6 AIDS and cancer in Africa

Introduction

The epidemic of the acquired immunodeficiency syndrome (AIDS) currently ravaging the world population was initially recognized in the early 1980s among the male homosexual community in the United States (CDC, 1981). An early manifestation, and one that was identified before the nature of the disease was recognized, was the occurrence of Kaposi sarcoma (KS)—normally an exceedingly rare cancer in the United States. This was the first signal that infection with the human immunodeficiency virus (HIV), later recognized as the etiological agent of AIDS, increases the risk of certain cancers. Subsequent observation has confirmed a greatly enhanced risk of not only KS, but also non-Hodgkin lymphoma (NHL), and these two diseases, along with cancer of the cervix, are now considered to be "AIDS-defining conditions"—that is, an HIV-positive subject with these cancers is considered to have AIDS (CDC, 1992). Subsequently, increased risks for several other cancers have been reported. The most convincing data come from follow-up of cohorts of HIV-positive subjects, comparing the occurrence of cancers with the number expected in the general population. Such studies suggest increased risks of several cancers, especially Hodgkin disease, anal cancer, seminoma, myeloma, and, less certainly, cancers of the lip, brain and lung (Goedert *et al.*, 1998; Grulich *et al.*, 1999; Frisch *et al.*, 2001). This relationship between HIV/AIDS and cancer has led to a better understanding of the immunology and biology of HIV infection, and indirectly to increasing knowledge about the relationship between viruses and cancer. The knowledge that these cancers occur in association with a virus that targets the immune system has led to the supposition that immunosuppression may be a strong factor in their pathogenesis. Cancer risk is also high in primary immunodeficiency states and organ transplant patients, but HIV-immunosuppressed populations seem to have higher rates of virus-associated cancers.

However, immunosuppression may not necessarily be the direct causal factor in HIV-associated cancers. The virus is not known to be oncogenic, but the infection induces production of various cytokines and growth factors, which can act as growth promoters.

Although the vast majority of research into the link between AIDS and cancer has been carried out in 'western' populations (mainly in the United States, and to a lesser extent in Europe and Australia), these populations account for only a minority of the cases of AIDS occurring in the world today, or of the numbers of individuals who are carriers of HIV. As described below, sub-Saharan Africa accounted for about 70% of all such persons in the world at the beginning of the 21st century. This chapter reviews what is known of the impact of the epidemic of HIV/AIDS on cancer in the African continent, and what this has contributed to knowledge of the role of HIV in cancer etiology.

The AIDS epidemic in Africa

Table 1 shows estimates from the United Nations Programme on HIV/AIDS (UNAIDS) on the extent of the epidemic worldwide, and in the countries of the African continent, at the beginning of the 21st century.

In Africa, there were an estimated 29 million persons infected with HIV at the end of 2001 (72.5% of the world total), of whom 28.5 million were in sub-Saharan Africa. The regions most affected are southern and eastern Africa, where 21% and 10%, respectively, of the adult population are infected with HIV. The figures suggest a fairly brisk increase in sufferers (from 24.5 million at the end of 1999 to 28.5 million at the end of 2001), although the estimated number of deaths (2.2 million) was the same in 1999 and 2001. There are now 12 countries in which more than one tenth of the adult population aged 15–49 years is infected with HIV. In seven countries, all in the southern cone of the continent, at least one adult in five is living with the virus. In Botswana, 38.8% of adults are now infected with HIV, while in South Africa, 20.1% are infected, an increase from 12.9% at the end of 1997. With a total of five million infected people, South Africa has the largest number of people living with HIV/AIDS in the world. While West Africa is relatively less affected by HIV infection, the prevalence rates in some large countries are creeping up. Prevalence in Côte d'Ivoire is the highest in the region (around 10%) while Nigeria, by far the most populous country in sub-Saharan Africa, has over 5% of adults infected with HIV (2.7 million persons). The prevalence rates in other West African countries remain below 3%. Infection rates in East Africa, once the highest on the continent, hover above those in the West of the continent but have been exceeded by the rates now being seen in the southern cone.

In Africa, AIDS was first recognized in the Rakai district of south-west Uganda in 1982, where it was known locally as "slim disease" (Serwadda *et al.*, 1985). It was characterized by fever, general malaise, itchy maculopapular rash, prolonged diarrhoea, oral candidiasis, occasional respiratory symptoms and profound wasting and weight loss.

Subsequently, descriptions of this disease were published in the international scientific literature, from Rwanda (Van de Perre *et al.*, 1984), Congo/Zaire (Piot *et al.*, 1984) and Zambia (Bayley, 1984). From this focus in East/Central Africa, the disease has spread to involve an increasingly wide area of the continent (Figure 1). The spread of this sexually transmitted disease has been aided and enhanced by the movement of troops and traders across borders. Though the main mode of transmission is sexual, particularly heterosexual sex in these areas, reuse of unsterilized injection needles and scarification marks are possible alternative routes that may have favoured the spread of the disease. In any event, as can be seen from the sex ratio of cases in Table 1, the disease is rather more common in women than in men in Africa, in contrast to other parts of the world, where homosexual intercourse or intravenous drug abuse are the major routes of transmission. The serious problem of HIV/AIDS in much of Africa is compounded by the lack of resources to manage the infection and its related issues. Unfortunately, various serious problems and determinants (e.g., wars, poverty) that fuel the spread of the epidemic abound in sub-Saharan Africa (Ateka, 2001). At the same time, it has been

Table 1. Estimates of HIV/AIDS in Africa

Region, Country	Estimated number of people living with HIV/AIDS, end 1999				Estimated AIDS deaths 1999: adults & children		Estimated number of people living with HIV/AIDS, end 2001			Estimated AIDS deaths 2001:adults & children	
	Adults and children	Sex ratio (M/F)	Prevalence adult (%)	Prevalence child (%)	Number	Rate per 1000	Adults and children	Prevalence adult (%)	Prevalence child (%)	Number	Rate per 1000
Northern Africa	**...**	**...**	**0.2**	**...**	**...**	**...**	**478 000**	**0.5**	**0.05**	**23 000**	**0.15**
Algeria	...	...	0.1	...	...	...	...	0.1*	...	...	...
Egypt	...	...	0.0	...	...	...	8000	<0.1	...	...	...
Libyan Arab Jamahiriya	...	...	0.1	...	...	...	7000	0.2	...	...	...
Morocco	...	...	0.0	...	...	...	13 000	0.1	...	...	...
Sudan	...	...	1.0	...	...	...	450 000	2.6	0.24	23 000	0.8
Tunisia	...	...	0.0	...	...	...	...	...	...	...	...
Western Africa	**4 788 600**	**0.84**	**4.6**	**0.22**	**463 410**	**2.4**	**5 672 400**	**4.9**	**0.49**	**363 200**	**1.74**
Benin	70 000	0.81	2.4	0.11	5600	1.0	120 000	3.6	0.40	8100	1.4
Burkina Faso	350 000	0.83	6.4	0.35	43 000	4.0	440 000	6.5	1.06	44 000	4.1
Cape Verde	...	...	...	...	...	...	...	...	...	...	...
Côte d'Ivoire	760 000	0.83	10.8	0.52	72 000	5.6	770 000	9.7	1.22	75 000	5.1
Gambia	13 000	0.82	2.0	0.10	1400	1.2	8400	1.6	0.09	400	0.3
Ghana	340 000	0.83	3.6	0.17	33 000	1.9	360 000	3.0	0.42	28 000	1.6
Guinea	55 000	0.79	1.5	0.08	5600	0.8	...	...	...	...	...
Guinea-Bissau	14 000	0.78	2.5	0.11	1300	1.2	17 000	2.8	0.28	1200	1.1
Liberia	39 000	0.76	2.8	0.16	4500	1.7	...	...	...	...	...
Mali	100 000	0.83	2.0	0.10	9900	1.0	110 000	1.7	0.24	11 000	1.0
Mauritania	6600	0.80	0.5	0.02	610	0.3	...	...	...	...	...
Niger	64 000	0.79	1.4	0.06	6500	0.7	...	...	...	...	...
Nigeria	2 700 000	0.86	5.1	0.24	250 000	2.5	3 500 000	5.8	0.51	170 000	1.6
Senegal	79 000	0.90	1.8	0.08	7800	0.9	27 000	0.5	0.07	2500	0.3
Sierra Leone	68 000	0.81	3.0	0.16	8200	1.9	170 000	7.0	0.79	11 000	2.7
Togo	130 000	0.82	6.0	0.32	14 000	3.5	150 000	6.0	0.73	12 000	2.8
Middle Africa	**2 242 100**	**0.81**	**5.4**	**0.23**	**205 720**	**2.4**	**3 085 900**	**6.5**	**0.72**	**244 370**	**2.76**
Angola	160 000	0.83	2.8	0.13	15 000	1.3	350 000	5.5	0.57	24 000	2.0
Cameroon	540 000	0.79	7.7	0.35	52 000	4.0	920 000	11.8	1.05	53 000	3.9
Central African Republic	240 000	0.77	13.8	0.58	23 000	7.2	250 000	12.9	1.54	22 000	6.6
Chad	92 000	0.80	2.7	0.12	10 000	1.5	150 000	3.6	0.48	14 000	1.9
Congo	86 000	0.82	6.4	0.30	8 600	3.3	110 000	7.2	1.04	11 000	3.9
Dem. Republic of the Congo	1 100 000	0.83	5.1	0.22	95 000	2.1	1 300 000	4.9	0.66	120 000	2.5

Table 1 (Cont.). Estimates of HIV/AIDS in Africa

Region, Country	Estimated number of people living with HIV/AIDS, end 1999				Estimated AIDS deaths 1999: adults & children		Estimated number of people living with HIV/AIDS, end 2001			Estimated AIDS deaths 2001:adults & children	
	Adults and children	Sex ratio (M/F)	Prevalence adult (%)	Prevalence child (%)	Number	Rate per 1000	Adults and children	Prevalence adult (%)	Prevalence child (%)	Number	Rate per 1000
Equatorial Guinea	1100	0.79	0.5	0.00	120	0.3	5900	3.4	0.20	370	0.9
Gabon	23 000	0.83	4.2	0.16	2000	2.0	...	...	...	...	...
Eastern Africa	**12 398 000**	**0.81**	**10.7**	**0.52**	**1 219 970**	**5.6**	**13 160 700**	**10.0**	**1.20**	**1 123 350**	**4.82**
Burundi	360 000	0.79	11.3	0.61	39 000	6.4	390 000	8.3	1.78	40 000	6.7
Comoros	...	...	0.1	...	...	...	...	...	...	...	...
Djibouti	37 000	0.84	11.8	0.55	3100	5.4	...	...	...	...	...
Eritrea	...	...	2.9	...	...	...	55 000	2.8	0.24	350	0.1
Ethiopia	3 000 000	0.81	10.6	0.54	280 000	5.1	2 100 000	6.4	0.79	160 000	2.8
Kenya	2 100 000	0.82	13.9	0.61	180 000	6.7	2 500 000	15.0	1.62	190 000	6.6
Madagascar	11 000	0.72	0.1	0.01	870	0.1	22 000	0.3	0.01	...	...
Malawi	800 000	0.81	16.0	0.81	70 000	7.2	850 000	15.0	1.21	80 000	7.6
Mauritius	...	...	0.1	...	...	...	700	0.1	...	<100	...
Mozambique	1 200 000	0.75	13.2	0.62	98 000	5.7	1 100 000	13.0	0.98	60 000	3.6
Réunion	...	...	...	...	...	...	...	...	...	...	...
Rwanda	400 000	0.76	11.2	0.69	40 000	6.1	500 000	8.9	1.85	49 000	6.7
Somalia	...	...	...	...	..		43 000	1.0		...	...
Uganda	820 000	0.83	8.3	0.51	110 000	5.6	600 000	5.0	0.93	84 000	3.8
United Republic of Tanzania	1 300 000	0.79	8.1	0.40	140 000	4.7	1 500 000	7.8	1.05	140 000	4.3
Zambia	870 000	0.84	19.9	0.96	99 000	11.9	1 200 000	21.5	3.03	120 000	12.4
Zimbabwe	1 500 000	0.75	25.1	1.08	160 000	14.6	2 300 000	33.7	4.13	200 000	17.0
Southern Africa	**5 020 000**	**0.79**	**20.7**	**0.76**	**315 100**	**7.9**	**6 090 000**	**21.3**	**1.99**	**436 000**	**9.86**
Botswana	290 000	0.87	35.8	1.49	24 000	16.6	330 000	38.8	4.28	26 000	18.4
Lesotho	240 000	0.85	23.6	0.99	16 000	8.8	360 000	31.0	3.34	25 000	14.0
Namibia	160 000	0.76	19.5	0.89	18 000	11.8	230 000	22.5	3.84	13 000	8.1
South Africa	4 200 000	0.78	19.9	0.70	250 000	7.3	5 000 000	20.1	1.68	360 000	9.3
Swaziland	130 000	0.79	25.2	0.93	7100	8.0	170 000	33.4	3.59	12 000	14.3
Sub-Saharan Africa	**24 500 000**	**0.81**	**8.6**	**0.38**	**2 200 000**	**4.1**	**28 500 000**	**9.0**	**0.92**	**2 200 000**	**3.8**
Global Total	**34 300 000**	**1.10**	**1.1**	**0.07**	**2 800 000**	**0.6**	**40 000 000**	**1.2**	**0.16**	**3 000 000**	**0.6**

Source: UNAIDS (http://www.unaids.org/epidemic_update/report/index.html)

estimated that close to 80% of resources earmarked for HIV/AIDS-related expenditure are utilized in regions accounting for less than 5% of the pandemic (Ateka, 2001).

According to UNAIDS, at the beginning of 2000, in most sub-Saharan countries adults and children were acquiring HIV at a higher rate than ever before: the number of new infections in the region during 1999 was 4.0 million. However, such rises are not inevitable. In Uganda, the prevalence of infection has decreased from around 14% in the early 1990s to about 5%. Studies of population-based cohorts have suggested that this is linked to changes in sexual behaviour (Mbulaiteye *et al.*, 2002). Similar observations have been made in Senegal (Meda *et al.*, 1999) and Zambia (Fylkesnes *et al.*, 2001).

In reviewing statistical data on HIV infection and AIDS, it is important to note that the clinical case definition for AIDS in Africa (WHO, 1986) relies on observed symptoms and signs, with almost no requirement for laboratory tests. The CDC/WHO definition for AIDS (CDC, 1987), which requires sophisticated laboratory support for diagnosis of opportunistic infections, estimation of CD4+ cell counts and exclusion of other known causes of immunodeficiency, is not a practical option in Africa and therefore not applied. Apart from the expense, the results of sero-diagnosis and confirmatory tests for HIV/AIDS in Africa are often complicated by the presence of cross-reacting antibodies from other common infections (Biggar, 1986). The clinical case definition, which was developed for the AIDS surveillance in Africa, lacks sensitivity and specificity. In addition, most of the data from sub-Saharan Africa relate to patients attending health centres, often the accessible and convenient study population, who unfortunately do not represent the general population, as usually only the sick attend health facilities and often only at late stages.

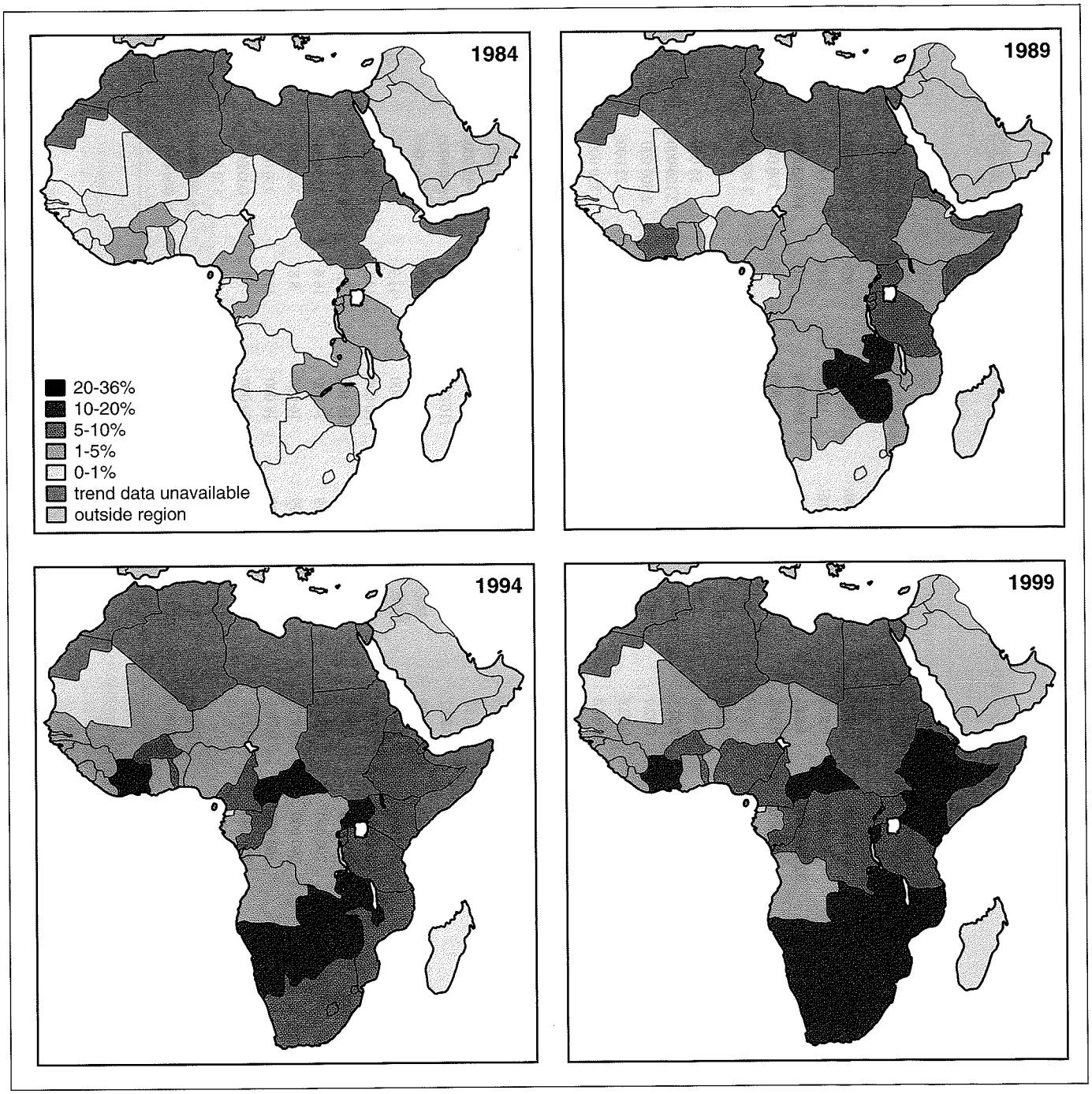

Figure 1. The spread of the AIDS epidemic in Africa, 1984–99
Source: UNAIDS (http://www.unaids.org/epidemic_update/report/index.html)

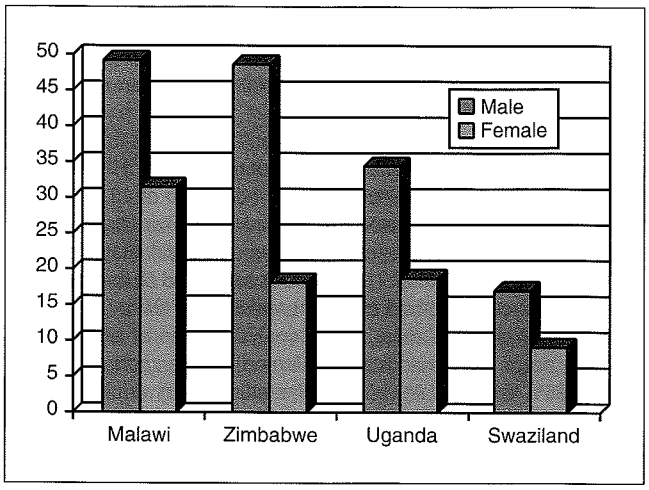

Figure 2. Incidence of Kaposi sarcoma in South and East Africa

As noted earlier, perinatal and heterosexual transmission predominate in Africa. The spectrum of associated diseases is rather different from the patterns in Europe and North America, with tuberculosis the main infectious complication (Lucas *et al.*, 1991; Berkley *et al.*, 1989). Several studies have suggested that the progression of HIV infection to clinical AIDS is more rapid in Africa than elsewhere (N'Galy *et al.*, 1988; Whittle *et al.*, 1992). However, there are few observations based upon incident infections (sero-converters). In the longitudinal, prospective population cohort study of people infected with HIV-1 and randomly selected subjects negative for HIV-1 antibodies in Uganda, the median time from seroconversion to death was 9.8 years, similar to that in developed countries before the use of anti-retroviral therapy. The median time from seroconversion to AIDS was 9.4 years and from AIDS to death was 9.2 months (Morgan *et al.*, 2002a). It was also observed that most of the clinical conditions and symptoms used to define the disease and its progression, although more frequent in HIV-positive individuals than in controls, were also common in the latter (Morgan *et al.*, 2002b), an observation similar to findings in Rwanda (Leroy *et al.*, 1995). Herpes zoster, oral candidiasis and pulmonary tuberculosis were, however, found to be more predictive of HIV infection. The high background levels of these defining conditions in the population, as a result of poverty, malnutrition, endemic malaria, infections, poor sanitation and inadequate health care, make it seem that the progression of HIV infection is more rapid in Africa.

Evidence for associations between HIV/AIDS and cancer in Africa

Routine surveillance of cancer incidence in high-risk populations was a valuable tool in identifying the increased risks of KS and NHL in populations at high risk of AIDS in the United States (Biggar *et al.*, 1984, 1985; Casabona *et al.*, 1993). In Africa, cancer registries face many difficulties in complete enumeration of cases (due to lack of access to limited health-care facilities and poor medical records), consistent recording and coding of diagnosis, and definition and enumeration of populations at risk (ill-defined place of residence, infrequent population censuses, and rural–urban migration). Nevertheless, some data are available from cancer registries in various countries on trends in incidence of different cancers in relation to the advancing epidemic of AIDS.

In theory, linkage studies between cohorts of AIDS patients and cancer registries (in areas where they exist) are feasible in Africa, but none have been performed. In contrast, several case–control studies have been reported, comparing prevalence of HIV infection in cancer cases and control populations. Some care is needed in interpreting the results. First, the cases are not always well defined, and may include 'cancers' diagnosed on clinical grounds only, without histological confirmation. The potential for bias due to inclusion of diseases related to HIV as cancer cases (for example, tuberculosis or HIV-related lymphadenopathy) should be considered. Secondly, as in all case–control studies, the nature of the control group must be carefully scrutinized—is it likely to represent the population from which the cases came, with respect to prevalence of HIV infection, or are persons included who are more, or less, likely to be infected?

Kaposi sarcoma

Before the onset of the HIV/AIDS epidemic, cumulative incidence of KS in the United States and Europe was ≤ 0.5 per 100 000, comprising about 0.3% of male and 0.1% of female cancers. Though the incidence was higher in East and Central Africa (comprising 3–10% of all cancers), it was rare in the western, northern and southern parts, where it accounted for ≤ 1% of cancers. The epidemiology of this 'endemic KS' in Africa is described in Chapter 4.6

In the United States and Europe, KS is the most frequently reported AIDS-associated cancer, its incidence being 1000–5000 times higher in some high-risk population groups with HIV infection than in the general population (Serraino *et al.*, 1997). In Africa, KS was reported to occur in 18% of AIDS cases in Rwanda (Van de Perre *et al.*, 1984), 16% and 10% of cases in Kinshasa, Congo (Democratic Republic) (Piot *et al.*, 1984; Nelson *et al.*, 1993) and 4% in Uganda (Berkley *et al.*, 1989).

Surveillance data from cancer registries have shown a large increase in incidence in many countries since the onset of the AIDS epidemic, and KS has become the most common cancer of men in Kampala, Uganda (Wabinga *et al.*, 2000), Harare, Zimbabwe (Chokunonga *et al.*, 1999), Blantyre, Malawi and Swaziland (this volume). Incidence is rather lower in women (Figure 2), but in these four countries, KS is second in frequency, behind cancer of the cervix.

In Bulawayo, Zimbabwe, the earlier (1963–72) estimated age-adjusted incidence rates in males and females were 2.3 and 0.3 per 100 000, respectively, but the recent rates from Harare (1993–95) are as high as 48.0 and 17.9 per 100 000 (Chokunonga *et al.*, 1999), with median ages of 35 and 32 years in males and females. In Kampala, Uganda, the age-standardized incidence of KS in 1960–71 was 3.6 per 100 000 in men and around 0.2 per 100 000 in women; these rates had increased to 39.3 and 21.8 per 100 000, respectively, in 1995–97 (Parkin *et al.*, 1999). Although the incidence of KS was low among the black population in South Africa until 1992, it approximately trebled between 1993 and 1995 (Sitas *et al.*, 1998).

In parallel with these increases in incidence, there have been a narrowing of the sex ratio to less than 2:1 (Figure 2) and a change in the age distribution, with, in the 1990s, a slight peak in childhood at ages 0–4 years, a decline until age 15 years and the main peak at 35–39 years in males and 25–29 years for females (see Figure 3 of Chapter 4.6)

The four case–control studies in Africa which have estimated relative risk are summarized in Chapter 4.6. They suggest moderately elevated risks of 35 in Rwanda (Newton *et al.*, 1995), 54 in Uganda (Newton *et al.*, 2001), and 62 and 22 in two studies in Johannesburg, South Africa (Sitas *et al.*, 1997, 2000). These risks are much lower than those reported in developed countries. Probably this relates to the much higher background incidence (non-HIV-related) in these populations, so that with similar levels of absolute risk in AIDS cases, relative risk is much lower in the African setting.

The relationship of KS to the associated oncovirus HHV-8 and the role that the epidemiology of this virus may have in the distribution of AIDS-related KS in Africa is reviewed in Chapter 4.6.

Lymphoma

The increased frequency of NHL in AIDS was noted in 1982 (Ziegler *et al.*, 1982) Since then, the elevated risk has been confirmed in studies in the United States and Europe (Beral *et al.*, 1991; Casabona *et al.*, 1991). About 3% of AIDS cases present with a lymphoma, but lymphomas may occur in up to 10% of AIDS cases at some point. Almost all lymphomas in AIDS cases are of B-cell type. The cohort study of Coté *et al.* (1997) provides the most accurate estimate of excess risk in AIDS—about 160 times that in HIV-negative subjects. Risk is highest for high-grade lymphomas, especially diffuse immunoblastic (x 630) and undifferentiated Burkitt lymphoma (BL) (x 220). Extranodal lymphomas are more common in AIDS than usual (Beral *et al.*, 1991), although this is probably because of the great excess of central nervous system lymphomas (15-fold increase); other extranodal lymphomas are not in excess (Coté *et al.*, 1997). Immunoblastic and central nervous system lymphomas occur later in the course of AIDS (with more profound immunosuppression) than do Burkitt-type lymphomas (Roithmann *et al.*, 1991). Males are more commonly affected, but this might be simply because of risk-group differences. Thus, the risk in females is 1.2 times that in males in heterosexually acquired cases of AIDS (Serraino *et al.*, 1992). Risk is higher in white (compared with black) patients, and in those of higher socioeconomic status (Beral *et al.*, 1991; Biggar & Rabkin, 1992; Franceschi *et al.*, 1999).

Chromosomal translocations have been found in AIDS-associated lymphomas. They include t(8;14)(q24;q32), t(8;22)(q24;q11) and t(2;8) (p12;q24) involving the c-*myc* locus, and rearrangements of the switch region of the heavy chains of immunoglobulins (chromosome 14) or light chains (chromosome 22 for λ, chromosome 2 for κ), especially for BL, but also in certain immunoblastic lymphomas with plasmocytic differentiation (Delecluse *et al.*, 1993). Rearrangements of *bcl* 6 situated in 3q27 were reported in 20% of diffuse large-cell lymphomas, but not small-cell types (Gaidano *et al.*, 1994). Mutations in *TP53* and n-*ras* are reported in a high proportion of AIDS-related BL and immunoblastic lymphomas (Ballerini *et al.*, 1993).

Epstein–Barr virus (EBV) is present in two thirds of AIDS-related lymphomas (Hamilton-Dutoit *et al.*, 1993) and may play an important role in lymphomagenesis (IARC, 1996, 1997). Its frequency varies by lymphoma type: it is found in almost all central nervous system lymphomas, 70–80% of immunoblastic lymphomas and 30–40% of small-cell/BL-type lymphomas.

– Non-Hodgkin lymphoma and AIDS in African adults

Relatively little is known concerning the effects of the AIDS epidemic on the occurrence of lymphomas in Africa, despite the very high seroprevalence of HIV in some countries. Particular care is needed in characterizing lymphomas when studying the possible link with HIV, since lymphadenopathy and lymphoid proliferation are common features of AIDS and the AIDS-related complex (Ioachim *et al.*, 1990; Baroni & Uccini, 1993), and a high percentage of persons undergoing lymph node biopsy in Africa now are therefore likely to be HIV-positive (Bem *et al.*, 1996).

Autopsy studies in Africa have found a very low prevalence of lymphomas in HIV-positive subjects. Abouya *et al.* (1992) found no cases among 53 subjects in Côte d'Ivoire, and Nelson *et al.* (1993) no cases among 63 subjects in Kinshasa, Congo (Democratic Republic). Lucas *et al.* (1994) detected seven cases of lymphoma among 247 autopsies (2.8%) in Côte d'Ivoire. Clinical descriptions of AIDS cases rarely mention lymphoma (Standaert *et al.*, 1988; Gilks *et al.*, 1992; Reeve, 1989; Karstaedt, 1992; Hira, 1990).

In Zimbabwe, Bassett *et al.* (1995) did not observe a very high incidence of NHL in the black population of Harare in 1990–92, although they did note that NHL comprised a rather higher percentage of lymphoreticular neoplasms than in an earlier series in 1979–84 (Levy, 1988). There are indications that incidence increased in the period 1991–95, at least in adult females (Chokunonga *et al.*, 1999).

In Uganda, the most recent data from the cancer registry in Kampala suggest that the incidence of NHL increased significantly between 1991–94 and 1995–97, especially in children and young adults (Parkin *et al.*, 1999).

To date, three studies have estimated the risk of NHL (all histological subtypes) in HIV-positive compared with HIV-negative subjects. Newton *et al.* (1995) found an odds ratio of 12.6 (95% CI 2.2–54.4) based on 19 cases tested for HIV in Rwanda, although some of these cases had been diagnosed on clinical suspicion only. In South Africa, Sitas *et al.* (1997, 2000) compared NHL cases with hospital 'controls', who had cancers unrelated to HIV or (in women) vascular disease. The most recent analysis (Sitas *et al.*, 2000) of 105 NHL cases (all histologically confirmed) gave an odds ratio (OR) of 5.0 (95% CI 2.7–9.5). In a similar study of 31 adult cases of histologically confirmed NHL in Uganda (Parkin *et al.*, 2000), the OR was 2.1 (95% CI 0.3–6.7); 12 of the cases (39%) were BL, of whom 3/7 (43%) were HIV-positive. Otieno *et al.* (2001) identified 29 cases of adult (age 16+) cases of BL from hospitals throughout Kenya in the period 1992–96. The number of cases identified in the main teaching hospital in Nairobi (19) was considered to be three times greater than in earlier years. Nineteen of the cases (66%) were HIV-positive, with ages typical of AIDS patients in Kenya (median 35 years) and a clinical presentation (diffuse lymph node involvement) differing from the HIV-negative cases, who were younger (16–25 years) and had a clinical picture reminiscent of typical endemic BL, with complete sparing of peripheral lymph nodes.

These are very low excess risks compared with those observed in Europe and the United States. Probably this relates to the poor prognosis of AIDS cases in Africa. The degree of immune dysfunction at AIDS diagnosis, as measured by CD4+ counts, is less in Africa than in industrial countries and median survival times are much shorter (Boerma *et al.*, 1998). Since the risk of NHL in AIDS (and other immunodeficiency states) is related to the degree of immune dysregulation, it could be that the apparently low risk of lymphoma in HIV-positive subjects in Africa is a result of competing mortality—particularly from infectious diseases—in AIDS patients with relatively low levels of immunosuppression. In the study in Uganda (Parkin *et al.*, 2000), the CD4+ cell count at diagnosis in HIV-positive lymphomas was higher than generally observed in Europe and North America (Roithmann *et al.*, 1991; Roithmann & Andrieu, 1992). Lucas *et al.* (1994) found that NHL was present undiagnosed at autopsy in 2.8% of HIV-positive subjects in Côte d'Ivoire (4% of subjects with AIDS), a figure not very different from the cumulative probability of developing a lymphoma observed in cohorts of AIDS patients in the USA (Coté *et al.*, 1997).

– Non-Hodgkin lymphoma of childhood

In the United States and Europe, NHLs are the most common malignancy in paediatric AIDS patients (Arico *et al.*, 1991; Serraino & Franceschi, 1996) and about one third are BL (Mueller, 1998). This form of BL is clinically and cytogenetically similar to BL as it is observed in non-AIDS cases (sporadic BL) in North America and Europe, and the proportion of cases with detectable EBV genome is similar (around 30%). It is thus quite distinct from the endemic form of BL that was common in equatorial Africa long before the AIDS epidemic. Endemic BL in some areas comprised more than 90% of NHL in children and its relationship with EBV and malaria is well documented (see Chapter 4.10). The effect of the AIDS epidemic on the occurrence of BL in these areas is therefore of considerable interest.

Hospital and autopsy series do not provide any evidence for an increased frequency of childhood BL cases since the onset of the AIDS epidemic. The autopsy series of Lucas *et al.* (1994) in Côte d'Ivoire found no NHL in 78 HIV-positive children, while in Zambia, there was a decrease in the number of histological diagnoses of BL in the main teaching hospital between 1980–82 (pre-HIV epidemic) and 1990–92 (during the HIV epidemic) (Chintu *et al.*, 1995).

However, in Uganda, one of the first countries in Africa to be affected by the AIDS epidemic in the early 1980s, registry data show a three-fold increase in the incidence in children (0–14 years) between the 1960s and 1995–97 (Parkin *et al.*, 1999).

In studies of childhood BL since the onset of the AIDS epidemic, it seems that cases remain predominantly of the endemic type, which is not associated with HIV. Among 56 childhood BL cases from Uganda (Parkin *et al.*, 2000), all were EBV-positive, and the median age of seven years, the predominance of males and the localization in facial and abdominal sites were characteristic of endemic BL. There was no association with HIV (OR = 1.0, 95% CI 0.3–3.9). In a previous study in Uganda, Mbidde *et al.* (1990) reported the absence of HIV infection among 50 children with BL studied early in the AIDS epidemic. All 17 cases of childhood BL in a series from the Nairobi Hospital, diagnosed in 1995–96, were HIV-negative (Lazzi *et al.*, 1998). In a larger series from Kenya, Otieno *et al.* (2001) reported that only 5/767 (0.65%) childhood cases of BL were HIV-positive—the sex ratio (2.5:1) and peak age at 5–7 years was typical of endemic BL. It is possible that the lack of an association between HIV and BL relates to the poor survival of children infected perinatally with HIV—only 34% of HIV-infected children in Uganda survived to the age of three years (Marum *et al.*, 1997).

It seems unlikely that the increased incidence of BL in Kampala, Uganda, is the consequence of the epidemic of HIV, and other factors, such as malaria infection, may be responsible.

– Hodgkin disease

Hodgkin disease represents one of the common tumours occurring in a context of immunodeficiency, including in HIV-infected populations, in whom 10-fold increases in risk have been observed (Dal Maso *et al.*, 2001). HIV-associated Hodgkin disease has been reported more often in European countries and to a lesser extent the United States. All series have documented unusually aggressive disease, including a higher frequency of the unfavourable histological subtypes (mixed cellularity and lymphocyte-depleted), advanced stages and poor therapeutic response compared with the behaviour of Hodgkin disease outside the HIV setting. Such increases have not been reported from sub-Saharan Africa and there is no change in the age-specific incidence pattern.

HPV-associated cancers and HIV/AIDS

Human papillomavirus (HPV)-associated malignancies occur frequently in patients with HIV infection and AIDS (Frisch *et al.*, 2000). In part, this may simply reflect the lifestyle factors associated with both infections; HIV-positive individuals are more likely to be infected with HPV. On the other hand, HIV may alter the natural history of HPV-associated oncogenesis through loss of immune control, facilitating infection with HPV or enhancing its persistence in cells and therefore increasing the development of squamous intraepithelial lesions (SIL).

– Cervical cancer

The Centers for Disease Control (CDC) designated high-grade SIL (HSIL) (moderate or severe dysplasia) as a category B defining condition, and invasive cervical cancer a category C defining condition of AIDS in 1993 (CDC, 1992). Although studies in the United States and Europe have reported 5–15-fold increases in risk of invasive cervical carcinoma in women who develop AIDS (Chapter 4.3), similar risks have not been demonstrated in sub-Saharan Africa. Numerous studies have investigated whether there is an increased risk of pre-invasive disease (cervical intraepithelial neoplasia (CIN) or SIL) in the presence of HIV infection.

Prevalence of CIN in relation to HIV status. In 4058 women attending two family planning clinics in Nairobi, Kenya, Maggwa *et al.* (1993) found a higher prevalence of cytologically diagnosed CIN in women who were HIV-positive compared with those who were negative (4.9% versus 1.9%). The OR was little affected by adjustment for reported sexual behaviour or prior history of sexually transmitted diseases (OR = 2.78, 95% CI 1.32–5.85). In a similar study in Abidjan, Côte d'Ivoire (La Ruche *et al.*, 1998a), the 2198 women were attending gynaecology clinics for various symptoms and hence had a relatively high prevalence of abnormal Pap smears (11.7% with low-grade SIL (LSIL) or worse). The prevalence of SIL was significantly higher in women who were HIV-positive (OR = 3.6 for LSIL and 5.8 for HSIL) and risk of LSIL (only) increased with increasing immunosuppression, as measured by CD4+ count. Kapiga *et al.* (1999) found that the risk of SIL among 691 HIV-positive women in Dar es Salaam, Tanzania, was increased among those with a CD4+ cell count below 200/μL. Leroy *et al.* (1999) tested pregnant women in antenatal clinics in Kigali, Rwanda, for HIV, in 1992–93. Among 103 HIV-positive and 107 HIV-negative women tested by Pap smears; the prevalence of SIL was significantly higher in the HIV-positive group (OR = 4.6, 95% CI 1.8–12.3), but, within this group, was not associated with immunosuppression.

CIN in relation to HPV and HIV infection. Studies in which HPV infection can be assessed as well as HIV are likely to be more informative concerning the contribution of HIV to cervical neoplasia. Most of these studies show that HPV infection is significantly more prevalent in women who are HIV-positive than in HIV-negative women (Laga *et al.*, 1992; Ter Meulen *et al.*, 1992; Seck *et al.*, 1994; Langley *et al.*, 1996; Miotti *et al.*, 1996; La Ruche *et al.*, 1998b; Piper *et al.*, 1999; Serwadda *et al.*, 1999; Temmerman *et al.*, 1999; Womack *et al.*, 2000), However, in other studies, there was no apparent association between the two infections. In their study of Nairobi prostitutes, Kreiss *et al.* (1992) found that HIV infection was associated with only a modest increase in HPV infection (37% versus 24%, OR = 1.7, not significant). In women attending an antenatal clinic in Mwanza, Tanzania, the OR of HPV infection in association with HIV was 1.02 (95% c.i. 0.6-1.6) (Mayaud *et al.*, 2001).

Because of the close association of HPV and HIV infection, it is not surprising that, in most studies, CIN/SIL is more prevalent in HIV-positive than in HIV-negative women. Laga *et al.* (1992), in a group of 95 prostitutes from Kinshasa, Zaire, observed a significantly higher prevalence of CIN in women positive for HIV (27%) than in those negative (3%) (OR = 14.7). Seck et al (1994) reported on 35 HIV-positive women (18 with HIV-1; 17 with HIV-2) and 58 HIV-negative women attending an infectious disease service in Dakar, Senegal; HIV infection was associated with the presence of dysplastic smears (OR = 5.5, 95% CI 1.02–29.7). Miotti *et al.* (1996) studied 268 post-partum women in Malawi; cytologically diagnosed SIL was significantly related to HIV status (OR = 2.2). Langley *et al.* (1996) found that SIL was associated with HIV-2 infection (the association with HIV-1 was not statistically significant) among 759 prostitutes in Dakar, Senegal. In a later study in Dakar, Vernon *et al.* (1999) observed a strong association between SIL and both HIV-1 and HIV-2 in women participating in a study of mother–child transmission of HIV, but there was no association in a group of 278 prostitutes. HSIL was strongly associated with HIV positivity (OR = 4.5, 95% CI 1.8–12.4) in family-planning attenders in Kenya (Temmerman *et al.*, 1999). However, in the studies in which HPV infection was not associated with HIV-positivity (Kreiss *et al.*, 1992; Mayaud *et al.*, 2001), there was no difference in CIN prevalence between women positive or negative for HIV, and in their series of gynaecology inpatients in Dar es Salaam, Tanzania, Ter Meulen *et al.* (1992) found that the prevalence of abnormal Pap smears did not differ between HIV-positive and -negative women.

The results of some of these studies allow the independent effects of HPV and HIV to be evaluated (Table 2). In the studies by Kreiss *et al.* (1992) and Mayaud *et al.* (2001), there was no

Table 2. Case–control studies of CIN and infection with HIV in women positive or negative for HPV infection

Reference	Location	Source of subjects	Measure of exposure	No. of cases/ no. of controls	Cases/controls HIV+ (%)	Odds ratio	95% CI
Kreiss *et al.* (1992)	Nairobi, Kenya	Prostitutes	Cytological CIN (all grades)	HPV– 3/34 HPV+ 13/13	66.7/61.7 69.2/76.9	1.24 0.68	0.06–78.6 0.08–5.34
Miotti *et al.* (1996)	Malawi	Women one year post-partum	Cytological SIL	HPV– 6/145 HPV+ 19/59	50/33.1 63.2/59.3	2.02 1.18	0.26–15.6 0.36–3.90
La Ruche *et al.* (1998b)	Abidjan Cote d'Ivoire	Gynaecology Outpatients	Cytological LSIL Biopsy/colposcopy HSIL	HPV– 57/292 HPV+ 151/95	19.3/14.7 53.6/31.6	1.38 2.51	0.62–3.03 1.42–4.46
Temmerman *et al.* (1999)	Nairobi Kenya	Family planning clinic attenders	HSIL on cytology	HPV– 11/421 HPV+ 22/59	27.3/6.9 37.5/22.0	5.07[a] 1.33[a]	0.82–22.5 0.35–4.55
Womack *et al.* (2000)	Chitungwiza Zimbabwe	Primary care attenders	SIL on biopsy or colposcopy	HPV– 29/217 HPV+ 87/133	41.4/35.5 83.9/65.4	1.28 2.76	0.54–3.01 1.34–5.73
Mayaud *et al.* (2001)	Mwanza Tanzania	Antenatal clinic attenders	SIL on cytology	HPV– 16/354 HPV+ 25/162	18.8/15.8 24.0/13.6	1.23 2.01	0.22–4.67 0.59–5.99

[a] OR for HSIL vs lesser abnormality and normal cytology

independent effect of HIV on risk of CIN—HIV did not influence risk of SIL, independent of HPV. A similar result is evident in the data presented by Miotti *et al.* (1996); however, at a follow-up visit, one year later, HPV infection in HIV-positive women was significantly more persistent (75% still positive) than in those women who were HIV-negative (23%).In the subset of subjects in the Abidjan study (described above) who were tested for the presence of HPV by polymerase chain reaction (PCR) analysis (La Ruche *et al.*, 1998b), HIV did not have a significant effect on the risk of SIL in women negative for HPV (OR for all grades of SIL combined = 1.38; 95% CI 0.62–3.03), although, in the presence of HPV, there was an additional effect of HIV on the risk (OR for all grades of SIL combined = 2.51; 95% CI 1.42–4.46)). HIV-infected women with abnormal cytology were not highly immunosuppressed (median CD4+ count 450/μL). A subset of 461 of the women from the screening study in Chitungwiza, Zimbabwe, were tested for HIV, as well as being examined for CIN (by colposcopy and/or biopsy); cells obtained by cytobrush were tested for HPV by hybrid capture II test (HC II) (Womack *et al.*, 2000). The prevalence of HSIL was almost three times higher in HIV-positive women than in HIV-negative (17.3% versus 5.9%, $p < 0.001$), but, in women negative for HPV, HIV did not have a significant effect on the risk of SIL (OR for all grades of SIL combined = 1.28; 95% CI 0.54–3.01). However, in the presence of HPV, there was an additional effect on the risk (OR for all grades of SIL combined = 2.76; 95% CI 1.34–5.73). HIV infection was associated with a seven-fold increase in HPV viral burden in women who were colposcopically normal.

The mechanism underlying the role played by HIV in the pathogenesis of cervical precancer has been the subject of much speculation. The most likely explanation seems to be that HIV infection leads to enhanced persistence of infection with HPV, as has been observed in various prospective studies, and that this may be related to immunosuppression (Jay & Moscicki, 2000). Studies so far performed in Africa suggest that immunosuppression (as measured by CD4 cell counts) is associated with a higher prevalence of HPV infection in seropositive women (Miotti *et al.*, 1996; Vernon *et al.*, 1999).

Invasive cancer of the cervix. With respect to invasive cervix cancer, the close association between HIV and HPV infection, as shown in these studies, should imply an increased risk in HIV-positive women, if only because of this confounding. However, in early studies, both Rogo & Kavoo-Linge (1990) and Ter Meulen *et al.* (1992) found prevalence of HIV in cancer patients to be lower than in the normal population. In 18 cervix cancer cases among gynaecology outpatients, the prevalence of HIV (22%) was the same as in subjects with normal Pap smears (La Ruche *et al.*, 1998a). Prevalence of HIV among 1323 cases of cervix cancer (almost all histologically confirmed) in Johannesburg was higher (12.6%) than in the comparison group of hospital patients with a mixture of non-HIV-related cancers or vascular disease (9.0%), yielding an OR of 1.6 (95% CI 1.1–2.3) (Sitas *et al.*, 2000). Newton *et al.* (2001) found a similar slight excess of HIV infection (32%) in 65 women diagnosed as having cervix cancer in Kampala, Uganda, compared with 21% in 'controls' with non-infection-related cancer or non-cancerous conditions (OR = 1.6; 95% CI 0.7–3.6).

The lack of a clear effect of HIV on the risk of invasive cancer may result from competing causes of mortality in HIV-infected women in Africa (mainly tuberculosis or other infections) during the long progression from HPV infection through CIN to invasive cancer. In a setting where an organized screening programme is not normally available, the suggestion that active screening among HIV-positive women may have prevented progression to invasive cancer is not a plausible explanation.

The observation of younger age of cases of cervix cancer who were HIV-positive, compared with those who were HIV-negative (Lomalisa *et al.*, 2000) has no etiological significance, merely reflecting the very different age structures of the respective populations at risk.

– Anal cancer

Various studies have indicated an association between HIV infection and anal cancer (Palefsky *et al.*, 1990), with the risk being higher in men than women in the United States (Frisch *et al.*, 2000) and in homosexual males compared with non-homosexual men (Melbye *et al.*, 1994). No change in incidence has been noted in Africa since the onset of the AIDS epidemic.

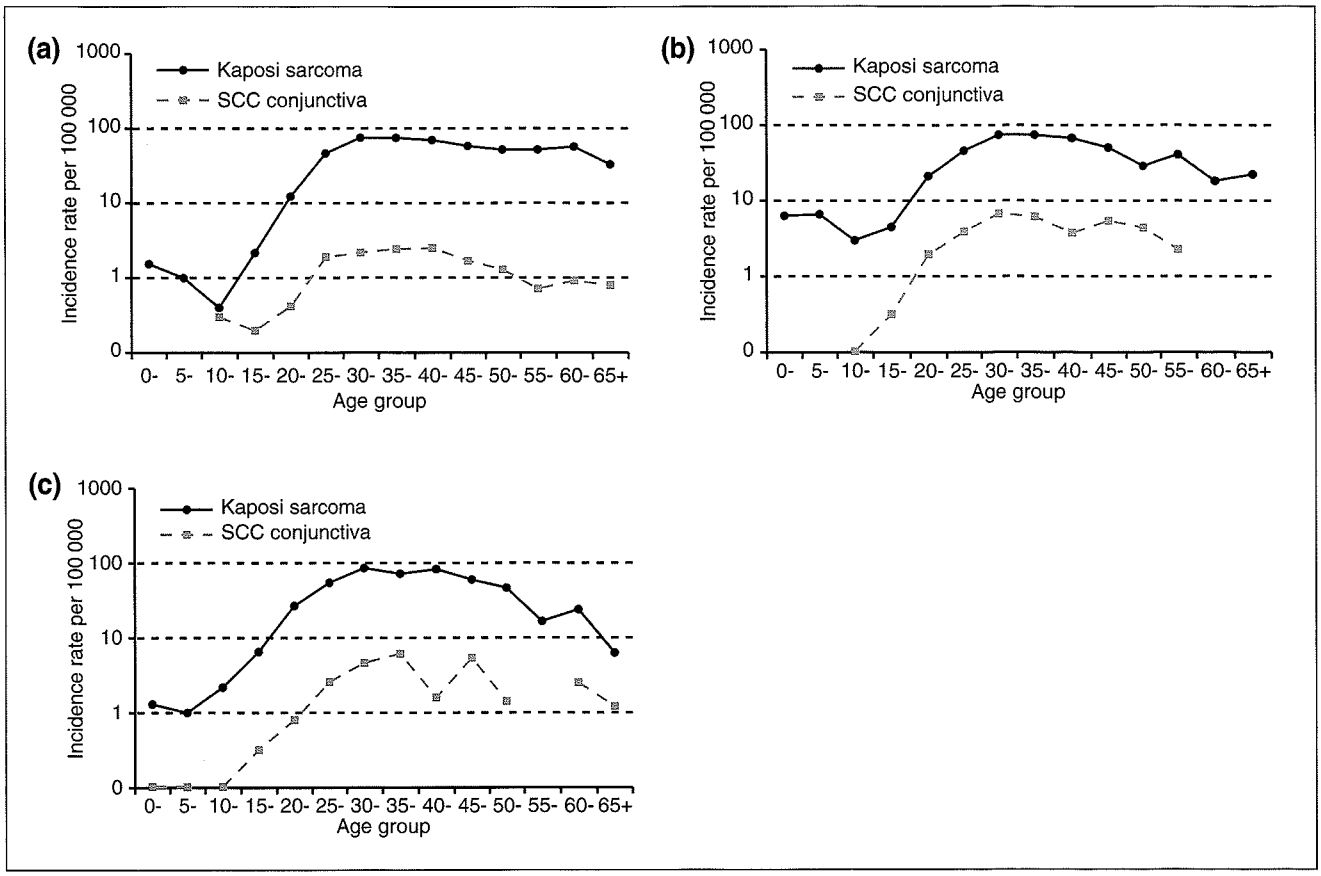

Figure 3. Incidence of Kaposi sarcoma and squamous cell carcinoma of the conjunctiva (both sexes) in (a) Harare, Zimbabwe, (b) Kampala, Uganda, and (c) Blantyre, Malawi

Ocular tumours

HIV infection is associated with a number of ocular manifestations. Ocular involvement by KS occurs and 20% of patients with systemic KS may develop the lesions on the eyelids, conjunctiva and rarely in the orbit. Although orbital lymphoma occurs in Africa, from observation, it is not common even in HIV-related cases.

HIV infection was suspected to be a risk factor for the development of squamous-cell dysplasia and neoplasia of the conjunctiva when striking increases in the number of patients with conjunctival neoplasms were noticed in Malawi, Rwanda and Uganda (Kestelyn *et al.*, 1990; Ateenyi-Agaba, 1995; Waddell *et al.*, 1996). In the pathology department at Moshi, Tanzania, about 10 cases of conjunctival squamous-cell cancer (SCC) were observed between 1976 and 1984, increasing to 40 cases by 1997 (Poole, 1999). The tumours occur at a relatively young age, mostly arising in the limbus of the eye, with duration of symptoms less than six months and an aggressive course. The Kampala cancer registry recorded a ten-fold increase in the incidence of conjunctival SCC between 1960–71 and 1995–97 (Parkin *et al.*, 1999). The high age-standardized rates of SCC of the conjunctiva now observed in registry data from Kampala, Uganda (2.0 per 100 000 in males and 2.3 in females) are also found in Blantyre, Malawi (2.1 per 100 000 in males and 2.8 in females) and Harare, Zimbabwe (1.5 per 100 000 in males and 2.5 in females). The close association with HIV infection is suggested by the age-specific incidence curve, which shows maximum rates at ages 30–39 years, very similar to the peak for age-specific incidence of Kaposi sarcoma (Figure 3) and reflecting the peak ages for HIV infection in these populations.

Five case–control studies have been completed in Africa, comparing prevalence of HIV infection in cases of SCC of the conjunctiva with that in control subjects (Table 3). All suggest a strong association, with an estimated OR between 8 and 13. The association has been confirmed in follow-up of cohorts of HIV-positive subjects in the United States (Goedert & Coté, 1995; Frisch *et al.*, 2001).

Since HPV (particularly type 16 and sometimes 6, 11, 18) has been found in some lesions (Newton, 1996), there is speculation that HIV plays a permissive role in enhancing the persistence of HPV and allowing its oncogenic potential to be expressed. HPV 16 was isolated in 7 out of 20 cases (35%) of conjunctival carcinoma samples from Uganda and Malawi (Waddell *et al.*, 1996). However, in the case–control study in Uganda (Newton *et al.*, 2002), no association was found with infection by HPV 16, 18 or 45 (as measured by serology), although the prevalence of infection by the latter two types was very low, and the estimates of risk were correspondingly imprecise.

Conjunctival SCC has always been comparatively more common in Africa than in Europe and America, as a result of the effects of ultraviolet light, the probable prime risk factor (Newton *et al.*, 1996b). High ambient solar ultraviolet radiation may act synergistically with HIV or potentiate the effects of the virus in promoting neoplastic transformation.

Other cancers

Leiomyosarcoma has been associated with HIV/AIDS, particularly in children, but there has been no evidence of an increase in this tumour in sub-Saharan Africa.

Incidence of liver cancer remains high in most regions in Africa, but there has been no significant increase associated with HIV/AIDS, in spite of the viral etiological basis. Nasopharyngeal cancer, associated with EBV, has also shown no increase.

Table 3. Case–control studies of infection with HIV and conjunctival cancers

Reference	Location	Cases	Controls	No. of cases/ no. of controls	Cases/controls HIV positive (%)	Odds ratio	95% CI
Kestelyn *et al.* (1990)	Kigali, Rwanda	Conjunctival squamous-cell neoplasms: 5 intraepithelial 6 invasive	Other eye clinic patients, age- and sex-matched	11/22	82/27	13.0	2.2–76.9
Ateeni-Agaba (1995)	Kampala, Uganda	Histologically confirmed SCC of conjunctiva	Other patients from same clinic, age- and sex-matched	48/48	75/19	13.0	4.5–39.4
Newton *et al.* (1995)	Kigali Rwanda	Eye cancer excl melanoma and KS	Other cancers excl. KS and NHL	8/200	25/4	8.4	0.8–96.9
Waddell *et al.* (1996)	Kampala, Uganda	Conjunctival squamous-cell neoplasms: 11 intraepithelial 27 invasive	Other eye clinic patients, age- and sex-matched	38/76	71/16	13.1	4.7–37.6
Newton *et al.* (2002)	Kampala, Uganda	Conjunctival tumours, 60% confirmed SCC	Other cancers (excl. cancers related to HIV, HPV, KSHV or sunlight)	60/1214	70/14.5	10.1[a]	5.2–19.4

[a]Adjusted for age and sex

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