2. Studies of Cancer in Humans

Most epidemiological studies of HIV have not differentiated between HIV-1 and the rarely seen HIV-2, which occurs almost exclusively in West Africa. In this section, unless specifically designated as HIV-2, the term HIV should be assumed to refer to HIV-1.

As described in Section 1.1.3, several different clades of both HIV-1 and HIV-2 have been defined. To date, there are no conclusive epidemiological data on the association between infection with specific clades and the occurrence of cancer in humans.

2.1 Kaposi's sarcoma

Kaposi's sarcoma is an AIDS-defining condition (see Section 1.4.4).

2.1.1 *Pathology and clinical disease*

In 1872, Dr Moriz Kaposi, a Hungarian dermatologist, first described an idiopathic, multiple, pigmented sarcoma, now called 'classic' Kaposi's sarcoma (Kaposi, 1872; Breimer, 1994). For many years, Kaposi's sarcoma was thought to be a lesion predominantly affecting elderly men of Mediterranean and eastern European origin (Dörffel, 1932; Landman *et al.*, 1984; Franceschi & Geddes, 1995). However, in the 1950s, as cancer registries became established in Africa, it was found that Kaposi's sarcoma comprised up to 8% of malignancies in some sub-Saharan regions, with an unusual endemic focus in parts of central Africa (Oettlé, 1962; Hutt & Burkitt, 1965). This 'endemic' Kaposi's sarcoma, like classic Kaposi's sarcoma, predominated in elderly men, but also occasionally affected children. In the 1960s and 1970s, Kaposi's sarcoma constituted up to 5% of cancers among immunosuppressed patients who had organ transplants (Penn, 1983, 1988a,b). In the early 1980s, a fourth variant of Kaposi's sarcoma, the so-called 'epidemic' Kaposi's sarcoma, heralded the onset of the AIDS epidemic in the United States (Hymes *et al.*, 1981).

The main pathological features of Kaposi's sarcoma are described in Section 4.2.1. The histopathology is identical in all variants (Templeton, 1981; Cockerell, 1991).

(*a*) *Clinical disease in HIV-seronegative individuals*

Classic or endemic Kaposi's sarcoma predominantly affects the skin of the lower limbs, and internal organs are rarely involved. The disease typically follows an indolent course, with patients surviving for an average of 10–15 years (Tappero *et al.*, 1993). Young children tend to have more severe disease than adults, often affecting the lymphatic system and internal organs rather than the skin, and shorter survival (Oettlé, 1962; Ziegler & Katongole-Mbidde, 1996). Adults develop plaques or nodules that may progress to sarcomatous or deeply infiltrative lesions (Taylor, 1971; Templeton, 1981). Kaposi's sarcoma in immunocompromised individuals (mainly transplant recipients and long-term users of steroids and cytotoxic drugs) often involves internal organs, lymph nodes and the face, mimicking the 'epidemic' type (Tappero *et al.*, 1993). In transplant recipients, Kaposi's sarcoma appears before most other tumours and may regress completely when immunosuppressive therapy is terminated (Penn, 1988a,b).

(*b*) *Clinical disease in HIV-seropositive individuals*

Kaposi's sarcoma may occur at milder levels of immunosuppression than other AIDS-defining illnesses. Lesions are usually multiple, progress rapidly, and may affect any area of the skin as well as internal organs. The tumours frequently begin as dusky-

red or violet macules, progressing over weeks or months to raised, painless, firm nodules and plaques. Although the tumour may affect the legs, as seen with classic Kaposi's sarcoma, lesions on the trunk, arms, genitalia and face are also common (Smith & Spittle, 1987). Lymph nodes and the oral cavity, most notably the palate, may be extensively involved. Oral Kaposi's sarcoma is often associated with involvement elsewhere in the gastrointestinal tract (Levine, 1993; Regezi *et al.*, 1993). Pulmonary Kaposi's sarcoma generally presents with shortness of breath and cough and is clinically difficult to distinguish from other pulmonary complications of AIDS (Levine, 1993).

Median survival following diagnosis of AIDS-related Kaposi's sarcoma is 14–18 months, a relatively long survival compared with other AIDS-defining illnesses (Casabona *et al.*, 1993; Jacobson *et al.*, 1993; Lundgren *et al.*, 1994; 1995; Luo *et al.*, 1995).

2.1.2 *Descriptive epidemiology of Kaposi's sarcoma*

(*a*) *Demographic variations: age and sex*

Formerly a tumour predominantly affecting the elderly (Oettlé, 1962; Templeton, 1981; Hutt, 1984; Geddes *et al.*, 1994; Hjalgrim *et al.*, 1996), Kaposi's sarcoma has shown a substantial alteration in age distribution in recent years, both in Africa and in Europe and the United States. In developed countries, the median age is now in the late thirties.

Age-specific incidence rates of Kaposi's sarcoma in Uganda and Zimbabwe in the early 1990s show a modest peak in children aged 0–4 years, a decline until age 15, and then the main peak at age 35–39 in men and age 25–29 in women (Wabinga *et al.*, 1993; Bassett *et al.*, 1995). In Europe and the United States, childhood Kaposi's sarcoma is very rare, only 32 cases having being recorded up to 1993 (Serraino & Franceschi, 1996a). Many of the European cases were in Romania, where intravenously acquired HIV infection had previously been documented (Hersh *et al.*, 1991; Orlow *et al.*, 1993).

Before the advent of AIDS, Kaposi's sarcoma was generally more frequent in men than in women, except among transplant recipients and children (Qunibi *et al.*, 1993; Serraino & Franceschi, 1996a,b), with a male : female ratio in developed countries as high as 15 : 1, although later studies found ratios of 2–3 : 1 in persons thought to be HIV-seronegative, possibly reflecting improved case ascertainment in women (Biggar *et al.*, 1984a; Franceschi & Geddes, 1995; Hjalgrim *et al.*, 1996). In Africa, male : female ratios above 10 from earlier surveys (Wahman *et al.*, 1991), have declined to about 3 : 1 more recently (Wabinga *et al.*, 1993; Bassett *et al.*, 1995; Newton *et al.*, 1996).

(*b*) *Geographical variations*

The incidence of Kaposi's sarcoma exhibits wide geographical variation.

In the 1960s, it represented up to 8% of all malignancies in some parts of sub-Saharan Africa (Table 6; Oettlé, 1962; Templeton, 1981; Hutt, 1984). Elsewhere, relatively high incidence rates were recorded in Israel (1970–79, 1.5/100 000 in both sexes combined; Landman *et al.*, 1984) and Italy (1976–84, 1.05/100 000 in men, 0.27/100 000 in women;

Geddes *et al.*, 1994), particularly in the south. The rates were lower in the United States (1973–79, 0.29/100 000 in men and 0.07/100 000 in women; Biggar *et al.*, 1984a) than in Europe (Grulich *et al.*, 1992; Hjalgrim *et al.*, 1996).

Table 6. Relative frequencies of Kaposi's sarcoma among all cancers in various areas of Africa

Reference	Location	Year(s) of study or report	Percentage of all cancers		
			Men	Women	Both
Oettlé (1962)	Belgian Congo	1956–57	–	–	9–13
	French Equatorial Africa	1953	–	–	5
	French West Africa	1954	–	–	1
	Gold Coast	1956	–	–	1
	Kenya	1948–61	–	–	2–4
	Mozambique	1958	–	–	2
	Natal	1957	–	–	1
	Nigeria	1934–44	–	–	2
	Rhodesia	1949	–	–	1
	South Africa	1960, 51	–	–	1–3
	Tanganyika	1960	–	–	3
	Tunisia	1960	–	–	< 1
Hutt & Burkitt (1965)	Uganda	1964	–	–	4
Bayley (1984)	Zaire	1983	–	–	9
Melbye *et al.* (1987)	Zaire	1984	16	–	–
Otu (1986)	Nigeria	1986	–	–	15–20
Ngendahayo *et al.* (1989)	Rwanda	1979–86	–	–	6
Wabinga *et al.* (1993)	Uganda	1989–91	49	18	–
Bassett *et al.* (1995)	Zimbabwe	1990–92	23	10	–
Newton *et al.* (1996)	Rwanda	1991–93	10	3	–
Patil *et al.* (1995)	Zaire	1980–89	–	–	7.0
Sitas *et al.* (1996)	South Africa				
	Black	1990–91	0.54	0.14	0.3
	White	1990–91	0.12	0.03	0.1

Since the advent of the AIDS epidemic, Kaposi's sarcoma has become even more common in parts of Africa (Table 6; Ziegler, 1993; Patil *et al.*, 1995). The prevalence of Kaposi's sarcoma in different areas of the world reflects both the proportion of homosexual and bisexual men and the proportion of people from high-risk countries such as Africa (see Section 2.1.5(*a*)).

Although widespread in parts of Africa before the AIDS epidemic, endemic Kaposi's sarcoma was not associated with HIV infection (Biggar *et al.*, 1984b). In some countries, modest increases in the incidence of Kaposi's sarcoma were already occurring before the onset of the AIDS epidemic (Dictor & Attewell, 1988; Hjalgrim *et al.*, 1996).

Volcanic dust has been proposed to contribute to the etiology of Kaposi's sarcoma. The evidence supporting this hypothesis came largely from the ecological observation that, for endemic Kaposi's sarcoma, the areas of highest incidence are located in seismically active regions around the Rift Valley of east Africa and (to a lesser extent) parts of Italy and Greece (Ziegler, 1993). One report described a two-fold increase (of borderline significance) in the risk for endemic Kaposi's sarcoma in a volcanic area of Italy (Montella *et al.*, 1996). However, many areas of endemic Kaposi's sarcoma are not volcanic regions. In a study of the distribution of endemic Kaposi's sarcoma in Italy, residence in flat lands and former malaria areas was a risk factor (Geddes *et al.*, 1995). [The Working Group noted that these hypotheses cannot explain the higher risk among homosexual men than other HIV-infected persons.]

(*c*) *Temporal changes*

The incidence of Kaposi's sarcoma increased dramatically with the arrival of the HIV epidemic. This increase is still being observed in some developing countries (Wabinga *et al.*, 1993; Bassett *et al.*, 1995) and some southern European countries, but the incidence appears to have reached a plateau in other developed countries, such as the United States (Dal Maso *et al.*, 1995).

2.1.3 *Descriptive epidemiological studies*

(*a*) *Studies in men in relation to marital status*

Studies of various types have attempted to quantify the incidence of Kaposi's sarcoma in groups affected by the HIV epidemic. Never-married young men were used as a surrogate representing homosexual men, who had the highest incidence of HIV infection in the populations studied (Table 7).

From 1973–80 to 1981–82, a significant increase in the odds ratio (OR) for Kaposi's sarcoma among never-married men compared to ever-married men was observed in San Francisco, CA, United States: 51.8 (95% confidence interval (CI)), 18.6–143.6), and in other areas covered by the Surveillance, Epidemiology and End Results (SEER) Program: 18.6 (95% CI, 2.2–154.5) (Biggar *et al.*, 1985). In San Francisco County, an OR of approximately 2000 was estimated in young single men when comparing data from 1973–79 and 1982. No similar increase was recorded among ever-married men. By 1984, Kaposi's sarcoma represented 56% of all malignancies among young never-married men in San Francisco city. In single men, the relative risk for Kaposi's sarcoma in 1984 compared with 1973–78 approached 2500 (Biggar *et al.*, 1987). In Los Angeles County, CA, United States, for never-married men, the proportionate OR for Kaposi's sarcoma in 1983–85 was nearly 100 times greater than that of 1972–79 (Bernstein *et al.*, 1989).

In 1985–87 in San Francisco County, compared with 1973–78, the incidence of Kaposi's sarcoma had increased over 5000-fold in single men under 50 years old and 200-fold in young married men. In the nine SEER areas combined (including low AIDS-incidence areas), the corresponding increase in young single men was 733-fold (Rabkin *et al.*, 1991).

Table 7. Increase in risk for Kaposi's sarcoma among never-married men since the beginning of the AIDS epidemic in the United States

Reference	Study area	Control group	Time period	Risk measure		95% CI[a] or χ^2_1 for trend
Biggar *et al.* (1985)	San Francisco County	Never-married men aged 20–49, 1973–79	1982	OR	2043	$p < 0.001$
	San Francisco area	Never-married men aged 20–49, 1973–80	1981–82	OR	52	19–144
	Other SEER areas	Never-married men aged 20–49, 1973–80	1981–82	OR	19	2–155
Biggar *et al.* (1987)	San Francisco City	Never-married men aged 20–49, 1973–78	1984	OR	2479	$p < 0.0001$
	San Francisco area	Never-married men aged 20–49, 1973–78	1984	OR	182	$p = 0.0001$
Rabkin *et al.* (1991)	San Francisco County	Never-married men aged 20–49, 1973–78	1985–87	RIR	5060	$p < 0.001$
	Total SEER areas	Never-married men aged 20–49, 1973–78	1985–87	RIR	733	$p < 0.002$
Bernstein *et al.* (1989)	Los Angeles County	Never-married men aged 18–54, 1972–79	1983–85	POR	96	$p < 0.0001$
Biggar *et al.* (1989)	Manhattan	Never-married men aged 20–49, 1973–76	1985	OR	1851	$p < 0.0001$
	Rest of New York City	Never-married men aged 20–49, 1973–76	1985	OR	484	$p < 0.0001$
	New York State	Never-married men aged 20–49, 1973–76	1985	OR	109	$p < 0.0001$

CI, confidence interval; OR, odds ratio; RIR, relative incidence ratio; SEER, Surveillance, Epidemiology and End Results; POR, proportionate OR

[a] In the absence of 95% CI, p value or χ^2_1 for trend is given

Rabkin and Yellin (1994) examined the incidence of Kaposi's sarcoma in a population-based study of never-married men, aged 25–54 years, in San Francisco, of whom an estimated 20 000 (24%) were HIV-seropositive in late 1984. In 1988–90, the estimated standardized incidence was 540/100 000, over 20 times higher than the concurrent rate in ever-married men (25/100 000; $p < 0.001$).

In 1985, the OR for Kaposi's sarcoma in single men in Manhattan, NY, United States, compared with the pre-AIDS period (1973–76), was 1851 (Biggar *et al.*, 1989). ORs were somewhat lower for the rest of New York City (484) and rest of New York State (109).

In New York City, small but consistent increases in the numbers of cases of Kaposi's sarcoma were seen also among married men and women of the same age group (Biggar *et al.*, 1989). Between 1976–78 (baseline period) and 1987–88, the annual incidence of Kaposi's sarcoma in women aged 20–49 years increased from 0 to 1.8/100 000 in black

women and 0 to 0.8/100 000 in white women in New York City, but did not change in the remainder of New York State (Rabkin *et al.*, 1993a).

(*b*) *Linkage studies between AIDS and cancer registries*

Record linkage between AIDS and cancer registration databases is an alternative methodology for examining associations between HIV infection and cancer in a population (Coté *et al.*, 1995). Such studies are facilitated by the relative completeness of AIDS and cancer registries with respect to Kaposi's sarcoma (Reynolds *et al.*, 1990; Barchielli *et al.*, 1995; Coté *et al.*, 1995). By matching 2528 AIDS registry cases with 62 500 cancer registry cases from the State of Illinois, United States, Coté *et al.* (1991) found a standardized incidence ratio (SIR) of Kaposi's sarcoma in AIDS patients of 972 compared with the general population of Illinois, an area of low risk for AIDS. This ratio was based on 137 linked cases of Kaposi's sarcoma.

Reynolds *et al.* (1993) linked 1454 cases of Kaposi's sarcoma in the California Tumor Registry (active since 1969) with all AIDS cases diagnosed in San Francisco since 1980. Before 1980, Kaposi's sarcoma was very rare. In 1980–87, the relative risk in AIDS patients was 716 compared with the general population.

Similar results have been reported from Italy and Switzerland (Franceschi *et al.*, 1992; Barchielli *et al.*, 1995; Serraino *et al.*, 1995a). Data for children are shown in Table 8 (Serraino & Franceschi, 1996a,b).

2.1.4 *Analytical studies*

(*a*) *Cohort studies*

Veugelers *et al.* (1994) from the Tricontinental Seroconverter Study studied 407 homosexual men with known date of HIV seroconversion, among whom 37 developed Kaposi's sarcoma.

Lundgren *et al.* (1995) studied 687 AIDS patients diagnosed in Denmark up to the end of 1990. Among these, 437 were homosexual or bisexual men who had died at the end of follow-up and 138 had developed Kaposi's sarcoma either at the time of AIDS diagnosis or during follow-up.

Dore *et al.* (1996) carried out a retrospective cohort study of 2580 people diagnosed with AIDS in Australia in 1983–94, among whom Kaposi's sarcoma was the AIDS-defining illness for 451, and among the remaining 2129 patients, Kaposi's sarcoma developed subsequently in 265.

[The Working Group noted that, although none of these studies reported the number of expected cases based on the incidence in the corresponding general population, the high proportions of persons in these cohorts who developed Kaposi's sarcoma must reflect a very high relative risk.]

Table 8. Odds ratio (OR) and 95% confidence interval (CI) for Kaposi's sarcoma (KS) according to selected characteristics and geographical area in children with AIDS, 1981–93

Characteristic	Europe			United States		
	KS/AIDS[a]	OR[b]	95% CI	KS/AIDS[a]	OR[c]	95% CI
Age (years)						
≤ 4[d]	5/3875	1		15/3796	1	
5–12	5/525	12.0	2.22–52.4	7/914	1.95	0.7–5.1
Gender						
Females[d]	3/1920	1		12/2224	1	
Males	7/2480	[1.5	0.3–7.2]	10/2486	0.8	0.3–1.9
Ethnic group						
White[d]		–		5/2136	1	
Black		–		17/2574	2.8	1.0–8.6
Transmission category						
Mother to child[d]	2/1802	1		20/4121	1	
Haemophiliacs and transfused	7/1671	3.13	0.4–162.1	2/523	0.9	0.1–4.2
Period of diagnosis						
≤ 1990[d]	[3/2440]	1		[20/3283]	1	
1991–93	[7/1788]	[2.3]	[0.5–12.5]	[2/1427]	[0.2]	[0.04–1.01]

Modified from Serraino & Franceschi (1996a,b)
[a] Some numbers do not add up to the same total because of missing values.
[b] Adjusted for age and European country
[c] Adjusted for age
[d] Reference category
[ ] calculated by the Working Group

(*b*) *Case–control studies*

Early studies measured the prevalence of antibodies to HIV in AIDS patients, including those with Kaposi's sarcoma, compared with various control groups. These studies established that antibodies to HIV were strongly associated with the development of Kaposi's sarcoma.

HIV infection was found in 11/18 Kaposi's sarcoma patients and in 8/200 control persons with other cancers in Rwanda (relative risk, 35.0; 95% CI, 8.2–206.7) (Newton *et al.*, 1995).

(*c*) *Analytical studies of the relationship between degree of immunosuppression and Kaposi's sarcoma among HIV-infected persons*

Muñoz *et al.* (1993) followed a cohort of HIV-infected homosexual and bisexual men during 1985–91. Among the 873 AIDS cases observed in the cohort, 194 had Kaposi's sarcoma as AIDS-defining illness. A diagnosis of Kaposi's sarcoma was strongly associated with $CD4^+$ T-cell count, with an incidence of 15/100 person-years for those with

$CD4^+$ count below 100 cells/mm^3 to 0.3/100 person-years for those with $CD4^+$ count above 500. Only 7.8% (12/153) of all initial AIDS-defining diagnoses of Kaposi's sarcoma were made in men with a $CD4^+$ count above 500 cells/mm^3. These data clearly show that the risk for Kaposi's sarcoma among AIDS patients is associated with the degree of immunosuppression.

In the early period of the AIDS epidemic, Kaposi's sarcoma was considered to be a relatively early manifestation of AIDS compared with, for example, lymphomas and many opportunistic infections. In recent years, Kaposi's sarcoma has been reported to occur later in the course of HIV disease than in the past. Lundgren *et al.* (1995) documented a significant decline in median $CD4^+$ count among AIDS patients from Denmark with Kaposi's sarcoma as initial AIDS diagnosis from 96 cells/mm^3 before 1987 to 28 cells/mm^3 in 1989–90.

Very similar results were obtained by Dore *et al.* (1996), who found a significant decline in median $CD4^+$ count for Kaposi's sarcoma patients as initial AIDS diagnosis from 92 cell/mm^3 in 1983–87 to 40 cells/mm^3 in 1991–94 ($p < 0.0005$).

Veugelers *et al.* (1995) studied the AIDS outcomes among 407 homosexual men. Their data showed that HIV-infected men who seroconverted before 1985 did not progress faster to Kaposi's sarcoma than men who seroconverted later.

2.1.5 *Factors influencing the occurrence of Kaposi's sarcoma in HIV-1-infected individuals*

(*a*) *Behavioural cofactors*

(i) *Descriptive studies*

The risk for Kaposi's sarcoma varies greatly with HIV transmission risk group, being particularly high in homosexual and bisexual men (see Tables 9–12, which were produced on the basis of AIDS surveillance data (Dal Maso *et al.*, 1995)). Figure 7 shows that even in young homosexual and bisexual men (aged 13–24 years), there is already an elevated proportion with Kaposi's sarcoma compared with other HIV-transmission groups. Since first homosexual intercourse must have been recent, this finding implies a rapid increase in risk following sexual transmission of the putative Kaposi's sarcoma agent (Franceschi & Serraino, 1995).

Beral *et al.* (1990) found that, among 88 739 AIDS patients in the United States, 13 616 (15%) developed Kaposi's sarcoma. The proportion varied from 21% in homosexual or bisexual men to 3% in heterosexuals, 2% in intravenous drug users, 3% in transfusion recipients, 1% in haemophiliacs and 1% in children infected by perinatal transmission.

In Spain, Casabona *et al.* (1990) found that, among 1074 AIDS patients, 124 presented with Kaposi's sarcoma: 36% in homosexual or bisexual men, 2% in intravenous drug users and none in 35 heterosexuals, 5 transfusion recipients, 23 haemophiliacs and 33 children infected by perinatal transmission.

Table 9. Numbers and proportions of male AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and HIV transmission group, in Europe and United States, 1981–94

Country[a]	Homo/bisexual men		Intravenous drug users		Heterosexuals				Haemophiliac and transfused		Other/ unknown		All	
	KS cases	(%)[d]	KS cases	(%)[d]	Pattern II countries[b]		Natives		KS cases	(%)[d]	KS cases	(%)[d]	KS cases	(%)[d]
					KS	(%)[d]	KS	(%)[d]						
Austria	106	(20)	2	(1)	0	(0)	3	(4)	0	(0)	9	(6)	120	(11)
Belgium	209	(28)	2	(2)	40	(14)	9	(5)	4	(7)	1	(2)	265	(19)
Denmark	217	(18)	0	(0)	1	(6)	2	(2)	1	(2)	1	(2)	222	(15)
France	5 396	(31)	122	(2)	94	(6)	157	(9)	34	(3)	188	(11)	5 991	(20)
Germany	2 151	(24)	35	(3)	10	(10)	22	(7)	5	(1)	88	(14)	2 311	(20)
Greece	107	(19)	2	(7)	2	(25)	8	(14)	2	(2)	18	(11)	139	(15)
Italy	934	(21)	300	(2)	10	(6)	96	(7)	21	(5)	100	(9)	1 461	(7)
Netherlands	493	(19)	0	(0)	1	(2)	8	(5)	0	(0)	4	(9)	506	(16)
Portugal	216	(28)	15	(2)	0	(0)	55	(12)	3	(3)	13	(14)	302	(15)
Spain	1 333	(26)	217	(1)	0	(0)	85	(5)	10	(1)	91	(5)	1 736	(7)
Sweden	134	(18)	0	(0)	4	(8)	5	(7)	1	(2)	0	(0)	144	(14)
Switzerland	480	(26)	28	(2)	6	(12)	38	(11)	2	(3)	9	(11)	563	(16)
UK	1 569	(20)	5	(1)	59	(12)	11	(5)	0	(0)	10	(6)	1 654	(17)
USA White	30 255	(21)	548	(4)	–[c]	–[c]	93	(5)	109	(2)	382	(8)	31 387	(19)
Black	4 198	(10)	711	(2)	–[c]	–[c]	101	(2)	30	(3)	331	(4)	5 371	(6)
Other	5 583	(19)	560	(3)	–[c]	–[c]	67	(4)	30	(4)	204	(6)	6 444	(12)

KS, Kaposi's sarcoma

[a] Only countries with > 100 cases of Kaposi's sarcoma over the period 1981–94 are included.

[b] Individuals originating from Pattern II countries (countries in which extensive spread of HIV began in the mid-to-late 1970s or early 1980s and in which heterosexual transmission has predominated and continues to)

[c] Data not available

[d] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective risk group

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Table 10. Numbers and proportions of female AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and HIV transmission group, in Europe and United States, 1981–94

Country[a]	Intravenous drug users		Heterosexuals		Haemophiliacs and transfused		Other/ unknown		All	
	KS cases	(%)[b]	KS cases	(%)[b]	KS cases	(%)[b]	KS cases	(%)[b]	KS cases	(%)[b]
Belgium	1	(3)	22	(7)	2	(4)			25	(5)
France	33	(1)	83	(3)	16	(2)	6	(1)	138	(2)
Italy	55	(2)	33	(2)	3	(2)	13	(4)	104	(2)
Spain	55	(1)	16	(7)	2	(1)			74	(1)
UK			42	(7)	1	(1)			43	(5)
US White	60	(1)	42	(1)	18	(1)	14	(2)	134	(1)
Black	136	(1)	48	(1)	9	(1)	46	(1)	250	(1)
Other	56	(1)	37	(1)	5	(1)	4	(1)	103	(1)

KS, Kaposi's sarcoma

[a] Only countries with > 25 cases over the period 1981–94 are included.

[b] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective risk group

[c] Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

In the United Kingdom, Beral *et al.* (1991a) found that, among 2830 AIDS patients, 566 developed Kaposi's sarcoma. The proportion varied from 23% in homosexual or bisexual men and 10% in heterosexuals to 0% in 83 intravenous drug users, 47 transfusion recipients, 163 haemophiliacs and 23 children infected by perinatal transmission.

European (Serraino *et al.*, 1992a; Franceschi *et al.*, 1995b; Serraino *et al.*, 1995b) and Australian (Elford *et al.*, 1993) surveillance data have confirmed that Kaposi's sarcoma is more common among homosexual and bisexual men and women who reported sexual rather than parenteral exposure to HIV. This finding is particularly notable since a high proportion of transfusion-associated AIDs cases have received blood from homosexual or bisexual men, so that even massive blood contact does not appear to increase the risk as much as sexual contact (Busch *et al.*, 1991).

Among people who acquired HIV by heterosexual contact, the risk for developing Kaposi's sarcoma varies according to country of origin: Kaposi's sarcoma occurred in 18% of AIDS cases in Rwanda (Van de Perre *et al.*, 1984), 16% in Zaire (Piot *et al.*, 1984), 13% of infected Africans resident in Belgium (Clumeck *et al.*, 1984), 8% of infected Africans resident in the United States, 6% of AIDS cases in Haitians resident in

the United States and 14% of infected Africans resident in the United Kingdom, as compared to 2–5% of AIDS patients in the United States or Europe (Beral *et al.*, 1990, 1991a) [Data calculated by Beral (1991a) from the original papers.]

Table 11. Numbers and proportions of AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and year of AIDS diagnosis, among homosexual and bisexual men in Europe and the United States, 1981–94

Country[a]	Year of diagnosis											
	Pre-1985		1985–86		1987–88		1989–90		1991–92		1993–94	
	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]
Austria	6	50	5	22	18	20	17	14	35	24	25	18
Belgium	4	29	15	35	30	29	41	23	64	29	55	28
Denmark	11	31	22	24	34	19	47	17	54	19	49	16[b]
France	107	45	485	41	968	33	1274	31	1353	30	1209	28[b]
Germany	53	39	227	36	420	26	538	25	547	24	366	17[b]
Greece			4	17	12	17	16	14	40	24	35	21
Italy	8	38	39	22	126	26	202	21	263	21	296	19[b]
Netherlands	17	35	44	24	97	21	115	18	135	19	85	15[b]
Portugal	3	100	13	36	29	30	46	24	77	32	48	24
Spain	12	60	54	33	181	29	313	25	429	27	344	22[b]
Sweden	4	25	22	30	25	21	31	17	33	21	19	10[b]
Switzerland	14	44	63	40	102	31	106	24	107	22	88	22[b]
UK	54	39	169	28	276	21	315	19	374	18	381	19[b]
USA												
White	2525	44	4603	29	6485	22	7260	21	7043	18	2339	15[b]
Black	249	20	460	13	741	10	1091	10	1112	8	545	8[b]
Other	292	32	678	26	1080	21	1370	19	1522	17	641	14[b]

KS, Kaposi's sarcoma

[a] Only countries with > 100 cases of Kaposi's sarcoma over the period 1981–94 are included.

[b] χ^2_1 for trend, > 3.84; $p < 0.05$

[c] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective calendar period

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Table 12. Numbers and proportions of AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and year of AIDS diagnosis, among men (other than homosexual and bisexual) and women in Europe and the United States, 1981–94

Country[a]	Year of diagnosis											
	Pre 1985		1985–86		1987–88		1989–90		1991–92		1993–94	
	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]
Men												
Belgium	8	12	8	14	13	14	9	8	10	6	8	5[b]
France	12	12	34	9	94	6	119	4	171	5	165	4[b]
Germany	6	16	13	9	37	8	28	4	44	6	32	5[b]
Italy	2	10	20	6	69	4	113	3	149	3	174	3[b]
Portugal			2	8	7	8	17	9	14	4	46	7
Spain	4	9	8	2	44	2	81	2	130	2	136	2
UK			2	2	8	4	15	4	31	6	29	5
USA												
White	40	7	83	5	165	4	272	5	349	5	223	5
Black	76	6	104	4	174	3	274	3	327	2	218	2[b]
Other	29	6	65	4	143	3	200		283	4	141	3[b]
Women												
France	3	8	12	5	22	3	28	2	36	2	37	2[b]
Italy			6	5	12	2	22	2	19	1	45	2
Spain	1	14	4	4	10	2	15	1	17	1	27	1
UK	3	43	1	5			5	3	18	6	15	4
USA												
White	17	9	24	3	26	1	39	1	48	1	21	1[b]
Black	23	5	28	2	56	2	83	1	107	1	65	1[b]
Other	1	1	17	3	29	2	41	2	52	2	30	1

KS, Kaposi's sarcoma

[a] Only countries with > 40 cases of Kaposi's sarcoma in each group over the period 1981–94

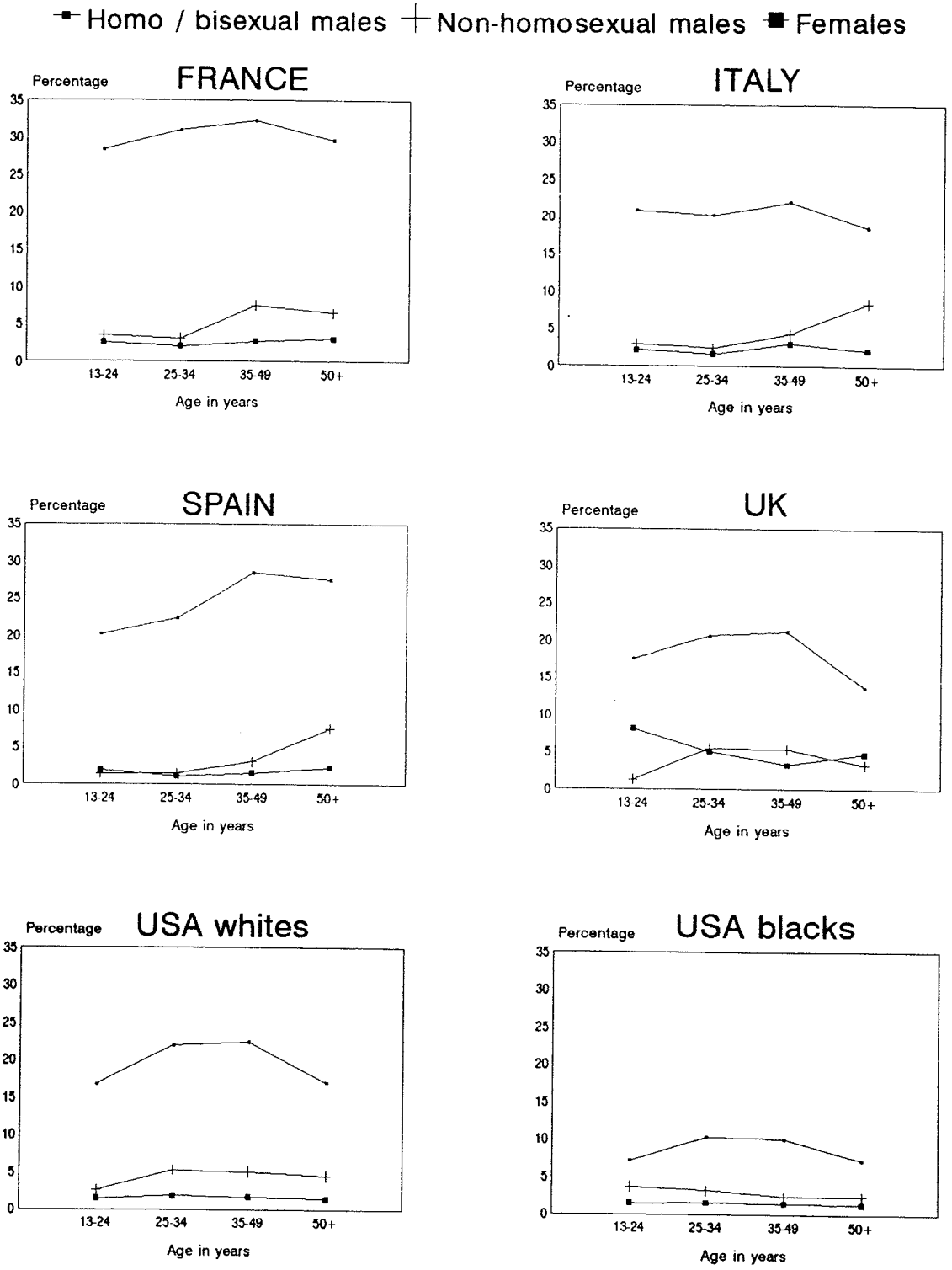
[b] χ^2_1, for trend, > 3.84; $p < 0.05$

[c] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective calendar period

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

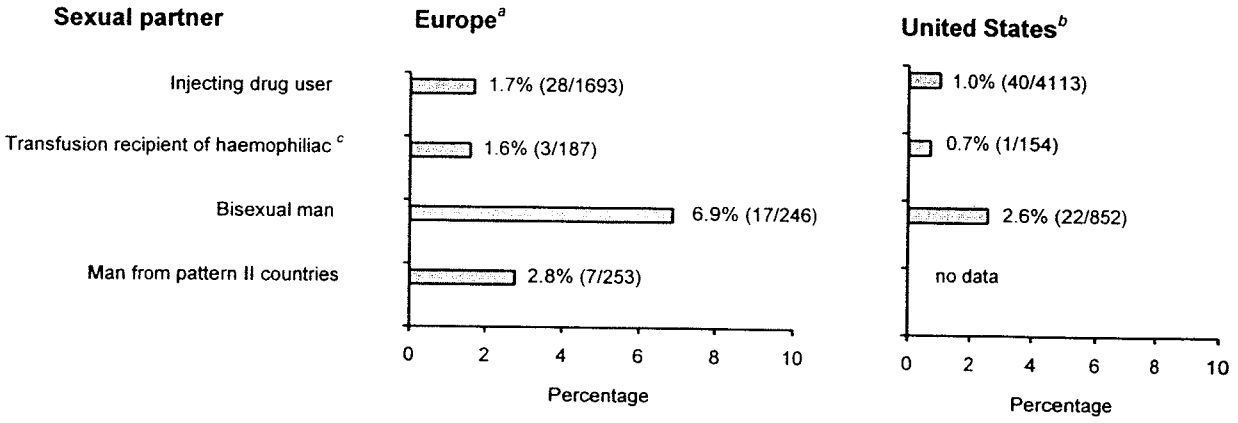
In addition, the proportion of sexually infected female AIDS patients presenting with Kaposi's sarcoma was highest in those whose reported sexual partners were bisexual men (2.6% in the United States, Peterman *et al.*, 1993; 6.9% in Europe, Serraino *et al.*, 1995b) (Figure 8).

Figure 7. Percentage of Kaposi's sarcoma as AIDS-defining illness by age in homosexual and non-homosexual males and females in selected European countries and the United States (whites and blacks), 1981–94



Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Figure 8. Percentage of Kaposi's sarcoma in women who acquired AIDS via heterosexual contact by their sexual partner's reported HIV-transmission group, Europe, 1981-93 and United States, [1981-91]



Pattern II countries: Extensive spread of HIV began in the mid-to-late 1970s or early 1980s. Heterosexual transmission has predominated and continues to.

[a] Modified from Serraino *et al.* (1995b)

[b] Modified from Peterman *et al.* (1993)

[c] In United States, transfusion recipient of haemophiliac. In Europe, blood recipient

(ii) *Analytical studies*

A number of studies have contrasted the sexual practices of homosexual men with Kaposi's sarcoma with those of men with opportunistic infections or other manifestations of AIDS (Tables 13 and 14).

Several studies have reported on the number of sexual partners among homosexual and bisexual men with Kaposi's sarcoma compared with homosexual and bisexual men with other AIDS manifestations (Table 13). Most of these studies (Haverkos *et al.*, 1985; Goedert *et al.*, 1987; Archibald *et al.*, 1990; Armenian *et al.*, 1993), but not all (Lifson *et al.*, 1990a,b), found that the Kaposi's sarcoma patients had a higher number of sexual partners. Goedert *et al.* (1987) also reported that Kaposi's sarcoma patients had more sexually transmitted diseases.

Similar studies have been undertaken of insertive oral–anal contact among Kaposi's sarcoma patients compared with men with other AIDS manifestations. Some studies (Archibald *et al.*, 1990; Beral *et al.*, 1992; Darrow *et al.*, 1992), but not all (Lifson *et al.*, 1990b; Elford *et al.*, 1992; Kaldor *et al.*, 1993; Page-Bodkin *et al.*, 1992; Armenian *et al.*, 1993) have found this sexual practice to be more common among Kaposi's sarcoma patients than among other AIDS patients (Table 14).

In conclusion, men who developed Kaposi's sarcoma have tended to be more sexually active, have had more sexually transmitted diseases and had more sexual partners from areas where Kaposi's sarcoma is common. In conjunction with the much higher risk for

Kaposi's sarcoma in homosexual men than in other HIV transmission groups, the data have led some authors to suggest that an infectious and sexually transmitted agent (independent of HIV) is associated with Kaposi's sarcoma. It should be noted that very few data on risk factors for Kaposi's sarcoma are available from Africa.

Table 13. Studies of the association between risk factors and Kaposi's sarcoma in homosexual men

Reference	Risk behaviour	AIDS manifestations	Proportion of cases	
			No.	%
Haverkos *et al.* (1985)	≥ 100 male sexual partners in year before illness	KS	29/47	61
		PCP	6/20	30
Goedert *et al.* (1987)	≥ 100 homosexual partners during the previous year	KS	3/8	38
		PCP	3/10	30
	≥ 3 STDs	KS	1/8	13
		PCP	0/10	
Archibald *et al.* (1990)[a]	> 20 male sexual partners in prior year	KS	19/25	76
		Other infections	25/48	52
	> 20 sexual partners from areas of high risk for KS[b]	KS	14/25	56
		Other infections	10/48	21
Lifson *et al.* (1990a,b)	Median no. of sexual partners: 300	KS	71 cases	
	Median no. of sexual partners: 278	Other	107 cases	
Armenian *et al.* (1993)[c]	≥ 49 male partners in the last 2 years	KS	159/314	51
		Non-cancerous AIDS controls	194/508	38
	Having partners from high risk areas[d]	KS	65/314	21
		Non-cancerous AIDS controls	61/508	12

KS, Kaposi's sarcoma; PCP, *Pneumocystis carinii* pneumonia; STD, sexually transmitted disease

[a] A reanalysis of the same cohort in 1992 found very similar results (Archibald *et al.*, 1992)

[b] San Francisco, Los Angeles, New York

[c] This cohort was first studied by Jacobson *et al.* (1990)

[d] From San Francisco for participants from other than Los Angeles

(*b*) *Infectious cofactors*

(i) *Human herpesvirus 8*

For a more detailed description of human herpesvirus 8 (HHV-8), see Section 4.2.4.

Chang *et al.* (1994) announced the discovery of a previously unknown human herpesvirus in Kaposi's sarcoma tissue of AIDS patients from the United States. The

Table 14. Studies of insertive oro-anal contact as a risk factor for Kaposi's sarcoma among AIDS patients

Reference	Location	Period of interview	Period of sexual behaviour assessed	KS post-AIDS included in cases	Index of IOAC	Proportion reporting IOAC[a] Numbers (%)	
						AIDS patients with KS	AIDS patients without KS
Armenian *et al.* (1993)	4 US cities	1984–85, 1987–91	2 years before enrolment	No	Being rimmed	240/314 (76%)	357/508 (70%)
Beral *et al.* (1992)	London, UK	1984-85	Previous five years	Yes	Insertive rimming, less than once a month and at least once a month but less than once a week	[14/30 (47%)]	[5/35 (14%)]
Darrow *et al.* (1992)	4 US cities	1981	Previous one year	No	> 10% of sexual contacts	22/49 (45%)	0/8
Archibald *et al.* (1990)	Vancouver, Canada	1982–84	At enrolment	Yes	Insertive fists	18/25 (72%)	23/48 (48%)
Lifson *et al.* (1990b)	San Francisco, USA	1983–86	1978–80 to 1983–84	Yes	Proportion of steady sexual partners with whom practised	4/71 (5%)	5/107 (5%)
Elford *et al.* (1992)	Sydney, Australia	1984, then 6-monthly[b]	1984 to diagnosis of AIDS	No	Any	29/55 (53%)	65/116 (56%)
Page-Bodkin *et al.* (1992)	San Francisco, USA	1984–91	2 years before interview	Yes	With some or most of sexual partners	43/87 (49%)	51/100 (51%)
Kaldor *et al.* (1993)	Sydney, Australia	1984–85	3 months before enrolment	No	[Insertive rimming]	[22/45 (49%)]	[34/88 (39%)][c]

KS, Kaposi's sarcoma; IOAC, insertive oro-anal contact

[a] Except where specified

[b] Self-administered questionnaire

[c] Numbers recalculated by the Working Group

virus, described as 'Kaposi's sarcoma-associated herpesvirus' (KSHV) or as human herpesvirus 8 (HHV-8), was identified by the use of representational difference analysis to discern DNA sequences in tumour tissue that were absent from normal DNA. The sequences, which showed similarity to a number of gammaherpesviruses (including Epstein–Barr virus (EBV)), were found in 21/27 (78%) people with AIDS-related Kaposi's sarcoma, 6/39 (15%) AIDS patients without Kaposi's sarcoma and 0/103 non-AIDS controls ($p < 10^{-7}$ using non-Kaposi's sarcoma controls).

A number of laboratories have since reported the detection of HHV-8 in biopsies of all epidemiological forms of Kaposi's sarcoma and/or in PBMCs from Kaposi's sarcoma patients (see Table 15). Overall, HHV-8 has been detected in more than 98% of Kaposi's sarcoma biopsies, but much less frequently and in lower amounts in skin of Kaposi's sarcoma patients. Using PCR, HHV-8 has been detected in PBMCs from about 50% of Kaposi's sarcoma patients (Ambroziak *et al.*, 1995 (in 100%); Howard *et al.*, 1995; Whitby *et al.*, 1995), but not at all (Ambroziak *et al.*, 1995; Whitby *et al.*, 1995) or in only 9% (Bigoni *et al.*, 1996) in those of healthy blood donors. In asymptomatic HIV-infected individuals, detection of HHV-8 in peripheral blood strongly predicts progression to Kaposi's sarcoma (Collandre *et al.*, 1995; Howard *et al.*, 1995; Whitby *et al.*, 1995). These findings suggest that HHV-8 has only a limited distribution in developed countries, but is an independent risk factor for classic (Mediterranean), African endemic and AIDS-associated Kaposi's sarcoma. However, the distribution of HHV-8 in the general population is not yet fully clear. Two groups have found HHV-8 in semen samples and prostate of healthy HIV-seronegative individuals (Lin *et al.*, 1995; Monini *et al.*, 1996), whereas others have not confirmed this observation (Ambroziak *et al.*, 1995; Li *et al.*, 1995).

Preliminary serological data also support the view that HHV-8 is infrequent in the general populations of developed countries. Antibodies to several proteins of HHV-8 can be detected in the majority of Kaposi's sarcoma patients, but only infrequently in HIV-infected individuals without Kaposi's sarcoma (Miller *et al.*, 1996; Moore *et al.*, 1996) and in the general population. These findings underline the strong association between detection of HHV-8 and the presence of Kaposi's sarcoma. However, in view of the conflicting PCR-based evidence, it needs to be established whether the presence of antibodies to HHV-8 reflects infection with, rather than reactivation of, HHV-8.

The advent of serological tests for HHV-8 should allow larger and more thorough epidemiological studies to be conducted, looking at the prevalence of the agent in populations at differing risk of developing Kaposi's sarcoma. If the virus is ubiquitous, it throws into question the issue of causality for Kaposi's sarcoma. Using an immunoblot assay for two latent nuclear antigens specific for HHV-8, Gao *et al.* (1996a) showed that the seroprevalence of HHV-8 did vary between groups with differing risk of Kaposi's sarcoma, being most prevalent in those at highest risk. Of 40 patients with Kaposi's sarcoma (recruited from the Multicentre AIDS cohort study (MACS)), 32 (80%) were positive for antibodies to HHV-8, compared to 7/40 (18%) homosexual men without the disease (just before the onset of AIDS). Of 122 HIV-seronegative blood donors and

Table 15. Proportion of patients with HHV-8 in relation to Kaposi's sarcoma and HIV/AIDS status

Reference	HHV-8-positive proportion of patients				
	AIDS/HIV+ KS+	AIDS/HIV– KS+	AIDS/HIV+ KS–	AIDS/HIV– KS–	Comments
Chang *et al.* (1994)	21/27		6/39[a]	0/103[b]	[a] Lymphomas, lymph nodes biopsies [b] Non-AIDS lymphomas, lymph nodes, cancers, other biopsies
Su *et al.* (1995)	4/4	2/3	0/5[a]	0/32[b]	[a] AIDS lymph nodes [b] Benign and malignant lymphoid tissue
Dupin *et al.* (1995)	4/4[a]	5/5[b]		0/6[c]	[a] Homosexual [b] Mediterranean KS [c] Other patients
Boshoff *et al.* (1995a)	14/14[a]	16/17[b] 8/8[d] 1/1[e]		0/11[c]	[a] 12 males, 2 females [b] Mediterranean patients [c] Various skin lesions (9 M, 2 F) [d] Organ transplant recipients [e] Homosexual
Ambroziak *et al.* (1995)	12/12[a] 7/7[b]	1/1[a] 3/3[b]	0/6[b]	0/14[b,c]	[a] Homosexual patients [b] HHV-8 detected in PBMCs [c] Healthy lab volunteers
Moore & Chang (1995)	10/11[a]	6/6[b] 4/4[a]		1/11 0/10[c]	[a] 10/11 Homosexual [b] Mediterranean 'classic' [c] PBMCs
Howard *et al.* (1995)	11/14[a,c] 0/6[b,c] 11/17[d]		1/19[c,e] 0/6[a]		All homosexual [a] Pulmonary and cutaneous KS [b] Cutaneous KS only [c] Bronchoalveolar lavage fluid [d] HHV-8 detected in PBMCs [e] The patient re-presented with [a] 3 months later

Table 15 (contd)

Reference	HHV-8-positive proportion of patients				Comments
	AIDS/HIV+ KS+	AIDS/HIV− KS+	AIDS/HIV+ KS−	AIDS/HIV− KS−	
Whitby *et al.* (1995)	24/46[a]		11/143[a]	0/160[a,b]	[a] HHV-8 detected in PBMCs [b] 134 blood donors, 26 cancer patients
Buonaguro *et al.* (1996)	19/19[a] 0/5[e]	42/42[b] 9/13[e]	0/15[c]	0/17[d]	[a] 5 Italian, 5 North American, 3 Ugandan, 3 Kenyan origin, KS tissues [b] 28 classic KS (5 Greek, 6 North American, 17 Italian), 2 iatrogenic (Greek), 12 African endemic KS (Ugandan) [c] PBMCs [d] Human biopsies from healthy individuals or affected by other pathologies [e] Autologous uninvolved skin of a and b
Chang *et al.* (1996)[a]	22/24	17/20	1/7	2/15	[a] Ugandan patients
Huang *et al.* (1995)	12/12[a]	14/18[b]			[a] US origin [b] Mediterranean (classic) and African origin
Lebbé *et al.* (1995)	2/2	14/14[a] 0/5[b]			[a] Immunosuppressed (1), classic (10), endemic (3) KS [b] PBMCs
Schalling *et al.* (1995)	17/17[a] 8/8[b]	18/18[a] 3/3[b]			[a] KS biopsies, Ugandan origin [b] KS biopsies, Swedish origin

Table 15 (contd)

Reference	HHV-8-positive proportion of patients				Comments
	AIDS/HIV+ KS+	AIDS/HIV– KS+	AIDS/HIV+ KS–	AIDS/HIV– KS–	
Bigoni *et al.* (1996)			0/10[b] – 4/58[d]	7/80[b] 1/11[c] 5/56[d]	[a] Italian patients [b] Non-Hodgkin's lymphoma patients [c] Reactive lymphadenopathy [d] HHV-8 detected in PBMCs
Prospective studies: Whitby *et al.* (1995)	No. developing KS[a] HIV+				[a] AIDS patients KS-free at recruitment; average 30 months follow-up [b] HHV-8 detected in PBMCs
	HHV-8+[b]	HHV-8–[b]			
	6/11 55% ($p < 0.00005$)	12/132 (9%)			

KS, Kaposi's sarcoma; PBMC, peripheral blood mononuclear cell; M, male; F, female

20 HIV-infected haemophiliacs, none were seropositive. The 40 patients with HIV-associated Kaposi's sarcoma had each been followed for a period of between 13 and 103 months before diagnosis of the disease (all were HIV-seropositive on entry). In that time, 11/40 (28%) were seropositive for HHV-8 throughout, 21 (52%) became positive between 6 and 75 months prior to diagnosis, 6/40 (15%) remained seronegative throughout and 2/40 (5%) changed from seropositive to seronegative during the course of the study. These data support the hypothesis that HHV-8 is causal for Kaposi's sarcoma and suggest that many of those who get the disease seroconvert to antibodies against the virus relatively soon before its onset. Further studies in these patients (using a different serological assay: an immunofluorescent assay) showed that they had an antigen profile suggestive of primary infection with HHV-8 rather that reactivation of a chronic existing infection (high titres of IgC and absence of IgA and IgM).

A second study by Gao *et al.* (1996b) compared the prevalence of HHV-8 in those with and without Kaposi's sarcoma from Uganda, Italy and the USA. There is a very strong association between seropositivity for HHV-8 and Kaposi's sarcoma, both in HIV-seropositive and in HIV-seronegative patients. However, the prevalence of HHV-8 in HIV-seronegative blood donors or patients with cancers other than Kaposi's sarcoma (for which there is no evidence of an association with HHV-8), varied dramatically between countries, being highest in Uganda (51%), followed by Italy (4%) and then the USA (0%). Kaposi's sarcoma remains virtually unknown outside of HIV-seropositive homosexual men in the USA (and some immigrant groups), but has existed at a low incidence in Italy and a considerably higher incidence in Uganda since well before the early 1980s (Templeton, 1973). Therefore, these results might be expected if HHV-8 were causal for Kaposi's sarcoma.

(ii) *Cytomegalovirus*

Even before the HIV epidemic, there were reports that cytomegalovirus antibody was more commonly present in persons with endemic forms of Kaposi's sarcoma (Giraldo *et al.*, 1975, 1978); cytomegalovirus genome was detected in Kaposi's sarcoma tissue from endemic cases (Giraldo *et al.*, 1980). Early in the AIDS epidemic, it was observed that the great majority of homosexual men had cytomegalovirus antibodies, compared with only half of the general population of the same age (Drew *et al.*, 1982; Melbye *et al.*, 1983; Rogers *et al.*, 1983), leading some investigators to suggest that it was a plausible candidate for the causal agent of AIDS itself (Urmacher *et al.*, 1982; Mintz *et al.*, 1983). However, other studies failed to confirm the consistent presence of the cytomegalovirus genome within Kaposi's sarcoma tissue (Ambinder *et al.*, 1987; Kempf *et al.*, 1995).

In retrospect, the reported associations between AIDS, immunosuppression or Kaposi's sarcoma and cytomegalovirus antibody prevalence or titre were probably due to failure to obtain controls adequately matched by sexual habits (Johnston *et al.*, 1990).

(iii) *Other infectious agents*

There is little evidence to support a relationship between human herpesvirus 6 (HHV-6) and Kaposi's sarcoma. One study failed to detect an elevated HHV-6 prevalence in

Kaposi's sarcoma tissue compared with normal skin; when detected, it was the more common B variant (Kempf *et al.*, 1995). However, another study reported that the less common A variant of HHV-6 was present in nearly a third of both endemic and HIV-related cases (Bovenzi *et al.*, 1993). Infection with HHV-6 occurs early in life and antibodies are common in adults (Krueger *et al.*, 1988; Dolcetti *et al.*, 1994).

Two studies have found human papillomaviruses (see IARC, 1995) in Kaposi's sarcoma tissue from AIDS cases, detected by PCR (Huang *et al.*, 1992) and by immunohistochemistry (Nickoloff *et al.*, 1992), but other investigations have failed to confirm these findings (Biggar *et al.*, 1992; Kaaya *et al.*, 1993a).

Rochalimaea henselae is a bacterium associated with angiomatoses that might be confused with Kaposi's sarcoma. It has been considered as a causal agent for Kaposi's sarcoma (Bignall, 1993) but is thought unlikely to be related to this disease (Taylor *et al.*, 1993).

Mycoplasma fermentans has been isolated from cells transformed with human DNA from Kaposi's sarcoma tissue (Lo *et al.*, 1989). However, there are no epidemiological data to support an association with Kaposi's sarcoma. Katseni *et al.* (1993) found HIV-positive and HIV-negative subjects to have comparable frequencies of *M. fermentans*. Another mycoplasma, *M. penetrans* (Lo *et al.*, 1991), seems to be more common in HIV-infected than in HIV-negative individuals, as shown by the prevalence of antibodies to this organism (Wang *et al.*, 1992). Serological evidence suggests that *M. penetrans* might be more common in HIV-infected homosexuals, but not in intravenous drug users or haemophiliacs, suggesting a link to those patient groups known to be at an increased risk for Kaposi's sarcoma (Wang *et al.*, 1993).

(*c*) *Genetic susceptibility*

In 1983, early in the AIDS epidemic, the HLA-DR5 haplotype was reported to be associated with the occurrence of Kaposi's sarcoma in homosexual men from New York City (Pollack *et al.*, 1983a; Prince *et al.*, 1984), an association also reported among cases of endemic Kaposi's sarcoma (Pollack *et al.*, 1983b; Contu *et al.*, 1984; Papasteriades *et al.*, 1984). Subsequent studies have failed to confirm such an association in either AIDS-related or endemic Kaposi's sarcoma (Melbye *et al.*, 1987; Brunson *et al.*, 1990; Mann *et al.*, 1990; Ioannidis *et al.*, 1995; Strichman-Almashanu *et al.*, 1995).

One suggestion to explain this discrepancy was that HIV-infected persons with elevated genetic susceptibility (in this case, DR5-positive) developed Kaposi's sarcoma sooner after infection and hence were not seen in later studies. However, large numbers of newly infected persons continue to enter the pool of persons at risk and exhaustion of the susceptible subgroups seems an unlikely explanation. Another explanation is that this marker is more common in some subgroups, particularly in Mediterranean and Jewish populations, and that control for this factor was inadequate. Reported associations with other HLA markers have not been confirmed (summarized by Ioannidis *et al.*, 1995), and the relationship between HLA and Kaposi's sarcoma is still controversial. [The Working Group noted that the multiple comparisons made in the analysis of the HLA data make it difficult to interpret the findings.]

(*d*) *Miscellaneous factors*

The use of amyl nitrite inhalants has been considered as a factor increasing risk for Kaposi's sarcoma in homosexual men. Use of these drugs was especially popular among very sexually active homosexual men at the time when the AIDS epidemic was emerging in the late 1970s and early 1980s (Jaffe *et al.*, 1983; Melbye *et al.*, 1983). They act as smooth muscle relaxants and potent vasodilators (Newell *et al.*, 1984) and are thought to be potentially carcinogenic (Jørgensen & Lawesson, 1982). Therefore, they seemed plausible candidate etiological agents for a tumour prominently involving blood vessels. Early studies found their use to be associated with both immunosuppression and with development of Kaposi's sarcoma (Goedert *et al.*, 1982; Marmor *et al.*, 1982; Haverkos *et al.*, 1985).

However, since nitrite inhalants were often used to facilitate anal intercourse, their use was correlated with the frequency of receptive anal intercourse with multiple partners. In one study, adjusting for anal intercourse eliminated the relationship between Kaposi's sarcoma and nitrite inhalant use (Darrow *et al.*, 1992), although in another study (Archibald *et al.*, 1990), a residual 'independent' effect remained. [The Working Group noted that, among homosexual men in developed countries, nitrite inhalant users also became HIV-infected early in the epidemic and thus manifested AIDS symptoms (including Kaposi's sarcoma) earlier. Thus, the evidence of the association between nitrite inhalants and Kaposi's sarcoma is not convincing.]

Data about androgen levels is conflicting. Klauke *et al.* (1995) report higher testosterone levels in 17 HIV-infected men with Kaposi's sarcoma than other HIV-infected men who had no symptoms (11), mild symptoms (12) or non-Kaposi's sarcoma AIDS (29). In contrast, Christeff *et al.* (1995) found higher levels of testosterone and dehydroepiandrosterone in 28 men with Kaposi's sarcoma compared to 34 HIV-infected men without Kaposi's sarcoma, after stratifying for $CD4^+$ T-cell count. Further studies are needed to clarify this issue.

Lunardi-Iskandar *et al.* (1995a) reported that Kaposi's sarcoma Y1 cells could not be grown in pregnant mice and that human chorionic gonadotropin (HCG) appeared to induce apoptosis in Kaposi's sarcoma derived cells in culture (see Section 4.2.1). The incidence of Kaposi's sarcoma in HIV-infected pregnant women (who would have high HCG levels soon after conception) in Africa was similar to that in post-pregnant women or women not recently pregnant, arguing against a role for HCG at physiological doses. Similarly, there was no difference between pregnant and non-pregnant women in the frequency of disseminated Kaposi's sarcoma lesions (Rabkin *et al.*, 1995a).

2.1.6 *Human immunodeficiency virus type 2*

Because of a paucity of data, it is unclear whether the clinical spectrum of diseases in HIV-2-infected individuals differs from that of HIV-1, particularly with respect to Kaposi's sarcoma (De Cock & Brun-Vézinet, 1989).

Kaposi's sarcoma in people with HIV-2 infection was reported in two patients from Senegal (Le Guenno *et al.*, 1987), one from France (Brücker *et al.*, 1987), four of 17 HIV-2-associated AIDS cases from western Africa (Clavel *et al.*, 1987), but not in two

follow-up studies, namely a one-year follow-up of 62 HIV-2-seropositive individuals (Poulsen *et al.*, 1989) and a two-year follow-up of 133 similar subjects from Guinea Bissau, a few of whom had an AIDS diagnosis (Ricard *et al.*, 1994).

No Kaposi's sarcoma was observed in a few case reports and small case series of HIV-2-seropositive individuals (Clavel *et al.*, 1986; Mølbak *et al.*, 1986; Ancelle *et al.*, 1987; Brun-Vézinet *et al.*, 1987; Burin Des Roziers *et al.*, 1987; Kroegel *et al.*, 1987; Saimot *et al.*, 1987; Veronesi *et al.*, 1987; Vittecoq *et al.*, 1987; Agut *et al.*, 1988; Centers for Disease Control, 1988; Hugon *et al.*, 1988)

2.2 Non-Hodgkin's lymphoma

In this monograph, Hodgkin's disease is covered under other cancers (Section 2.3.3).

2.2.1 *Description of the clinical disease and pathology*

Lymphomas have been classified on the basis of pathological appearance in various classification schemes. The use of different schemes and changes in these over time have complicated comparisons of the occurrence of non-Hodgkin's lymphoma between places and between time periods.

Non-Hodgkin's lymphoma is a recognized complication of other immunosuppressed conditions. Both primary and iatrogenic immunosuppression are associated with increased risk for non-Hodgkin's lymphoma (see Section 4.3.1). In particular, Burkitt's lymphoma incidence is increased in X-linked lymphoproliferative disease and ataxia telangiectasia, but not in relation to iatrogenic immunosuppression (Filipovich *et al.*, 1994).

Non-Hodgkin's lymphoma accounts for approximately 4% of cancer cases and 4% of cancer deaths in the general population not infected with HIV (Parkin *et al.*, 1992). Incidence rates for non-Hodgkin's lymphoma rise exponentially with age, and there is a male predominance (ratio 3 : 2), which is more marked at younger than older ages. The incidence has been rising steadily for several decades, since long before the advent of HIV. Among United States men aged 0–64 years, the increase over the past 40 years has been estimated to be above 40%. Even after accounting for the effect of HIV, the incidence of non-Hodgkin's lymphoma has continued to increase more rapidly than that of most other tumours (Devesa *et al.* 1987; Coleman *et al.*, 1993). The incidence of high histological grades of disease has increased more than that of low-grade ones, and extranodal disease has increased more rapidly than nodal disease (Rabkin *et al.*, 1993b). The reasons for these increases are not understood. Even after accounting for the impact of changes in diagnosis and well established risk factors on the trends, there remains an unexplained increase in the incidence of non-Hodgkin's lymphoma in the United States (Hartge & Devesa, 1992).

(*a*) *Classification of AIDS-related lymphomas*

Most types of non-Hodgkin's lymphoma are AIDS-defining conditions.

Non-Hodgkin's lymphoma can arise either in the lymph nodes or in extranodal lymphoid tissue. In the absence of HIV infection, approximately three quarters of the cases have a nodal primary site and one quarter originate extranodally. The central nervous system is an unusual site of non-Hodgkin's lymphoma in the absence of HIV infection. In 2687 HIV-negative cases reported to a Danish Lymphoma Registry, the central nervous system was the primary site in 4.2% of extranodal non-Hodgkin's lymphomas and in 1.6% of all non-Hodgkin's lymphomas (Krogh-Jensen *et al.*, 1994).

HIV-associated lymphomas are distinctive in their site distribution. Nearly half of the cases of HIV-associated lymphoma have an extranodal primary site. The central nervous system is a particularly favoured primary site, accounting for about 20% of all AIDS-related non-Hodgkin's lymphoma in the United States (Beral *et al.*, 1991b).

As shown in Table 16, the spectrum of HIV-related lymphoproliferative disorders includes: (i) systemic non-Hodgkin's lymphomas; (ii) body cavity-based lymphoma; (iii) primary lymphoma of the brain; and (iv) multicentric Castleman's disease.

(i) *Systemic non-Hodgkin's lymphomas*

Systemic AIDS-related non-Hodgkin's lymphomas are a heterogeneous group of malignancies, usually of the B-cell phenotype. The overwhelming majority fall within three Working Formulation histological categories: large non-cleaved-cell lymphoma; large-cell immunoblastic lymphoma; and small non-cleaved-cell lymphoma, which includes Burkitt's tumour. It has been proposed that large non-cleaved-cell lymphoma and large-cell immunoblastic lymphoma be classified as a single category under the term 'diffuse large-cell lymphoma'. This latter definition has been further expanded to include also $CD30^+$ anaplastic large-cell lymphoma of B-cell origin (Harris *et al.*, 1994). $CD30^+$ anaplastic large-cell lymphomas constitute a heterogeneous group of high-grade lymphomas at the borderline between Hodgkin's disease and non-Hodgkin's lymphomas, and have been described in association with AIDS (Carbone *et al.*, 1991; Chadburn *et al.*, 1993; Tirelli *et al.*, 1995a).

An interesting feature of systemic lymphomas in HIV patients is the frequency of pleomorphic features, with overlap between established histological subtypes (Raphael *et al.*, 1991). An atypical variant made up mainly of blastic cells exhibiting features intermediate between small non-cleaved-cell lymphoma with plasma-cell differentiation and immunoblastic plasmacytoid cells has also been observed in HIV patients (Lennert & Feller, 1990; Carbone *et al.*, 1995a). These atypical morphological features may bias a correct discrimination of small non-cleaved-cell lymphoma from large-cell immunoblastic lymphoma. This intermediate variant also includes Burkitt-like tumours (Harris *et al.*, 1994).

Whether extramedullary plasmacytoma should be included among AIDS-related lymphomas is still debated (reviewed by Levine, 1993).

(ii) *Body cavity-based lymphoma*

Body cavity-based lymphoma, growing in the pleural, pericardial and peritoneal cavities as primary lymphomatous effusions, represents an additional rare AIDS-related non-Hodgkin's lymphoma variant (Knowles *et al.*, 1989; Cesarman *et al.*, 1995). This

lymphoma has morphological features between those of large-cell immunoblastic lymphoma and anaplastic large-cell lymphoma (Ansari *et al.*, 1996; Carbone *et al.*, 1996a; Cesarman *et al.*, 1996). Its identification is based on pathology, clinical features, phenotype, genotype and etiology (Jaffe, 1996).

Table 16. Pathological features of AIDS-related non-Hodgkin's lymphomas and other lymphoproliferative disorders

Non-Hodgkin's lymphomas
Systemic lymphomas
(*a*) *'Blastic'[a] cell lymphomas*
Large non-cleaved cell (G - WF)
Immunoblastic (H - WF) with or without plasma cell differentiation
Small non-cleaved cell (J - WF) with or without plasma cell differentiation
Extramedullary (plasmacytoma)[b]
Blastic cells with 'intermediate' features
(*b*) *'Anaplastic'[c] cell lymphomas*
Anaplastic large cell (CD30/Ki-1$^+$)
(*c*) *Others (rare types)*
Body cavity-based lymphoma
Primary brain lymphoma (immunoblastic)
Multicentric Castleman's disease

Updated and adapted from Gaidano & Carbone (1995)
WF, International Working Formulation for non-Hodgkin's lymphomas
[a] The term 'blastic' is used in analogy with the suffix 'blastic' used in the Kiel Classification (Stansfeld *et al.*, 1988).
[b] Whether extramedullary plasmacytomas should be included among HIV-related lymphomas is still debated.
[c] The term 'anaplastic' is used in analogy with the term used in the definition of CD30$^+$ anaplastic large-cell lymphomas; it indicates blastic large cells which display marked pleomorphism, with giant cells possessing bizarre and irregular nuclei and large nucleoli (Harris *et al.*, 1994).

(iii) *Primary lymphoma of the brain*

Unlike the heterogeneous systemic AIDS-related non-Hodgkin's lymphomas, non-Hodgkin's lymphomas arising in the central nervous system represent a more uniform group and, in the majority of cases, tend to display histological features consistent with immunoblastic–plasmacytoid lymphomas (Remick *et al.*, 1990; Camilleri-Broët *et al.*, 1995).

(iv) *Multicentric Castleman's disease*

Multicentric Castleman's disease, also called multicentric angiofollicular lymphoid hyperplasia, is an atypical, usually polyclonal lymphoproliferative disorder which involves multiple lymphoid organs. Multicentric Castleman's disease in HIV-infected individuals is a distinct clinicopathological entity (Oksenhendler *et al.*, 1996). It is characteristically associated with Kaposi's sarcoma, which occurs during the clinical course of most HIV-associated cases of multicentric Castleman's disease (Soulier *et al.*, 1995).

(*b*) *Phenotypic and genotypic features*

The vast majority of AIDS-related non-Hodgkin's lymphomas are B-cell neoplasms (reviewed by Levine, 1993). Most of them, especially systemic and primary brain lymphomas, express monotypic surface immunoglobulin or B-cell antigens (CD19, CD20, and CD22), but lack T-cell-associated antigens (reviewed by Knowles, 1993). The remaining AIDS-related B-cell non-Hodgkin's lymphomas, particularly $CD30^+$ anaplastic large-cell lymphomas (Carbone *et al.*, 1993a, 1996b) and those preferentially involving body cavities (Knowles, 1993; Cesarman *et al.*, 1995), usually exhibit an indeterminate immunophenotype. Both lymphoma types lack surface immunoglobulin and B-cell-associated antigens, but express the leukocyte common antigen and various antigens associated with activation (Cesarman *et al.*, 1995; Carbone *et al.*, 1996b).

Almost all AIDS-related non-Hodgkin's lymphomas, including those displaying B-cell phenotypes as well as those displaying indeterminate phenotypes, exhibit clonal immunoglobulin heavy-chain and light-chain gene rearrangements and lack clonal T-cell receptor β-chain gene rearrangements (reviewed by Knowles, 1993). A higher proportion of anomalously matured B-cell neoplasms has been observed in HIV-infected individuals than among non-Hodgkin's lymphomas in the general population (Boiocchi *et al.*, 1990).

Polyclonality has been reported in rare instances, based on absence of immunoglobulin heavy chain gene rearrangements in three B-cell tumours (McGrath *et al.*, 1991). However, Raphael *et al.* (1994) reported that two cases without rearrangement did have clonal EBV termini. Similarly, Boiocchi *et al.* (1993a) noted clonal light chain rearrangement in all of three cases of AIDS-associated non-Hodgkin's lymphoma without heavy chain rearrangement.

2.2.2 *Descriptive epidemiology of non-Hodgkin's lymphoma*

As a primary AIDS-defining illness, non-Hodgkin's lymphoma accounts for 2.9% of AIDS cases in United States (Beral *et al.*, 1991b; Biggar & Rabkin, 1992) and 3% in European (Serraino *et al.*, 1992b) surveillance data. However, at least as many non-Hodgkin's lymphomas occur as a clinically recognized secondary diagnosis after another AIDS-defining illness. In the United States death certification data for 1992, 5.7% of persons dying of HIV infection had non-Hodgkin's lymphoma recorded (Selik *et al.*, 1995).

(a) Cancer registry data

Population-based cancer registration data yield indirect estimates of HIV-associated risk for non-Hodgkin's lymphoma based on surrogate indicators of groups at risk for HIV infection, such as never-married marital status as a surrogate indicator of homosexuality among men (see Table 17).

Table 17. Increase in risk for non-Hodgkin's lymphoma among US never-married men since beginning of the AIDS epidemic

Reference	Study area	Age group	Time period		Relative risk	*p* value
			Before	After		
Kristal *et al.* (1988)	New York City, high AIDS mortality neighbourhood	25–54	1980	1984	[2.6	< 0.01]
Biggar *et al.* (1989)	Manhattan	20–49	1973–76	1985	6.2	< 0.01
Harnly *et al.* (1988)	San Francisco	25–44	1975	1985	5.3	< 0.01
Ross *et al.* (1985)	Los Angeles	18–54	1972–79	1983	1.6	< 0.05
Rabkin & Yellin (1994)	San Francisco	25–54	1973–79	1988–90	20	< 0.01

Ross *et al.* (1985) studied the incidence of non-Hodgkin's lymphoma in never-married men aged 18–54 years in Los Angeles, CA, United States, from 1972 to 1983. Starting in 1982, there was a 60% increase in incidence; increases were especially marked for Burkitt-like lymphoma and immunoblastic sarcoma (lymphoma). During 1980–83, these high-grade tumours accounted for 20% of all cases of non-Hodgkin's lymphoma.

Kristal *et al.* (1988) examined cancer surveillance data and mortality statistics for residents of New York City, NY, United States, aged 25–54 years for the period 1980–85. They detected a three-fold increase in the incidence of non-Hodgkin's lymphoma up to 1984 among never-married men living in neighbourhoods with high AIDS mortality.

Biggar *et al.* (1989) examined lymphoma incidence among never-married men aged 20–49 years in Manhattan, NY, United States, from 1973 through to 1985. They detected a six-fold increase from baseline rates by the end of their study period. Increases were greatest for Burkitt-like lymphoma and immunoblastic lymphoma.

Harnly *et al.* (1988) examined cancer incidence in never-married men aged 25–44 years in San Francisco, CA, United States, for the period 1975–85. In census tracts with a high incidence of AIDS, the incidence of non-Hodgkin's lymphoma was increased five-fold by 1985.

Rabkin and Yellin (1994) found that the incidence of non-Hodgkin's lymphoma in never-married men aged 25–54 years in San Francisco increased 20-fold between 1973–79 and 1988–90. However, the increases were not uniform for all sub-types of non-Hodgkin's lymphoma. Burkitt-like tumours peaked in incidence in 1985–87, then decreased in 1988–90, whereas incidence of immunoblastic lymphomas increased continuously through to 1990. The incidence of extranodal (especially central nervous system) lymphoma increased more rapidly than that of nodal disease, accounting for half of the incidence in the most recent period. [On the basis of the estimated 25% prevalence of HIV in this population, the incidence of non-Hodgkin's lymphoma in HIV-infected San Francisco men was 0.7% per year in 1988–90.]

Rabkin *et al.* (1993a) examined cancer registration data for New York women at high risk for HIV infection. Between 1976–78 and 1987–88, the incidence of non-Hodgkin's lymphoma doubled in black women, but not in white women, consistent with the distribution of AIDS, which was also primarily concentrated among black women.

Another set of studies has relied on linkage between cancer registry and AIDS registry data.

Coté *et al.* (1991) used linkage of AIDS and cancer registries in Illinois, United States, to detect cases of non-Hodgkin's lymphoma in patients diagnosed with AIDS between 1 January 1981 and 15 February 1989. Compared with general population rates, they found a 140-fold increase in incidence of non-Hodgkin's lymphoma among AIDS patients.

Reynolds *et al.* (1993) linked AIDS and cancer registry data in San Francisco for the period 1980–87. Risk for non-Hodgkin's lymphoma was increased 71-fold over concurrent general population incidence rates and 97-fold over the 1973–77 rates in the same geographical area. [The Working Group noted that the former risk estimate may be biased downwards by HIV-associated non-Hodgkin's lymphoma not being recognized as AIDS, whereas the latter may be biased upwards by the temporal trend in non-Hodgkin's lymphoma independent of HIV infection.]

(*b*) *Cohort data*

Lyter *et al.* (1995) examined the incidence of non-Hodgkin's lymphoma in 430 HIV-seropositive homosexual men in Pittsburgh, PA, United States, between 1984 and 1993. The annual incidence was [0.6%], which was 83 times that of contemporaneous population rates.

Ragni *et al.* (1993) followed a cohort of 1295 HIV-positive haemophiliacs in a collaborative study. The overall incidence of non-Hodgkin's lymphoma was 0.16 case/100 person-years, which constituted a 36.5-fold increase over expected rates.

Peters *et al.* (1991) reported a case-series of 347 AIDS patients treated at a hospital in London, United Kingdom, between October 1982 and December 1989. They found that the proportion of AIDS deaths due to lymphoma increased from 0 to 16% between 1984 and 1989. [The Working Group noted that these figures may be confounded by the introduction of *Pneumocystis carinii* pneumonia prophylaxis.]

2.2.3 *Role of immunosuppression*

Non-Hodgkin's lymphoma is considered to be a relatively late manifestation of AIDS, compared with Kaposi's sarcoma and some opportunistic infections.

Muñoz *et al.* (1993) analysed the incidence of non-Hodgkin's lymphoma in 2627 HIV-infected homosexual men in four United States cities between 1985 and 1991. They noted a nonsignificant increase with decreasing $CD4^+$ T-cell count: the relative risk for non-Hodgkin's lymphoma as an initial AIDS-defining illness was 0.38 (95% CI, 0.14–1.09) with 101–200 $CD4^+$ cells/mm^3 versus ≤ 100 cells/mm^3.

Rabkin *et al.* (1992) followed a cohort of 1701 haemophiliacs, of whom 1065 (63%) were HIV-seropositive. The incidence of non-Hodgkin's lymphoma after HIV seroconversion averaged 0.15 cases/100 person-years and rose exponentially with increasing duration of HIV infection. However, $CD4^+$ T-cell counts of cases of non-Hodgkin's lymphoma were similar to those in AIDS-free subjects after the same duration of HIV infection. Haemophiliac patients without HIV infection showed no increased risk for non-Hodgkin's lymphoma.

In clinical trials of zidovudine and dideoxyinosine in AIDS and AIDS-related complex patients, the three-year cumulative incidence of non-Hodgkin's lymphoma among 116 patients was 19%. There was no significant difference between subjects receiving the two antiretroviral treatments (Pluda *et al.*, 1990, 1993). Patients with less than 50 $CD4^+$ T-cells/mm^3 were at significantly higher risk for primary central nervous system lymphoma, but not for systemic lymphoma (Pluda *et al.*, 1993).

Moore *et al.* (1991) followed 1030 patients with AIDS or advanced AIDS-related complex receiving zidovudine at 12 sites in the United States between 1987 and 1990. The incidence of non-Hodgkin's lymphoma was 1.6 cases/100 person-years. Kaposi's sarcoma, oral hairy leukoplakia and cytomegalovirus disease, markers of immune dysfunction, were each independently associated with increased risk for non-Hodgkin's lymphoma.

The association between immune decline and non-Hodgkin's lymphoma appears to differ with the subtype of the disease. Roithmann *et al.* (1991) reported 131 HIV-associated non-Hodgkin's lymphomas recorded at a French registry during 1987–89. The median $CD4^+$ T-cell count was significantly higher in cases of small non-cleaved-cell lymphoma (266/mm^3) than in those of large-cell (125/mm^3, $p < 0.05$) or immunoblastic (80/mm^3, $p < 0.01$) lymphoma.

These studies have consistently found increasing risk of non-Hodgkin's lymphoma with increasing duration of HIV infection and with progression in immune dysregulation. It is not clear what aspect of immune dysfunction corresponds directly to this risk.

The potential role of HIV as a direct cause of non-Hodgkin's lymphoma is addressed in Section 4.3.

2.2.4 *Co-factors*

(*a*) *Demographic*

The proportion of AIDS patients presenting with non-Hodgkin's lymphoma is greater in adults than in children. In United States surveillance data, 0.5% of AIDS cases under one year and 1.9% of cases one to nine years of age had non-Hodgkin's lymphoma (Beral *et al.*, 1991b). Children were somewhat more likely to have Burkitt-like lymphoma, and older adults were more likely to have immunoblastic or large-cell lymphoma. In this series, women were one third to one half less likely than men to have non-Hodgkin's lymphoma as an AIDS-defining illness.

Biggar and Rabkin (1992) reviewed United States AIDS surveillance data for AIDS-defining lymphomas. The proportion of AIDS cases presenting with non-Hodgkin's lymphoma was higher in older persons, men and whites. As the authors noted, these same characteristics are associated with increased risk for non-Hodgkin's lymphoma in non-HIV-infected individuals, suggesting that an environmental cofactor(s) for AIDS lymphoma is unlikely to be important.

In European surveillance data, the proportion of AIDS patients presenting with non-Hodgkin's lymphoma is also greater in adults than in children (Serraino *et al.*, 1992c). In cases reported up to the end of June 1991, among intravenous drug users, females had a relative risk for non-Hodgkin's lymphomas of 0.7 (95% CI, 0.6–0.9) compared with males in the same risk group, whereas among AIDS patients with heterosexually acquired HIV infection, females had a relative risk of 1.2 (95% CI, 0.8–1.8).

(*b*) *Geographic*

Non-Hodgkin's lymphoma accounts for a similar proportion of AIDS cases in various locations. In surveillance data, non-Hodgkin's lymphoma accounted for 2.9% of United States AIDS cases recorded up to June 1989 and 3.0% of European cases up to June 1991 (Beral *et al.*, 1991b; Serraino *et al.*, 1992c). In European surveillance data, there was little difference between four regions (northern, central, southern and eastern) in the fraction of AIDS with non-Hodgkin's lymphoma as the initial diagnosis (Serraino *et al.*, 1992c).

Casabona *et al.* (1991) analysed national surveillance data from 15 European countries up to March 1989. They found similar proportions of AIDS-related non-Hodgkin's lymphoma in three regions (northern, central, southern) for homosexual men and for other risk groups, and there was no consistent variation in the geographic pattern with time for either transmission category.

Data from Africa are less complete and it is unclear whether the risk for non-Hodgkin's lymphoma is the same as that observed in developed countries. In South African AIDS surveillance data, seven (5.6%) of the first 126 cases reported between 1982 and 1988 had non-Hodgkin's lymphoma (Sitas *et al.*, 1993). However, most of these patients were of Caucasian origin.

Lucas *et al.* (1994) reported an autopsy study of HIV-positive adults and children admitted in 1991 and 1992 to the largest hospital in Abidjan, Côte d'Ivoire. In this series, 7/247 (2.8%) adult (> 14 years) decedents had non-Hodgkin's lymphoma at autopsy

versus 0/78 paediatric decedents. The proportion was similar in patients seropositive for HIV-1 and HIV-2.

Bassett *et al.* (1995) examined cancer incidence rates in the African population of Harare, Zimbabwe, for 1990–92 and compared them with rates in Bulawayo, Zimbabwe, 20–30 years earlier. With the advent of the AIDS epidemic, annual age-standardized (world standard) Kaposi's sarcoma incidence increased by [22 and 88/100 000] in men and women, respectively. In contrast, the respective increases in non-Hodgkin's lymphoma incidence were only [2 and 3/100 000], similar to increases over this period in populations without HIV infection.

Wabinga *et al.* (1993) examined cancer surveillance data for Kampala, Uganda, for the period between September 1989 and December 1991. They noted a marked increase in Kaposi's sarcoma compared with baseline data from 1954–1960. In contrast, there was no detectable increase in the incidence of non-Hodgkin's lymphoma. Annual age-standardized (world standard) rates of non-Hodgkin's lymphoma actually decreased slightly between these two periods, from 3.9 to 3.2/100 000 for men and from 2.9 to 2.6/100 000 for women.

Newton *et al.* (1995) reported 245 cancer cases registered in Butare, Rwanda, between October 1992 and April 1994. Seven (37%) of 19 patients with non-Hodgkin's lymphoma were HIV-seropositive compared with 4% of control cancer cases, corresponding to an odds ratio of 12.6 (95% CI, 2.2–54.4).

[The Working Group noted that the apparent deficit of AIDS-associated non-Hodgkin's lymphoma in Africa cannot be explained by underdiagnosis only. It is possible that patients with severe immunodeficiency in this part of the world tend to die from infectious diseases before manifesting non-Hodgkin's lymphoma.]

(*c*) *Behavioural*

In contrast to the variation in risk for Kaposi's sarcoma, there are relatively small differences in risk for non-Hodgkin's lymphoma between HIV exposure groups in developed countries.

As seen in Tables 18 and 19, the proportion of AIDS cases presenting with non-Hodgkin's lymphoma is consistently between 2 and 5% in western European countries and the United States, and varies little between HIV-exposure categories.

In United States surveillance data up to 30 June 1989, 5.2% of haemophilic AIDS cases, 3.4% of homosexual or bisexual male cases and 1.6% of intravenous drug user cases were reported with non-Hodgkin's lymphoma (Beral *et al.*, 1991b).

Reynolds *et al.* (1993) linked AIDS and cancer registries in San Francisco, CA, United States, for an analysis of cancers diagnosed during 1980–87. Intravenous drug users comprised 2% of 3826 AIDS cases without cancer versus 1% of 234 AIDS-associated non-Hodgkin's lymphoma, but this difference was not statistically significant.

Serraino *et al.* (1992c) analysed data on 53 042 AIDS cases reported from the World Health Organization European Region as of June 1991. Non-Hodgkin's lymphoma accounted for 1% of initial AIDS diagnoses among HIV-infected children and 4% among

Table 18. Numbers and proportions of male AIDS cases with non-Hodgkin's lymphoma as the AIDS-defining condition, by country and HIV transmission group in Europe and the United States, 1981–94

Country	Homo/ bisexual men		Intravenous drug users		Heterosexuals (Pattern II countries)[b]		Heterosexuals (other)		Haemophiliacs and transfused		Others/ unknown		Total NHL	
	NHL cases	%[c]	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%
Austria	14	3	8	3	0	0	5	7	2	3	7	5	36	3
Belgium	26	3	3	3	7	3	15	9	0	0	3	10	54	4
Denmark	45	4	2	3	1	6	6	5	4	4	2	5	60	4
France	642	4	204	3	25	2	84	5	61	5	50	5	1096	4
Germany	372	4	37	3	1	1	11	3	31	5	52	9	504	4
Greece	16	3	0	0	1	12	3	5	5	5	6	4	31	3
Italy	168	4	386	3	6	4	54	4	16	4	50	5	682	3
Netherlands	105	4	5	2	1	2	6	4	1	2	1	2	119	4
Portugal	19	2	6	1	0	0	8	2	1	1	2	3	36	2
Spain	160	3	265	2	0	0	36	2	25	4	49	3	535	2
Sweden	38	5	4	5	0	0	1	1	2	3	0	0	45	4
Switzerland	68	4	23	2	0	0	14	4	1	2	1	2	107	3
United Kingdom	246	3	15	4	14	3	12	5	28	5	5	3	320	3
United States White	3821	3	301	2	–[d]	–[d]	53	3	137	3	146	3	4518	3
Black	549	1	315	1	–[d]	–[d]	57	1	19	2	103	1	1043	1
Other	581	2	284	1	–[d]	–[d]	26	1	20	2	69	2	980	2

NHL, non-Hodgkin's lymphoma

[a] Only countries with > 30 cases of NHL over the period 1981–94 are included.

[b] Individuals not originating from Pattern II countries (countries in which extensive spread of HIV began in the mid-to-late 1970s or early 1980s and in which heterosexual transmission has predominated and continues to) which include Africa and the Caribbean.

[c] Number of NHL cases as percentage of total AIDS cases in the respective risk group

[d] Data not available

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Table 19. Numbers and proportions of female AIDS cases with non-Hodgkin's lymphoma as the AIDS-defining condition, by country and HIV transmission group in women in Europe and the United States, 1981–94

Country[a]		Intravenous drug users		Heterosexual (Pattern II countries)[b]		Heterosexual (other)		Haemophiliacs and transfused		Other/ unknown		Total NHL	
		NHL cases	%[c]	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%
France		55	3	17	2	50	3	18	2	21	4	161	3
Germany		14	2	1	1	8	2	3	2	6	5	32	2
Italy		79	2	2	3	32	2	5	4	9	2	127	2
Spain		36	1	0	0	24	2	2	1	9	3	71	1
Switzerland		13	2	0	0	8	3	0	0	0	0	21	2
United Kingdom		5	3	6	2	7	3	5	7	1	1	24	3
United States	White	43	1	–[d]	–[d]	80	2	32	2	24	2	179	2
	Black	60	0	–[d]	–[d]	80	1	10	1	38	1	188	1
	Other	38	1	–[d]	–[d]	42	1	8	2	13	1	101	1

[a] Countries with > 30 cases of NHL over the period 1981–94 are included.

[b] Individuals not originating from Pattern II countries (countries in which extensive spread of HIV began in the mid-to-late 1970s or early 1980s and in which transmission has predominated and continues to), which include Africa and the Caribbean.

[c] Number of NHL cases as percentage of total AIDS cases in the respective risk group

[d] Data not available

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

haemophiliacs; homosexual men were significantly more likely to have non-Hodgkin's lymphoma than intravenous drug users.

Pedersen *et al.* (1995) investigated 6550 European patients with AIDS followed at 52 centres, diagnosed with AIDS from 1979 up to the end of 1989. In this study, non-Hodgkin's lymphoma constituted a higher fraction of AIDS-defining illnesses in intravenous drug users (4.1%) than in homosexual men (3.0%); however, lymphoma incidence after AIDS diagnosis was significantly lower among intravenous drug users than among homosexual men. The authors suggested that their results indicate that national surveillance data may underreport AIDS-related non-Hodgkin's lymphoma in drug users.

Similarly, the Italian Cooperative Group for AIDS-Related Tumours (GICAT) (1988) reported that intravenous drug users accounted for a slightly higher proportion of AIDS-associated non-Hodgkin's lymphoma than of total AIDS cases in Italy. They identified 93 AIDS-associated non-Hodgkin's lymphomas diagnosed between January 1980 and November 1987, of which 63 (68%) were in intravenous drug users as compared with 59% of all AIDS cases in the United States.

(*d*) *Infections*

AIDS-associated non-Hodgkin's lymphoma is a heterogeneous entity, and subsets of cases have been associated with various viruses, particularly two herpes viruses, EBV and HHV-8.

(i) *Epstein–Barr virus*

Monoclonal Epstein–Barr virus (EBV) infection is found in AIDS-related non-Hodgkin's lymphomas, especially those in the central nervous system, which are almost always EBV-positive (MacMahon *et al.*, 1991). Table 20 lists studies in which central nervous system lymphomas have been tested for EBV. MacMahon *et al.* (1991) found EBV in all of 21 cases of AIDS-related central nervous system lymphoma, and this high prevalence is consistent with results of most other studies (DeAngelis *et al.*, 1992; Cinque *et al.*, 1993; Arribas *et al.*, 1995). An exception is the study by Morgello (1992), which reported only 50% of cases to be EBV-positive, perhaps because of a less sensitive method of detection. Cinque *et al.* (1993) found EBV in cerebrospinal fluid to be highly predictive of central nervous system lymphoma at subsequent necropsy. These data suggest that EBV is necessary for lymphomagenesis in the central nervous system in patients with AIDS.

In AIDS-related systemic non-Hodgkin's lymphoma, EBV is less frequently detected (Table 21). It is found preferentially in tumours with immunoblastic histology. The prevalence of EBV-positivity reported has varied from 28% (Ernberg & Altiok, 1989) to 66% (Shibata *et al.*, 1993). No single histological type was uniformly positive for EBV, which suggests that the systemic AIDS-related lymphomas have a more complex etiology than primary central nervous system disease. However, where EBV clonality has been examined, EBV-positive tumours have been uniformly monoclonal (Ballerini *et al.*, 1993; Shibata *et al.*, 1993). Thus, EBV infection precedes clonal outgrowth of

Table 20. Prevalence of Epstein–Barr virus in central nervous system non-Hodglkin's lymphoma and control tissue in relation to HIV status

Reference	Study area	Lymphoma site	EBV detection method	EBV+ non-Hodgkin's lymphoma cases		EBV+ controls		Comments
				HIV+	HIV–	HIV+	HIV–	
MacMahon *et al.* (1991)	Baltimore, USA	CNS	EBER1 ISH	21/21	2/15	0/13	0/6	1/1 HIV–transplant patient EBV-positive
DeAngelis *et al.* (1992)	New York, USA	CNS	BamHI-W PCR	11/13	7/13			
Morgello (1992)	New York, USA	CNS	EBNA-1 PCR	6/12				
Cinque *et al.* (1993)	Stockholm and Milan	CNS	EBER ISH	16/16				
				0/2				
		CSF	EBNA-1 PCR	17/17	1/66		0/10	
				0/2				
Arribas *et al.* (1995)	St Louis, MO, USA	CNS	LMP PCR	6/6				
				1/1				Systemic lymphoma
		CSF	EBNA-1 PCR	4/7[a]		0/16		
				1/1				Systemic lymphoma
			BamHI-W PCR	6/7[b]		1/16		
				1/1				Systemic lymphoma

Abbreviations: CNS, central nervous system; EBER, Epstein–Barr encoded RNA; ISH, in-situ hybridization; EBNA, Epstein–Barr nuclear antigen; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; BamHI-W, first internal repeat sequence; LMP, latent membrane protein

[a] Including 3/6 patients with CNS lymphoma

[b] Including 5/6 patients with CNS lymphoma

Table 21. Prevalence of Epstein–Barr virus in systemic lymphoma tissue in relation to HIV status

Reference	Study area	Histology	EBV detection method	EBV+ non-Hodgkin's lymphoma cases		Comments
				HIV+	HIV–	
Ernberg & Althiok (1989)	Sweden		Southern blot	7/25		1/7 PGL nodes also positive
MacMahon *et al.* (1991)	Baltimore, USA		EBER1 ISH	3/7	0/2	
Shibata *et al.* (1993)	Los Angeles, USA	Diffuse large-cell Immunoblastic Small non-cleaved-cell	EBNA-1 PCR + (EBER-1 ISH or Southern blot)	6/11 17/20 16/28	0/12 1/13 1/12	EBV clonal in 12/12 cases
Carbone *et al.* (1993b)	Aviano, Italy	Diffuse large-cell Immunoblastic Small non-cleaved-cell Anaplastic large-cell	EBER1/2 ISH	1/6 1/1 2/4 3/4		
		Immunoblastic Small non-cleaved-cell Anaplastic large-cell	BamHI-W PCR	2/6 4/11 10/12		
		Diffuse large-cell Immunoblastic Small non-cleaved-cell Anaplastic large-cell	LMP PCR	0/6 3/7 0/15 9/12		
Ballerini *et al.* (1993)	New York, USA	Diffuse large cell Immunoblastic Small non-cleaved cell	Southern blot	1/4 4/4 5/16		EBV clonal in all positive cases
Finn (1995)	New York, USA		Immunohistochemistry	8/17	9/23	Head and neck lymphomas

Abbreviations: PGL, persistent generalized lymphadenopathy; EBER, Epstein–Barr encoded RNA; ISH, in-situ hybridization; EBNA, Epstein–Barr nuclear antigen; PCR, polymerase chain reaction; BamHI-W, first internal repeat sequence; LMP, latent membrane protein

these tumours, which is consistent with an etiological role of this virus. The specific role of EBV in lymphomagenesis is uncertain.

Detection of EBV in lymph nodes from patients with persistent generalized lymphadenopathy has been associated with subsequent non-Hodgkin's lymphoma. Shibata *et al.* (1991) studied 32 patients with persistent generalized lymphadenopathy who were non-Hodgkin's lymphoma-free. Two of 10 patients with EBV-positive lymph nodes versus one of 22 patients with EBV-negative lymph nodes developed non-Hodgkin's lymphoma over a median follow-up of 12 months ($p > 0.1$). [The Working Group noted that insufficient data were presented to allow analysis by survival methods accounting for duration of follow-up.]

(ii) *HHV-8*

HHV-8 is a recently identified human herpes virus that is a nearly universal infection in Kaposi's sarcoma tissues (see Section 2.1.5). In the first report of this virus, Chang *et al.* (1994) examined 27 AIDS lymphomas and 29 non-AIDS lymphomas by PCR. Three (11%) of the AIDS lymphomas and none of the non-AIDS lymphomas had HHV-8 sequences in the tumour tissue.

In a follow-up to this study, Cesarman *et al.* (1995) reported on an examination of 193 AIDS-associated lymphomas in 42 patients from New York, United States, which included the 27 from the report by Chang *et al.* (1994). HHV-8 was detected in all eight tumors associated with lymphomatous effusions (body-cavity based), but not in 185 others without effusions. Furthermore, there were on average 40–80 copies of the HHV-8 sequence per cell, whereas Kaposi's sarcoma tissue contained 1–2 copies per cell. Significantly, all eight tumors also contained EBV detected by PCR, which was clonal by Southern blot in 6/6 cases.

Pastore *et al.* (1995) tested 180 lymphoid malignancies in Italy and Spain. HHV-8 was present in all of three cavity-based lymphomas, but was not found in 177 other non-Hodgkin's lymphomas.

(iii) *HHV-6*

In a French study, the presence of HHV-6 DNA was determined by PCR in HIV-positive and HIV-negative patients with non-Hodgkin's lymphoma or lymph node follicular hyperplasia. Twelve (44%) of the 27 AIDS-associated lymphomas versus seven (35%) of the 20 lymphomas from HIV-seronegative patients contained HHV-6 DNA ($p = 0.51$) (Fillet *et al.*, 1995). HHV-6 prevalence was similar in the hyperplastic lymph nodes from both HIV-positive (2/4, 50%) and HIV-negative patients (5/9, 55%).

In an Italian study, HHV-6 DNA was detected by PCR in DNA extracted from paraffin-embedded tissue from 16 (89%) of 18 HIV-infected individuals. However, nine (64%) of 14 non-lymphoma tissue samples from the same patients also contained detectable HHV-6 (Trovato *et al.* 1995).

In summary, EBV and HHV-8 are almost always found in AIDS-related lymphoma of the brain and body cavity-based lymphomas, respectively, and may be found in other AIDS lymphomas (HHV-8 has been detected in all (14/14) cases of HIV-associated

lymphomas). Their role in the etiology of these malignancies will be examined in Section 4.3. HHV-6 has not been specifically related to non-Hodgkin's lymphoma.

(*e*) *Zidovudine and other therapy*

As non-Hodgkin's lymphoma occurs more frequently in advanced-stage HIV infection, concern has been raised regarding a potential role of antiretroviral therapy in lymphomagenesis. An exceptionally high risk of non-Hodgkin's lymphoma was found in Phase I trials of nucleoside analogues in patients with advanced HIV infection at the National Institutes of Health in the United States (Pluda *et al.*, 1990, 1993). Patients treated with either zidovudine or dideoxyinosine had a 19% risk of non-Hodgkin's lymphoma three years after starting therapy, with no significant difference between these two antiretroviral agents.

Levine *et al.* (1995) performed a case–control study of AIDS-related non-Hodgkin's lymphoma compared with other AIDS diagnoses. The matched odds ratio for prior use of zidovudine was 0.43 (95% CI, 0.17–1.12).

Muñoz *et al.* (1993) examined antiretroviral therapy as a risk factor for non-Hodgkin's lymphoma in a cohort study of homosexual men. They found a protective effect of treatment, with a relative risk of 0.47, which was not statistically significant.

Coté and Biggar (1995) linked AIDS and cancer registries to compare risk for non-Hodgkin's lymphoma before and after zidovudine therapy became available in 1987. The observed : expected ratios for non-Hodgkin's lymphoma incidence were 222 pre-zidovudine (1981–86) and 193 post-zidovudine (1988–90).

Rabkin *et al.* (1993c) examined the incidence of non-Hodgkin's lymphoma in relation to $CD4^+$ count in a cohort of HIV-infected homosexual men. They compared incidence in the periods before and after January 1988 to assess changes after zidovudine was introduced. The cumulative risk for non-Hodgkin's lymphoma at 50 $CD4^+$ cells/mm^3 was $25 \pm 12\%$ before January 1988 and $10 \pm 5\%$ after that date ($p = 0.4$).

In summary, there is no consistent evidence from these studies that antiretroviral therapies increase the risk for non-Hodgkin's lymphomas in AIDS patients.

2.2.5 *HIV-2 and non-Hodgkin's lymphoma*

When they occur, HIV-2-associated non-Hodgkin's lymphomas appear to have clinical features similar to those of HIV-1-associated non-Hodgkin's lymphomas. In a report of three cases of non-Hodgkin's lymphomas associated with HIV-2 infection, all were high-grade malignancies with B-cell immunophenotype (Forjaz Lacerda *et al.*, 1990).

In the study from the Côte d'Ivoire by Lucas *et al.* (1994) (see Section 2.2.4), 7/247 HIV-positive adult decedents had non-Hodgkin's lymphoma. The proportion was similar in patients who were seropositive for HIV-1 (5/154), HIV-2 (1/40) and both (1/53).

2.3 Cervical, anal and other cancers

Cancers other than Kaposi's sarcoma and non-Hodgkin's lymphoma have been studied considerably less often and reported in far fewer HIV-positive patients. Some

positive findings may have been inflated by publication bias, surveillance bias or misclassification with Kaposi's sarcoma and non-Hodgkin's lymphoma; confounding is also possible on account of the existence of several risk factors shared by HIV infection and some neoplasms. Data on cancer occurrence in HIV-infected individuals are particularly inadequate in developing countries, where the largest numbers of AIDS cases occur.

Research attempting to clarify the potential relationship between HIV and anogenital cancers has so far been based primarily on small cross-sectional and case–control studies of populations at particular risk for HIV infection and with the outcome variable being precancerous lesions rather than invasive cancer. The short existence of the HIV epidemic, the initial male predominance, and the young populations at risk have in particular limited the possibilities for studying large numbers of HIV-infected female cases — especially HIV-infected cases with cervical cancer.

Specific genital types of human papillomavirus (HPV) are involved in the etiology of invasive cervical cancer and in some of its precursor lesions. There is also preliminary evidence for an association with anal cancer and anal intraepithelial lesions (IARC, 1995). Both HIV and most known oncogenic types of HPV are sexually transmitted. Therefore, the ability to control for confounding is particularly essential in studying the influence of HIV on anogenital malignancies. The small sample size in many of the studies undertaken so far has limited their ability to control adequately for behavioural covariates and risk factors associated with HIV infection.

2.3.1 *Cervical intraepithelial neoplasia and invasive cancer*

The influence of HIV on invasive cervical cancer and its precursor lesions has been reviewed (Palefsky, 1991; Rabkin & Blattner, 1991; Sillman & Sedlis, 1991; Northfelt & Palefsky, 1992; Braun, 1994; Stratton & Ciacco, 1994).

(*a*) *Precancerous lesions*

(i) *Association with HIV*

In the late 1980s, the first case reports and case series were published which suggested an association between HIV infection and cervical intraepithelial neoplasia (CIN) (Bradbeer, 1987; Byrne *et al.*, 1989; Henry *et al.*, 1989). In a review by Mandelblatt *et al.* (1992), 21 of the earliest case reports and series were described in more detail. Table 22 summarizes relevant data.

In a blind cytological analysis of cervicovaginal smears, a significantly higher percentage of cytological squamous atypia was documented in HIV-positive (11/35; 31%) than HIV-negative women (1/23; 4%) (Schrager *et al.*, 1989). Furthermore, cytological or histopathological findings suggestive of HPV infection were observed in 26% of HIV-positive women compared with 4% of HIV-negative women. [The Working Group noted that the controls in this study were not comparable with HIV-positive cases in terms of sexual behaviour, history of sexually transmitted diseases or frequency of barrier methods used.]

Fruchter *et al.* (1994) estimated that approximately 13% of 482 women referred to a public colposcopy clinic in Brooklyn, NY, United States, with abnormal Papanicolaou

Table 22. Studies of precancerous lesions of the uterine cervix in HIV-infected persons

Reference, study area	No. and type of HIV+ cases	No. and type of HIV− controls	HPV prevalence			Cervical abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	Percentage		Odds ratio (95% CI)			
Schrager *et al.* (1989) USA	35	23	HIV+ HIV−	26% 4%		*Squamous atypia* HIV+ HIV−	31% 4%		Cytological or histopathological findings	Pap smear	HIV-infected: fewer barrier methods, more STD
Feingold *et al.* (1990) USA	35	32	HIV+ HIV−	49% 25%		*SIL* HIV+ HIV−	40% 9%		Southern blot (cervico-vaginal lavage)	Pap smear	48 IVDU 18 heterosexual partners of IVDU
Vermund *et al.* (1991a) USA	51 (18 asymptomatic 33 symptomatic)	45	HIV+ symptomatic asymptomatic HIV−	53% 70% 22% 22%		*SIL* HIV+ symptomatic asymptomatic HIV−	 42% 17% 13%	 12 (1.3–108) [2.0 (0.1–30)] 4.6 (0.8–28)	Southern blot (lavage)	Pap smear	IVDU, heterosexual contacts with IVDU
Byrne *et al.* (1989) UK	19 recruited from HIV+ STD clinic attenders					3 CIN III 1 CIN II 1 Atypia 1 SPI 1 HPV			Colposcopy	Pap smear and biopsy	
ter Meulen *et al.* (1992) Tanzania	46 gynaecological in-patients	313 gynaecological in-patients	*Any type* HIV+ HIV− *HPV 16/18* HIV+ HIV−	 78% 56% 30% 14%	*HPV (total)** 2.5 ($p = 0.02$) *HPV-16/18** 2.4 ($p = 0.02$)	HIV+ HIV−	2.4% 2.8%		PCR	Pap smear	*Adjusted for age
Kreiss *et al.* (1992) Nairobi, Kenya	147 prostitutes	51 prostitutes	HIV+ HIV−	37% 24%	1.7 (0.8–3.6)*	*CIN* HIV+ HIV− *HPV+* HIV+ HIV− *HPV−* HIV+ HIV−	 26% 24% 47% 57% 9% 7%	 0.9 (0.2–3.5) 9.4 (1.7–52.1) 17.3 (1.4–217)		Cytology	*Adjusted for age and years of prostitution

Table 22 (contd)

Reference, study area	No. and type of HIV+ cases	No. and type of HIV– controls	HPV prevalence			Cervical abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	Percentage		Odds ratio (95% CI)			
Laga *et al.* (1992) Kinshasa, Zaire	47 prostitutes	48 prostitutes	HIV+ HIV– HIV+/CIN+ HIV+/CIN–	38% 8% 73% 30%	6.8 (1.9–26.8) 6.2 ($p = 0.02$)	*CIN* HIV+ HIV–	 27% 3%	 14.7 (1.8–95.3)	ViraType™ Southern blot	Cytology	13 Pap smears inadequate for interpretation
Conti *et al.* (1993) Italy	273 former IVDU	161 former IVDU				HIV+ HIV–	42% 8%	4.2 (2.1-8.4) *HPV–/HIV+* 1.2 (0.2-0.6) *HPV+/HIV–* 10.8 (2.8–41.6) *HPV+/HIV+* 64.0 (19.2–214)	Cytological diagnosis	Cytology confirmed by biopsy	Cross-sectional study, potential selection bias (inflated), odds ratios *CIN II,III/HIV+* CD4⁺ ≥ 500 1.0 CD4⁺ < 500 5.4 (2.6–11)
Maggwa *et al.* (1993) Nairobi, Kenya	205 attenders, family planning clinic	3853 attenders, family planning clinic				HIV+ HIV–	4.9% 1.9%	2.8 (1.3-5.9) adj. sexual behaviour, demographic variables		Cytology	
Van Doornum *et al.* (1993) The Netherlands	25 IVDU and prostitutes	44 IVDU and prostitutes	HIV+ HIV–	32% 7%	6.4 (1.3–40.1)	HIV+ HIV–	0% 4.6%		PCR	Cytology	HIV–: More clients per month than HIV+ women
Smith *et al.* (1993b) UK	43 mostly IVDU	43 matched to HIV+ cases	*HPV-6/11* HIV+ HIV– *HPV-16* HIV+ HIV–	 11.6% 2.3% 11.6% 4.7%		HIV+ HIV–	14% 9%		Southern blot	Histology	Tendency to increased CIN prevalence in HIV+ women with increasing immunosuppression
Ho *et al.* (1994) New York, USA	97 IVDU, HIV-related disease, IVDU partner	110 same	*All HPV types* HIV+ HIV– CD4⁺ > 20% CD4⁺ ≤ 20% *Oncogenic types* HIV+ HIV–	 49.5% 22.7% 45.0% 60.7% 14.4% 6.4%	 3.3 (1.8–6.1) 2.8 (1.3–6.0) 5.3 (2.2–12.7) 3.5 (1.3–9.2)				Southern blot hybridization		*Strong HPV signal*, odds ratios: HIV– 1.0 HIV+ CD4⁺ > 20% 2.6 CD4⁺ ≤ 20% 5.9

Table 22 (contd)

Reference, study area	No. and type of HIV+ cases	No. and type of HIV– controls	HPV prevalence		Cervical abnormality		HPV test	Pathology reading	Comments
			Percentage	Odds ratio (95% CI)	Percentage	Odds ratio (95% CI)			
Klein *et al.* (1994) New York, USA	114 IVDU, HIV-related disease, sex partner IVDU	139 same			HIV+ 21.9% HIV– 10.1% CD4 > 20% 16.7% CD4 ≤ 20% 35% *Multivariate analysis* HPV infection high-risk HPV Strong HPV signal Low CD4⁺ count	2.5 (1.2-5.1) 1.8 (0.7–4.6) 4.8 (2.0–11.6) 6.8 (2.9–15.7) 11.8 (4.1–34.1) 10.8 (3.5–33.7) 3.1 (1.0–9.5)	Southern blot hybridization	Cytology	No demographic or behavioural variables associated with SIL
Williams *et al.* (1994) San Francisco, USA	55 IVDU	59 IVDU	*Dot blot* HIV+ 19% HIV– 5% *PCR* HIV+ 57% HIV– 13%		9 out of 11 abnormal smears in HIV+	6.1 (1.2–60.5)	ViraType™ and PCR	Cytology	Recruited from larger cohort, see also Table 23
Sun *et al.* (1995) New York, USA	344 cross-sectional	325	*All HPV types* HIV+ 60% HIV– 36% *HPV-16* HIV+ 27% HIV– 17% *HPV-18* HIV+ 24% HIV– 9%	< 0.001	*All HPV types* HIV+/CIN II/III 53% HIV–/CIN II/III 50% *HPV-16* HIV+/CIN II/III 35% HIV–/CIN II/III 0 *HPV-18* HIV+/CIN II/III 35% HIV–/CIN II/III 50%		PCR	Cervico-vaginal lavage, colposcopy and sometimes biopsy	HIV+ HPV+ women had more CIN irrespective of CD4⁺ level than HIV– HPV+ women
Langley *et al.* (1996) Senegal	HIV-1 68 HIV-2 58 both 14 commercial sex workers	619 commercial sex workers	HIV-1+ 57% HIV-2+ 50.0% both 75.0% HIV– 40.1%	2.3 (1.4–3.7) 1.7 (1.0–3.0) 3.9 (1.9–8.1) 1.0	HIV-1 7.5 HIV-2 11.1 both 16.7 HIV– 6.8	1.8 (0.7–4.7) 2.9 (1.2–7.2) 5.2 (1.4–19.6) 1.0 Adjusted for no. of sexual partners and study site	PCR	Cytology	No analysis of the independent effect of HIV and HPV on CIN development was presented

STD, sexually transmitted disease; SIL, squamous intraepithelial lesions; CIN, cervical intraepithelial neoplasia; SPI, subclinical papillomavirus infection; PCR, polymerase chain reaction; IVDU, intravenous drug user; [ ] calculated by the Working Group

smears were HIV-seropositive. A more detailed characterization of 208 of these women showed the 47 HIV-positive women had more advanced CIN, larger cervical lesions and more associated vulvo-vaginal lesions than the 161 HIV-seronegative women.

Johnstone *et al.* (1994) conducted a retrospective case–control study in Edinburgh, United Kingdom, which included IVDU women or women having a seropositive IVDU partner and computer-matched neighbourhood controls. Cytological smears were retrieved subsequently for both cases and controls. There were more abnormal smears from the HIV-seropositive group than from the drug-related seronegative ($p < 0.01$) group or the neighbourhood control group ($p < 0.001$). [The Working Group noted that no information on HPV was presented.]

(ii) *Association with HIV and HPV*

Vermund *et al.* (1991) extended a study by Feingold *et al.* (1990) on HPV-associated disease in women taking intravenous drugs in the United States. In this study of 96 women, non-white subjects were disproportionately represented among HIV-infected women but other behavioural and sociodemographic characteristics were similar. Symptomatic HIV-positive women had more HPV DNA (70%), measured by Southern blot hybridization, compared with asymptomatic (22%) and seronegative women (22%). Among symptomatic HIV-positive women, a strong association between HPV and squamous intraepithelial lesions was documented (odds ratio, 12; 95% CI, 1.3–108), whereas the association was nonsignificant for the other two groups. These and other studies conducted in the late 1980s and early 1990s suggest that more severe HIV disease might exacerbate HPV-mediated cervical cytological abnormalities (Maiman *et al.*, 1991; Schäfer *et al.*, 1991; Johnson *et al.*, 1992; Conti *et al.*, 1993).

In a cross-sectional study of 359 gynaecological in-patients without cancer in Tanzania (ter Meulen *et al.*, 1992), 1/42 (2.4%) HIV-positive women compared with 8/285 (2.8%) HIV-negative women had an abnormal Pap smear. However, none of the HIV-positive women was suspected to be severely immunosuppressed, in view of the lack of severe HIV-related symptoms. HIV-positive women were 3.3 times more likely to be positive for HPV types 16 or 18, as detected by PCR, after adjusting for differences in sexual behaviour, history of sexually transmitted diseases and other factors. [The Working Group noted that no analysis of the association between HPV and smear abnormality by HIV status was presented.]

Kreiss *et al.* (1992) performed a nested case–control study of 147 HIV-positive and 51 HIV-negative women within a large cohort of prostitutes in Nairobi, but did not observe a significant difference with respect to the prevalence of HPV DNA between the two groups (adjusted odds ratio, 1.7; 95% CI, 0.8–3.6). A strength of this study is that the populations studied were relatively homogeneous with respect to sexual behaviour and condom use. Papanicolaou smears were available only for the most recently enrolled 63 women in the study. Among women with cervical HPV DNA, HIV infection was not associated with an increased prevalence of CIN (47% in HIV-positive versus 57% in HIV-negative women).

In contrast, in a somewhat smaller but otherwise similarly designed study conducted in Kinshasa, Zaire, Laga *et al.* (1992) found a significantly higher prevalence of HPV

DNA in HIV-positive cases (18/47; 38%) than in HIV-negative controls (4/48; 8%; odds ratio, 6.8; 95% CI, 1.9–26.8). HPV was detected both by ViraType™ and Southern blot. Eight (73%) of 11 HIV-positive women who had CIN also had HPV DNA detected compared with nine (30%) of 30 with no CIN (Fisher's exact test $p = 0.02$). Cases and controls in this study did not differ in terms of important demographic or sexual behavioural characteristics, but clinical AIDS was more frequent (7% of HIV-positive cases) than in the population studied by Kreiss *et al.* (0.7%).

In a large study of 4058 women attending two semi-urban family planning clinics in Nairobi, Kenya, Maggwa *et al.* (1993) observed CIN on Pap smears of 10/205 (4.9%) HIV-positive women compared with 72/3853 (1.9%) HIV-seronegative women (odds ratio, 2.8; 95% CI, 1.3–5.9) controlled for sexual behaviour and other risk factors. [The Working Group noted that the association with HPV was not evaluated in this study.]

Langley *et al.* (1996) studied the effect of both HIV-1 and HIV-2 on the development of CIN lesions in a cross-sectional analysis of 759 female commercial sex workers in Senegal. After adjustment for number of sexual partners per week and study site, HIV-2 seropositivity was associated with a 2.9-fold increased risk for CIN (95% CI, 1.2–7.2) compared with a 1.8-fold (0.7–4.7) risk in HIV-1 infected women. Women infected with both HIV types had a 5.2-fold increased risk (1.4–19.6). [The Working Group noted that the authors did not report HPV status or $CD4^+$ T-cell counts in these analyses.]

(iii) *HIV, HPV and $CD4^+$ T-cell counts*

Whereas most studies reviewed above have used either HIV-positivity *per se* or degree of severity of HIV-associated disease as a surrogate marker for level of immune status, recent studies have often included an evaluation by $CD4^+$ T-cell count. Ho *et al.* (1994) found that among 207 primarily intravenous drug-using women, young age (less than 35 years) (odds ratio, 2.5; 95% CI, 1.3–4.8) and HIV-positivity (3.0; 1.5–5.7) were the only independent covariates associated with HPV DNA positivity. The association with HIV changed only marginally between the univariate and the multivariate analysis, indicating little influence of confounding. Prevalence of HPV increased with decreasing $CD4^+$ count, from 23% among immunocompetent HIV-negative subjects to 45% in mild or moderate immunosuppressive conditions (HIV-positive and $CD4^+$ percentage > 20%) and to 61% in severe immunosuppression ($CD4^+$ percentage < 20%). Oncogenic HPV types (16, 18, 31, 33 and 35) were not particularly strongly associated with HIV-positivity. A general increase in the quantity of viral copies of HPV detected was indirectly supported by the finding of a significant association between strong Southern blot hybridization signal strength and increasing HIV-induced immunosuppression (see Table 22). Among 29 study subjects who had no sexual exposure in the previous year, 1/16 (6.3%) HIV-seronegative women were HPV-positive compared to 8/13 HIV-positive women (61.5%). [The Working Group noted that this observation supports the conclusion that individuals with HIV-induced immunosuppression are prone to persistent HPV infection rather than self-limiting infection].

The influence of immunosuppression was also evaluated in a cross-sectional study by Williams *et al.* (1994) of 114 intravenous drug users in San Francisco. A close association between HIV, HPV and abnormal cervical cytology was observed (see Table 23).

In a multivariate model of risk factors for cervical epithelial abnormalities which excluded those showing only atypia with inflammation, both cervical HPV detected by dot blot (odds ratio, 32.1; 95% CI, 2.9–354) and HIV-seropositivity with $CD4^+$ T-cell count below 250 cells/mm^3 (odds ratio, 126.8; 95% CI, 7.5–2133) were independent predictors.

Table 23. Relation between human immunodeficiency virus serostatus, presence of cervical human papillomavirus, and cervical cytology (from Williams *et al.*, 1994)

HPV/HIV status	Cervical cytology		Odds ratio	95% CI	*p* value[a]
	Abnormal	Normal			
Dot blot					
HPV–/HIV–	0	47	1		
HPV–/HIV+	5	31	7.3	0.7–354	0.08
HPV+/HIV–	1	2	15.7	0.2–1254	0.2
HPV+/HIV+	4	4	37.6	2.7–1888	0.001
PCR					
HPV–/HIV–	0	41	1		
HPV–/HIV+	3	17	6.8	0.5–367	0.1
HPV+/HIV–	1	6	5.8	0.07–471	0.3
HPV+/HIV+	6	18	12.9	1.4–610	0.009

[a] *p* values compared with referent values (negative/negative)

In a population-based study of HIV-positive women exposed by intravenous drug use or from partners using intravenous drugs in Edinburgh, United Kingdom, Johnstone *et al.* (1994) found an association between prevalence of abnormal smears and reduced $CD4^+$ count ($p < 0.0005$), but there was no clear relation between $CD4^+$ count and the severity of the lesions.

Sun *et al.* (1995) conducted a large cross-sectional study in New York including 325 HIV-seronegative and 344 HIV-seropositive women. The two groups had similar age distribution, income and education. HPV of any type was detected in 60% of HIV-positive women and 36% of seronegative women. HPV-positive women who were also HIV-positive were significantly more likely to have CIN than were HPV-infected HIV-seronegative women. This difference was observed at all levels of immunosuppression. [The Working Group noted that these epidemiological data suggest that the association between HIV and CIN lesions cannot be explained exclusively by activation of a latent HPV infection mediated by HIV-induced immunosuppression. Thus, HIV could have an effect on the development of CIN which is independent of systemic immunosuppression. Such an effect could reflect a direct biological action but could also be a result of confounding by factors for which no adjustment was made, e.g., a behavioural variable linked with HIV seropositivity and often associated with CIN lesions.]

(iv) *Progression of disease and treatment of CIN lesions*

Adachi *et al.* (1993) conducted a prospective study among 48 women with abnormal Papanicolaou smear out of an original cohort of 232 women at high risk for HIV infection in the Bronx, New York. Subsequent colposcopic or histological findings in 36/38 were no more severe than those observed by cytology, indicating that abnormal cytological smears accurately reflect the severity of cervical and vaginal disease in HIV-positive women. Similar results were obtained by Korn *et al.* (1994) and Johnstone *et al.* (1994). A follow-up of between 3 and 37 months, based on small numbers, showed that all three HIV-negative and five out of ten HIV-positive women had normal examinations, whereas three HIV-positive women had persistent disease and two had progression to condyloma (Adachi *et al.*, 1993).

Sha *et al.* (1995) followed 82 HIV-positive women who were seen between 1986 and 1992 at a hospital in Chicago, IL, United States. Among 10 who presented with CIN confirmed by Papanicolaou smears, none developed invasive cervical cancer during a median follow-up time of 13 months (range, 3–61 months).

Maiman *et al.* (1993a) in Brooklyn, NY, found an equal distribution of CIN severity and lesion size among 44 HIV-positive and 125 HIV-negative women. However, more HIV-positive women (39%) developed biopsy-proven recurrent CIN after treatment than HIV-negative women (9%), and, among HIV-positive women, recurrent disease was clearly associated with degree of immunosuppression as measured by $CD4^+$ T-cell count.

Wright *et al.* (1994) performed a retrospective chart review of patients treated by electrosurgical excision for CIN at a hospital in Manhattan, NY, United States, during 1991–92. All patients had at least six months of follow-up or had documented recurrent and/or persistent disease during less than six months of follow-up. Age-distribution and grading of disease stage were similar in HIV-positive and -negative patients, but recurrent and/or persistent CIN occurred significantly more frequently in HIV-positive women (56%, 19/34) than in HIV-negative women (13%, 10/80; $p < 0.001$). In HIV-positive women, the occurrence of recurrent and/or persistent CIN was associated with degree of immunosuppression (> 500 $CD4^+$ cells/mm^3: 20%; ≤ 500 $CD4^+$ cells/mm^3: 61%).

These studies suggest that HIV infection and/or HIV-related immunosuppression accelerate the progression of CIN.

(*b*) *Invasive cervical cancer*

Since January 1993, CDC included invasive cervical cancer as an AIDS-defining illness in HIV-positive women (Centers for Disease Control and Prevention, 1992a) (see Table 5).

(i) *Case series*

Maiman *et al.* (1993b) studied 16 HIV-positive women (19%) out of 84 women below 50 years of age with invasive cervical cancer, at a hospital in Brooklyn. Three were known to be HIV-positive before enrolment whereas 81 were subsequently tested

for HIV. Almost 70% of the HIV-positive patients were at clinical stage III or IV disease, compared with 28% in the HIV-negative group ($p = 0.01$).

Zanetta *et al.* (1995) made a retrospective evaluation of all patients referred during 1991–94 to a hospital in Milan, Italy, with a diagnosis of invasive cervical carcinoma. Six (1.8%) out of 340 women with invasive cervical carcinoma were HIV-positive. The mean age at diagnosis was 30 years (range, 27–36) for the HIV-seropositive women, but 49 for the remaining population. Furthermore, HIV-seropositive women had more advanced disease ($p = 0.04$). [The Working Group noted that four out of the six seropositive women were intravenous drug addicts ($p < 0.0001$).]

(ii) *Prognosis*

Maiman *et al.* (1990, 1993b) reported a poorer response to therapy and a poorer prognosis among HIV-infected patients with invasive cervical cancer in Brooklyn, with higher recurrence and death rates compared with HIV-uninfected patients. The patient's immune status had a significant impact on subsequent disease. Thus, only seropositive patients with $CD4^+$ counts greater than 500 cells/mm^3 had prolonged or disease-free follow-up.

(iii) *Descriptive epidemiology*

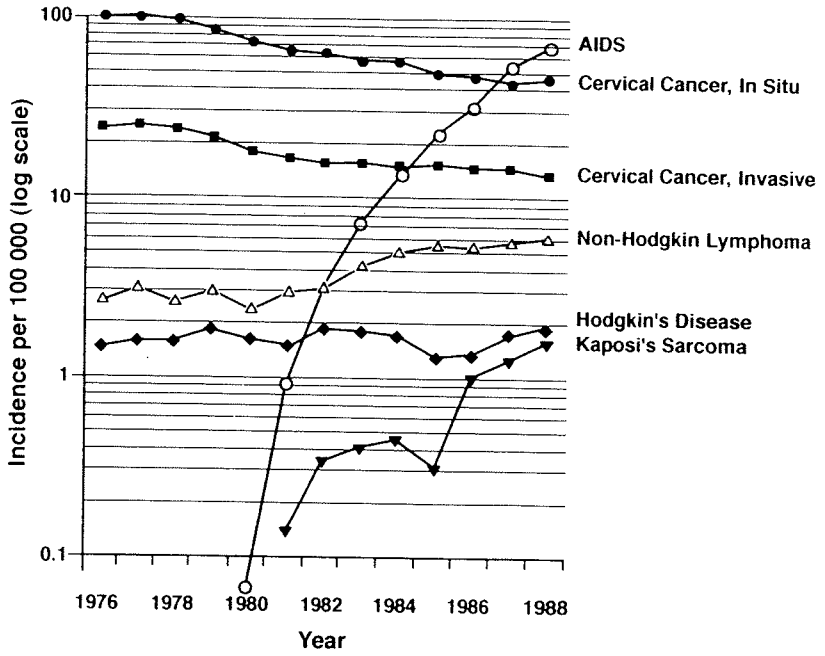
Rabkin *et al.* (1993a) used cancer registry incidence data from New York and northern New Jersey in the United States to study time trends in cervical cancer rates. The annual incidence of AIDS among women in upstate New York is low among white women and also significantly lower in black women compared to women from New York City and northern New Jersey. Nevertheless, cervical cancer in New York and northern New Jersey blacks declined during the study period (1976–88) by approximately 40% for invasive tumors and 50% for in-situ lesions (Figure 9). Because the incidence in whites remained rather stable, the ratio of incidence of invasive cervical carcinoma in blacks to incidence in whites decreased in all three regions.

Data from a pathological review of cervical cancer series from Lusaka, Zambia (Rabkin & Blattner, 1991; Patil *et al.*, 1995) indicated that both the total incidence and the age-distribution of cervical cancer remained stable during the period between 1980 and 1989 when HIV was rapidly spreading to large segments of the population. Nearly 10% of pregnant women and 18% of normal blood donors were already HIV-infected by 1985 (Melbye *et al.*, 1986).

Wabinga *et al.* (1993) compared cervical cancer incidence data for different time periods based on the cancer registry in Kyadondo County in Uganda. Invasive cervical cancer almost doubled from 22.2/100 000 in 1954–60 to 43.6 in 1989–91. The overall increase in cancer incidence during the same period was nearly 50%. [The Working Group noted that the quality of the data is uncertain and the incidence of cervical cancer appears to have been increasing in this population before the advent of HIV.]

In a large linkage study between AIDS and cancer registries in seven health departments in the United States, published as an abstract, Coté *et al.* (1993) found invasive cervical carcinoma in AIDS patients to be only marginally increased over background.

Figure 9. Incidence per 100 000 of AIDS and selected cancers in black New York City women aged 20–49, 1976–1988. Data smoothed by 3-point moving means



From Rabkin *et al.* (1993a)

(iv) *Case–control studies*

In Tanzania, ter Meulen *et al.* (1992) found that 8/270 (3%) cases of invasive cervical cancer were HIV-seropositive compared with 46/359 (13%) controls. [The Working Group noted that many of the controls were gynaecological patients and may have had conditions associated with other sexually transmitted diseases.]

In a study of cancer patients in Rwanda (Newton *et al.*, 1995), 0/23 cases of cervical cancer were HIV-seropositive compared to 8/200 (4%) in controls comprising other cancers.

In summary, the above studies are generally consistent in demonstrating an association between late-stage HIV infection and increased prevalence of CIN. However, there is at present no evidence of a significantly increasing incidence of invasive cervical carcinoma as a consequence of the HIV epidemic. This lack of increased risk of invasive disease may be partly explained by the late spread of HIV infection in the female population. In addition, active screening programmes among HIV-infected women may reduce the likelihood of progression to invasive cervical carcinoma. One result could be that HIV-infected women die from other causes before CIN progresses to invasive cervical carcinoma. HIV-infected women have in general higher rates of sexually transmitted diseases than women in the general population and are therefore more likely to be in close contact with the health care system both before and after their HIV infection.

2.3.2 *Anorectal intraepithelial neoplasia and invasive cancer*

A comprehensive and detailed review of anal cancer in HIV-infected individuals has been presented by Palefsky (1994).

The assessment of anorectal epithelial cytology poses special problems because of variable quality of sample collection and faecal contamination. Furthermore, biopsy materials have only rarely been obtained for confirmation of cytological results. A significant association between cytological and histopathological findings was observed in one study (Palefsky *et al.*, 1990), whereas Surawicz (1993) reported a three-fold greater prevalence of dysplasia for biopsy evaluation than by cytology in 90 homosexual men referred for internal lesions from a cross-sectional community-based study (see Table 24).

Table 24. Correlation of anal abnormalities with histological diagnosis

Anoscopic abnormalities	Negative	Low grade (AIN I)	High grade (AIN II-III)	Total
Discrete warts	3	26	8	37[a]
Circumferential ring of warts	2	14	7	23
Flat white epithelium	1	11	6	18
Normal or non-HPV-associated findings	7	0	1	8[a]
Total	13	51	22	86[a]

From Surawicz *et al.* (1993)

AIN, anal intraepithelial neoplasia

[a]Biopsies from two HIV-seronegative men in each of these categories were unsatisfactory.

(*a*) *Precancerous lesions*

(i) *Association with HIV*

Denis *et al.* (1992) studied 190 patients diagnosed with advanced HIV-associated disease (Group IV, CDC). Thirty-five patients had anal abnormalities, including one case of non-Hodgkin's lymphoma, but there was no case of anal carcinoma.

(ii) *Association with HIV and HPV*

The main features and results of published studies are summarized in Table 25.

Frazer *et al.* (1986) reported, from a prospective study of 61 homosexual men in Australia, cytological evidence of dysplasia with concomitant features of HPV infection in 24 men and of HPV without dysplasia in a further 26 men. HIV infection was associated with dysplasia in a univariate analysis, but the small sample size hindered more sophisticated analyses.

Table 25. Studies of precancerous lesions of the anorectal region in HIV-infected persons

Reference, study area	No. and type of HIV+ cases	No. and type of HIV− cases	HPV prevalence			Anal abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	% HIV+/HIV-		Odds ratio (95% CI)			
Frazer *et al.* (1986) Australia	20 homosexual men	41 homosexual men				HIV+ HIV−	[45%] [15%]		Cytological reading	Cytology	
Palefsky *et al.* (1990) San Francisco, USA	97 homosexual men with CDC group IV disease	None	HPV, all types HPV-6/11* HPV-16/18* HPV-31,33,35*	54% 23% 29% 20%		HIV+ condyloma atypia AIN I AIN II	39% 4 19 11 4		ViraType™	Cytology + histology	*Alone or in combination
Melbye *et al.* (1990) Denmark	33 homosexual men	87 homosexual men	HIV+	61.1%				*ASIL+HPV* CD4⁺/CD8⁺ ratio ≥ 1.0 < 1.0	ViraType™ 5.9 30.0	Cytology (ASIL)	
Caussy *et al.* (1990) USA	43 homosexual men	62 homosexual men	HIV+ HIV−	53% 29%	$p = 0.01$	HIV+ HIV−	24% 7%	$p = 0.03$	ViraType™ and PCR	Cytology (ASIL)	
Kiviat *et al.* (1990) USA	49 homosexual men	47 homosexual men	HIV+ HIV−	26% 6%					ViraType™		
Critchlow *et al.* (1992) USA	26 consecutive homosexual men for HIV testing	119 same	HIV+ HIV−	31% 8%	5.8 (1.1–30.1) adj. for STD history, age, anorectal symptoms				Dot filter hybridization		HIV positivity did not influence type of HPV. HPV prevalence up with severity of HIV-disease
Bernard *et al.* (1992) France	54 homosexual and IVDU men	54 partners of women with genital HPV or cervical dysplasia	*HIV+* Any type HPV-6/11 HPV-16/18 and/or 31/35/51 *HIV−* Any type HPV-6/11 HPV-16/18 and 1/35/51	 [66%] 17% 83% [54%] 62% 38%					In situ hybridization		Link between CMV and high-risk HPV observed irrespective of HIV status

Table 25 (contd)

Reference, study area	No. and type of HIV+ cases	No. and type of HIV– cases	HPV prevalence			Anal abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	% HIV+/HIV-		Odds ratio (95% CI)			
Kiviat *et al.* (1993) USA	285 homosexual men seeking HIV testing	204 same	*Southern blot*		4.0 (2.7–6.2)	HIV+	26%	5.6 (3.0-10.5)	Southern transfer hybridization and PCR	Cytology Bethesda recommendation	*Southern transfer hybridization*
			HIV+	55%		HIV–	8%	*HIV+*			CD4⁺ ≤ 500 2.6 (1.2-5.7)
			HIV–	23%		*HIV+ only*					CD4⁺ > 500 1.0
			PCR			Atypia:		Atypia:			*PCR alone*
			HIV+	92%	3.1 (1.6–5.8)	CD4⁺ < 200	28%	4.2			CD4⁺ ≤ 500 6.3 (0.8-72.2)
			HIV–	78%		200–500	25%	3.3			CD4⁺ > 500 1.0
						501–800	25%	2.7			
						> 800	30%	2.6			
						ASIL:		ASIL:			
						CD4⁺ < 200	36%	9.9			
						200–500	35%	8.7			
						501–800	25%	5.1			
						> 800	8%	1.3			
Breese *et al.* (1995) Denver, USA	93 homosexual men	116 homosexual men	*HIV+*						ViraPap™/ ViraType™	None	HPV prevalence associated with increasing immunodeficiency
			HPV, any type	61%							
			HPV-6/11	8%							
			HPV-16/18	12%							
			HPV-31/35/35	18%							
			Mixed HPV-16/18+	19%							
			Mixed HPV-16/18–	4%							
			HIV–								
			HPV, any type	17%							
			HPV-6/11	4%							
			HPV-16/18	7%							
			HPV-31/33/35	0.8%							
			Mixed HPV-16/18+	4%							
			Mixed HPV-16/18–	0.8%							

ASIL, anal squamous intraepithelial lesions; PCR, polymerase chain reaction; IVDU, intravenous drug users; STD, sexually transmitted disease; CMV, cytomegalovirus

Kiviat *et al.* (1990) reported that 13/49 (26.5%) HIV-infected homosexual men compared with 3/47 (6.4%) HIV-negative homosexual men had detectable anal HPV by dot-blot hybridization ($p = 0.002$). No data on anal cytology or histology were available.

Critchlow *et al.* (1992) reported a significant association between HIV infection and HPV DNA as measured by dot filter hybridization, after adjustment for sexually transmissible disease history, age and current anorectal disease (odds ratio, 5.8; 95% CI, 1.1–30.1). HIV infection was not associated with the type of HPV detected but the severity of HIV-related disease was positively related to HPV prevalence.

In anal swabs or biopsies from homosexual men, Critchlow *et al.* (1995) reported a progressive increase in the detection of HPV-16 or HPV-18 DNA with declining $CD4^+$ T-cell count.

Bernard *et al.* (1992) studied 54 HIV-positive and 54 HIV-negative men, all presenting with anogenital lesions such as flat condyloma or condyloma acuminata. HIV-positive subjects were homosexual men (71%) or intravenous drug users (24%). HIV-negative subjects were partners of women with genital HPV infection or cervical dysplasia. High-risk types of HPV (16, 18, 31, 35, 51) were more prevalent (83.4%) in HIV-positive persons and the low-risk HPV types (6, 11) were more common in HIV-negative subjects (62.1%). Anal intraepithelial neoplasia (AIN) II/III was highly associated with high-risk HPV types (15/16, 94%) compared with low-risk HPV (1/24, 6%).

(iii) *HIV, HPV, and $CD4^+$ T-cell count*

Palefsky *et al.* (1990), in their study of 97 homosexual men with advanced HIV infection in San Francisco, CA, United States, found HPV DNA (detected by ViraPap™/ViraType™) in 54% and abnormal anal cytology in 39% (for details see Table 25). AIN was diagnosed in 15 specimens (15%). Abnormal cytology was significantly associated with anal HPV infection (odds ratio, 4.6; $p = 0.003$) and, among those infected with two or more HPV types, 10/12 had abnormal anal cytology (odds ratio, 39.0). $CD4^+$ counts obtained from medical records were inversely associated with cytological abnormality but did not contribute significantly in a multiple regression model which also included HPV.

Caussy *et al.* (1990) found that 41 (39%) of 105 homosexual men from Washington DC, and New York, United States, had infection with HPV-6/11, -16/18, or -31,33,35. The corresponding figures were 53% in 43 HIV-infected subjects and 29% in 64 HIV-negative subjects ($p = 0.01$). In HIV-infected subjects, low $CD4^+$ count was independently associated with anal HPV detection, whereas the number of partners and the frequency of receptive anal intercourse were unimportant. Abnormal cytology was seen in 9/37 (24%) HIV-infected men and in 4/55 (7%) HIV-negative men ($p = 0.03$) and was strongly associated with the detection of any HPV genotype. None of 15 subjects with HPV detected only by PCR had anal epithelial abnormality.

In a sample of 112 Australian homosexual men consecutively presented for routine screening for sexually transmitted diseases and HIV infection, 19% showed evidence of mild to moderate dysplastic changes (AIN I or AIN II). HPV DNA (types 6/11, 16/18) by dot blot hybridization was detected in 40% (6/11 in 18%; 16/18 in 11%; both groups in

12%). There was a significant association between presence of HPV-16/18 and anal dysplasia, but not between HPV infection or anal dysplasia and HIV-positivity, immune status, sexual practices or other sexually transmitted diseases (Law *et al.*, 1991).

In a larger study (Kiviat *et al.*, 1993), a random sample of 285 HIV-positive and 204 HIV-negative homosexual men was surveyed. HPV DNA was found by Southern blot hybridization in 55% and 23% (odds ratio, 4.0; 95% CI, 2.7–6.2) of HIV-positive and -negative men and by PCR in 92% and 78% (odds ratio, 3.1; 95% CI, 1.6–5.8), respectively. Each specific group of HPV DNA types surveyed was most common in HIV-infected men (Table 26). Detection of HPV by both Southern blot hybridization and PCR (high-level HPV infection) was significantly associated with anal intraepithelial lesions. However, after adjustment for level of HPV DNA, severely immunosuppressed HIV-positive men ($CD4^+$ count < 500 cells/mm^3) were at higher risk for anal intraepithelial lesions than men with a $CD4^+$ count of more than 500 cells/mm^3 (odds ratio, 2.9; 95% CI, 1.4–6.2). [The Working Group noted that this finding indicates a possible independent role of immunosuppression in addition to that of HPV].

Table 26. Prevalence of anal HPV DNA in HIV-positive and HIV-negative homosexual men as detected by dot-filter hybridization, low- and high-stringency Southern transfer hybridization, and PCR

	HIV+	HIV–	OR	95% CI
Dot blot	(*n* = 304)	(*n* = 211)		
Any HPV	52%	18%	5.1	3.3–7.9
Southern	(*n* = 285)	(*n* = 204)		
Any HPV	55%	23%	4.0	2.7–6.2
HPV-16,18[a]	21%	7%	5.0	2.6–9.6
HPV-31,33,35[a]	15%	3%	8.7	3.5–25.7
HPV-6,11[a]	21%	7%	5.0	2.6–9.6
Unclassified	16%	8%	3.7	1.7–6.3
Multiple	15%	3%	8.5	3.4–25.2
PCR	(*n* = 241)	(*n* = 152)		
Any HPV	92%	78%	3.1	1.6–5.8
HPV-16,18	53%	38%	3.6	1.8–7.2
HPV-31,33,35	43%	15%	7.4	3.4–16.2
HPV-6,11	47%	39%	3.1	1.6–6.2
Unclassified	19%	22%	2.2	1.0–4.9
Multiple	44%	23%	4.9	2.4–10.1

From Kiviat *et al.* (1993)
[a] Alone or in combination

Sixty-six (22%) HIV-positive and 24 (11%) HIV-negative men from the above-mentioned study were referred for biopsies of internal anorectal lesions (Surawicz *et al.*, 1993). Whereas only 31 (36%) had dysplasia diagnosed by cytology, 73/86 (85%) had dysplasia evident on biopsy (26% high-grade). The correlations of anal abnormalities

with histological diagnosis are presented in Table 24. HIV status did not influence the prevalence of high-grade lesions. Both high- and low-risk HPV types were common in many of the biopsy specimens.

In a study of 37 HIV-positive and 28 HIV-negative homosexual men, Palefsky *et al.* (1994) found both anal intraepithelial lesions and the presence of HPV to be closely associated with HIV-positivity in men with $CD4^+$ T-cell counts below 200 cells/mm^3. Furthermore, multivariate analysis indicated a possible influence of current smoking.

Several studies among women are in progress, but the results of only one have been published (Williams *et al.*, 1994). Among 114 intravenous drug users, anal infection with HPV was twice as frequent as cervical infection and was associated with HIV-positivity by both dot blot (odds ratio, 2.5; 95% CI, 0.9–7) and PCR (2.6; 1.03–6.8). Anal intraepithelial lesions were seen in 14% (15/109) of the women, of whom 11 were HIV-infected (odds ratio, 3.4; 95% CI, 0.9–15.5). The presence of anal squamous intraepithelial lesions (ASIL) was closely associated with a simultaneous high level (dot blot positive) of HPV DNA and HIV-positivity (odds ratio, 9.2; 95% CI, 1.6–63.6), whereas no association was found with $CD4^+$ count.

Breese *et al.* (1995) studied the expression of HPV in a cross-sectional, follow-up study of 116 HIV-seronegative and 93 HIV-seropositive homosexual men. HPV was significantly more common among HIV-positive persons and HPV types 16/18 accounted for more than 50% of the infections. HPV prevalence increased significantly with decreasing $CD4^+$ count; persistence of HPV during a six-month follow-up was also more common among men with clinical signs of severe immunosuppression (AIDS/ARC (AIDS-related complex)) (95%) compared with asymptomatic HIV-seropositive men (62%) and HIV-seronegative men (61%).

(iv) *Progression of disease*

Irrespective of HIV status, there are few data available relevant to the association between the different intraepithelial lesions and invasive anal cancer.

In San Francisco, Palefsky *et al.* (1992) followed 37 homosexual men with advanced HIV disease prospectively for an average of 17 months and found an increase in anal epithelial abnormality from 27% to 65%. The percentage of men with AIN increased from 8 to 32% and that of men with high-grade AIN from 0 to 16%. Presence of HPV DNA (detected by Virapap™/Viratype™) increased from 60 to 89%.

Morgan *et al.* (1994) identified all patients who had undergone excision biopsy of anal condylomata during 1984–88 at a hospital in London, United Kingdom. Overall, 27 had evidence of AIN and for these patients, results of HIV testing were traced. Five of six patients having carcinoma *in situ* (AIN III) were found to be HIV-seropositive and were followed for between four and six years without any evidence of progression of disease.

(*b*) *Invasive anal cancer*

(i) *Case reports and series*

Only a few case reports and series describe invasive anal cancer in HIV-infected persons (Rüdlinger & Buchmann, 1989; Lorenz *et al.*, 1991; Chadha *et al.*, 1994; Jebakumar *et al.*, 1994; Nasti *et al.*, 1994). Most cancers occurring in the anal region are of the (transitional) epidermoid type. Other anal cancers associated with HIV include small-cell carcinoma (Read *et al.*, 1985; Smitherman *et al.*, 1990; Nakahara *et al.*, 1993), non-Hodgkin's lymphoma and Kaposi's sarcoma.

(ii) *Prognosis*

Very little information is available on the possible influence of HIV infection on the prognosis of anal cancer. Some cases have shown an aggressive clinical course with low response to treatment (Lorenz *et al.*, 1991; Jebakumar *et al.*, 1994), whereas others have not (Chadha *et al.*, 1994; Nasti *et al.*, 1994).

(iii) *Descriptive epidemiology*

Reports from Sweden, Denmark and the United States have shown significant increases in the incidence of epidermoid anal cancer over the last 30 years, not only during the period of the AIDS epidemic (Goldman *et al.*, 1989; Frisch *et al.*, 1993; Melbye *et al.*, 1994a). The increase has been more pronounced in women than in men and more in urban than in rural areas. Furthermore, black people are at higher risk than whites and never-married men are at higher risk than ever-married men. The increased risk of anal cancer in never-married men has been documented as early as the 1940s and 1950s (Frisch *et al.*, 1993). These trends suggest that important behavioural and environmental changes were taking place before the beginning of the AIDS epidemic.

Melbye *et al.* (1994a) compared the proportion of men who were never-married (as a surrogate for homosexuality) among anal cancer patients with that in colon cancer patients (controls) in four metropolitan areas (San Francisco–Oakland, CA; Detroit, MI; Seattle, WA; Atlanta, GA) included in the SEER Programme in the United States. The relative risk for anal cancer patients rose from 5.8 (95% CI, 3.9–8.7) in 1973–78 to 6.7 (4.7–9.5) in 1979–84 and 10.3 (7.5–14.1) in 1985–89 ($p_{trend} = 0.02$). Among white men from the San Francisco Bay area, the incidence of anal cancer increased from 0.5/100 000 in 1973–75 to 1.2/100 000 in 1988–89 ($p_{trend} < 0.001$).

Biggar *et al.* (1987) and later Rabkin and Yellin (1994) used data from the SEER programme to study the evolution in anal cancer incidence in single, young (25–54 years) men within the city of San Francisco. The incidence of anal cancer in 1973–79 was 9.9 (95% CI, 4.5–18.7) times that expected from general population rate and in 1988–90 was 10.1 (95% CI, 5.0–18.0) times that expected.

Biggar *et al.* (1989) used a proportional incidence method to study cancers (period 1973–85) occurring among single young men and married young men in New York. A significant increase in anal/anorectal cancers was recorded for single but not for married men. However, the increase appeared to have already occurred by 1979–80, without a clear increasing trend thereafter.

Reynolds *et al.* (1993) linked AIDS registry files (San Francisco residents only) with the California Tumor Registry (period 1980–87) and compared the incidence of cancer in the AIDS population with that of the general population of the San Francisco Bay Area. Six cases of anal or rectal cancer were seen among the AIDS patients, which were more than expected (standardized incidence ratio [SIR], 3.5; 95% CI, 1.3–7.5). In-situ cancer of the anorectal area was also significantly elevated among persons with AIDS (7 cases; SIR, 65; 95% CI, 26.1–134). The SIR analysis included cancers that occurred before, concurrently with and subsequent to the diagnosis of AIDS.

Melbye *et al.* (1994b) used a linkage between AIDS (50 050 reports) and cancer (859 398 reports) registries in seven health departments in the United States to investigate the association between HIV infection and epidermoid anal cancer. Compared with general population rates, the relative risk for anal cancer at and after AIDS diagnosis was 84.1 (95% CI, 46.4–152) among homosexual men and 37.7 (9.4–151) among non-homosexual men. The relative risk was 13.9 (6.6–29.2) for occurrence of anal cancer in the period two to five years before AIDS diagnosis and 27.4 (15.9–47.2) during the two years before AIDS diagnosis (p for trend = 0.004) (Table 27).

Table 27. Relative risk (observed/expected ratio) of epidermoid anal and anorectal cancer among AIDS patients compared with population controls matched for age, sex, and race

Time from AIDS diagnosis	No. of cases		Relative risk (95% CI)
	Observed	Expected	
2–5 years before	7	0.502	13.9 (6.6–29.2)
0.25–2 years before	13	0.475	27.4 (15.9–47.2)
0.25 years before or after	9	0.113	79.6 (41.4–153)
0.25–0.75 years after	3	0.072	41.7 (13.4–129)
> 0.75–2.25 years after	4	0.082	48.7 (18.3–130)

From Melbye *et al.* (1994b)

In summary, the above studies are generally consistent in demonstrating an association between HIV infection (and the associated immunodeficiency) and anal dysplasias. However, even in the absence of HIV infection, anal cancer is more common in AIDS risk groups. Thus, a specific association of HIV infection with invasive cancer has not been convincingly demonstrated.

2.3.3 *Hodgkin's disease*

Misclassification of non-Hodgkin's lymphoma cases as cases of Hodgkin's disease occurs (Herndier & Friedman, 1992; Reynolds *et al.* 1993; Rabkin & Yellin, 1994; Knopf & Locker, 1995) and may at least partly explain the reported increased rates of Hodgkin's disease in HIV-positive persons. Non-Hodgkin's lymphoma incidence is

greatly increased in HIV-positive persons and only a small misclassification rate of these cases would cause a false impression of an elevation in rates of Hodgkin's disease (Glaser & Swartz, 1990). Assignment to a specific type is particularly difficult for those cases of Hodgkin's disease that have been reported in HIV-positive persons with an atypical lymphoid background. Sometimes even unusual atypical reactive processes make a firm diagnosis rather difficult (Herndier & Friedman, 1992).

(*a*) *Distribution of histological types*

(i) *Hodgkin's disease in HIV-uninfected persons*

Hodgkin's disease is a heterogeneous entity which is often described as two different diseases. In developed countries, it has a bimodal age–incidence curve with a first peak at 15–34 years and another among persons older than 55 years of age. Histologically, nodular sclerosis is primarily diagnosed in young Hodgkin's disease patients, whereas mixed cellularity predominates in the older age groups. Population-based data from the SEER programme show a significant increase in the incidence of nodular sclerosis, particularly in adolescents and young adults, whereas the mixed cellularity type has remained stable over time. A decrease in incidence in recent years among older age groups was explained by earlier misclassification of non-Hodgkin's lymphoma as Hodgkin's disease. Among 9418 microscopically confirmed cases of Hodgkin's disease reported to the SEER programme between 1973 and 1987, 51.0% were of the nodular sclerosis type, 23.8% of mixed cellularity, 6.7% with lymphocytic predominance, 5.7% with lymphocytic depletion and 12.8% were miscellaneous Hodgkin's disease (Medeiros & Greiner, 1995).

(ii) *Hodgkin's disease in HIV-infected persons*

Since the mid-1980s, a large number of case reports and small case series of Hodgkin's disease in HIV-infected persons have appeared (see Rubio, 1994) which, together with larger and more recent case series (Table 28), describe a particular natural history and histological distribution of Hodgkin's disease which are different from those of Hodgkin's disease in HIV-uninfected persons. Despite a young median age of the patients, mixed cellularity and lymphocyte depletion are the predominant histological features. The majority of cases have B symptoms and approximately 80% have advanced disease (stages III or IV). Extranodal dissemination and, in particular, bone marrow involvement are common, whereas mediastinal involvement is less frequent than is observed in HIV-uninfected persons (Rabkin & Blattner, 1991; Tirelli *et al.*, 1995b).

The Italian Cooperative Group on AIDS-related Tumors (GICAT) in 1988 and subsequently Monfardini *et al.* (1991), Tirelli *et al.* (1992), Serraino *et al.* (1993), Errante *et al.* (1994) and Tirelli *et al.* (1995b) have described cases of Hodgkin's disease in HIV-infected persons. Among 63 cases in intravenous drug users (median age, 27 years), reported to the organization during 1980–89, 74% were histologically characterized as showing mixed cellularity or lymphocyte depletion. Overall, 83% were in advanced stage, but atypical presentations (central nervous system, skin, endobronchial site or lung involvement with lack of mediastinal adenopathy) were uncommon (Monfardini *et al.*, 1991).

Table 28. Characteristics of Hodgkin's disease in HIV-infected persons (only studies with more than 20 cases)

Reference	Period	*N*	Age median (range)	Male no.	Female no.	Histopathology				Advanced stage (III, IV)	B symptoms	Extra nodal	Bone marrow involvement
						Mixed cellularity	Lymphocyte depletion	Nodular sclerosis	Lymphocytic predominance				
Rubio (1994) Spain	1984–91	46	27 (mean) (18–55)	43	3	41%	22%	22%	4%	89%	83%	50%	41% at diagnosis
Andrieu *et al.* (1993) France	1987–89	45[a]	30	39	6	49%	4%	40%	0	75%	80%	in all stage IV	[24%]
Monfardini *et al.* (1991) Italy	1980–89	63	27 (20–44)	59	4	48%[b]	23%	23%	0	83%	NR		
Tirelli *et al.* (1995b) Italy	1986–94	114[c]	29 (19–57)	103	11	45%	21%	30%	4%	81%	77%	63%	
Ree *et al.* (1991) USA	1983–90	24	34 (24–51)	23	1	100%	0	0	0	92%	100%		50% at presentation, confirmed in 25% by biopsy

[a] Three cases had undetermined histological subtype.
[b] 3% had lymphocyte depletion and mixed cellularity
[c] Seven cases not classified histopathologically

Tirelli *et al.* (1995b) compared 114 HIV-positive cases reported to GICAT during 1986–94 with 104 HIV-negative cases of Hodgkin's disease from a single institution. HIV-positive cases included a higher percentage of stage IV disease despite a lower median age.

Andrieu *et al.* (1993) compared all 45 cases of Hodgkin's disease collected by the French registry of HIV-associated tumours between 1987 and 1989 with a cohort of 407 HIV-negative Hodgkin's disease patients for whom similar diagnostic criteria had been used. The groups had a similar median age (30 and 31 years) but differed significantly with respect to advanced clinical stage (75% versus 33%), proportion of mixed cellularity (49% versus 20%) and absence of mediastinal disease (87% versus 29%).

In a series of 46 patients with Hodgkin's disease and HIV infection diagnosed in 1984–91 in nine hospitals in Madrid, Spain, 41% were classified as being of mixed cellularity, 22% with lymphocytic depletion, 22% with nodular sclerosis and 4% with lymphocytic predominance. Advanced disease (stages III or IV) was found in 89%; 83% had B symptoms and 41% had bone marrow involvement (Serrano *et al.*, 1990; Rubio, 1994).

(iii) *Prognosis*

Hodgkin's lymphoma in the immunocompromised host is particularly aggressive and difficult to treat (Carbone *et al.*, 1991).

Errante *et al.* (1994) studied treatment response and survival in 84 Italian HIV-negative and 92 HIV-positive patients. Remission was achieved in 51% of HIV-infected patients and in more than 90% of the HIV-negative patients. When HIV-infected patients were compared with only the older HIV-negative patients, who were primarily diagnosed with the mixed cellularity type of Hodgkin's disease, similar differences were observed. The estimated four-year survival was 33% in HIV-positive patients compared with 88–100% in HIV-negative patients, depending upon the age group.

In the French study, Roitmann *et al.* (1992), Andrieu *et al.* (1993) and Lévy *et al.* (1995) found a high rate (79%) of complete remission after standard therapy in 45 HIV-positive Hodgkin's disease patients, but haematological and infectious complications were very frequent. Overall, two-year survival was 41%.

Other authors have found full remission in HIV-positive persons to range between 47% and 58% (Serrano *et al.*, 1990; Monfardini *et al.*, 1991; Tirelli *et al.*, 1995b).

(*b*) *Descriptive epidemiology*

Already in the early 1980s, analyses of data from the SEER programme detected marked increases in the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma among never-married young men, but no similar increase in Hodgkin's disease was observed (Biggar *et al.*, 1985; Bernstein *et al.*, 1989). Among never-married young men from San Francisco, CA, United States, Biggar *et al.* (1987) found a small but non-significant increase while Rabkin and Yellin (1994) observed an increase which predated the AIDS epidemic and which was not restricted to the mixed cellularity subtype most often associated with HIV-positive cases of Hodgkin's disease. Analyses of data from a cancer registry in New York State, not part of the SEER programme, revealed an abrupt

increase in Hodgkin's disease among never-married men in 1985 (Biggar *et al.*, 1989), whereas a study of women based on cancer registry data from New York and New Jersey did not detect an increase in the incidence of Hodgkin's disease during 1976–88 (Rabkin *et al.*, 1993a).

Medeiros and Greiner (1995) studied trends in Hodgkin's disease over three time periods (1973–77, 1978–82 and 1983–87), using data from the SEER programme. In San Francisco County, where young men are known to have a high prevalence of HIV infection, the age-specific incidence rates for Hodgkin's disease of mixed cellularity increased for men and was the most common subtype by the age of 50. This was in contrast to an unchanged age-adjusted rate among men based on the entire SEER database.

In another study based on SEER data, the risk was evaluated of developing another primary cancer after a diagnosis of Kaposi's sarcoma. Because of the more than 40 000-fold increase in risk for Kaposi's sarcoma among never-married men since the beginning of the HIV epidemic, this tumour was used as a surrogate for HIV-positivity. No indication of an increased risk for Hodgkin's disease was found among never-married men with Kaposi's sarcoma (Biggar *et al.*, 1994).

(*c*) *Cohort studies*

Reynolds *et al.* (1993) linked data from AIDS and cancer registries in San Francisco between 1980 and 1987. Compared with concurrent population rates for the same geographical area, the SIR for Hodgkin's disease in men with AIDS increased from 1.9 in 1980–81 to 18.3 in 1986–87. This observation was based on only 16 cases and the standardized intervals overlapped for each of the four periods studied. [The Working Group noted that the SIR analysis included 14 cases in which Hodgkin's disease was diagnosed before the AIDS diagnosis. This would tend to overestimate the risk in AIDS patients when comparing with population rates, because these cases entered the analysis only if they survived until AIDS diagnosis.]

Hessol *et al.* (1992) compared the risk for Hodgkin's disease in a cohort of 6704 homosexual men from the San Francisco City Clinic Cohort study with population-based rates from the SEER programme. Information on cancer events in the cohort was obtained by computer-matched identification of participants with the records of the Northern California Cancer Center registry. Among HIV-infected men, the age-adjusted standardized relative risk for Hodgkin's disease was 5.0 (95% CI, 2.0–10.3).

Ragni *et al.* (1993) found no increased incidence of Hodgkin's disease among 3041 haemophiliacs from the United States during 1978 and 1989. In fact, no case of Hodgkin's disease was reported among the 1295 HIV-positive patients.

In the NCI Multicenter Haemophilia Cohort Study, there were two cases of Hodgkin's disease among 1065 HIV-seropositive subjects and one case among 636 HIV-seronegative subjects (Rabkin *et al.*, 1992). These cases were 6.6 and 8.2 times the expected frequencies in HIV-seropositive and HIV-seronegative subjects, respectively, although neither excess was statistically significant.

Lyter *et al.* (1995) studied cancer events occurring during 1984–93 in a cohort of 769 HIV-seronegative and 430 HIV-seropositive homosexual men in Pittsburgh, PA, United States. Cancer information was collected through semiannual visits, medical records and death certificates. There was no difference in Hodgkin's disease rates between the seronegative homosexual men and the general male population of Pennsylvania, whereas two cases observed in the HIV-seropositive group were more than expected (SIR, 19.8; 95% CI, 2.4–71.5).

(*d*) *Cofactors*

Little is known about potential cofactors for Hodgkin's disease occurring in HIV-positive persons. HIV-positive persons express a higher proportion of EBV-positive B-lymphocytes that are capable of spontaneous outgrowth *in vitro* than HIV-uninfected persons (Birx *et al.*, 1986).

Moran *et al.* (1992) used PCR to detect the presence of EBV DNA sequences in 10 HIV-positive patients with Hodgkin's disease. Eight (80%) were positive for EBV, compared with 23 (40%) of 57 specimens from HIV-negative patients with Hodgkin's disease.

Tirelli *et al.* (1995b) observed the expression of the EBV-encoded latent membrane protein-1 (LMP-1) in the diagnostic Reed–Sternberg cells (Mueller, 1996) in 14/18 (78%) HIV-positive and 27/104 (25%) HIV-negative Hodgkin's disease patients ($p < 0.001$). Monoclonal expression of EBV genomes was found in 8/10 (80%) tumours from HIV-infected persons compared with 12/44 (38%) tumours from HIV-negative individuals. Using PCR-based amplification of EBNA-2-specific sequences, the authors showed 6/11 EBV-positive tumours in HIV-positive persons to contain type 2 EBV compared with 1/26 such tumours from HIV-negative persons. The great majority of tumour biopsies from HIV-1-positive patients with Hodgkin's disease have been consistently found to be positive for the EBV genome or viral proteins (Mueller, 1996).

In summary, the above studies indicate that Hodgkin's disease in the presence of HIV infection is more likely to have mixed cellularity or lymphocyte-depleted histology and is clinically more aggressive. Absolute Hodgkin's disease incidence may also be elevated in HIV-infected persons, particularly injecting drug users, but an association is not proven because of the modest magnitude of the observed increases and the diagnostic overlap with non-Hodgkin's lymphoma.

2.3.4 *Testicular cancer*

The incidence of both testicular germ-cell tumours and infection with HIV is highest in young men aged 20–40 years. It is to be expected that a proportion of testicular cancer patients will be HIV-positive by chance.

(*a*) *Case reports and series*

A number of case reports and small case series of testicular cancer in HIV-infected men have been published. Some of these have been summarized by Csiszar and Zimmern (1993) and Buzelin *et al.* (1994) and together with other series (Moyle *et al.*, 1991;

Bernardi *et al.*, 1995; Timmerman *et al.*, 1995) constitute a total of at least 120 cases. Of these, five were reported as being lymphomas, often with accompanying extensive systemic disease. The remaining cases were testicular germ-cell tumours. Seminomas were the most frequently observed histological type of germ-cell tumour (49–67%). Non-seminomatous tumours comprised a proportion similar to that reported in uninfected individuals with testicular germ-cell tumours (Einhorn *et al.*, 1993).

Moyle *et al.* (1991) reported three testicular seminomas among 2205 known HIV-seropositive patients attending a hospital clinic in London, United Kingdom. They calculated the risk among HIV-infected persons to be increased 68-fold compared with expected rates.

Timmerman *et al.* (1995) reviewed 294 cases of testicular germ-cell tumours diagnosed between 1980 and 1993 at four hospitals in San Francisco, CA, United States, using cancer registry files and pathology reports. Overall, 11 HIV-seropositive cases (4%) were identified. These were further evaluated together with four additional seropositive cases diagnosed at private medical centres in San Francisco and compared with the remaining 279 cases without evidence of HIV infection. There was no difference in tumour stage at presentation (low-stage (I and IIA) tumours in HIV-positive persons, 67%; those in HIV-negative persons, 63%). Standard therapy including orchiectomy, retroperitoneal lymph node dissection, radiation therapy and chemotherapy was well tolerated. In these HIV-positive patients, there was no indication of a more aggressive course of disease compared with that seen in HIV-negative patients.

Bernardi *et al.* (1995) performed a retrospective analysis of 26 cases of testicular germ-cell tumours diagnosed between 1986 and 1994 in HIV-positive men in Italy. Of these patients, 61% had low-stage tumours (stages I to IIb) and only 35% had advanced disease, a proportion similar to that observed among HIV-seronegative patients. The complete response rate of 95% and overall three-year survival of 65% in this series did not differ substantially from those in HIV-uninfected persons (Kaplan, 1995). The median $CD4^+$ T-cell count at presentation was 261 cells/mm^3 (range, 2–1229) and only six had a $CD4^+$ count below 200 cells/mm^3, which suggests that the clinical behaviour of testicular cancer in HIV-positive persons is not directly related to level of immunosuppression.

(*b*) *Descriptive and cohort studies*

Descriptive studies based on cancer incidence data from various parts of the United States have unanimously failed to show a link between cancer of the testis and the HIV epidemic. Biggar *et al.* (1987) used never-married men as a surrogate for homosexuality in their study of cancer incidence trends in San Francisco from 1973 to 1984. Neither this study nor that of Rabkin and Yellin (1994), with the same data series updated to 1990, showed any indication of an increasing trend in the 1980s for cancer of the testis. In an analysis of cancer incidence data from New York City based on the period 1973–85, Biggar *et al.* (1989) similarly found no increasing trend for cancer of the testis.

Reynolds *et al.* (1993), using data from population-based registries for AIDS and cancer for San Francisco residents for the period 1980–87, found no indication of an

increased risk for testis cancer in AIDS patients (1973–77: SIR, 1.0; 95% CI, 0.2–2.8); 1980–87: SIR, 0.7; 95% CI, 0.2–2.2).

Lyter *et al.* (1995) found two cases of testicular seminoma in a prospective cohort study of 430 HIV-infected men (SIR, 8.2 (95% CI, 1.0–30)). When a third case of extragonadal seminoma was included and the age-adjusted population rates for all seminomas were compared, a 21-fold increase ($p < 0.001$) in the HIV-infected cohort was observed.

In summary, there is some suggestion of an association of testicular cancers with HIV infection, but the studies are not yet conclusive.

2.3.5 *Non-melanoma cancers of the skin*

Skin cancers and, in particular, squamous-cell carcinomas have been associated with a wide variety of immunodeficiency conditions (Hintner & Fritsch, 1989). Transplant patients who are immunocompromised have a disproportionately high incidence of squamous-cell carcinomas as compared to basal-cell carcinomas, in a ratio of 15 : 1 according to one study (Barr *et al.*, 1989) (see Section 4.1).

(*a*) *Case reports and series*

A number of case reports on skin cancers other than Kaposi's sarcoma in HIV-infected persons have been published (for references see Smith *et al.*, 1993c). However, only one large series has been described.

Lobo *et al.* (1992) identified all HIV-infected male patients with a non-melanoma skin cancer diagnosed in the dermatology clinic at the University of California, San Francisco, United States, and performed a retrospective case–control study with age-matched controls. Overall, 116 non-melanoma skin cancers were identified in 48 patients, 101 occurring in 47 patients were basal-cell carcinomas and 15 in 10 patients were squamous-cell carcinomas. The basal-cell : squamous-cell carcinoma ratio (6.7 : 1) was similar to that observed in HIV-uninfected persons in the same area but different from that observed among transplant patients, as discussed above. The major risk factors associated with non-melanoma skin cancer in this group of men were the same as those in the normal population: fair skin, a family history of skin cancer and sun exposure.

(*b*) *Descriptive and cohort studies*

Reynolds *et al.* (1993) found, in their linkage study of AIDS and cancer cases among San Francisco residents, three non-melanoma skin cancers (one dermatofibroma, one haemangiosarcoma, one sarcoma unspecified), a significantly higher number than expected (SIR, 10.0). Because the study was purely registry-based, it was impossible to confirm that these cases were not misclassified Kaposi's sarcoma cases.

Non-melanoma skin cancers are not registered in the SEER programme. The incidence of melanoma of the skin has been found to be marginally increased among never-married men from New York City and from San Francisco (Biggar *et al.*, 1989; Rabkin & Yellin, 1994), but these findings are possibly related to the specific behaviour of single men in terms of recreational sun exposure, rather than to the HIV epidemic. No increase incidence with time was observed in any of the studies.

Smith *et al.* (1993c) followed 724 HIV-infected military employees in the United States for a period of 36 months and diagnosed 13 cases of basal-cell carcinoma (1.8%), two cases of squamous-cell carcinoma (0.3%) of the face, 2 cases of squamous-cell carcinoma (0.3%) in the anus and three malignant melanomas (0.6%). The basal-cell : squamous-cell carcinoma ratio was more similar to that of the general population than to that observed among transplant recipients. Most of the patients studied were at an early stage of their HIV disease and not severely immunosuppressed, and had lightly pigmented skin.

In their cohort study of 1701 haemophiliacs (see Section 2.2.3), Rabkin *et al.* (1992) observed five cases of basal-cell carcinoma (2 in HIV+, 3 in HIV– persons), corresponding to rates of [0.2 and 0.8 per 1000 person-years] in HIV-infected and HIV-uninfected subjects, respectively. No comparison was made with rates in the general population.

Ragni *et al.* (1993) performed a retrospective cohort study of 3041 haemophiliacs (56.6% HIV-infected) from 18 haemophilia centres in the United States during the period 1978–89. The incidence of basal-cell carcinoma in HIV-infected patients was 18.3 times greater than that in HIV-uninfected patients ($p < 0.0001$) but 11.4 times greater than that in the general population, a finding which remains unexplained. Among HIV-infected patients, the observed-to-expected ratio was 2.0 ($p < 0.001$).

In a large cohort study of 1199 homosexual men (period 1984–1993) (Lyter *et al.*, 1995) found three cases of basal-cell carcinoma in HIV-infected persons and seven cases of basal-cell carcinoma and two of squamous-cell carcinoma in seronegative men. No more cases were found in either HIV-infected or -uninfected men than expected from general population rates.

In a study of 1073 homosexual and bisexual men (434 HIV+) in three United States cities, followed for over 10 000 person-years, the relative risk for incidence of skin cancers —25/35 basal-cell carcinomas — was 2.2 in HIV-infected compared with uninfected men (Holmberg *et al.*, 1995b).

In summary, there is conflicting evidence regarding an association between non-melanoma skin cancers and HIV infection. [The Working Group noted that the diagnosis and reporting of these tumours are highly variable and this possible association may be particularly difficult to investigate.]

2.3.6 *Conjunctival tumours*

Although rare in Europe and North America, squamous-cell carcinoma of the conjunctiva was already more common in Africa before the advent of AIDS (Templeton, 1973; Newton *et al.*, 1996). Strong associations have been reported between dysplasia and invasive carcinoma of the conjunctiva and HPV (IARC, 1995).

(*a*) *Case reports*

Two case reports of squamous-cell carcinoma of the conjunctiva in HIV-seropositive men in the United States (Winward & Curtin, 1989; Kim *et al.*, 1990), coupled with a dramatic increase in the number of tumours being seen by ophthalmologists in at least two African centres, led to the suggestion of an association with HIV infection (Kestelyn

et al., 1990; Ateenyi-Agaba, 1995). Several studies from Africa and one from the United States have investigated this association.

(*b*) *Descriptive study*

In an analysis based on the Multistate AIDS-Cancer Match Registry in the United States, Goedert and Coté (1995) found four AIDS patients with a diagnosis of conjunctival squamous-cell carcinoma, a significantly higher number than expected (observed : expected, 13 [95% CI, 4–34]).

(*c*) *Case–control studies*

In Rwanda, Kestelyn *et al.* (1990) found that 9/11 cases of conjunctival squamous-cell carcinoma were HIV-seropositive, compared with 6/22 controls (odds ratio, 13.0; 95% CI, 2.2–76.9).

In Uganda, Ateenyi-Agaba (1995) found that 36/48 cases of conjunctival squamous-cell carcinoma were HIV-seropositive, compared with 9/48 controls (odds ratio, 13.0; 95% CI, 4.5–39.4).

In Rwanda, Newton *et al.* (1995) examined the association of HIV infection with all ocular tumours, excluding retinoblastoma and melanoma. The proportion of HIV-positive cases was 2/8 versus 8/200 controls (odds ratio, 8.4; 95% CI, 0.8–96.9).

In summary, HIV infection has been consistently associated with conjunctival carcinoma in case–control studies in several African locations. The association has been inconsistent in western countries and the discrepancy between these regions may be due to the lower background rates of this tumour in developed countries.

2.3.7 *Leiomyosarcoma*

Leiomyosarcoma is an extremely rare tumour in childhood, with an annual incidence of less than two cases per 10 million children (Lack, 1986). It has been reported in immunocompromised children following liver and renal transplantation (Ha *et al.*, 1993).

(*a*) *Case reports and series*

Spindle-cell tumours (leiomyoma and leiomyosarcoma) in HIV-infected children have been described relatively frequently, at sites such as the gastrointestinal tract (Chadwick *et al.*, 1990; McLoughlin *et al.*, 1991; Mueller *et al.*, 1992), liver (Mueller *et al.*, 1992; Ross *et al.*, 1992; Levin *et al.*, 1994), tracheobronchial tree (Martinez *et al.*, 1990; Balsam & Segal, 1992), lung (Chadwick *et al.*, 1990) and subcutaneous tissue (Orlow *et al.*, 1992). Several of the cases were discovered only at autopsy as solitary small spherical tumour masses.

DiCarlo *et al.* (1990) described eight cancers in 102 HIV-infected children followed at the Children's Hospital AIDS programme of New Jersey, NY, during 1984–88, of which one was an unusually aggressive case of leiomyosarcoma.

The above reports and a further one by McClain *et al.* (1995, 6 cases in 5 children) document at least 14 spindle-cell tumours in HIV-infected children, a much higher

number than expected considering that less than 10 000 children are infected with HIV in developed countries.

A few cases of spindle-cell tumours of the liver, colon, adrenal glands and spinal cord in HIV-infected adults have also been reported (Radin & Kiyabu, 1992; Steel *et al.*, 1993; Prévot *et al.*, 1994; McClain *et al.*, 1995).

(*b*) *Descriptive studies*

Rabkin and Yellin (1994) found, using cancer incidence data from the SEER programme, an increasing although nonsignificant trend in the observed-to-expected ratio of leiomyosarcomas among never-married men resident in San Francisco, CA, United States.

(*c*) *Cofactors*

McClain *et al.* (1995) suggested that EBV may contribute to the pathogenesis of leiomyomas and leiomyosarcomas in HIV-infected patients but not in HIV-uninfected persons. Using in-situ hybridization, they detected EBV genomes in all muscle cells of five leiomyosarcomas and two leiomyomas from six HIV-infected persons but not in three leiomyosarcomas or four leiomyomas from HIV-uninfected persons. Quantitative PCR showed high levels of EBV in the tumour tissues. Furthermore, separate tumours in the same patients contained different episomal EBV clones, signifying the presence of distinct monoclonal EBV-related tumours.

Lee *et al.* (1995) studied three children who developed smooth muscle tumours following organ transplantation. In each case, clonal EBV genome was detected in tumour tissue. In the two cases studied, the tumours were positive for EBNA-2 and the tumours from each of the patients were positive for EBERs. Both viral protein products expressed in latent infection.

In summary, leiomyomas and leiomyosarcomas appear to be associated with HIV infection in children. EBV appears to be an important etiological co-factor. The association is not apparent in HIV-infected adults.

2.3.8 *Other cancers*

There have been a large number of case reports and small case series of tumours other than those described above in HIV-infected persons.

Apart from effects on specific tumours, HIV infection and associated immunosuppression have been suspected of causing a global increase in the incidence of cancers of all types. This hypothesis has been examined in cohort studies (Rabkin & Yellin, 1994; Lyter *et al.*, 1995) and in analyses of registry data (Coté *et al.*, 1991; Reynolds *et al.*, 1993; Biggar *et al.*, 1994). Excluding cases of Kaposi's sarcoma and non-Hodgkin's lymphoma, total incidence of other cancers was either not increased or minimally increased. Since HIV-infected persons may have increased exposure to other cancer risk factors (e.g., cigarette smoking), the significance of the elevations seen in some of these studies is uncertain.

A small increase in the number of registered hepatomas at the SEER cancer registry in San Francisco, CA, United States, was observed among single white men between 1973–78 (baseline) and 1984 (Biggar *et al.*, 1987). However, there was no obvious further increase in incidence when the data were followed through to 1990 (Rabkin & Yellin, 1994). No case of liver cancer was recorded in a cohort of San Francisco AIDS patients followed from 1980 to 1987 (Reynolds *et al.*, 1993). Similarly, no case of liver cancer was found among 1065 HIV-infected haemophiliacs in the United States followed over 12 years (Rabkin *et al.*, 1992). In another study of United States haemophiliacs (Ragni *et al.*, 1993), no significant difference in liver cancer was seen in HIV+ and HIV– patients. In a study of 1227 HIV-infected haemophiliacs in the United Kingdom between 1985 and 1992, the risk of death from liver cancer (compared with the United Kingdom population) was similar in the HIV-infected (observed : expected, 15.1) and HIV-uninfected cohorts (observed : expected, 18.7) (Darby *et al.*, 1995). No association between HIV infection and liver cancer was found in Rwanda (Newton *et al.*, 1995); 1 person out of 35 (3%) with liver cancer was HIV-positive versus 7/165 (4%) controls.

In a large linkage analysis based on AIDS and cancer records from different regions within the United States, no association between EBV-associated nasopharyngeal carcinoma and AIDS was found (Melbye *et al.*, 1996).

Oral squamous-cell carcinomas have been hypothetically linked to infection with HPV. A small number of case reports have described these tumours, primarily located on the tongue, in HIV-infected persons (Salas-Buzon & Saez-Eligido, 1992). However, there are no data to support an association with HIV-infection (Ficarra & Eversole, 1994). *Nasal cavity tumours* were in excess ($n = 2$) in a linkage study of AIDS and cancer registry data from San Francisco (Reynolds *et al.*, 1993) but the authors ascribed this finding to possibly misclassified Kaposi's sarcoma cases.

Plasma-cell tumours that have been hypothetically linked with EBV infection have been described at unusual sites with widespread dissemination and a clinically aggressive course in HIV-infected persons (Israel *et al.*, 1983; Vandermolen *et al.*, 1985; Kaplan *et al.*, 1987; Monfardini *et al.*, 1989; Voelkerding *et al.*, 1989; Kumar *et al.*, 1994). *Lymphomatoid granulomatosis* (Mittal *et al.*, 1990) and a number of typical and more atypical cases of *acute myeloblastic leukaemia* have been reported (Al-Bahar *et al.*, 1994; Rabaud *et al.*, 1995). However, there has been no indication from either registry studies or cohort studies of an increased risk for leukaemia associated with the HIV epidemic (Biggar *et al.*, 1989; Rabkin & Yellin, 1994; Ragni *et al.*, 1993; Reynolds *et al.*, 1993; Lyter *et al.*, 1995).

Reports on *lung cancer* in HIV-infected persons have reflected differences in the clinical course in comparison with HIV-uninfected persons. Survival is short and appears to be worse than that seen in HIV-uninfected lung cancer patients (Flores *et al.*, 1995). However, these data probably reflect the dismal course of infection with HIV. Rabkin and Yellin (1994) reported a small relative increase in lung cancer among never-married men in San Francisco, but unrelated behavioural risk factors such as cigarette smoking may be responsible.

Other tumours that have been reported in HIV-positive persons but for which an association with the infection is not convincing include *mesothelioma* (Behling *et al.*, 1993), *cerebral glial tumours* (Chamberlain, 1994; Moulignier *et al.*, 1994) and *cancer of the colon* (Kaplan *et al.*, 1987; Cappell *et al.*, 1988), *pancreas* (Kaplan *et al.*, 1987; Monfardini *et al.*, 1989) and *kidney* (Monfardini *et al.*, 1989).

In summary, the available data do not support an association of these other tumours with HIV infection.