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HIV-Associated Cancers and Related Diseases

Robert Yarchoan, M.D., Thomas S. Uldrick, M.D.

HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD.

Abstract

Clusters of cases of pneumocystis pneumonia and Kaposi's sarcoma in New York and California in men who had sex with men were early harbingers of the acquired immunodeficiency syndrome (AIDS) epidemic.¹ The syndrome was also soon noted to be associated with a high incidence of aggressive B-cell lymphomas. As the AIDS definition crystallized, Kaposi's sarcoma, aggressive B-cell lymphomas, and invasive cervical cancer were considered to be AIDS-defining cancers when they developed in patients with human immunodeficiency virus (HIV) infection.² Additional cancers are now known to be associated with HIV (Table 1). The term HIV-associated cancer is used here to describe this larger group of cancers (both AIDS-defining and non-AIDS-defining cancers) that have an increased incidence among patients with HIV infection. In addition, incidental cancers also may develop in patients with HIV infection.

Epidemiology and Pathogenesis of HIV-Associated Cancers

Kaposi's sarcoma and several types of aggressive B-cell lymphomas occur most often in patients with CD4+ T-cell lymphocytopenia. Before the development of effective anti-HIV therapy, these cancers occurred in 30% or more of patients who had AIDS. After the introduction of zidovudine and didanosine, the incidence of these tumors began to decrease. The incidence dropped by 70% or more in the United States after the introduction of three-drug antiretroviral therapy (ART) regimens in the mid-1990s, with a continued and more modest decrease after 2000.^{4,5} However, as combination ART has dramatically improved the survival of patients with HIV infection and AIDS, the number of persons living with AIDS has more than doubled in the United States and the age of this population has increased (Fig. 1A). A large proportion of persons with HIV infection or AIDS are currently at an age at which the risk of cancer is increased, and a wide variety of cancers now develop in patients with HIV infection in association with a range of CD4+ counts.^{3,4,6,7} The burden of AIDS-defining cancers has remained relatively steady for the past two decades, but the burden of non-AIDS-defining cancers has increased and accounts for an increasing proportion of cancer-related morbidity and mortality in this population (Fig. 1B). As shown in a study in France, cancer is the leading cause of death in HIV-infected persons in highly developed countries.⁸

Address reprint requests to Dr. Yarchoan at the National Cancer Institute, 10 Center, Dr., Rm. 6N106, MSC1868, Bethesda, MD, 20892, or at robert.yarchoan@nih.gov.

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Epidemiologic patterns, including the observation that Kaposi's sarcoma was much more common in men who have sex with men than in other groups at risk for HIV infection, suggested that Kaposi's sarcoma was caused by a second infectious agent.⁹ In 1994, Chang et al. discovered a new gammaherpesvirus in Kaposi's sarcoma lesions (Kaposi's sarcoma-associated herpesvirus [KSHV], also known as human herpesvirus 8 [HHV-8]) and showed that it was the cause of Kaposi's sarcoma.¹⁰ With this finding, it became apparent that most HIV-associated cancers are caused by oncoviruses such as KSHV, Epstein-Barr virus (EBV), high-risk human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and Merkel-cell polyomavirus. In patients with HIV-induced immune dysregulation, immunologic control of these viruses and virus-infected cells is impaired, which permits the development of cancer. HIV prevalence is greatest in low- and middle-income countries in which the burden of virally associated cancers is also high. In some of these countries, Kaposi's sarcoma and cervical cancer are among the most common cancers.

Various factors contribute to increased cancer incidence. Persons with HIV infection have chronic antigenic stimulation, inflammation, and cytokine dysregulation (even with HIV control and preserved CD4+ counts), which contribute to the development of lymphoma and other cancers.¹¹ Also, persons at risk for HIV infection have increased rates of infection with oncoviruses.¹² KSHV, HPV, and HBV are sexually transmitted, and their prevalence is increased in persons with multiple sexual contacts. HBV and HCV can be spread by needle sharing. Smoking prevalence is high in some populations of persons with HIV, which contributes to an increased incidence of lung and other smoking-related cancers. HIV infection also increases the incidence of pneumonia, which in turn increases the risk of lung cancer in this population.¹³ Finally, in an aging HIV-positive population, an increasing proportion of cancers (e.g., colon, breast, and prostate cancer) are common incidental cancers.

Kaposi's Sarcoma

Kaposi's sarcoma is a multicentric tumor characterized by lesions ranging from a few indolent skin lesions to multiple lesions involving one or more organs, especially the oral mucosa, gastrointestinal tract, lymph nodes, lungs, and bones (Fig. 2). The epidemiologic types of Kaposi's sarcoma are the classic form, which typically occurs in elderly men in Mediterranean regions and is relatively indolent; the endemic form, occurring in persons in sub-Saharan Africa, often involving lymph nodes; the transplantation-associated form; and the epidemic (AIDS-associated) form. KSHV is the etiologic agent for all forms, which may have different natural histories but are considered the same disease. The prevalence of KSHV infection, unlike that of other herpesviruses, varies in different populations.¹⁴ The prevalence is substantially higher in men who have sex with men and in regions such as sub-Saharan Africa and countries bordering the Mediterranean Sea; less than 5% of the general U.S. population is infected. Kaposi's sarcoma develops in relatively few persons with KSHV infection who are otherwise healthy. The risk of HIV-associated Kaposi's sarcoma is inversely related to the CD4+ count, yet the risk remains substantially elevated as compared with the risk in the general population, even among patients who receive effective combination ART for years, have normal CD4+ counts, or both.¹⁵ Although the incidence of

HIV-associated Kaposi's sarcoma has declined overall in the United States,^{3,6} recent evidence shows an increase among black men in the southern United States.¹⁶

Kaposi's sarcoma lesions are characterized by proliferation of spindle cells of endothelial origin, with varying degrees of abnormal vascularity, inflammatory infiltrates, and fibrosis. Red cells and hemosiderin deposits give lesions their characteristic purplish color. Spindle cells are infected with KSHV and express latency-associated nuclear antigen (LANA), a viral protein that tethers KSHV episomes to chromatin. KSHV encodes a number of genes that induce proliferation, cytokine production, and angiogenesis and thereby contribute to pathogenesis.¹⁷ Studies in animals suggest that a constitutively active G-protein-coupled receptor encoded by the lytic open reading frame 74 gene (*ORF74*) is particularly important.¹⁸ Kaposi's sarcoma lesions often develop on the feet, which are relatively hypoxic, and tumor development may be facilitated by KSHV-encoded genes that are activated by hypoxia-inducible factors.¹⁹ Clonality remains an area of uncertainty.^{20,21} Kaposi's sarcoma is generally considered to be multiclonal, but there is some evidence that more advanced disease may be oligoclonal or monoclonal.

Criteria originally developed by the AIDS Clinical Trials Group are used to stage AIDS-related Kaposi's sarcoma and assess patients' responses to therapy.^{22,23} Kaposi's sarcoma can be rapidly progressive, and advanced disease is associated with a high mortality. Combination ART is a cornerstone for the treatment of AIDS-related Kaposi's sarcoma. Estimates of responses to ART alone vary greatly. Tumor reduction or resolution occurs over a period of several months in 20% to 80% of patients with AIDS-related Kaposi's sarcoma who are receiving ART, especially those with limited disease who have not previously received antiretroviral treatment.^{24,25} In some patients, initial development of a tumor or tumor exacerbation occurs after the initiation of ART; this may be due to a form of the immune reconstitution inflammatory syndrome (IRIS).²⁶ The use of glucocorticoids, a common treatment for other forms of IRIS, can exacerbate the tumor and should be avoided when possible.²⁷

Local therapies, including radiation, topical 9-*cis*-retinoic acid (alitretinoin), and intralesional therapy, usually add little to ART and are now rarely used. Surgery plays little role other than for diagnosis or for treatment of an anatomically dangerous lesion.

Patients who do not have a response to ART or have extensive disease are best treated with systemic therapy. Indications for systemic therapy include visceral disease, painful or ulcerated lesions, edema, extensive cutaneous disease, rapidly progressive disease, Kaposi's sarcoma IRIS, or psychological withdrawal because of the stigma of visible lesions. Pegylated liposomal doxorubicin is the most common systemic therapy, which even in the pre-ART era was associated with a response rate of approximately 45%.^{28,29} Paclitaxel, with a response rate of 55 to 70%, is associated with more toxic effects and is generally used as second-line therapy.^{29,30} More recently, pomalidomide and lenalidomide have shown activity in both AIDS-associated and classic Kaposi's sarcoma.^{31,32} Agents such as doxorubicin, bleomycin, vincristine, and etoposide have less favorable activity and side-effect profiles in cases of Kaposi's sarcoma but are often administered with ART in sub-Saharan Africa, because they are available and because of the high cost of liposomal

doxorubicin or paclitaxel.^{33,34} Preliminary results from an ongoing trial (<https://ClinicalTrials.gov/> number,) conducted in five countries in Africa and in Brazil by the AIDS Clinical Trials Group and the AIDS Malignancy Consortium have shown that etoposide is inferior either to paclitaxel or to bleomycin plus vincristine in advanced disease.³⁵

Regardless of which drug is used, patients should receive treatment as long as they continue to improve; once there is a plateau in the response, if the response is adequate, therapy should be stopped, sometimes after a period of reduced intensity. However, if substantial disease remains after the response plateau, consideration should be given to switching to a different therapy. With the use of available therapies, many patients achieve long-term control, especially with the immune reconstitution that is induced by ART. However, KSHV cannot be eradicated, and tumors may recur and require additional therapy. In sub-Saharan Africa, patients with AIDS-related Kaposi's sarcoma have a risk of death that is three times as high as the risk among patients with AIDS who do not have Kaposi's sarcoma; patients with AIDS-related Kaposi's sarcoma also often have severe complications that can lead to limb amputation.^{33,36} There is a need for new, effective anti-Kaposi's sarcoma therapies, in part because of the cumulative toxic effects associated with currently available agents (e.g., cardiac toxicity associated with doxorubicin, as well as bone marrow toxicity). There is also a need for affordable agents that are suitable for use in resource-limited settings.

Other Diseases Caused by KSHV

KSHV is the cause of primary effusion lymphoma (a rare lymphoma), KSHV-associated multi-centric Castleman's disease (Fig. 3), and a KSHV inflammatory cytokine syndrome (KICS).³⁷⁻³⁹ Two or more of these diseases may develop in a patient, and clinicians should be vigilant for their co-occurrence. Primary effusion lymphoma is a rare clonal B-cell cancer that typically is manifested as a body-cavity effusion but can also appear as noncavitary disease (Table 2). All cases of primary effusion lymphoma have KSHV infection of tumor cells, and 80% have EBV coinfection.^{37,40} Primary effusion lymphoma may arise from KSHV-infected mesothelial cells that differentiate into tumor cells with features similar to B1 cells (a subset of B cells that secrete broadly reactive low-affinity antibodies and are enriched in murine pleural and peritoneal cavities).⁴¹ Patients with primary effusion lymphoma often present with inflammatory symptoms. Elevated serum levels of inflammatory cytokines, ferritin, and IgE are associated with a poor outcome.⁴² Combination chemotherapy regimens that are used in aggressive B-cell lymphomas, combined with ART, can lead to long-term remission in approximately 40% of patients, and therapy should be undertaken with curative intent.^{40,42}

KSHV-associated multicentric Castleman's disease is a B-cell lymphoproliferative disease characterized by inflammatory symptoms, including high fevers, night sweats, cachexia, and weight loss.^{38,43,44} Patients often have lymphadenopathy, splenomegaly, and edema, as well as respiratory, gastrointestinal, dermatologic, or neurologic symptoms. The course is characterized by intermittent flares, and patients can become critically ill. Laboratory abnormalities include an elevated C-reactive protein level, a decreased albumin level, and an increased KSHV viral load, as well as anemia, thrombocytopenia, and hyponatremia. The disease is often misdiagnosed, especially in sub-Saharan Africa.³⁴ Diagnosis requires biopsy

of an affected lymph node. Characteristic findings on examination of biopsy specimens include LANA-expressing plasmablasts in the mantle region and regressed germinal centers with a vascularized core. Inflammatory symptoms result from KSHV-encoded viral interleukin-6 and from increased levels of other cytokines, including human interleukin-6 and interleukin-10.^{45–47} Until recently, median survival was less than 2 years. However, several new therapies have been developed, including rituximab, rituximab plus liposomal doxorubicin, and high-dose zidovudine plus valganciclovir.^{48–51} The majority of patients can now have long-term remission, and the prognosis is markedly improved.

KICS, a syndrome characterized by severe multicentric Castleman's disease–like inflammatory symptoms without Castleman's disease, develops in some patients with KSHV infection.^{39,52} A high percentage of patients with KICS have Kaposi's sarcoma or primary effusion lymphoma. Treatment of the underlying tumor in patients with KICS can be challenging, and initial reports show that KICS is associated with a poor prognosis. Additional research is needed to understand this condition and improve treatment options.

HIV-Related Lymphomas

Lymphomas that were initially included in the Centers for Disease Control definition of AIDS were Burkitt's, immunoblastic, and primary central nervous system (CNS) lymphoma.² Since then, lymphoma classification has evolved and new forms (e.g., primary effusion lymphoma and plasmablastic lymphoma) have been identified.^{37,53} The definition of "AIDS-defining lymphoma" has not been officially revised, but it generally refers to aggressive B-cell non-Hodgkin's lymphomas arising in patients who have HIV infection (Table 2). The presence of HIV also increases the risk of classic Hodgkin's lymphoma,^{3,6,7,54} which is not AIDS-defining.

Many HIV-associated lymphomas consist of EBV-infected tumor cells, including AIDS-related primary CNS lymphoma,⁵⁵ plasmablastic lymphoma,⁵³ and Hodgkin's lymphoma.⁵⁴ However, many cases of HIV-associated Burkitt's lymphoma and diffuse large-B-cell lymphoma are EBV-negative. Plasmablastic lymphoma is an aggressive EBV-associated tumor originally described as jaw lesions in HIV patients; a number of these tumors have *c-myc* translocations.⁵⁶ In HIV-associated Hodgkin's lymphoma, mixed cellularity is the most common histologic type, the Reed–Sternberg cells are generally EBV-infected, and the tumor microenvironment has unique features. Clinically, the distinguishing features of HIV-associated Hodgkin's lymphoma as compared with Hodgkin's lymphoma in the general population include occurrence at an older age and the more frequent occurrence of B symptoms (i.e., weight loss, night sweats, and fever), organ involvement, and unusual presentations, such as bone-only disease.⁵⁴

Lymphoma may be the presenting symptom of HIV infection, and all patients with aggressive B-cell lymphomas or Hodgkin's lymphoma should be tested for HIV.⁵⁷ Diagnosis of lymphoma requires pathological confirmation. For most patients with aggressive HIV-associated lymphoma, staging should include evaluation for CNS involvement. Cytologic analysis of the cerebrospinal fluid (CSF) may be associated with a high rate of false negative

results; therefore, flow cytometric analysis of the CSF is useful in evaluating for leptomeningeal involvement.⁵⁸

HIV-infected patients with ring-enhancing CNS masses should be evaluated for primary CNS lymphoma. Magnetic resonance imaging with gadolinium and ¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG-PET) are diagnostically useful. Diagnosis is aided by lumbar puncture with evaluation of CSF for cell counts, EBV and *Toxoplasma gondii* polymerase chain reaction (PCR), and cytologic and flow cytometric analysis for assessment of leptomeningeal B-cell lymphoma involvement, as well as other routine and other microbial studies as clinically indicated. An elevated EBV viral load supports the diagnosis of lymphoma, and cytologic analysis supported by flow cytometry can be diagnostic. Conversely, other positive microbiologic results may render a diagnosis of infection. Because these patients have advanced AIDS, concurrent lymphoma and infection may be observed. Biopsy of the CNS mass is the most reliable test and is recommended if there is a high index of suspicion for lymphoma and a diagnosis cannot be established through CSF evaluation and imaging. Stereotactic needle biopsy is generally safe. However, in patients with advanced AIDS in whom a biopsy is not possible, the combination of an FDG-avid CNS lesion and an elevated EBV viral load in the CSF has a high positive predictive value and can be used to justify therapy.⁵⁹ Before the availability of ART, a trial of empirical toxoplasmosis therapy was recommended, because differentiating toxoplasmosis from lymphoma was difficult, and resolution of the mass with treatment of toxoplasmosis would rule out a diagnosis of lymphoma. However, because of the potential to cure primary CNS lymphoma with lymphoma-directed therapy, empirical toxoplasmosis therapy alone is no longer appropriate, since timely establishment of a definitive diagnosis of primary CNS lymphoma minimizes the risk of neurologic deterioration.

Overall survival for patients with HIV-associated lymphoma has increased from less than 20% during the pre-ART era, with dose-reduced regimens, to more than 80% in the current era. Survival outcomes similar to those in the general population have been shown for diffuse large-B-cell lymphoma, Burkitt's lymphoma, and Hodgkin's lymphoma when patients are treated with full-dose regimens that are appropriate for the particular histologic diagnosis.⁶⁰⁻⁶³ A pooled analysis showed that rituximab, concurrent ART, and dose-adjusted etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide (EPOCH) were associated with longer survival among patients with CD20+ HIV-associated lymphoma.⁶⁴ The efficacy of treatment with standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with HIV-associated Hodgkin's lymphoma is similar to the efficacy in those with HIV-negative Hodgkin's lymphoma.⁶³ Hematopoietic cell transplantation is feasible in patients with HIV, and early studies suggest survival outcomes similar to those in the general population.⁶⁵ Rarer lymphomas, such as plasma-blastic lymphoma and primary effusion lymphoma, should also be managed with curative intent.^{66,67} For primary CNS lymphoma, radiation therapy was previously recommended but can cause late neurotoxic effects. Preliminary data suggest that immunochemotherapeutic approaches that incorporate ART and rituximab can lead to long-term remission in more than 70% of patients, without radiotherapy.⁶⁸ This treatment paradigm parallels that of primary CNS lymphoma in the general population.

Concurrent ART is advised in the treatment of HIV-associated lymphomas; however, a review of potential drug interactions is required before starting lymphoma therapy. HIV medications with strong effects on the cytochrome P-450 enzyme CYP3A4, including ritonavir and cobicistat, should be avoided in patients who are undergoing treatment with commonly used lymphoma regimens.⁶⁹ If the toxic effects of ART compromise delivery of curative treatment of cancer, modification of ART is required. Integrase strand-transfer inhibitor–based regimens that do not contain cobicistat are preferred. In patients with lymphomas who need to initiate ART, it is reasonable to defer ART and then introduce it soon after administration of the first cycle of chemotherapy. Likewise, in patients who need to modify ART, it is reasonable to discontinue concurrent ART and then reintroduce it soon after administration of the first cycle of chemotherapy. Attention to supportive care, including prophylaxis of opportunistic infections, is required.

Non–AIDS-Defining Cancers

In persons with HIV, all cancers except Kaposi’s sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer are considered non–AIDS-defining cancers. These include HIV-associated tumors and incidental cancers. The following five cancers make up approximately one half of these tumors among patients with HIV in the United States: lung cancer, anal cancer, hepatocellular cancer, Hodgkin’s lymphoma, and oropharyngeal cancer.³ In addition, HIV increases the risk of several other cancers, including squamous-cell skin cancer, Merkel-cell carcinoma, the myelodysplastic syndrome, polycythemia vera, and (especially in sub-Saharan Africa) squamous-cell carcinoma of the conjunctiva.^{4,70} Early in the AIDS epidemic, patients with AIDS were often too fragile to receive standard cancer therapy. However, this situation has changed with the use of ART; non–AIDS-defining and incidental cancers should generally be managed according to the standard of care. In cases in which no good standard treatment options exist, referral of patients to enrollment in clinical trials should be considered. The National Cancer Institute, the Food and Drug Administration (FDA), the American Society of Cancer Research, and the Friends of Cancer Research support the inclusion of patients with HIV in cancer-related clinical trials when appropriate.^{71–73} In the management of cancer, HIV should be treated as a chronic condition and attention should be paid to potential drug interactions among HIV medications and cancer therapy, as well as to the prevention of opportunistic infections.

Human Papillomavirus–Related Cancers

Cervical and anal cancers are the most common HPV-associated tumors in people with HIV.³ An estimated 30% of head and neck cancers and a majority oropharyngeal cancers in people with HIV are HPV-related.^{74,75} People with HIV are at increased risk for chronic infection with high-risk HPV and for associated cervical and anal pre-malignant high-grade squamous intraepithelial lesions.^{76–78} The risk of such lesions is associated with immunosuppression. Detection and management of premalignant lesions is important for the prevention of many HPV-associated cancers. Cervical cancer screening is particularly important in HIV-infected women. The Department of Health and Human Services recommends that HIV-infected women who are younger than 30 years of age undergo annual screening Papanicolaou (Pap) tests after diagnosis. After three negative annual Pap

tests, a screening interval of 3 years is appropriate.⁷⁹ For women 30 years of age or older, the recommendation is for either Pap tests or cotesting with Pap tests and tests for oncogenic HPV strains. For HIV-infected women, it is recommended that screening tests continue throughout their lifetime. These guidelines are in flux and are regularly updated at <https://aidsinfo.nih.gov/>.⁷⁹ New screening approaches for HPV-associated tumors in resource-limited settings include screen-and-treat programs and the performance of PCR assays for various HPV types.⁸⁰ Anal cancer develops most often in men who have sex with men. Screening programs for anal cancer have been developed in accordance with cervical cancer models and include anal Pap tests and colposcopy. However, the risk–benefit ratio is unclear in the treatment of anal high-grade squamous epithelial lesions. The National Cancer Institute is sponsoring a multicenter randomized, controlled trial — the Anal Cancer HSIL [high-grade squamous intraepithelial lesion] Outcomes Research (ANCHOR) study — to determine whether screening for and treatment of high-grade lesions prevents the development of invasive anal cancer, as compared with monitoring alone.

Prevention of HIV-Associated Cancers

Most HIV-associated tumors are caused by oncogenic viruses or other exogenous agents and are potentially preventable.⁸¹ Most important are early diagnosis and treatment of HIV with ART. In addition, HPV-associated cancers can be prevented by vaccination.⁸² HPV vaccines are most effective if administered to both girls and boys before sexual debut and is FDA-approved for women and for men who have sex with men up to the age of 26 years for the prevention of HPV-associated diseases. The quadrivalent HPV vaccine, Gardasil, is immunogenic in people with HIV, especially those with CD4+ counts above 200 cells per cubic millimeter.⁸³ HBV vaccination, as well as programs to reduce needle sharing, are important to reduce the risk of liver cancer. KSHV-related tumors could be prevented by blocking KSHV infection. KSHV is transmitted largely by saliva,⁸⁴ and behavioral interventions could feasibly reduce transmission. There is little knowledge about KSHV in populations at risk, and men who have sex with men continue to have a high rate of KSHV infection.^{85–87} Use of saliva in a range of sexual activities, including use as a lubricant, may contribute to infection risk. Similarly, specific practices such as pre-mastication of food may spread KSHV in sub-Saharan Africa. It seems reasonable to suggest that patient education and public health measures that are focused on reducing the transmission of KSHV by saliva could be effective, although this has not been shown in controlled trials. Additional studies are needed to inform preventive strategies.

Smoking cessation is of particular importance. Smoking prevalence is substantially higher in many HIV-infected populations than in the general public, and lung cancer is one of the most common causes of cancer-related mortality. Smoking cessation also has benefits in terms of the reduction in the risk of other cancers. Lung cancer screening with the use of low-dose computed tomography (CT) is being evaluated in HIV-infected people with a heavy smoking history to better understand the sensitivity, specificity, and best use of CT in this population.⁸⁸ According to current U.S. Preventive Services Task Force recommendations, patients from 55 to 80 years of age with a smoking history of 30 pack-years or more should be screened for lung cancer annually with low-dose CT. Finally,

patients with HIV infection should undergo age-appropriate screening for incidental cancers, such as colon and breast cancer.

Conclusions

Although the development of ART has done much to improve overall survival and reduce the incidence of AIDS-defining cancers, other cancers have come to the forefront and have become common causes of complications and death among persons with HIV infection. As the HIV-infected population ages, a wide variety of HIV-associated cancers have become increasingly important. These cancers pose both challenges and opportunities. The National Cancer Institute sponsors a range of clinical studies in the United States and globally to prevent and treat HIV-associated cancers through the AIDS Malignancy Consortium, the Intramural Program, the Cancer Immunotherapy Trials Network, and the Bone and Marrow Transplant Clinical Trials Network. Results from previous studies support evidence-based guidelines for the treatment of several HIV-associated cancers.⁸⁹ However, many questions remain. Addressing these questions will open new approaches for the prevention, diagnosis, and treatment of cancer among the more than 35 million people globally who are infected with HIV.

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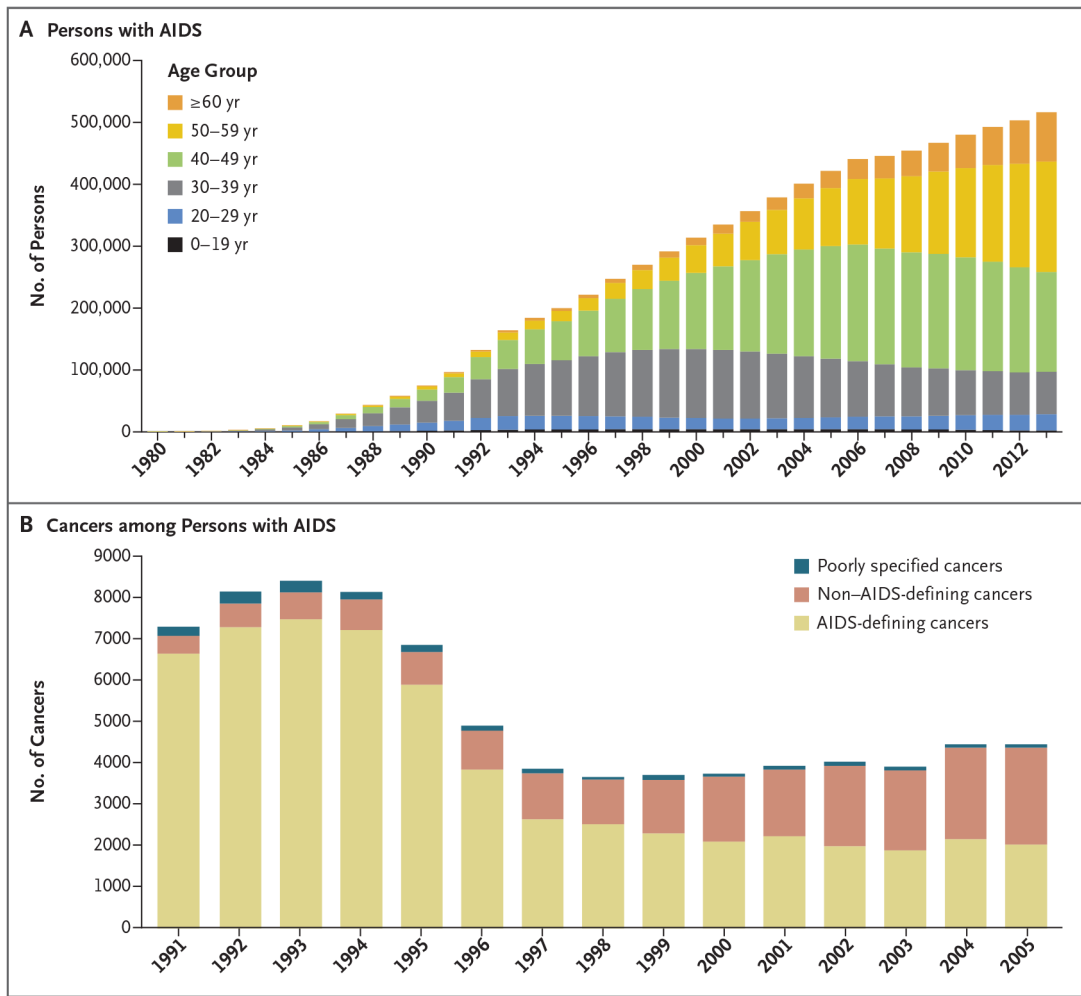


Figure 1. Trends in AIDS and in Cancers among Persons with AIDS.

Panel A shows the AIDS population in the United States according to year and age group. Data are from the National HIV Surveillance System, Centers for Disease Control and Prevention. Panel B shows estimated numbers of cancers among people living with AIDS in the United States according to year, stratified according to AIDS-defining cancers, non-AIDS-defining cancers, and poorly specified cancers.³



Figure 2. Selected Clinical Manifestations of Kaposi's Sarcoma.

In Panel A, advanced Kaposi's sarcoma with tumor-associated edema and ulceration are shown on the thigh of a patient with Kaposi's sarcoma–associated herpesvirus (KSHV) inflammatory cytokine syndrome (KICS). In Panel B, the CT scan shows diffuse, infiltrative pulmonary Kaposi's sarcoma. In Panel C, Kaposi's sarcoma of both legs and both feet, with associated “woody” edema, is shown in a patient with well-controlled HIV infection and a preserved CD4+ count. Panel D shows Kaposi's sarcoma of the oral cavity, and Panel E shows characteristic Kaposi's sarcoma lesions on the skin of the back.

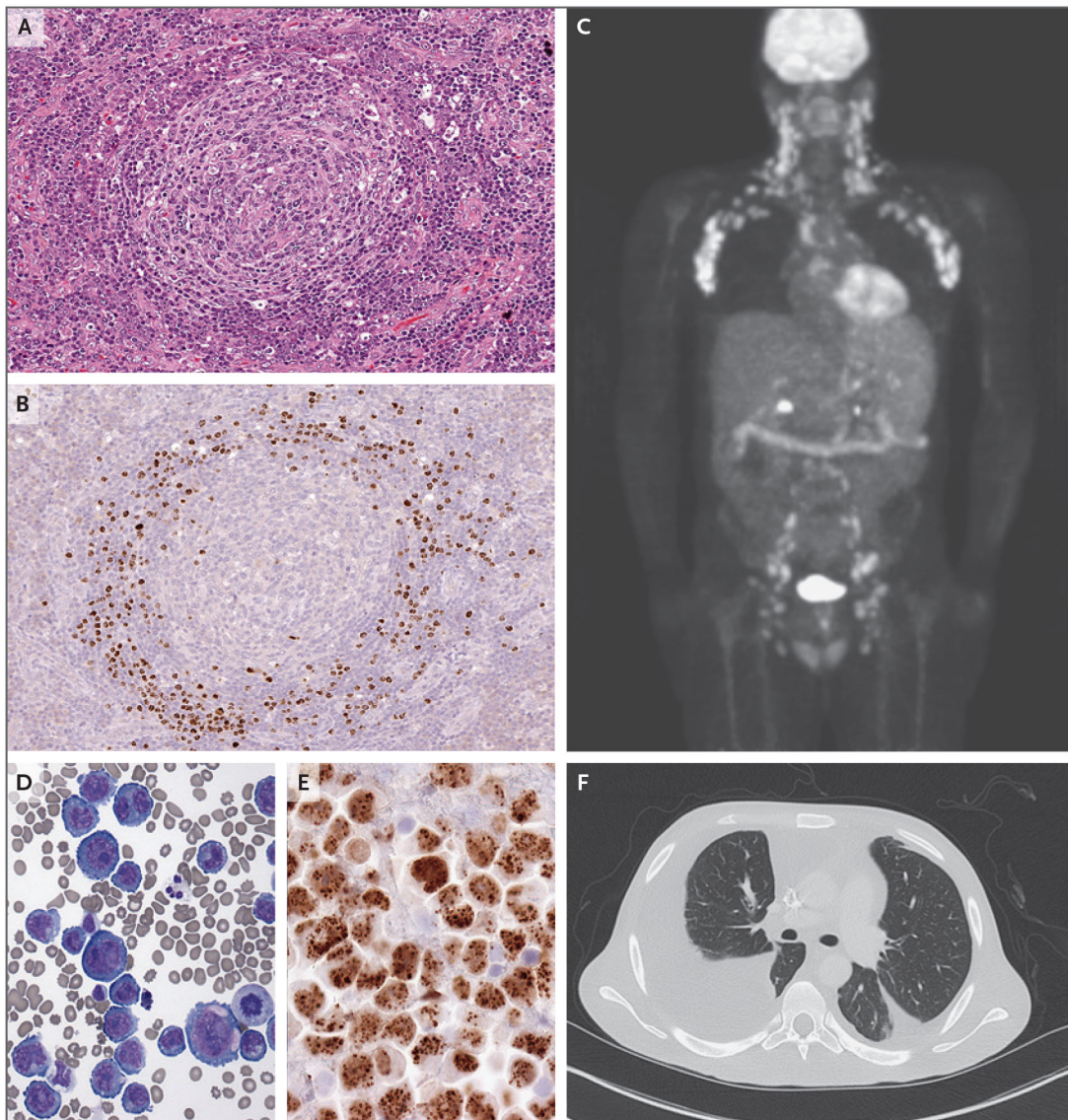


Figure 3. Pathological and Imaging Findings in KSHV-Associated Multicentric Castleman's Disease and Primary Effusion Lymphoma.

In KSHV-associated multicentric Castleman's disease (Panel A, hematoxylin and eosin), the involved lymph nodes often have regressed germinal centers surrounded by layered mantle cells, vascular proliferation and hyalinization, and interfollicular plasmacytosis. KSHV-encoded latency-associated nuclear antigen 1 (LANA-1) staining highlights KSHV-infected plasmablasts (Panel B). In a patient with KSHV multicentric Castleman's disease (Panel C), ^{18}F -fluorodeoxyglucose (FDG) positron-emission tomography shows symmetric FDG-avid lymph nodes noted in cervical, axillary, and inguinal chains; increased uptake of FDG is also noted in the enlarged spleen. In primary effusion lymphoma (Panel D), staining with modified rapid Wright–Giemsa (Diff-Quik) reveals large malignant lymphoid cells with basophilic cytoplasm and prominent nucleoli. LANA-1 staining (Panel E) highlights KSHV-infected lymphoma cells. In a case of primary effusion lymphoma (Panel F), a CT scan

reveals pleural effusions. The pathological images are from Stefania Pittaluga and Hao-Wei Wang, Laboratory of Pathology, National Cancer Institute.

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Principal HIV-Associated Tumors.*

Table 1.

Cancer	Estimated No. of Cases/yr in the United States among Persons with AIDS [†]	SIR after Combination ART in the United States [‡]	Role of Immunosuppression from HIV Infection	Etiologic Virus	Other Causative Factors
AIDS-defining					
Non-Hodgkin's lymphoma	1194	11.5	++ to ++++ for different types	EBV [§]	
Kaposi's sarcoma	765	498.1	+++	KSHV	
Cervical cancer	106	3.2	+	HPV	Tobacco
Non-AIDS-defining					
Lung cancer	376	2.0	+	?	Smoking, pulmonary infections
Anal cancer	313	19.1	+	HPV	
Hodgkin's lymphoma	179	7.7	++	EBV	
Oral cavity and pharyngeal cancer	100	1.6 [¶]	0 to + for different types	HPV	Tobacco, alcohol
Hepatocellular carcinoma	117	3.2	0 or +	HBV, HCV	Alcohol, other hepatic insults
Vulvar cancer	15	9.4	+	HPV	
Penile cancer	13	5.3	+	HPV	

* Shown are the principal tumors that are associated with an increase in the standardized incidence ratio (SIR) among persons with human immunodeficiency virus (HIV) infection in the United States. Plus signs (from 0 to +++) indicate the relative association of the cancer with immunosuppression and low CD4+ counts, with 0 indicating no association and ++++ indicating a substantial association. ART denotes anti-retroviral therapy, EBV Epstein-Barr virus, HBV hepatitis B virus, HCV hepatitis C virus, HPV human papillomavirus, and KSHV Kaposi's sarcoma-associated herpesvirus.

[†]The information in this column is based on 2001–2005 data from Shiels et al.³ The total number of cases per year of non-AIDS-defining cancers in persons with HIV infection (with or without AIDS), on the basis of 2004–2007 data from Shiels et al.,³ is approximately 32% higher than the numbers listed here.

[‡]The information in this column is from Hernández-Ramírez et al.⁴

[§]EBV is the cause of approximately 30 to 100% of the various forms of AIDS-defining non-Hodgkin's lymphoma; two exceptions are primary effusion lymphoma and large-B-cell lymphoma that develops in KSHV-related multicentric Castlemann's disease, which are caused by KSHV. Approximately 80% of persons with primary effusion lymphoma are coinfecting with EBV.

[¶]The SIR is for HPV-associated cancers; for HPV-unrelated cancers, the SIR is 2.2.

Table 2.

Lymphoproliferative Disorders Strongly Associated with HIV Infection.

Tumor Type	Key Immunohistochemical and Molecular Diagnostic Findings	Unique Features in Patients with HIV
Diffuse large-B-cell lymphoma*	CD20+, may have <i>c-myc</i> translocation	Is the most common lymphoma in patients with HIV; may have CNS involvement
Burkitt's lymphoma*	CD20+, CD10+, <i>c-myc</i> translocation	Immunoblastic morphologic features may be noted
AIDS-related primary CNS lymphoma*	CD20+, EBV+	Generally occurs in patients with CD4+ counts <100 cells per microliter; concurrent CNS infections may be observed; median patient age is less than that for primary CNS lymphoma in the general population
Primary effusion lymphoma*	CD20-, KSHV+, EBV+ (in approximately 80% of cases)	Was originally described as an effusion lymphoma; other nodal and extranodal presentations are possible; concurrent Kaposi's sarcoma is common
Plasmablastic lymphoma*	CD20-, EBV+, may have <i>c-myc</i> translocation	Was originally described as jaw lesion; other nodal and extra-nodal presentations are possible
KSHV-associated multicentric Castlemans disease	KSHV+, lambda-restricted plasmablasts; a proportion of infected cells are viral interleukin-6+	Features include weight loss, night sweats, fever, anemia, hypo-albuminemia, thrombocytopenia; patients have elevated levels of circulating viral interleukin-6, human interleukin-6, and other cytokines and an increased KSHV viral load
Classic Hodgkin's lymphoma	Often EBV+, Reed-Sternberg cells	Extranodal disease is frequently seen in patients with HIV, including presentations of bone-only disease; median age is higher than that for Hodgkin's lymphoma in the general population

* This lymphoma is generally considered AIDS-defining. CNS denotes central nervous system.