

The Epidemiology of Acquired Immunodeficiency Syndrome Malignancies

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The acquired immunodeficiency syndrome (AIDS) results in an extraordinary increase in the risk of two malignancies: Kaposi's sarcoma (KS; relative risk [RR], >10,000) and B-cell non-Hodgkin's lymphoma (NHL; RR, >100). KS appears to result from uncontrolled expression of latency genes of human herpes virus-8 (HHV-8). KS is exquisitely sensitive to immune deficiency, and its incidence has declined during the late 1990s with the advent of highly active antiretroviral therapy (HAART) against human immunodeficiency virus (HIV). The risk of NHL is highest with high-grade histologies, and the incidence has declined only slightly with HAART. The risk of KS and NHL is decreased for people with the CCR5 Δ 32 polymorphism, and NHL risk is increased with the SDF1-3'A polymorphism. Children with AIDS have a similar pattern of risk, but also have a high risk of leiomyosarcoma (RR, ~10,000). AIDS-related immune deficiency also increases the risk of Hodgkin's disease (RR, 8), probably multiple myeloma (RR, 5), and possibly other tumors in adults. Although the occurrence of cervical cancer (RR, 3) and anal cancer (RR, 30) is excessive among persons with AIDS, most or all of this excess results from sexually acquired human papillomavirus (HPV) infection and not from immune deficiency. Future efforts need to focus on understanding how the immune perturbation of AIDS results in a limited spectrum of tumors and most urgently on controlling the underlying HIV epidemic.

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KAPOSI'S SARCOMA (KS) and non-Hodgkin's lymphoma (NHL) were recognized as epidemic, life-threatening opportunistic diseases in the early 1980s and were quickly incorporated in the national surveillance definition of the acquired immunodeficiency syndrome (AIDS). The most important discovery during those first years was that AIDS is caused by infection with human immunodeficiency virus (HIV). Much also has been learned during these first two decades of the epidemic about KS, NHL,

and other malignancies that occur in people with AIDS.

The epidemiology of AIDS malignancies has been reviewed several times, including a comprehensive summary in 1996.¹ That year proved to be a watershed, with the licensure of anti-HIV protease inhibitors and dramatic evidence of a therapeutic benefit for combination anti-HIV chemotherapy, conventionally termed highly active antiretroviral therapy (HAART). HAART, however, has not been uniformly effective against all manifestations of HIV and AIDS. This chapter will consider principles of the epidemiology of AIDS and cancer, the occurrence of cancer in the first two decades of AIDS, the specific malignancies associated with AIDS, and finally changes in cancer risk for persons with HIV and AIDS during these first years of HAART.

ISSUES PARTICULAR TO THE EPIDEMIOLOGY OF AIDS-RELATED MALIGNANCIES

The immune deficiency of AIDS presents the special opportunity to understand the etiologies or pathogenesis for cancer. However, because the cases of interest have two diseases, AIDS and cancer, there is considerable risk for epidemiologic studies to make erroneous associations due to confounding. For example, exposures such as intravenous drug use, promiscuity, or smoking are more common in the HIV/AIDS population than in the general population and thus come to light simply because of HIV/AIDS. To minimize confounded associations, the hypotheses must be carefully considered and the comparison populations carefully defined.

One approach is to conduct cancer analyses within an HIV/AIDS risk group, although HIV-uninfected homosexual men or intravenous drug users differ from their HIV-infected counterparts. While helpful, residual confounding persists, as illustrated by higher levels of cigarette smoking among HIV-positive compared with persistently HIV-negative homosexual men.² Cigarette smoking in the latter 20th century reflects risky sexual and other behaviors. Because cigarette smoking is associated with the risk of HIV infection, it would

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be difficult to know if cigarettes also were associated with lung cancer in this population.

An optimal approach is to analyze risk factors for cancer in prospective cohort studies of HIV-infected subjects, using cancer-free but HIV-infected controls. Preliminary results are discussed below for KS, NHL, and cervical and anal precancerous lesions. The available cohorts generally are not sufficiently large to evaluate other types of cancer. The exception is to examine time trends of risk among persons who have been reported to AIDS surveillance, specifically to test whether progressive HIV-related immune deficiency is associated with increasing risk of specific cancers. Such analyses are in progress in Italy,³ Australia,⁴ and, the largest to date, the AIDS-Cancer Match Registry in the United States and Puerto Rico.⁵

In considering the results of any study, histopathologic confirmation of the reported malignancies should be required, and ideally should be validated through an independent review by expert pathologists. In the AIDS-Cancer Match Registry, 86 tumors of unspecified histology were found among 98,336 people with AIDS. There was a highly significant 10-fold increased risk in these undefined tumors compared with the general population, as well as a highly significant trend of increasing risk from pre-AIDS to 2 years after an AIDS-defining opportunistic illness. Because the histology was undefined, it is likely that this merely reflected histologically undefined KS or NHL.⁵ A similar and probably trivial association was noted with poorly defined leukemias among persons with AIDS (relative risk [RR], 11.0; 95% confidence interval [CI], 3.0 to 28.3).⁵

SURVEILLANCE FOR AIDS-DEFINING CANCERS AND OTHER ILLNESSES IN THE UNITED STATES

Cumulatively through the end of 1998, 56,615 cases of KS, 18,729 cases of NHL, and 1,166 cases of invasive cervical cancer have been reported among persons with AIDS in the United States (Fig 1). To put this in perspective, 203,289 *Pneumocystis carinii* pneumonia (PCP) AIDS cases have been reported. These numbers crudely reflect the effect of AIDS on specific diseases, but they do not reflect time trends in the spread of HIV nor in the latency before a disease is clinically apparent.

Surveillance for AIDS-defining cancers and other opportunistic illnesses was substantially altered in

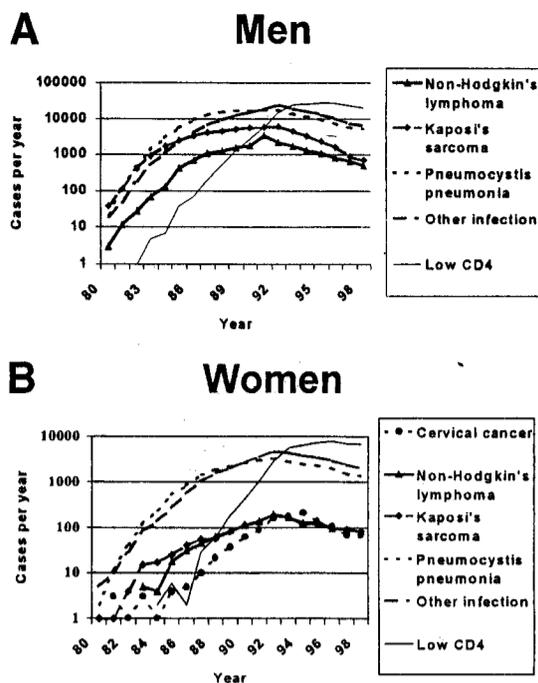


Fig 1. Incidence of AIDS-defining opportunistic infections and malignancies in the United States, 1981-1998, among men (A) and women (B). Data kindly provided by Drs John Karon and Lisa Lee, Division of HIV/AIDS Prevention—Surveillance and Epidemiology, Centers for Disease Control and Prevention.

1993, when the US Centers for Disease Control and Prevention (CDC) made major changes in the AIDS definition, particularly the inclusion of severely immune deficient HIV-positive patients, those with CD4⁺ a lymphocyte count less than 200 cells/ μ L, even in the absence of a life-threatening illness. This inclusion of subclinically immunodeficient patients instantaneously increased the number of persons with AIDS and also caused an artifactual deficit in cases of KS, NHL, and the other AIDS clinical illnesses that developed and would otherwise have been reported later in a patient's course. With that change, the apparent incidence of AIDS in the United States peaked in 1993 with 78,711 cases, and subsequently declined to approximately 45,000 cases per year.

The outbreak of PCP and KS signaled the onset of the epidemic in 1981. PCP has continued to be the most common presenting manifestation of AIDS despite development of prophylaxis. The incidence of PCP increased through 1992, at which time it was exceeded by the aggregate of other opportunistic infections (Fig 1). In contrast,

at least among men, KS incidence has declined, both in AIDS surveillance data (Fig 1A) and in population-based cancer surveillance in San Francisco, one of the original epicenters of the AIDS epidemic.⁶ The incidence of NHL has generally mirrored the epidemic as a whole. Cervical cancer was added as an AIDS-defining condition in 1993, and has since been reported about as often as KS and NHL among women with AIDS (Fig 1B).

KS AND HUMAN HERPES VIRUS 8

In 1872, Mor Kaposi, a Hungarian dermatologist working in Vienna, described what now is called classical KS, a relatively indolent skin tumor of the hands, or especially the feet and legs, occurring mostly among elderly men.⁷ During the intervening century, classical KS was seen with regularity among Mediterranean, central European, and Jewish populations. In central Africa, KS was observed in younger men, women, and even children.⁸ This disease, termed African or "endemic" KS, involves lymph nodes and viscera more often than does classical KS. Lastly, KS risk was noted to be increased among transplant recipients,⁹ showing that iatrogenic immune suppression was important in disease pathogenesis.

The outbreak of KS in the late 1970s coincided with or possibly antedated the outbreak of PCP among homosexual men in the United States. Not only were cases of these conditions reported to the CDC contemporaneously in 1981,^{10,11} Biggar et al also noted a sudden increase of KS cases beginning in 1977 among never-married young men in New York City.¹² The outbreak was readily detected for two reasons. First, KS had been quite rare in the United States, with age-adjusted annual incidence rates of 0.29 and 0.07 for males and females, respectively.¹³ Second, as revealed years later and relevant to the HAART era, KS and PCP risk are exquisitely sensitive to HIV-related immune deficiency.

AIDS KS in the United States occurs predominantly, but not exclusively, among homosexual men (Table 1). The risk of KS was so strongly associated with numerous male homosexual partners that it could be detected in our prospective New York and Washington, DC Gay ("DCG") Men's study of only 42 subjects, among whom 10 developed KS within 3 years of follow-up.¹⁴ This and similar findings¹⁵ prompted searches for a sexually transmissible "KS agent," culminating in

Table 1. Estimated Risk of Various Malignancies Among Persons With AIDS Compared With the General US Population

Malignancy	Estimated Relative Risk
Strongly related to immune deficiency	
Kaposi's sarcoma	73,000
Homosexual men	106,000
Nonhomosexual men	13,000
Women	Unknown
Leiomyosarcoma	10,000
Non-Hodgkin's lymphoma	
Children	1,203
Adults	165
Hodgkin's disease	7.6
Possibly related to immune deficiency	
Multiple myeloma	4.5
Seminoma	2.9
Brain cancer	3.5
Anal cancer	31.7
Squamous cell conjunctival cancer	13.0
Lip cancer	4.1
Weak or no relationship to immune deficiency	
Cervical cancer, invasive	2.9
Nonseminoma male germ cell	1.5
Lung adenocarcinoma	2.5
Lung nonadenocarcinoma	1.2
Melanoma	1.1
Lymphoid leukemia	1.4
Myeloid leukemia	3.0
Insufficient data	
Nonmelanoma skin cancer	5.4
Hepatocellular carcinoma	Undefined
Penile cancer	Undefined
Vaginal and vulvar cancer	Undefined

NOTE. Data from the AIDS-Cancer Match Registry and others as noted in the text.^{4,5,6,61,80} Reference population is the US Surveillance, Epidemiology and End Results (SEER) cancer registry program.

the discovery in 1994 by Yuan Chang, Patrick Moore, and their colleagues of a previously unknown herpes virus, termed Kaposi's sarcoma-associated herpes virus or human herpes virus-8 (HHV-8).¹⁶ As reviewed elsewhere,¹⁷ HHV-8 has numerous genes capable of deregulating mitosis, interrupting apoptosis (programmed cell death), increasing angiogenesis, and blocking presentation of antigenic epitopes. The control and sequence of expression of these genes, as well as the precise carcinogenic mechanism, are still under investigation, as is the epidemiology of HHV-8 transmission and its noncarcinogenic manifestations.

Prototype assays for detecting HHV-8 DNA and antibodies have been developed and have provided insight into likely modes of its transmission and natural history. Virtually 100% of KS lesions have HHV-8 detectable by polymerase chain reaction.¹⁶ HHV-8 DNA cannot be readily detected in the peripheral blood with current methods, but when such viremia is detected, the risk of KS during the subsequent 3 years is increased significantly.¹⁸ Testing for HHV-8 latency-associated nuclear antibodies, using cryopreserved sera from our DCG cohort, has revealed concurrent HHV-8 and HIV epidemics among homosexual men during the early 1980s.¹⁹ In this and other studies, HHV-8 seroprevalence and seroincidence are associated with numerous homosexual partners.^{19,20} However, unlike the strong relationship of HIV with unprotected receptive anal intercourse, no specific sexual practice has been linked to HHV-8.¹⁹

Aside from homosexual men, HHV-8 infection has only weak or even no association with sexual practices or HIV infection. This is in line with weak if any clustering of classical KS in spouses.²¹ Mother-to-infant transmission of HHV-8 has been reported from Africa,^{22,23} which is plausible given the occurrence of KS in African children. Transmission by HHV-8-seropositive mothers to their infants could not be detected in our study in New York City.²⁴ As with the closest relative of HHV-8, Epstein-Barr virus (EBV), it currently appears likely that most transmissions may occur via saliva to the oropharynx. HHV-8 can be detected in saliva and pharyngeal swabs, occasionally at relatively high levels.²⁵ Recent studies of families in Israel and French Guyana found HHV-8 seropositivity was associated with detection of HHV-8 antibodies in a subject's sibling or mother, but not in his or her father.^{26,27} However, much more work is needed to prove nonsexual transmission of HHV-8.

Without AIDS or iatrogenic immune deficiency, the risk of KS is low. For example, in parts of Italy that have an HIV-8 seroprevalence of 20%, the annual incidence of classical KS is 6.2 and 2.5 per 10,000 males and females, respectively.²⁸ With the plausible assumption that classical KS occurs only with HHV-8 seropositivity, the annual risk of KS is less than 1 per 1,000.

In contrast, homosexual men with HIV have an enormous risk of KS. Compared with the general US population, KS risk is increased approximately

100,000-fold for homosexual men with AIDS and approximately 13,000-fold for others with AIDS (Table 1). The sevenfold higher risk for homosexual men compared to others with AIDS approximately reflects their higher prevalence of HHV-8. Likewise, the absolute risk of AIDS KS is great: 35% within 10 years of HIV and HHV-8 coinfection in our DCG study of homosexual men.¹⁹ The risk of AIDS KS is not due to HIV infection per se, but rather to the level of immune deficiency, as measured by the CD4⁺ lymphocyte count. During the first 3 years of our DCG study, KS developed in four (12.5%) of the 23 subjects who had an enrollment CD4⁺ lymphocyte count less than 300 cells/ μ L, compared with none of those who enrolled with at least CD4⁺ lymphocyte counts \geq 550/ μ L.¹⁴ Even higher risks of KS have been noted with lower CD4⁺ lymphocyte counts.

Cofactors for AIDS and non-AIDS KS are poorly defined and must be re-examined incorporating the discovery of HHV-8. Despite similar HHV-8 seroprevalence rates by sex, it appears that in all populations males are at higher risk of KS than females. This male excess holds even among African children,⁸ and it remains unexplained.

NON-HODGKIN'S LYMPHOMA

The risk of NHL for persons with AIDS is increased approximately 150- to 250-fold compared with the general population. However, while very high, the level of risk varies substantially by histologic type of NHL (Table 2). Three NHLs are AIDS-defining: high-grade immunoblastic, or diffuse large cell; small noncleaved (Burkitt, Burkitt-like, or non-Burkitt); and primary NHLs of the CNS most of which are immunoblastic. The AIDS-Cancer Match Registry provided a wider and histologically more specific assessment, revealing that AIDS increased the risk of many other types of NHL.²⁹ In general, the risk with AIDS was highest for high-grade NHL histologies (RR, 348), intermediate for intermediate-grade histologies (RR, 113), and lower for low-grade histologies (RR, 14). Within these grades, risk varied markedly, from follicular, small-cleaved cell NHL (RR, 3) to diffuse immunoblastic (RR, 627). Of note, persons with AIDS had an extraordinarily high risk of unspecified histologic types of NHL (RR, 580). As a note of caution, this could be an artifact of more complete histologic information in the general US reference population (the Surveillance,

Table 2. Risk of Non-Hodgkin's Lymphoma Among Persons With AIDS

Working Group Formulation	Observed	Expected	Relative Risk
High grade			
Diffuse, immunoblastic	11	0.183	627
Lymphoblastic	4	0.095	42
Undifferentiated Burkitt's	38	0.173	220
Subtotal	157	0.451	348
Intermediate grade			
Diffuse, large cell	142	0.934	145
Diffuse mixed	10	0.186	54
Diffuse, small cell	6	0.209	29
Follicular, large cell	2	0.093	21
Subtotal	160	1.422	113
Low grade			
Follicular, mixed small cleaved and large cell	1	0.156	6
Follicular, small cleaved	1	0.337	3
Small lymphocytic	8	0.214	37
Subtotal	10	0.707	14
Other specified	6	0.240	25
Not otherwise specified	183	0.315	580
Total	516	3.137	165
Data from Cote et al. ²⁹			

Epidemiology and End Results [SEER] registry system) than in the larger AIDS population.

Risk factors for AIDS NHL mirror those of non-AIDS NHL, being approximately twofold higher in men than women, higher for whites than non-whites, and exponentially higher with older age.³⁰ As described in more detail below, Rabkin et al recently noted that risk of AIDS NHL was related to a polymorphism in the stromal cell-derived factor 1 (SDF1-3'A), which is associated with increased levels of B-cell chemokines.³¹ The SDF1-3'A allele is twofold more common in whites than blacks. NHL risk was increased twofold for whites who were heterozygotic and fourfold for those who were homozygotic for SDF1-3'A.³¹

Prior to the era of HAART, approximately 3% of newly diagnosed AIDS cases in the United States had NHL, and an equal proportion developed NHL after some other AIDS-defining opportunistic illness.³² In some closely monitored cohorts, AIDS NHL was reported to occur in nearly 30% of subjects within 3 years of a CD4⁺ lymphocyte count less than 50 cells/ μ L.³³ However, the association of NHL risk with worsening immunity is much

stronger for large cell, immunoblastic, and especially for CNS lymphoma, than it is for Burkitt's lymphoma.³⁴

Herpes virus infections play a distinct role in AIDS NHLs. HHV-8 was discovered in essentially every case of the newly defined clinicopathologic condition currently termed "primary effusion lymphoma" (PEL, formerly "body cavity-based lymphoma").^{35,36} PEL manifests as a lymphomatous effusion in the pleural, pericardial, or peritoneal cavity, often with no apparent tumor mass. PEL cells are clonal, often coinfecting with EBV, and grow readily in culture, providing reagents for HHV-8 research and immunofluorescent antibody assays (IFAs). PEL is extremely rare, with only perhaps a dozen cases in the world literature.

EBV can be detected in virtually 100% of CNS lymphomas.³⁴ This suggests that the CNS can be a sanctuary for EBV-infected malignant cells. It also has prompted studies indicating that detection of EBV in cerebral spinal fluid may be a useful diagnostic marker of CNS lymphoma, particularly in AIDS patients who have mass lesions on radiographic studies.^{37,38} Outside of the CNS, EBV can be detected in approximately 40% of AIDS NHLs, including both Burkitt (and Burkitt-like) and large cell, immunoblastic histologies.³⁴ This is useful information, as it shows that the majority of non-CNS AIDS lymphomas are not related to EBV.

AIDS Burkitt (and Burkitt-like) lymphomas virtually always have a pathognomonic 8;14 chromosomal rearrangement, in which the immunoglobulin heavy-chain gene (*Ig μ*) is translocated upstream from the *c-myc* proto-oncogene.³⁹ With this molecular signature, they resemble classical African Burkitt lymphomas rather than sporadic, non-African Burkitt lymphomas, many of which lack the 8;14 translocation. We noted that clones of peripheral blood lymphocytes with this 8;14 translocation could be detected in some 9% of homosexual men who had been infected with HIV for more than 6 years.⁴⁰ This rate was much higher than that found in HIV-negative men in the same cohort. It also appeared to be specific, as HIV was not associated with an increased prevalence of the 14;18 translocation that is characteristic of low-grade, follicular small cell lymphomas.⁴¹ Despite the high prevalence of the Burkitt-like 8;14 translocation in peripheral blood cells, it was not predictive of AIDS NHL in general, although most

of these NHLs were large cell, immunoblastic and not Burkitt histologies.⁴²

HODGKIN'S DISEASE

Several series of Hodgkin's disease cases among persons with HIV infection or AIDS have been reported, including a well-characterized series of 114 cases from the Italian Cooperative Group on AIDS and Tumors.⁴³ However, because Hodgkin's disease and AIDS both have peak incidence among young adults, the validity of these series was uncertain. Hessol et al matched AIDS registries and the Northern California Cancer Center registry to the identifying information from the 6,704 homosexual men who had enrolled in the San Francisco City Clinic cohort study of hepatitis B in 1978 through 1980.⁴⁴ This showed 90 cases of NHL and eight cases of Hodgkin's disease. The age-adjusted morbidity ratios were 37.7 (95% CI, 30.3 to 46.7) for NHL and 5.0 (95% CI, 2.0 to 10.3) for Hodgkin's disease. Five of the Hodgkin's disease cases occurred in close proximity to an AIDS-defining opportunistic illness; two others were HIV-seropositive, and the eighth lacked an HIV result. Thus, homosexual men with HIV infection and especially those with AIDS appeared to be at significantly increased risk for Hodgkin's disease.

In the AIDS-Cancer Match Registry, we found 140 cases of Hodgkin's disease among persons who had or later developed AIDS.⁵ These included 13 cases among persons with a previous AIDS-defining opportunistic illness, which was 7.6-fold higher (95% CI, 4.1 to 13.1) than expected in the general population. Of particular note, the risk of Hodgkin's disease was significantly higher post-AIDS than pre-AIDS ($P < .0001$), supporting the hypothesis that the elevated risk was linked with immune deficiency and not with sexual activity or some other confounding variable. We also examined the possibility that some AIDS NHL cases may have been misdiagnosed as Hodgkin's disease, through independent hematopathologic validation of 16 of the AIDS Hodgkin's disease cases.⁵ A similar level of risk of Hodgkin's disease for persons with AIDS (RR, 8.5; 95% CI, 4.1 to 16) was noted in the Australian AIDS-cancer match.⁴

As for some NHLs, Hodgkin's disease among young adults, and particularly Hodgkin's disease with AIDS, has been associated with EBV, which can be detected and which is actively expressed in

the vast majority of Reed-Sternberg cells of AIDS-Hodgkin's cases.^{5,45,46}

MULTIPLE MYELOMA

An increased risk of multiple myeloma was found among HIV-positive homosexual men in the Multicenter AIDS Cohort Study. Specifically, three of 2,683 HIV-positive subjects developed myeloma, compared with one of 2,896 HIV-negative subjects; the rate in the HIV-positive subjects was 14-fold higher compared with the general US population.⁴⁷ We confirmed this association and refined it to show that the risk of myeloma not only was elevated (RR, 4.5), but that it was significantly higher post-AIDS than pre-AIDS ($P = .015$).⁵ A high risk of multiple myeloma also was noted in the AIDS-cancer match in Australia (RR, 5.8; 95% CI, 1.2 to 17).⁴ Persons with other immunodeficiency states have not been noted to have excess myeloma, but the substantially and consistently elevated risk of NHL and Hodgkin's disease with AIDS makes an excess of myeloma plausible. The elevated risk of multiple myeloma was not preponderantly among homosexual men with AIDS, as might be expected if it were related to HHV-8 infection.^{5,48,49}

CERVICAL CANCER

Although invasive cervical cancer among HIV-positive women was included in the National Surveillance Definition of AIDS in 1993, there is little or no evidence that the risk of this tumor relates to HIV-induced immune deficiency. Women at high risk for sexually acquired HIV are also at high risk for sexually acquired infection with oncogenic types of human papillomavirus (HPV). HPV-16, HPV-18, and a few other strains are the primary etiologic agents of cervical cancer. There is good evidence that, compared with HIV-negative women, the oncogenic HPVs not only are highly prevalent among HIV-infected women, but also that they persist for longer times and at higher levels.⁵⁰ These persistent, high-level HPV infections result in cervical squamous intraepithelial lesions (SIL),⁵¹ but seemingly are not sufficient to induce cervical cancer at a higher rate than found in the general population.

Analyses of populations with high rates of Papanicolaou screening are difficult but nonetheless provide insight. For example, invasive cervical cancer among women in New York and New Jersey

declined steadily during the 1980s, at the time when the epidemic of AIDS KS and AIDS NHL was readily detected.⁶ Likewise, in the AIDS-Cancer Match Registry, from 5 years before to 2 years after an AIDS-defining illness, we noted a flat or even decreasing risk of invasive cervical cancer mirrored by an increasing risk of in situ cervical cancer near the time of an AIDS-defining illness, presumably the result of Papanicolaou screening.⁵ The lack of an association of invasive cervical cancer with HIV/AIDS also has been reported in populations that lack screening, including women in Zambia, Rwanda, South Africa, and the Ivory Coast.^{6,52-54} The absence of evidence for an association does not prove there is no association, as discussed for anal cancer, below.

ANAL CANCER

Like cervical cancer, squamous cell carcinoma of the anus derives from cloacogenic cells and is caused by oncogenic types of HPV. Moreover, as for AIDS and cervical cancer, confounding results in an association between AIDS and anal cancer, simply because both are caused by sexually transmitted viruses. Unlike cervical cancer, however, there is some evidence, albeit weak, that anal cancer risk is increased with AIDS.

The confounding was illustrated in the AIDS-Cancer Match Registry analysis, wherein anal cancer risk was 15-fold higher among people who would develop AIDS 2 to 5 years later, compared with the general population.⁵ Of greater interest, the anal cancer risk doubled to approximately 30-fold among people who had already had an AIDS-defining opportunistic illness. This increasing risk with worsening immune deficiency was nearly statistically significant ($P = .085$) and implies that immune deficiency, not merely sexual activity, increases the risk of anal cancer. Given the evidence that HIV-related advanced immune deficiency is associated with persistent, high level HPV infection and squamous intraepithelial lesions of the anus,⁵⁵⁻⁵⁷ an increased risk of cancer would be expected. Perhaps this increase is relatively small, such as twofold, and can be detected only in populations, such as HIV-infected homosexual men, that do not undergo cytologic screening for premalignant lesions but that have ready access to high-quality diagnostic procedures and treatment for cancer. Whether or not anal cancer risk is increased with AIDS rather than merely with

sexual activity, it is sufficiently high that homosexual men or others who engage in receptive anal intercourse with multiple partners should be monitored for premalignant and malignant anal lesions.⁵⁸

SQUAMOUS CELL CARCINOMA OF THE CONJUNCTIVA

Squamous cell carcinoma of the conjunctiva (SCCC) has been associated with chronic, intense ultraviolet light exposure, typically near the equator, and with HPV infection.⁵⁹ Marked increases in SCCC incidence have been reported by Kestelyn et al and by Ateenyi-Agaba from Rwanda and Uganda, respectively.^{60,61} In the latter study, the incidence SCCC increased from six cases per million in 1972 through 1988 to 36 cases per million in 1990 through 1992.⁶¹ Case-control studies at both sites, comparing SCCC with age- and sex-matched controls with other eye diseases, found HIV antibodies in 75% to 82% of those with SCCC compared with 19% to 24% in the controls. The RR of SCCC with HIV antibodies was increased 13-fold and was highly significant in both studies.^{60,61} Among the four SCCC cases noted in the AIDS-Cancer Match Registry, there appeared to be an association with advanced immune deficiency rather than HIV alone,⁶² but there were too few cases for a rigorous analysis.⁵

TESTICULAR AND OTHER CANCERS IN ADULTS

An increased risk of testicular cancer, specifically seminoma, but not nonseminomatous germ cell tumors, was found among HIV-positive homosexual men in the Pittsburgh component of the Multicenter AIDS Cohort Study. During a mean follow-up of 5.4 years, there were two testicular and one extragonadal seminomas in the cohort of the 430 HIV-positive subjects, which was 21-fold higher than expected in the general Pennsylvania population.⁶³ We confirmed this association and refined it to show that the risk of seminoma not only was elevated, but that it was significantly higher post-AIDS than pre-AIDS.⁵ There was no association between AIDS and nonseminoma male germ cell tumors. Although this consistency and specificity is reassuring, because there were only six post-AIDS cases (compared with 2.09 expected), this apparent association of elevated seminoma

risk with AIDS needs to be corroborated in other populations.

Brain cancers, particularly malignant gliomas, were noted to be elevated after an AIDS-defining opportunistic illness (RR, 3.5; 95% CI, 1.4 to 7.2) and significantly higher than in the pre-AIDS period ($P = .006$).⁵ However, this analysis was based on only 22 cases, and independent histopathological verification has not been performed.

Cancer of the lip has been noted to be significantly elevated in the linkage of AIDS and cancer registries in Australia (RR, 4.1; 95% CI, 1.6 to 9.5)⁴ and also appears to be elevated among renal transplant patients.⁶⁴ Lip cancer risk was not elevated among persons with AIDS in the United States.⁵ An approximately twofold increased risk of lung cancer has been noted among people with AIDS, but the approximately equal risk pre- and post-AIDS ($P \geq .13$) suggests that the risk is likely attributable to higher levels of cigarette smoking or other confounding rather than to immune deficiency.⁵ Persons with AIDS, particularly those with high rates of hepatitis B and C infection, are at elevated risk for hepatocellular carcinoma. However, this risk elevation is equivalent in HIV-positive and -negative hemophiliacs,⁶⁵ and also pre- and post-AIDS,⁵ suggesting that the hepatoma risk is attributable to hepatitis viruses and not to HIV-related immune deficiency.

CANCER AMONG CHILDREN WITH AIDS

Data on cancer among children with AIDS are sparse, but a pattern is beginning to emerge. First, NHL is the most common neoplasm, including 42 (65%) of the 64 cases reported by Granovsky et al in the United States⁶⁶ and seven of the nine cases reported by Evans et al in the United Kingdom.⁶⁷ As in adults with AIDS, the NHLs in children were predominantly of B-cell lineage and had an immunoblastic, large cell or small-noncleaved cell (Burkitt or Burkitt-like) histology.⁶⁶ Of eight children with AIDS and neoplasms reported by Di-Carlo et al, three had CNS lymphoma, one had NHL of the lung, and two others had polyclonal B-cell lymphoproliferative disease of the lung.⁶⁸ Gastrointestinal and CNS extranodal sites were relatively common.⁶⁶ The RR of NHL among children with AIDS was estimated to be 1,203 (95% CI, 688 to 1,949).⁶⁶

Granovsky et al also reported two cases of Hodgkin's disease,⁶⁶ perhaps also paralleling the

experience in adults with AIDS. Unlike adults, however, there were four cases of mucosa-associated lymphoid tissue (MALT) lymphomas among children.⁶⁶

Three cases of KS were reported by Granovsky et al⁶⁶ and two by Evans et al.⁶⁷ Given the rarity of KS among children, these five cases are surely far more than would be expected in the general population. KS is a greater problem among African children, including but not limited to those with AIDS.⁶⁹

Children, but not adults, with AIDS have been noted to have an extraordinary risk of leiomyoma and leiomyosarcoma, which appear to be related to unregulated, clonal infection of smooth muscle cells with EBV.⁷⁰ In the series of Granovsky et al, there were 11 cases of these smooth muscle tumors, second most common after NHL.⁶⁶ Based on two leiomyosarcoma cases occurring during prospective evaluation, the risk compared with the general population was extraordinary (RR, 10,000; 95% CI, 1,210 to 36,100).⁶⁶

HOST GENETIC SUSCEPTIBILITY

Polymorphisms in certain chemokine receptors and their chemokine ligands have a substantial effect on susceptibility to HIV infection, to AIDS-free survival, or both. CC-chemokine receptor 5 (CCR5) was discovered as the essential coreceptor for infection by macrophage-tropic HIV. Because these HIV strains account for nearly all transmissions, people who are homozygotes for an inactivating 32-basepair deletion (CCR5 $\Delta 32/\Delta 32$) are largely resistant to HIV infection.⁷¹ Rare cases HIV infections with CCR5 $\Delta 32/\Delta 32$ appear to result from T-cell tropic HIV, which uses CCR2 as its coreceptor.⁷²

Heterozygotes for CCR5 (+/ $\Delta 32$) or for a polymorphism in CCR2b (+/64I) have better AIDS-free survival compared to people with wildtype genes (+/+).⁷³ In one report,⁷⁴ homozygotes for a polymorphism in a CCR2 ligand called stromal cell-derived factor 1 (SDF1-3'A/3'A) also had better AIDS-free survival.

Recent data indicate that these polymorphisms may have different effects on specific AIDS-defining opportunistic illnesses. The risk for AIDS KS and NHL appears to be substantially reduced with CCR5 +/ $\Delta 32$.^{31,75} In contrast, whereas CCR2b +/64I is associated with a reduced risk of opportunistic infections and better post-AIDS survival, it

appears to have little effect on the risk of NHL. Of substantial interest, increased risk of AIDS NHL, especially Burkitt and Burkitt-like histologies, was noted with the SDF1-3'A polymorphism. With a median follow-up of 12 years in three prospective HIV-1-infected cohorts, 5% of the SDF1 wildtype (+/+) subjects had developed NHL, compared with 10% of those with SDF1 +/3'A and 19% of those with SDF1-3'A/3'A.³¹ These data implied a gene dosage effect, with a RR of 2.0 (95% CI 1.3 to 3.1) per SDF1-3'A allele. It is possible that SDF1-3'A, which is twofold more common among whites than blacks, accounts for some of the well-documented twofold increased risk of non-AIDS NHL among whites. However, no excess of SDF1-3'A was found among 24 whites with non-AIDS Burkitt or Burkitt-like NHL.³¹

TRENDS IN AIDS MALIGNANCIES IN THE ERA OF HAART

The CDC recently published data from their Adult/Adolescent Spectrum of HIV Disease project, summarizing trends in the incidence of AIDS-defining opportunistic illnesses among 22,558 HIV-infected people in 11 US cities.⁷⁶ In this study, 12,982 opportunistic illnesses were diagnosed during the 6-year interval from 1992 through 1997. For all opportunistic illnesses the incidence declined from 327 to 148 per 1,000 person-years. Of 21 specific opportunistic infections, 14 decreased significantly during the 6 years and none increased. In contrast, of five AIDS-defining malignancies, only KS declined significantly, from 61 to 20 per 1,000 person-years (Fig 2). There were nonsignificant declines in the incidence of immunoblastic lymphoma and primary brain lymphoma, but not in Burkitt's lymphoma or invasive cervical cancer (Fig 2). One could speculate that these trends in particular diseases reflect the effect, or lack of effect, of partial restoration of immunity with HAART.

FUTURE PERSPECTIVE

During the 1990s, as the HIV/AIDS epidemic has attenuated only slightly in some areas of sub-Saharan Africa and Thailand, it has expanded in eastern Europe and Latin America and has exploded in India and other areas of southeast Asia. Meanwhile in the United States and western Europe, the HIV/AIDS epidemic has become endemic among homosexual men and increasingly

Incidence of AIDS Diseases, 1992-97

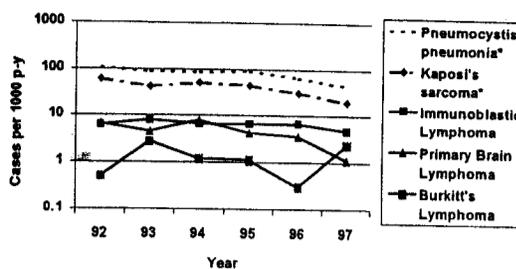


Fig 2. Incidence of AIDS-defining malignancies among HIV-infected subjects in the Adult/Adolescent Spectrum of Disease project, 1992 to 1997.⁷⁶ Significant declines ($P < .05$ by Cochran-Mantel-Haenszel trend test) were noted in PCP (and most of the opportunistic infections) and in Kaposi's sarcoma, but not in the three histologic types of AIDS-defining non-Hodgkin's lymphoma nor in invasive cervical cancer (not shown).

among the lowest socioeconomic strata of the populations, especially among racial and ethnic minority teenagers and young adults.⁷⁷ Evidence for re-emergence of sexually transmitted diseases including HIV among homosexual men in the United States is particularly worrisome.⁷⁸ Given that the natural incubation period from HIV infection to an AIDS-defining disease, including KS, is at least 8 years, the continuing incidence of sexually transmitted diseases among homosexual men in the United States is likely to presage a continuing incidence of AIDS-associated malignancies.

There are, however, rays of hope. Although still high, risky sexual activity among US urban high school students appears to have declined from 1991 to 1997.⁷⁷ It also is encouraging that cost-effective prevention of mother-to-infant HIV transmission with zidovudine or nevirapine may lead to a reduction in HIV-infected children and pediatric AIDS, even in developing countries.⁷⁹ As we nonetheless toil on, however, we must recognize that safe sex and HAART have relatively small effects on the pandemic. Meanwhile, the holy grail, a safe and effective HIV vaccine, remains years away from our grasp.

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