

Chapter 2

Epidemiology of AIDS-Defining Malignancies

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Abstract AIDS-defining malignancies are a subset of HIV-associated malignancies that include Kaposi sarcoma, some forms of non-Hodgkin lymphoma (NHL), and invasive cervical cancer (see also Chap. 3). Kaposi sarcoma along with *Pneumocystis carinii* pneumonia was among the first diseases that comprised the original surveillance definition of AIDS in the USA. Subsequently NHL (1985) and invasive cervical cancer were added (CDC 1992). Compared to non-AIDS-defining malignancies, Kaposi sarcoma and NHL demonstrated the highest incidence in the early AIDS epidemic. As shown in the first figure of this chapter, with the introduction of highly active antiretroviral therapy (HAART) in 1996, the incidence patterns of these cancers with the exception of cervical cancer dropped significantly. It is hypothesized that HAART restores immune function and delays progression to AIDS. However, even with improved clinical outcomes, HAART has not eliminated the risk of AIDS-defining malignancies. HIV-positive persons still remain at a substantially increased risk of developing these cancers as compared to the general population and AIDS-related and non-AIDS-related cancers combined are the most frequent underlying causes of death in AIDS in the USA.

2.1 Epidemiology of Kaposi Sarcoma Before HAART

Prior to the AIDS epidemic Kaposi sarcoma (KS) was a cancer with an incidence in white males of 0.3 per 100,000 in the USA (1973–1978) (Mbulaiteye et al. 2003). With the advent of the AIDS epidemic in 1981, a new form of KS, classified as “epidemic” or AIDS-associated KS, was identified. In the initial definition of AIDS, it was considered

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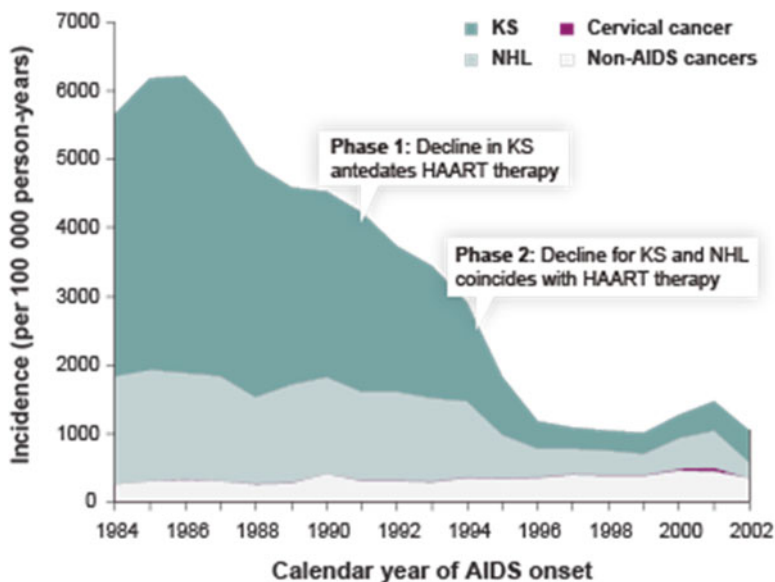


Fig. 2.1 Cancer incidence among people with AIDS in the USA (1984–2002). Incidence is shown as a function of calendar year of AIDS onset for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), cervical cancer, and non-AIDS-defining cancers. Incidence estimates for each cancer are stacked on top of each other to depict the proportion of total cancer incidence contributed by each cancer type. Analysis was restricted to the 2-year period 4–27 months after AIDS onset. Engels EA, et al., Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS* 2006;20:1645–54, by permission of Wolters Kluwer Health

an AIDS-defining illness because epidemiologically these cases [characterized by young age at onset, high prevalence among men who have sex with men (MSM), and association with unexplained immunodeficiency] were distinct from the other three recognized patterns of KS (classic KS—elderly Mediterranean men, endemic KS—sub-Saharan Africa, and iatrogenic KS—associated with therapeutic immunosuppression) and they tended to occur in individuals with other manifestations of this new syndrome. Beginning with the first report of KS among MSM in 1981, incidence rapidly increased and peaked in 1985–1986. By 1989–1991, incidence was 8.9 per 100,000 with nearly 40–50 % of men who have sex with men (MSM) presenting with KS as their AIDS-defining illness (Fig. 2.1) (Mbulaiteye et al. 2003). KS became the most common AIDS-associated cancer in the USA in 1990–1995 and it was associated with a 53,000-fold higher risk compared to the general population (Engels et al. 2006). AIDS-associated KS generally presented not only with purple or black cutaneous lesions but also frequently with organ involvement, especially among those with advanced immunodeficiency. Survival prior to antiretroviral treatment was at most 12–18 months (Bower et al. 2006) and for the cases with extensive involvement of internal organs and concurrent opportunistic infections, prognosis was particularly poor.

Epidemiological studies documented an association of epidemic KS with high rates of sexual partner exchange, co-incident sexually transmitted infections (particularly oral gonorrhea), anal intercourse, fecal-oral exposure [particularly oral anal insertive sex (rimming)], fisting (insertion of the hand into the partner's rectum), usage of nitrite (a smooth muscle relaxant used to facilitate anal sex), and contact of KS cases with a sex partner from the New York and San Francisco epicenter. These associations, plus a discordance in KS rates between MSM compared to those who acquired AIDS through parenteral [transfusion (4 %) and injection drug use (10 %)] and perinatally (3 %) (Mbulaiteye et al. 2003), supported the hypothesis that a sexually transmitted factor independent of HIV was responsible.

Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), was discovered by Chang and Moore in KS lesions, and this virus is now established as the causative agent of KS. Epidemiological analyses established that HHV-8 is a necessary but not sufficient cause of KS, based on cross-sectional and longitudinal studies of MSM that documented that all AIDS-associated KS cases were HHV-8 positive. Also, these studies revealed that a substantial fraction of MSM, especially in the New York and San Francisco epicenters, were carriers of the virus. Seroepidemiological studies further documented that not only was HHV-8 linked to AIDS-associated KS, but that HHV-8 is also detected in cases with classic, endemic, and iatrogenic KS. By contrast, the prevalence of HHV-8 infection was low in blood donors in the USA. To better understand the complex epidemiological relationship between HIV and HHV-8, several epidemiological studies documented that anal-related sexual activities were independent risk factors for acquisition of both viruses, confirming the hypothesis that co-epidemics of HIV and HHV-8 accounted for the emergence of AIDS-associated KS. These co-epidemics were most prominent in the New York and San Francisco epicenters and this pattern explained the association with sexual contact with someone from New York or San Francisco as a risk factor for KS in populations outside of the New York and San Francisco areas. In summary both HIV and HHV-8 share some overlapping risk factors, particularly fecal-oral exposure for HHV-8 and the closely related penile-anal exposure for HIV.

The AIDS-associated KS epidemic in Africa has a different epidemiological pattern, essentially reflecting the super-imposition of HIV upon an existing endemic pattern of HHV-8 infection that drives the occurrence of endemic KS. Epidemiological data suggest that in this setting, HHV-8 was highly prevalent before the AIDS epidemic and like other herpesviruses is associated with oral exposure resulting from poor hygiene and practices such as pre-mastication of food during infant feeding common in the African setting. The sexual risk factors detected in the African KS setting (e.g., high rates of sexual partner exchange, commercial sex worker exposure, etc.) are associated with acquisition of HIV infection rather than with the acquisition of HHV-8. This super-infection with HIV in an HHV-8 infected person and its attendant HIV-induced immunosuppression accelerates and amplifies the imposition of epidemic KS on a background of endemic KS.

2.2 Epidemiology of Kaposi Sarcoma After HAART

As shown in Fig. 2.1 the phase 1 decline in KS incidence commencing in 1986 likely represented the rapid expansion of AIDS beyond the original epicenters with high rates of HHV-8, changes in sexual behaviors, and modest impacts of early mono and dual antiretroviral HIV therapy. A more dramatic declination occurred in 1994–1996 (Fig. 2.1) in the USA coincident with the introduction of highly active antiretroviral therapy (HAART), a pattern observed in other populations when effective treatment was implemented. In the Multicenter AIDS Cohort Study (MACS) of MSM, the incidence of KS declined by 87 % in the post-HAART era (1996–2007) as compared to the pre-HAART era (1984–1995) (Seaberg et al. 2010). In the Swiss HIV Cohort study, the standardized incidence rates of KS declined from 1,375 to 67 per 100,000 in 1985–1996 and 2002–2006 periods, respectively (Franceschi et al. 2010). Similarly, the incidence rate of KS declined significantly from 15.2 to 4.9 per 1,000 person-years in the 1992–1996 and 1997–1999 periods, in a collaborative study of 23 prospective studies from North America, Europe, and Australia (International Collaboration on HIV and Cancer 2000). HAART was also associated with improved survival of KS. The mortality rate from KS decreased fourfold for persons with AIDS and nearly 70 % of persons survived up to 3 years (Simard et al. 2010; Spagnuolo et al. 2012).

Regardless of these improvements, individuals continue to present with AIDS-associated KS (Fig. 2.2). KS is currently associated with a 3,640-fold higher risk in HIV-infected individuals compared to the general population (Engels et al. 2006). KS has been documented in individuals with failing HAART, individuals with immune reconstitution inflammatory syndrome (IRIS) after initiating HAART for the first time, and those who have steady suppressed HIV viral loads and relatively high CD4+ T cells. Children diagnosed with AIDS before the age of 14 years have significantly elevated risk of developing KS in the post-HAART era as compared to the general population. The current risk of AIDS-associated KS remains elevated, even though the risk has decreased significantly since the pre-HAART era.

Risk factors associated with KS in the post-HAART era primarily include low CD4 cell counts and high plasma HIV RNA levels. In particular, low CD4+ T cell counts (<50 cells/ μ l) were associated with an increased risk of KS for those taking HAART in the Swiss HIV Cohort (Franceschi 2008). Additional risk factors specific to the post-HAART era include older age and IRIS. HIV-infected individuals may be surviving longer and becoming at risk of KS independent of restored immunity from HAART. With IRIS, there is a transient increased incidence of KS after initiation of therapy independent of current CD4 counts. Starting HAART in a proportion of treatment naïve individuals may stimulate a heightened inflammatory response that induces KS, perhaps in part by provoking HHV-8 activation from latent to active gene expression. The relationship between HIV-related immune suppression and HHV-8 activation is dynamic and understanding the relevance of the current risk factors, such as age and IRIS, may be better understood at a molecular rather than population level.

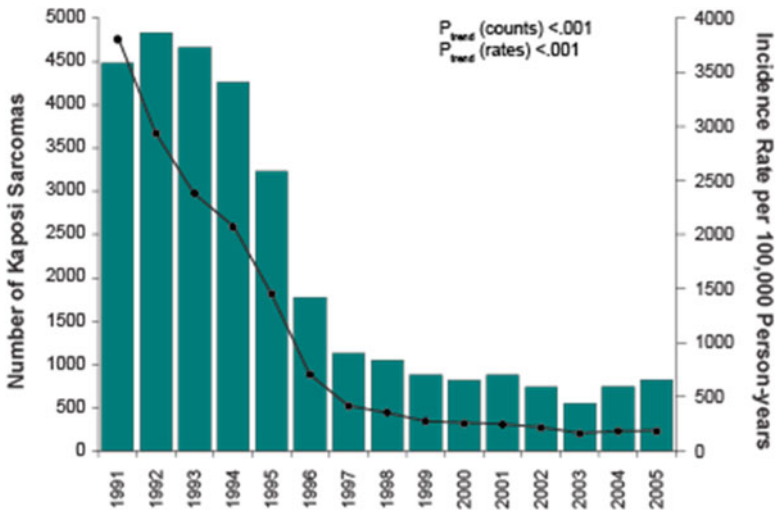


Fig. 2.2 Cancer burden of Kaposi sarcoma among people living with AIDS in the USA during 1991–2005. Bars depict estimated counts (i.e., number of cancers) and points connected by lines depict the incidence rates standardized to the 2,000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided P values were calculated using the χ^2 test. Shiels MS, et al., Cancer Burden in the HIV-Infected Population in the United States. J Natl Cancer Inst. 2011;103(9):753–62, by permission of Oxford University Press

More recently, host and viral cofactors are emerging as recognized factors in the development of KS. Molecular epidemiologic studies suggest that polymorphisms in host genes involved with inflammation or immune responses are associated with a slightly increased risk of KS. Host factors include a positive association between KS and substitution of phenylalanine for glycine at position 13 in the HLA-DRB1 locus, suggesting a role for immunogenetic factors. Also, a specific polymorphism in the IL-8 promoter (TT is protective versus AT) is associated with both the occurrence and severity of KS. Additional host factors include a decrease in NK cells and immune activation measured by elevated cytokine levels.

A number of HHV-8 genes have functions that can promote tumorigenesis. Like other herpesviruses, HHV-8 has “picked up” host genes that encode for key cell cycle regulatory genes [e.g., human complement-binding protein, IL-6, BCL-2, cyclin-D, Flice inhibitory protein (FLIP)] and some DNA altering genes (e.g., dihydrofolate reductase, thymidine kinase, thymidylate synthetase, and DNA polymerase). These “accessory” genes are thought to be integral to KS oncogenesis on the molecular level. HIV-1 itself has a viral protein, Tat (trans-activating factor) that may synergize with HHV-8 to foster angiogenesis, disease progression, and promote tumor survival. The potential synergistic effect of host and viral cofactors on KS progression may further disrupt immune control of HHV-8 and explain the more advanced clinical state of KS among HIV-1 infected individuals as compared to immunosuppressed organ transplant recipients.

An emerging risk factor in the post-HAART era is ineffective treatment. Ineffective HAART may be the result of poor adherence resulting in insufficient immune restoration and the development of drug-resistant strains. Ineffective therapy may also be associated with interrupted treatment. In the Swiss HIV cohort study, absence of antiretroviral therapy (ART) for 3 months was associated with an eightfold increased risk of KS (Franceschi 2008). In a randomized clinical trial, KS incidence was higher among those with intermittent therapy as compared to those on continuous therapy (Silverberg et al. 2007). These relapses in HIV viremia may have a direct effect on viral and host interactions, ultimately altering host susceptibility to KS disease progression.

2.3 Epidemiology of Non-Hodgkin Lymphoma Before HAART

Non-Hodgkin lymphoma (NHL) was the second most common cancer early in the AIDS epidemic and it was included as an AIDS-defining illness by the Centers of Disease Control (CDC) in 1985. The background prevalence of NHL in the USA prior to the AIDS epidemic was much higher than KS, so incidence trends were not as striking. In a period analysis, the incidence of NHL from 11 regions in the USA in the Surveillance Epidemiology and End Results (SEER) Program was 21.1 per 100,000 white men in 1995 as compared to 10.4 per 100,000 white men in 1973 (Mbulaiteye et al. 2003). For those with HIV infection, the incidence of NHL was 60–200 times higher as compared to HIV-negative individuals (Bower et al. 2006). Five to ten percent of all HIV-infected individuals were expected to develop lymphoma as either the first or subsequent AIDS-defining malignancy (Hamilton-Dutoit et al. 1991). Overall survival from NHL was worse than KS, less than a year (Bower et al. 2006).

AIDS-related lymphomas (ARL) are cancers of the lymphatic system. These NHL are predominantly of B-cell origin, intermediate to high-grade malignancies, and often have extensive extranodal involvement, such as the central nervous system. The prevalence of high-grade malignancy is much higher among AIDS patients (80–90 %) as compared to HIV-uninfected individuals (10–15 %) (Levine 1993). They occur late in HIV infection, and in general, their incidence is not affected by transmission group or geographic region in the USA. Women have a slightly lower incidence of ARL, but that is similar to the gender distributions of lymphomas in HIV-uninfected individuals. The strongest risk factors are duration of HIV infection, low CD4+ T cell counts at lymphoma diagnosis, and having a prior AIDS-defining illness. Of the 35 different histological types of NHL, four are associated with AIDS-defining malignancies by the 1985 definition of the Centers for Disease Control: diffuse large B-cell lymphoma (DLBCL) with centroblastic features; DLBCL with immunoblastic features; primary central nervous system lymphoma (PCNS); and Burkitt's lymphoma (BL). The nomenclature for lymphomas has changed since then, and while it is hard to map the DLBCL in the 1985 nomenclature to current lymphoma types, it is generally accepted that DLBCL of either the

germinal center subtype or activated B-cell subtype can be considered AIDS-defining. Three additional lymphomas that rarely occur in immunocompetent patients, but are more specific to HIV infection are primary effusion lymphoma (PEL), plasmablastic lymphoma (often of the oral cavity), and large B-cell lymphoma arising in HHV-8-associated multicentric Castleman's disease. About 70 % of the ARL are of the DLBCL histologic type which also includes variants or subtypes such as PCNS, PEL, and plasmablastic lymphoma.

Epstein-Barr virus (EBV), which had previously been identified as an etiologic agent of certain lymphomas, is a major contributor to AIDS-related lymphoma. EBV is ubiquitous in the general population and it has been associated with transplant-related lymphomas and primary immunodeficiency-associated lymphoma. Another oncogenic virus more recently linked to NHL is HHV-8, which like EBV is specifically associated with a subset of AIDS-associated lymphomas. EBV occurs in 30 % of centroblastic-DLBCL, 90 % of immunoblastic-DLBCL, 100 % of PCNS, 30–50 % of Burkitt-like lymphoma, and 50 % of plasmablastic lymphoma (Carbone 2003). PEL is associated with both EBV (about 80 %) and HHV-8 (100 %) (Carbone 2003). With varying prevalence of oncogenic viruses, no clear transmission patterns, and a multitude of host and viral risk factors, the only common risk among the ARL is HIV-related immunosuppression. Fortunately for those who were most susceptible to NHL, HAART significantly changed the incidence of the disease.

2.4 Epidemiology of NHL After HAART

Upon the introduction of HAART the incidence of NHL declined in the USA, but not as dramatically as KS (Fig. 2.1). Further unlike KS, which showed a biphasic decline, the decline for ARL was only observed during the 1994–1996 period when HAART was introduced (Fig. 2.3). In the MACS of MSM, the incidence of NHL declined by 77 % in the post-HAART era (1996–2007) as compared to the pre-HAART era (1984–1995) (Seaberg et al. 2010). In the Swiss HIV Cohort study, the standardized incidence rates of NHL declined from 952 to 98.4 per 100,000 in the 1985–1996 and 2002–2006 periods, respectively (Franceschi et al. 2010). Similarly, the incidence rate of NHL declined from 6.2 to 3.6 per 1,000 person-years in the 1992–1996 and 1997–1999 periods, respectively based on a collaborative study of 23 prospective studies from North America, Europe, and Australia (International Collaboration on HIV and Cancer 2000). In looking more specifically at the histologic types that comprise ARL, HAART has been particularly effective at reducing the incidence of PCNS and immunoblastic DLBCL, but it appears to have less impact on the incidence of Burkitt's lymphoma. Both mortality and survival improved for NHL in the post-HAART era, but the changes were more gradual. NHL mortality rate decreased twofold for persons with AIDS and about 56 % had an overall survival of 3 years with HAART and improved lymphoma therapies (Simard et al. 2010; Spagnuolo et al. 2012). HIV-positive individuals continue to present with NHL (Fig. 2.3) and are at a 23-fold increased risk compared to the general

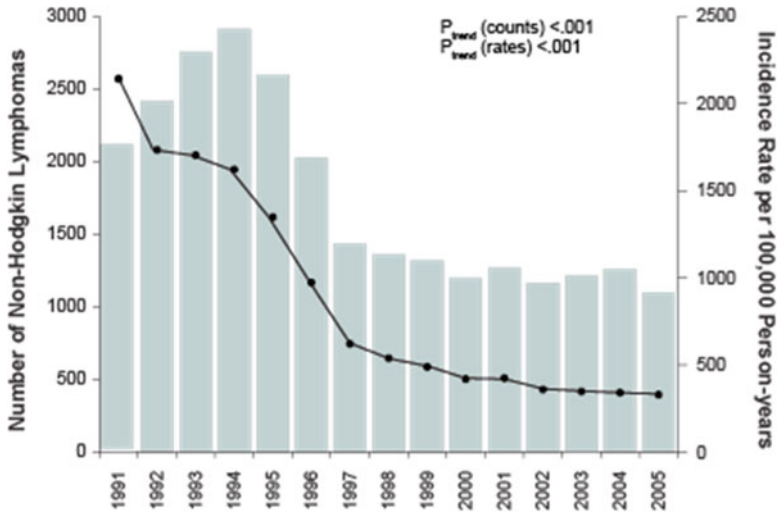


Fig. 2.3 Cancer burden of non-Hodgkin lymphoma among people living with AIDS in the USA during 1991–2005. *Bars* depict estimated counts (i.e., number of cancers) and *points connected by lines* depict the incidence rates standardized to the 2,000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided P values were calculated using the χ^2 test. Shiels MS, et al., Cancer Burden in the HIV-Infected Population in the United States. *J Natl Cancer Inst.* 2011;103(9):753–62, by permission of Oxford University Press

population (Engels et al. 2006). In several recent studies in the USA and Europe, NHL has emerged as the most common AIDS-associated malignancy. For example, in a record linkage study that evaluated the cumulative incidence of all cancers across the pre- and post-HAART eras, NHL surpassed KS as the most prevalent cancer in the post-HAART era (Simard et al. 2011). One risk factor in the post-HAART era driving this increase is a larger and aging AIDS population. The AIDS population has grown fourfold and is comprised of a higher proportion of individuals aged 40 years or older (Shiels et al. 2011). For those on HAART, older age (45 years+) is independently associated with a threefold increased risk of NHL (Polesel et al. 2008). Cases currently present with the same stages of disease as seen early in the epidemic, but they are older, less likely to have a prior AIDS diagnosis, and have a higher CD4+ T cell count at NHL diagnosis. As a result, current epidemiologic studies have focused less on markers of immune suppression and more on the molecular markers of pathogenesis to better understand risk factors in the post-HAART era.

Studies of archived pre-lymphoma samples from the MACS document that several markers of immune function are altered years before AIDS-associated lymphoma development. CXCL13 (a chemokine promoting B-cell chemotaxis) is significantly elevated particularly among EBV-negative compared to EBV-positive cases (Husain et al. 2010). CD23 (a B-cell stimulatory factor), IgE, IL6, CD27, and IL10 as well as the IL10 promoter 592C/C genotype are all elevated a year or more before lymphoma development compared to age and immune status matched

controls, demonstrating underlying markers of immune activation associated with future risk for HIV-associated lymphoma (Breen et al. 2011). An emerging risk factor in the post-HAART era is HIV viral replication as measured by cumulative or intermittent viremia (linked to treatment interruption) (Silverberg et al. 2007; Zoufaly 2009). Recent epidemiologic studies have found that HIV may upregulate activation-induced cytidine deaminase (AID) prior to NHL diagnosis. AID's normal function is to promote hypermutation of immunoglobulin genes associated with increasing affinity of the antibody during normal development of memory B cells and to promote class switching of antibody isotypes (i.e., IgM to IgG). The genetic modifications induced by AID sometimes lead to mistakes, such as chromosomal translocations or point mutations in immunoglobulin and/or oncogenes. The chromosomal translocations of the c-MYC gene common in HIV-associated Burkitt's lymphoma may be related to this upregulation of AID. Other early genetic modifications in HIV-related lymphomas include alterations of the BCL-6, a transcription repressor gene and point mutations or deletions in proto-oncogenes (Ras) and tumor suppressor genes (P53) (Carbone 2003). The decreased functionality of EBV-specific CD4+ and CD8+ T lymphocyte cells affects the cell-mediated responses necessary to control reactivation and replication of EBV-associated lymphomas. Any combination of these risk factors may have a multiplicative effect on developing NHL. While the pattern of HIV-associated lymphomas has changed in the post-HAART era (Fig. 2.3), there remains the paradox of emerging lymphoma risk particularly for some histological types not previously linked to HIV, such as certain T-cell lymphomas. In summary, lymphoma remains a major cause of mortality among HIV-infected patients even in the HAART era.

2.5 Epidemiology of Cervical Cancer Before and After HAART

Invasive cervical cancer occurring in HIV-infected women was added as an AIDS-defining condition in 1993. Its inclusion at the time was somewhat controversial, as the incidence of cervical cancer was not substantially increased in AIDS patients. However, the increase in cervical cancer in HIV-infected patients has since become more apparent. It takes approximately 10–15 years for a cervical abnormality to become invasive and during those years it progresses through stages of cervical intraepithelial neoplasia (CIN 1,2,3). The benefit of HAART in delaying the progression of HPV disease in HIV-infected women remains unclear. As seen in Fig. 2.4, the pattern of HIV-associated cervical cancer differs from the patterns for KS and NHL where in the pre-HAART era, rates were exceptionally high and declined after the introduction of HAART. In the case of HIV-associated cervical cancer the initially high incidence rate in the early 1990s may be attributed to a lack of regular screening and management of abnormal pap smears in HIV-infected women. As screening and treatment of precursor lesions improved, the incidence rate stabilized. HIV-infected women compared to the general population maintained

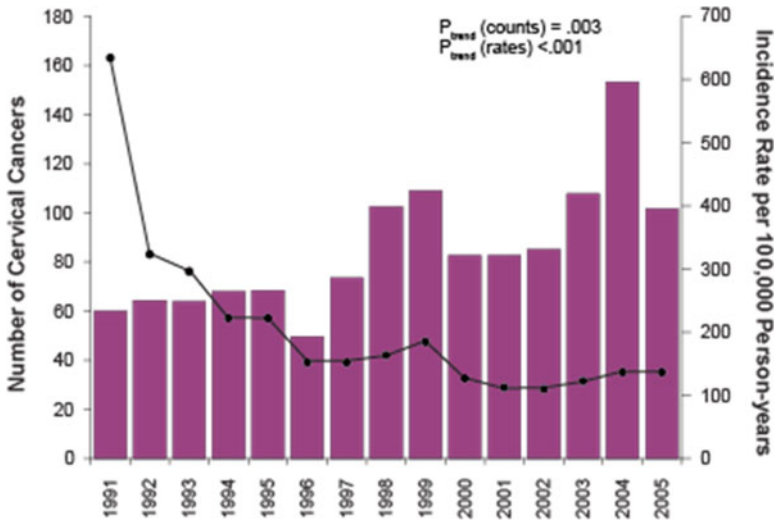


Fig. 2.4 Cancer burden of cervical cancer among people living with AIDS in the USA during 1991–2005. *Bars* depict estimated counts (i.e., number of cancers) and *points connected by lines* depict the incidence rates standardized to the 2,000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided P values were calculated using the χ^2 test. Shiels MS, et al., Cancer Burden in the HIV-Infected Population in the United States. *J Natl Cancer Inst.* 2011;103(9):753–62, by permission of Oxford University Press

a similar risk of cervical cancer through the introduction of HAART (1990–1995, SIR:4.2; 1996–2002, SIR:5.3) (Engels et al. 2006). The 5-year cumulative incidence of cervical cancer in the post-HAART era (0.64 %, 1996–2006) is similar to the pre-HAART era (0.63 %, 1980–1989; 0.73 %, 1990–1995) among those living with AIDS (Simard et al. 2011). Additionally, a collaborative study of 23 prospective studies from North America, Europe, and Australia found no change in the incidence of cervical cancer in the post-HAART era (International Collaboration on HIV and Cancer 2000). HAART appears to have had little or no impact on the incidence of cervical cancer so far and HIV-infected women remain at an elevated risk of developing the disease. However, it is possible that HAART may in the future be found to have effects on cervical cancer after a number of years.

For HIV-infected women who do develop cervical cancer, the disease is more aggressive, develops at younger age with more advanced disease that relapses after treatment (Pantanowitz and Michelow 2010). AIDS-defining cervical cancer progresses more rapidly and has a worse median survival compared to cervical cancers among HIV-negative women (Bower et al. 2006). The aggressive nature of cervical cancer in HIV-infected individuals would suggest that HIV-related immunosuppression may play a role in disease progression. However, HAART has had little impact on the incidence or progression rates of cervical lesions (Bratcher et al. 2010). Declining levels of CD4+ counts have not been shown to be a strong risk factor for disease progression. This is further supported by the observation that there is no difference in severity of neoplasia in women with asymptomatic HIV as com-

pared to women with AIDS (Clarke and Chetty 2002). It is possible that oncogenic changes that result in genetically unstable precancerous lesions determine progression rates independent of any restored immunity from HAART. There is also the possibility that the inconsistent findings in the prior research have been biased by the variability in cervical detection methods, follow-up time, duration of HAART, and small numbers of incident cases of cervical cancer.

The strongest risk factor for cervical cancer is persistent infection of high-risk types of the sexually transmitted virus, human papillomavirus (HPV). HPV is comprised of at least 40 different genotypes that infect the genital tract, 15 of which are considered high oncogenic risk. Genotypes HPV 16 and HPV 18 carry the highest risk and account for nearly 70 % of cervical cancers in the USA. HPV is highly transmissible particularly among younger women at sexual debut where an immunologically naïve host first experiences viral exposure. Risk factors associated with HPV acquisition include lifetime number of sexual partners, frequency of sex, partner's sexual history and behavior, parity, hormonal contraception, smoking, HIV, and other sexually transmitted infections. For most women, nearly 90 % of the infections are cleared by cell-mediated immunity within 2 years. For those co-infected with HIV, the course of HPV disease differs significantly.

HIV-infected women have a higher incidence, prevalence and number of concurrent HPV infections than HIV-negative women, and this is compounded by the sexual risk factors shared between HIV and HPV. Cervical HPV infection persists longer in HIV-infected women and has a higher probability of progressing from low to high-grade lesions. The regression rates of low grade cervical lesions decrease from 60 % in uninfected women to 27 % in HIV-infected women (Clarke and Chetty 2002). The burden of HPV infections increases as CD4 counts decline and HIV-1 viral loads increase. It is believed that selective depletion of effective CD4+ T cells results in poor responses by local CD8+ T cells in promoting clearance or regression of HPV (Clarke and Chetty 2002). A decrease in Langerhans cells in the cervical epithelium where HPV resides results in fewer numbers of antigen presenting cells needed to activate a cell-mediated response (Clarke and Chetty 2002). HIV may also release viral proteins, such as Tat, in the local environment that can enter cells and interfere with repair of DNA double strand breaks resulting in mutations and genetic instability (Nunnari et al. 2008). Tat may also activate gene transcription which may not be specific to the host or virus. Tat has been found to increase expression of early HPV genes that promote cell cycle progression (Clarke and Chetty 2002). Further studies of novel cofactors, such as HIV viral proteins, are needed to understand malignant transformation and development of cervical cancer. Any restored immunity from HAART may be too late depending on when therapy is initiated relative to the oncogenic events occurring with HPV.

Central to HPV's oncogenic potential are two viral gene products viral proteins termed E6 and E7 that increase cell proliferation, immortalization, and transformation. The E6 protein, particularly from HPV 16 and HPV 18, is efficient at binding the tumor suppressor protein, p53 leading to degradation. Loss of p53 prevents DNA repair and apoptosis and allows cell cycle progression regardless of any DNA damage. The E6 protein also increases telomerase activity and promotes cell immortalization. The E7 protein binds and inactivates another tumor suppressor,

retinoblastoma gene protein (pRB), resulting in activation of gene transcription and cell cycle progression. Unlike low risk HPV types that are not associated with pre-cancerous lesions, high-risk types are more likely to integrate HPV's episomal chromosome into the host DNA. This disrupts a regulatory gene, viral E2, resulting in over expression of E6 and E7 proteins. Viral integration confers an advantage of cell cycle progression, but it is not in itself sufficient for malignant transformation. The majority of invasive cancers, particularly for HPV 18, have integrated HPV genomes, but there are still a proportion of invasive cervical cancers with episomal genomes. Recently, HPV DNA methylation has been described as a potential biomarker that may be able to distinguish the HPV infections that will progress to precancerous lesions (Clarke et al. 2012). HPV has conserved sites of CpG that when methylated by the host cell's DNA methyltransferase may, by mechanisms that are not completely understood, promote pathogenesis. Increased methylation in the capsid genes, L1 and L2, has been associated with increased risk of CIN2+ lesions (Clarke et al. 2012). However, methylation of the promoter and enhancer regions upstream of E6 are mixed and further studies are needed (Clarke et al. 2012). As more studies explore the epigenetic changes in precancerous lesions, the role of HIV and the host's genetic background in enhancing HPV infection will be better understood. In summary, HIV is a strong risk factor for more aggressive cases of cervical cancer, but widespread use of HAART so far appears to have little effect on the incidence, progression, or mortality rates of cervical cancer.

2.6 Conclusion

Most studies evaluating the changes in morbidity and mortality of AIDS-defining malignancies across calendar time rely on record linkage studies. This is an effective way to evaluate the cumulative effect of changing treatment strategies on cancer risk, given the power of the large sample sizes. A number of studies have shown that HAART on a population level has significantly decreased the rates of KS and NHL but has had little impact on cervical cancer. However, in part because the AIDS population is increasing and ageing, and fewer patients are dying of other manifestations of AIDS, cancer is increasing as a cause of death in the USA among HIV-infected individuals. Further studies that evaluate HAART on the level of the individual are needed to identify molecular factors involved with the pathogenesis of these different malignancies. More specifically, studies need to evaluate the role of HIV and its viral proteins in driving lytic replication in KS, somatic hypermutations and chromosomal translocations in NHL, or early gene expression in cervical cancer. A common theme across all these malignancies is that they often present with more aggressive cases during HIV infection. Therefore, cohort studies that dive deeper into the molecular interactions will offer new insights into the continued burden of AIDS-defining malignancies and potentially lead to new therapies and prevention measures in the current era of HAART.

References

- Bower M, Palmieri C, Dhillon T. AIDS-related malignancies: changing epidemiology and the impact of highly active antiretroviral therapy. *Curr Opin Infect Dis.* 2006;19:14–9.
- Bratcher LF, Sahasrabudde VV. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. *Infect Agents Cancer.* 2010;5:8.
- Breen EC, Hussain SK, Magpantay L, Jacobson LP, Detels R, Rabkin CS, Kaslow RA, Variakojis D, Bream JH, Rinaldo CR, Ambinder RF, Martinez-Maza O. B-cell stimulatory cytokines and markers of immune activation are elevated several years prior to the diagnosis of systemic AIDS-associated non-Hodgkin B-cell lymphoma. *Cancer Epidemiol Biomarkers Prev.* 2011;20(7):1303–14.
- Carbone A. Emerging pathways in the development of AIDS-related lymphomas. *Lancet Oncol.* 2003;4:22–9.
- Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep.* 1992;41(RR-17):1–19.
- Clarke B, Chetty R. Postmodern cancer: the role of human immunodeficiency virus in uterine cervical cancer. *Mol Pathol.* 2002;55(1):19–24.
- Clarke MA, Wentzensen N, Mirabello L, Ghosh A, Wacholder S, Harari A, Lorincz AT, Schiffman M, Burk RD. Human papillomavirus DNA methylation as a potential biomarker for cervical cancer. *Cancer Epidemiol Biomarkers Prev.* 2012 [October 3; Epub ahead of print].
- Elton MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J Natl Cancer Inst.* 2002;94(16):1204–10.
- Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ, for the HIV/AIDS Cancer Match Study. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS.* 2006;20(12):1645–54.
- Franceschi S, Dal Maso L, Rickenbach M, Polesel J, Hirschel B, Cavassini M, Bordoni A, Elzi L, Ess S, Jundt G, Mueller N, Clifford GM, the Swiss HIV Cohort Study. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *Br J Cancer.* 2008;99:800–4.
- Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, Bouchardy C, Dehler S, Jundt G, Ess S, Bordoni A, Konzelmann I, Frick H, Dal Maso L, Elzi L, Furrer H, Calmy A, cavassini M, Ledergerber B, Keiser O, the Swiss HIV Cohort Study. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer.* 2010;103:416–22.
- Hamilton-Dutoit SJ, Pallesen G, Franzmann MB, Karkov J, Black F, Skinhoj P, Pedersen C. AIDS-related lymphoma. Histopathology, immunophenotype, and association with Epstein-Barr virus as demonstrated by in situ nucleic acid hybridization. *Am J Pathol.* 1991;138(1):149–63.
- Husain S, Widney D, Jacobson L, Breen E, Levine A, Detels R, Zhang Z, Martínez-Maza O. Elevated serum levels of CXCL13 precede HIV-associated non-Hodgkin's lymphoma. *Infect Agents Cancer.* 2010;5(Suppl. 1) (A24).
- International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst.* 2000;92(22):1823–30.
- Levine AM. AIDS-related malignancies: the emerging epidemic. *J Natl Cancer Inst.* 1993;85(17):1382–97.
- Mbulaiteye SM, Parkin DM, Rabkin CS. Epidemiology of AIDS-related malignancies an international perspective. *Hematol Oncol Clin N Am.* 2003;17:673–96.
- Nunnari G, Smith JA, Daniel R. HIV-1 Tat and AIDS-associated cancer: targeting the cellular anti-cancer barrier? *J Exp Clin Care Res.* 2008;27:3.

- Pantanowitz L, Michelow P. Review of human immunodeficiency virus (HIV) and squamous lesions of the uterine cervix. *Diagn Cytopathol.* 2010;39(1):65–72.
- Polesel J, Clifford GM, Rickenbach M, Dal Maso L, Battegay M, Bouchardy C, Furrer H, Hasse B, Levi F, Probst-Hensch NM, Schmid P, Franceschi S, the Swiss HIV Cohort Study. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS.* 2008;22:301–6.
- Seaberg EC, Wiley D, Martinez-Maza O, Chmiel JS, Kingsley L, Tang Y, Margolick JB, Jacobson LP. Cancer Incidence in the Multicenter AIDS Cohort Study before and during the HAART era. *Cancer.* 2010;116:5507–16.
- Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, Bhatia K, Uldrick TS, Yarchoan R, Goedert JJ, Engels EA. Cancer Burden in the HIV-infected population in the United States. *J Natl Cancer Inst.* 2011;103:753–62.
- Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, Hidalgo J, Lourtou L, Neaton JD, Tambussi G, Abrams DI. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS.* 2007;21:1957–63.
- Simard EP, et al. Cancer as a cause of death among people with AIDS in the United States. *Clin Infect Dis.* 2010;51(8):957–62.
- Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. *Cancer.* 2011;117:1089–96.
- Spagnuolo V, Galli L, Salpietro S, Gianotti N, Guffanti M, Cossarini F, Bigoloni A, Cinque P, Bossolasco S, Travi G, Fumagalli L, Lazzarin A, Castagna A. Ten-year survival among HIV-1 infected subjects with AIDS or non-AIDS-defining malignancies. *Int J Cancer.* 2012;130:2990–6.
- Zoufaly A, Stellbrink H-J, an der Heiden M, Kollan C, Hoffmann C, van Lunzen J, Hamouda O, the ClinSurv Study Group. Cumulative HIV viremia during Highly Active Antiretroviral Therapy is a strong predictor of AIDS-Related Lymphoma. *J Infect Dis.* 2009;200:79–87.

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