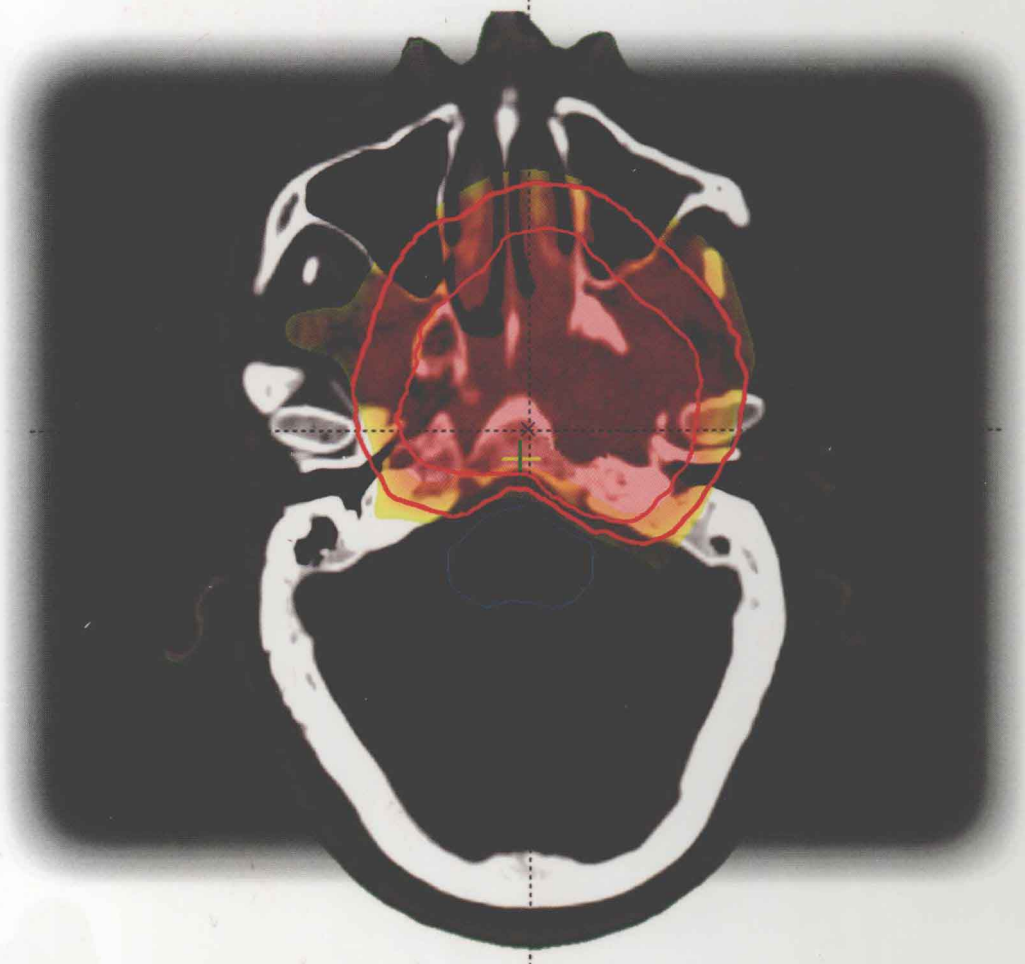
VIRAL AND IMMUNOLOGICAL MALIGNANCIES



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06 07 08 09/WPC/9 8 7 6 5 4 3 2 1

ISBN 1-55009-256-1
Printed in the United States of America by Walsworth Publishing Company
Production Editor: Maria L. Reyes; Typesetter: Jansom; Cover Designer: Lisa Mattinson

Sales and Distribution

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Preface

Viruses can cause cancer and cancers are more common in the setting of immune deficiency. Examples of these relationships have been known for decades, but newer molecular tools and the human immunodeficiency virus (HIV) epidemic have shed vital new light on this active and interesting area of research. Rarely, in humans, viruses can be directly oncogenic. Much more commonly, the role of viruses in human cancer is indirect, requiring an interaction with a second infection, chronic inflammation, or other host factor. In many cases, the precise relationship between viral infection and malignancy remains an epidemiologic association and the subject of active investigation. Nonmalignant hematologic disorders have a similarly complex relationship with cancer-associated viruses and may offer insight into the pathogenesis of oncogenesis. This book explores the relationships between viral infections, immune impairments, and hematologic and malignant diseases, particularly against the backdrop of the HIV epidemic.

Cancers were among the earliest recognized manifestations of acquired immune deficiency syndrome (AIDS), and efforts to understand them helped lead to the discovery of HIV infection. Prior to the AIDS epidemic, Kaposi's sarcoma (KS) was a rare cancer in most areas, usually confined to very elderly men in whom it typically followed a slowly progressive course. Because KS often is immediately visible involving the skin, and has a characteristic histology, its appearance in young previously healthy men in the early 1980s was a striking alert to the onset of the AIDS epidemic. Not long thereafter, non-Hodgkin's lymphomas were also appreciated to be part of the clinical spectrum of AIDS.

In the early stages of HIV infection, lymphatic proliferation causes diffuse generalized lymphadenopathy. HIV was, in fact, first isolated from an excised node, and the clinical description of generalized adenopathy was instrumental in understanding that AIDS as initially defined did not capture the full spectrum of HIV disease, later shown to include even completely asymptomatic individuals.

The lymphomas associated with AIDS are themselves complex and instructive. Peripheral lymphomas often arise in extranodal sites rarely affected in non–HIV-infected persons and follow an aggressive clinical course. Lymphomas in the central nervous system (CNS) in HIV-infected persons are a marker of extremely advanced immune deficiency and are almost always associated with evidence of Epstein-Barr virus (EBV) coinfection. Primary effusion lymphomas, first recognized in HIV-infected patients, follow an aggressive clinical course.

The theme of viral coinfection is a recurring one in AIDS-associated malignancies. The striking epidemiology of KS led to the identification of a novel human herpes virus, HHV-8. This virus is associated with all groups affected by KS, but dramatically so with HIV coinfection. Viral coinfections are also studied in HIV-infected persons with respect to cancers associated with EBV (non-Hodgkin's lymphoma), HHV-8 (KS and primary effusion lymphoma), and human papillomavirus (anal and cervical cancers), as well as coinfection with hepatitis viruses B and C (hepatocellular cancer).

The immune impairment of HIV infection is also an important setting in which to explore potential oncogenesis of other viral infections long suspected to be linked to human cancer. Here, studies of

simian virus 40 and human T-lymphotropic virus infections come to mind, as well as cancers suspected but not proven to be virally induced, including those arising in immunosuppressed patients after organ transplantation.

HIV infection clearly causes hematologic and oncologic sequelae, but the immune restoration seen in HIV treatment offers further insight. Antiretroviral therapy differentially alters the incidence of associated malignancies and can even cause tumor regression. KS incidence is relatively more decreased in treated HIV-infected populations than peripheral non-Hodgkin's lymphomas, whereas CNS lymphomas have nearly disappeared. HIV therapy can lead to KS regression and is, in fact, now the preferred treatment for that formerly aggressive cancer. HIV therapy does not typically cause lymphoma regression, but has substantially improved overall treatment response and survival. Even more interesting are the reports of clinical flares in KS after antiretroviral therapy initiation. This immune response inflammatory syndrome is well described in those with underlying opportunistic infection and presumably follows the recovery of antigen-driven immune response.

The hematology of HIV infection is similarly revealing of biologic insights. HIV infection itself causes anemia, probably in the majority of patients during their disease course. Anemia is, in fact, an important and independent survival predictor along with CD4 cell count and HIV viral load. As in other patient groups, anemia adversely affects quality of life. Whether the reversal of anemia prolongs survival is unproven, but it clearly reduces associated symptoms. Thrombocytopenia is also seen in HIV infection. Interestingly, thrombocytopenia may decrease in severity as HIV disease stage advances. Clinically significant coagulopathies are uncommon in HIV infection, but thrombotic thrombocytopenic purpura is substantially increased in incidence, as are serologic abnormalities, including the lupus-like anticoagulants.

Clearly, our understanding of the intricate interrelationships between immune surveillance, immune deficiency, and human cancer biology has been advanced through the study of HIV infection. In many cases, the specific pathogenesis relationship between HIV, coincident infections, and the host immune response still requires further investigation. It is hoped that the monographs collected in this volume will serve as an effective overview of current research and clinical consequences.

Finally, creating this book benefitted enormously from the talented editorial assistance of Ms. Carrie Clark Walsh. The editors also gratefully acknowledge the contributions of Dr. Susan Krown for providing key clinical illustrations.

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Epidemiology of Cancer in the Pre-HAART and HAART Eras

SUSAN SCHEER
NANCY A. HESSOL

In the 1970s, the increasing use of immune suppressive drugs for organ transplantation led to the discovery that the risk of certain cancers was elevated in transplant recipients. A decade later, scientists recognized that the risk of some cancers was also elevated in people with severe immunodeficiency owing to HIV infection. With the advent of more powerful anti-HIV treatment, termed highly active anti-retroviral therapy (HAART), in the mid-1990s, a noticeable decline in the incidence of AIDS-defining cancers occurred.

Unquestionably, the introduction and widespread use of HAART has led to reduced AIDS morbidity and mortality among people with HIV infection (Figure 1–1). However, longer life expectancy may also lead to the development of diseases that require a longer latency period, such as cancer. Under these conditions, it is important to closely monitor for emerging epidemiologic trends to accurately determine the risks of malignancy in this population. Implementation of appropriate cancer prevention, screening, and treatment recommendations requires a better understanding of the etiology, epidemiology, and natural history of AIDS defining and non–AIDS-defining malignancies.

After briefly reviewing cancers found to be associated with immunosuppression in non–HIV-infected patients, this chapter will focus on those cancers, both AIDS-defining and non–AIDS-defining, that have an increased occurrence in people with HIV infection. Particular attention will be given to contrasting the risk of cancer in the time period prior to HAART and in the HAART era. The majority of the data cited for this chapter draws upon results from large cohort studies and linkage studies between HIV/AIDS and cancer registries that quantified cancer risk and survival. The mainly descriptive data from case reports were used to assess change in cancer presentation.

CANCERS ASSOCIATED WITH IMMUNOSUPPRESSION PRIOR TO HIV

Independent of HIV infection, the occurrence of a number of cancers is associated with severe immunodeficiency.[1,2] Cancers resulting from congenital

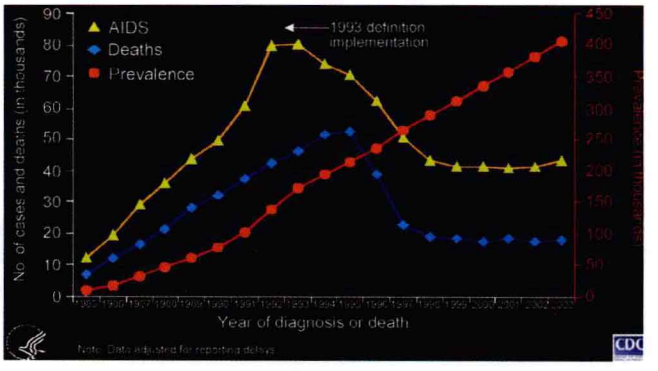

Figure 1–1. Estimated number of AIDS cases, deaths, and persons living with AIDS, 1985–2003, United States. Data adjusted for reporting delays. From Centers for Disease Control & Prevention, National Center for HIV, STD, and TB Prevention. Last updated: July 15, 2003. Available at: http://www.cdc.gov/hiv/graphics/surveill.htm (accessed Aug 22, 2005).

immunosuppression related to autoimmune diseases have long been found in children. Increases in organ and tissue transplantation in the 1970s, and the resulting use of immunosuppressive drugs, have caused the relative risk of a number of cancers, specifically non-Hodgkin's lymphoma (NHL), Kaposi's sarcoma (KS), hepatocellular carcinoma, and squamous cell carcinoma of the skin, to increase dramatically.[1] Cancers associated with immunosuppression in transplant recipients appear to be more aggressive than in the general population. However, discontinuation of the immunosuppressive therapy can stop or even reverse tumor growth. In addition, the same risk factors that predict cancers in the general population also influence the development of a malignancy among those with immunosuppression. For example, transplant recipients who are fair skinned and/or have high lifetime exposures to the sun are at greater risk for developing skin cancer than other transplant recipients.[1] Cancers associated with immunodeficiency are summarized in Table 1–1. As survival among persons with AIDS increases, the role of immunosuppression and its association with malignancies will become increasingly important.

AIDS-DEFINING CANCERS, PRE-HAART VERSUS HAART ERA

Current estimates are that 30 to 40% of persons with HIV infection develop a malignancy at some point in the course of their disease.[3] As people with HIV live longer, especially with advances in anti-retroviral therapies, more people are expected to develop malignancies, including cancers not currently associated with HIV or AIDS.

The Centers for Disease Control and Prevention (CDC) currently considers three cancers to be AIDS-defining conditions: (1) KS, (2) intermediate or high-grade B-cell NHL, and (3) invasive cervical cancer.[4] For each of these three cancers, the etiologic agent, risk groups and geography, incidence and presentation, and survival time are discussed below.

Kaposi's Sarcoma

KS is a multifocal endothelial tumor that can involve skin, mucous membranes, lymph nodes, and internal organs. In 1872, Moritz Kaposi reported odd skin tumors in five men in their sixties and seventies.[5] Commonly referred to as "classic KS," it was characterized as a benign tumor usually occurring in men between the ages of 50 and 60 who were of Eastern European and Mediterranean ancestry. Tumor progression tended to be slow, and lesions were usually confined to the skin of the lower extremities with no internal organ involvement. It was common for people to survive 8 to 10 years with KS and then die of an unrelated cause.

Etiologic Agent

Prior to 1994, the cause of KS among persons with HIV infection was unknown. However, the pattern of occurrence in persons with AIDS suggested that KS had an infectious etiology and was sexually transmitted in the same manner but less efficiently than HIV. In 1994, a newly identified virus, human herpesvirus type 8 (HHV-8) was determined to be the etiologic agent for KS.[6] HHV-8 has been found in over 90% of KS lesions, supporting the role of HHV-8 in the development of KS.[2]

The mode of HHV-8 transmission is not clearly understood. Given the early detection of KS in men who have sex with men (MSM) in the United States,

Table 1–1. IMMUNODEFICIENCY-ASSOCIATED CANCERS

Type of Cancer	Type of Immunosuppression	Infectious Agent or Underlying Condition
KS (transplant or iatrogenic)	Resulting from tissue/organ transplant	Human herpesvirus 8
NHL		Epstein-Barr virus
Hepatocellular carcinoma		Hepatitis B and C viruses
Squamous cell carcinoma of the skin		Human papillomavirus types
Anogenital cancer		Human papillomavirus types
Lymphoma	Congenital defect	X-linked gamma globulinemia or ataxia telangiectasia

KS = Kaposi's sarcoma; NHL = non-Hodgkin's lymphoma.

KS was originally thought to be sexually transmitted, particularly through oral anal contact. Recent studies[7] have found that HHV-8 DNA is more readily detected in saliva than in genital secretions. Supporting this theory is the occurrence of KS among families in areas where HHV-8 is endemic, such as Africa and Israel.[8]

Numerous studies now indicate that HHV-8 is necessary but not sufficient for the development of KS.[8,9] The risk of KS is increased by the detection of HHV-8 DNA in peripheral blood and is correlated with HHV-8 viral load. Additionally, both KS and HHV-8 are inversely correlated with immune competence.[8] Clearly, underlying host immunosuppression plays a role in development of KS among persons with HHV-8 infection.

It has also been suggested that Tat, a protein expressed by HIV, is associated with increased KS incidence, but again, incidence is only increased in those who are immunocompromised.[10,11]

Risk Group and Geography

With the establishment of cancer registries in the 1950s, KS was found to be endemic in Central and Eastern Africa. Following advances in transplant medicine, another form of KS associated with immune deficiency was found. Patients who took immunosuppressive regimens to prevent graft rejections after a transplant began to develop KS. This form of KS, also known as post-transplant or iatrogenic KS, often resolves when immunosuppressive therapy is stopped.[8]

Prior to the onset of the HIV/AIDS epidemic, KS was extremely rare in the United States,[12] with an expected rate in men of 0.29 cases per 100,000 annually.[13] In the late 1970s and early 1980s, an outbreak of KS was identified in young homosexual men.[14] These men had an observed rate of KS more than 2,000 times higher than the expected rate among never-married men of the same ages. As a result, KS became one of the first recognized indicators of AIDS.[14,15]

Since the risk of KS increases as immunosuppression increases,[8] people infected with HIV have a higher risk of developing KS than those not infected with HIV. By destroying $CD4^+$ T lymphocytes and compromising the host immune system,[16] HIV increases one's susceptibility to KS. Among persons with HIV/AIDS, KS tumors most commonly involve mucocutaneous sites. KS may also involve visceral organs, including the lungs, in about one-third to one-half of persons with KS.

KS became the first malignancy identified as an AIDS-defining illness when it was incorporated into the original CDC AIDS case definition.[14] The number of KS cases continued to increase rapidly, and KS continues to be the most common HIV-associated malignancy.[17]

The risk of KS among HIV-infected MSM is five- to 10-fold higher than in other risk groups for HIV and AIDS.[3] In Spain and Italy where injection drug users (IDUs) make up the majority of AIDS cases, the occurrence of KS is much lower than in the United States and Northern Europe, where MSM account for the majority of AIDS cases.

Women with KS have a poorer survival and generally present with more advanced KS than men.[18] Women also have an increased incidence of lymphedema, lymph node disease, and visceral disease. The increased proportion of women with KS with visceral disease and their poorer survival has been found independent of adjustment for CD4 lymphocyte count.[18–20]

Incidence and Presentation

Significant declines in the incidence of KS as a presenting AIDS diagnosis were seen prior to the widespread use of HAART (Figure 1–2). A number of possible factors, including a decreased exposure to HHV-8 through the use of safer sex practices to prevent HIV, an expansion of the AIDS case definition to include conditions that usually precede KS, use of antiviral drugs that have anti-herpetic properties, and/or a decrease in the identification or the reporting of KS, could explain these declines.[17]

To examine whether increased HAART use was primarily responsible for a decrease in the incidence of KS and a decrease in HHV-8 virus prevalence and transmission rates, Osmond and colleagues tested stored blood samples from MSM in San Francisco in three time periods, 1978 to 1979, 1984 to 1985, and 1995 to 1996.[21] They did not find any significant declines in the prevalence of HHV-8

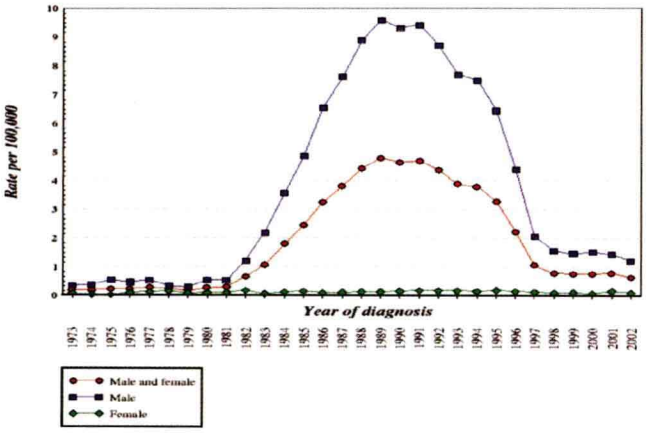

Figure 1–2. Age-adjusted incidence rates for Kaposi's sarcoma, by sex, 1973–2002, United States SEER 9 registries. From Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, (1973–2002). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission. Available at: http://www.cdc.gov/hiv/graphics/surveill.htm (accessed Aug 22, 2005).

during these time periods and also reported that the proportion of men practicing unprotected oral sex remained the same during these periods. They concluded that the decline in KS was, therefore, not a result of HHV-8 prevalence or changes in sexual behaviors, but instead was due to improvements in immune function and decreases in HIV-1 viral load as a result of HAART use, and that prior to HAART use, immune function improvement could be attributed to zidovudine monotherapy.

One of the most dramatic changes in the AIDS epidemic has been the decline in KS among persons with AIDS associated with their use of HAART. When the period before HAART was compared to 1996 and beyond, the incidence of KS declined by about two-thirds, with KS now being a relatively uncommon diagnosis in people with AIDS.[11]

Numerous studies have reported significant declines in the incidence of KS. The Multicenter AIDS Cohort Study (MACS) reported rates of KS declining by 66% between the pre-HAART years 1989 to 1994 and the years 1996 to 1997, after HAART became readily available.[22] The International Collaboration on HIV and Cancer pooled data from 47,936 HIV-infected persons in 23 prospective studies and found that the overwhelming majority of cancers (more that 90%) during the period of 1992 to 1999 were either KS or NHL. They reported that KS incidence declined from 15.2 per 1,000 person-years in the period 1992 through 1996 (1,489 cases) to 4.9 per 1,000 person-years in 1997 through 1999 (190 cases).[23] In addition, analyses looking individually at the 23 studies found that KS incidence declined in each, with many of the declines statistically significant.

Investigators from the Swiss HIV Cohort Study reported that KS incidence substantially decreased immediately following the initiation of HAART.[24] When the period before HAART was compared with the 15 months after HAART initiation, KS risk decreased by 66% ($p = .001$), suggesting that the impact of HAART is rapid. A population-based linkage of the HIV and cancer registries in Australia found that KS started declining between July 1990 and June 1994 (a pre-HAART period when zidovudine monotherapy was standard practice) and that there was a significant overall decline ($p = .045$) over the four time periods covered (prior to July 1990, July 1990–June 1994, July 1994–July 1996, and July 1996–December 1998).[25]

A linkage study between the San Francisco, California, AIDS registry and the California state cancer registry identified 3,407 cases of KS between 1988 and 2000 and found a statistically significant decreased adjusted rate ratio (RR) for KS in the HAART versus the pre-HAART time period (RR = 0.55, 95% CI 0.51–0.59).[26]

KS as the initial AIDS-defining illness has continued to decrease, but as people live longer on HAART, KS as a secondary AIDS diagnosis has increased from 23% in the 1980s to 50% in 1996 to 1997.[17,27] Nonetheless, overall the incidence of KS has significantly declined in the era following the introduction of HAART.

Survival

In addition to declining incidence, survival with KS has significantly improved with HAART use. The MAC Study reported an 81% reduced risk of death among KS patients who received HAART.[28] Additionally, survival with pulmonary KS, the most severe form of KS, has improved with HAART. Prior to HAART, 90% of AIDS patients who developed pulmonary KS progressed and died, whereas

after the introduction of HAART, only 47% of patients with pulmonary KS died.[29]

In the linkage study between the San Francisco, California, AIDS registry and the California state cancer registry, median survival among persons with KS in the pre-HAART time period was 19 months (95% CI 18–20 months) and during the HAART era median survival increased to 93 months (95% CI 79 –upper bound not achieved), a statistically significant difference ($p < .001$)[30] (Figure 1–3).

Recent studies have found that both protease inhibitor–based and non-nucleoside reverse transcriptase inhibitor–based anti-retroviral treatment combinations may lead to an undetectable HHV-8 viral load, which is in turn associated with KS regression.[31]

Persons with pulmonary KS generally live about 4 to 6 months; with chemotherapy, median survival may increase to 9 to 11 months.[32]

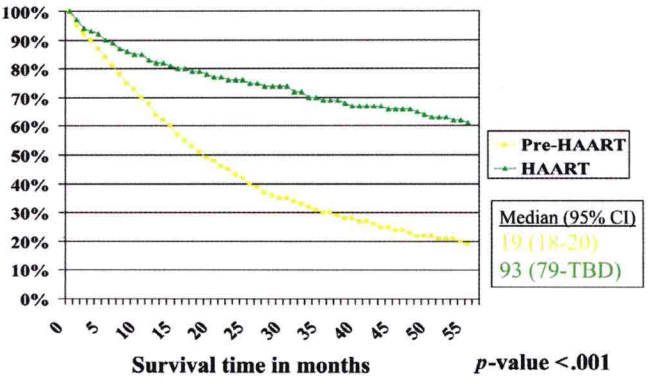

Figure 1–3. Kaplan-Meier survival time estimates for Kaposi's sarcoma, stratified by HAART time period, San Francisco AIDS cases, 1990–2000. Reproduced with permission from Hessol and Scheer.[30]

Non-Hodgkin's Lymphoma

The first cases of AIDS-related NHL, specifically advanced stage Burkitt's-like lymphoma, were identified about one year after the first reports of AIDS in MSM,[33] As a result, in 1985, the CDC added diffuse, undifferentiated Burkitt's and Burkitt's-like lymphoma to the list of AIDS-defining illnesses.[34,35] As the AIDS epidemic progressed, a number of studies of NHL in persons with AIDS reported that the incidence of NHL and, specifically, clinically aggressive, high-grade NHL was increasing.[33,36] Again, the CDC expanded the AIDS-defining illnesses to include diffuse aggressive, intermediate-grade or high-grade NHL or B-cell or indeterminant phenotype occurring in an HIV-seropositive individual.[37,38]

Almost all AIDS-related NHLs derive from B cells. AIDS-related NHLs are extremely aggressive and are located in sites usually not found in other lymphomas,[39] AIDS-related NHLs tend to develop later in the course of HIV infection when compared to other AIDS-defining conditions, such as KS, and are characterized by clinical and histological heterogeneity.

AIDS-related NHLs are divided into three broad groups based on the anatomic site of origin: (1) systemic (nodal or extranodal), (2) primary central nervous system (CNS), and (3) body-cavity–based or primary effusion lymphomas.[38]

Systemic NHLs make up approximately 80% of all AIDS-related NHLs. Approximately 85% of systemic NHLs have extranodal involvement, usually occurring in the central nervous system, the gastrointestinal tract, bone marrow, or the liver.[38] These include Burkitt's and Burkitt's-like lymphomas. Primary CNS lymphomas include immunoblastic lymphomas that present most commonly in the brain. They are usually large and multifocal occurring in the cerebrum, but they also occur in the cerebellum, basal ganglia, and the brain stems; they account for approximately 20% of AIDS-related NHLs.[38] Primary effusion lymphomas account for approximately 3% of all AIDS-related NHLs. These lymphomas are referred to as body cavity lymphomas because they usually remain localized in the body cavity of origin and usually do not spread to the lymph nodes or to distant sites.[38]

Etiologic Agent

NHL is associated with a viral pathogen, the Epstein-Barr virus (EBV). However, unlike KS and its association with the Kaposi's sarcoma herpesvirus (KSHV), EBV is not uniformly present in NHLs. EBV sequences are estimated to be present in approximately 30% of Burkitt's lymphoma and 80% of large-cell immunoblastic lymphomas.[40] Primary CNS lymphoma, however, is strongly associated with the presence of EBV, which is present in almost 100% of CNS lymphomas.[38,41–43] A study by MacMahon found