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EDITORIAL

HIV-associated malignancies at 40: much accomplished but much to do

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Abstract: The report in 1981 of a cluster of cases of Kaposi sarcoma (KS) in homosexual men in New York and California was one of the earliest harbingers of the AIDS pandemic, and association of cancer with HIV/AIDS has been one of the key features of this disease since. Looking back at year 40, the development of anti-retroviral therapy markedly reduced the incidence of AIDS-related cancers that occur at low CD4 counts, and this has been one of the most impressive advances in cancer prevention over the past half-century. There have also been advances in prevention and treatment of various HIV-associated tumors. However, as AIDS patients are living longer, there has been an increase in other cancers. Cancer continues to be one of the most frequent causes of death in persons living with HIV, and further basic, translational, clinical, and epidemiologic research in this area is urgently needed.

***Keywords*:** HIV, AIDS, Kaposi sarcoma, KSHV, PLWH

In July, 1981 the United States Centers for Disease Control reported a cluster of cases of Kaposi sarcoma (KS) in 26 homosexual men in New York and California (*1*). This report, along with another from the previous month describing 6 cases of community-acquired *Pneumocystis carinii* pneumonia were the first indications of the worldwide AIDS pandemic, which has since killed more than 36 million people worldwide. It soon became evident that this new immunodeficiency disorder, which was by 1984 shown to be caused by a novel retrovirus, human immunodeficiency virus (HIV), was associated with a marked increase in certain tumors, especially KS and high-grade B cell lymphomas, but not others. KS had previously been an extremely rare skin tumor in the Unites States, and its particular association with HIV/AIDS in gay men was initially quite puzzling. However, in 1994, the team of Patrick Moore and Yuan Chang showed that KS was caused by a novel gammaherpesvirus, which they named Kaposi sarcoma-associated herpesvirus (KSHV) and is also referred to as human herpesvirus-8 (HHV-8) (*2*). With this discovery, it became clear that most of the tumors whose incidence is increased in HIV/AIDS are caused by oncogenic tumor viruses, especially KSHV, Epstein Barr virus (EBV), and human papillomavirus (HPV) (*3*). We now know that KSHV is excreted in saliva and that the marked association between KS and AIDS was because of an otherwise silent epidemic of KSHV in gay men that was occurring at the same time as the HIV pandemic.

For some time after its recognition as a new disease, AIDS was almost always a death sentence; patients usually died within a couple of years, and a high percentage of these deaths were from AIDS-associated cancers. The first breakthrough came with the development of the initial antiretroviral drugs: AZT (zidovudine) and other nucleoside reverse transcriptase inhibitors (*4,5*). These increased the CD4 counts and significantly increased the survival of patients with AIDS, especially when used in combination. In addition, they reduced the incidence of HIV-associated malignancies. However, resistance to these early antiretrovirals often developed. The subsequent development and widespread use of HIV protease inhibitors starting around 1996 enabled the advent of 3-drug regimens which could essentially completely thwart HIV replication and changed AIDS into a chronic manageable disease. In addition, combination antiretroviral therapy (ART) markedly reduced the incidence of AIDS-related tumors that occur at low CD4 counts (Table 1), and in fact this has been one of the most impressive recent advances in cancer prevention in the past 50 years (*6*). Along with this, we have seen marked advances in the treatment of HIV-associated cancers. These advances have in part been enabled by the development of new anti-cancer drugs and regimens, and in part by the immune restoration caused by ART, which has enabled the use of full-dose therapies used in the general population. In particular, there have been dramatic improvements in the survival of PLWH with high-grade B cell lymphomas, with KS, and with a form of multicentric Castleman disease caused by KSHV (*3*).

At the same time, along with their increased longevity, PLWH are experiencing more cancers that

Table 1. Estimated numbers of selected cancers in people living with AIDS in the United States in different time periods

Association	Cancer	1991-1995	1996-2000	2001-2005
Associated with low-CD4 counts	Kaposi sarcoma	21,483	5,727	3,827
	Non-Hodgkin lymphoma	12,778	7,292	5,968
Some immunologic association	Cervical carcinoma	327	419	530
	Anal cancer	206	770	1,564
	Hodgkin lymphoma	426	682	897
	Lung cancer	875	1,383	1,882
No immunologic association	Colon cancer	108	230	438

Estimated numbers of cancers in people living with AIDS in the United States in different time periods: pre-three drug antiretroviral therapy (1991-1995); early post three-drug therapy (1996-2000); and later post three-drug therapy (2001-2005). From Shiels *et al*., (*6*).

are associated with advancing age (*6*). These include increases in certain other HIV-associated tumors that are not strongly linked to low CD4 counts, such as anal cancer or lung cancer (Table 1). In addition, along with the increasing number of older patients with HIV infection, there are increases in other common cancers that are not linked to immune defects in this population, such as prostate cancer or breast cancer. And, we continue to see severe cases of KS and other AIDS-related tumors associated with significant immunosuppression among patients who are not diagnosed with HIV until late in the course of infection. Cancer is now one of the most frequent causes of death in people living with HIV (PLWH) in developed nations. Moreover, HIV-associated malignancies are a major health problem in sub-Saharan Africa and other resource-limited regions; in some countries in sub-Saharan Africa, KS is the most common tumor overall in men (*7*). And in resource rich countries, like the United States, KS and other HIV-associated malignancies disproportionately affect individuals experiencing health disparities (*8*).

So while much progress has been made, there is much to do.

The most important task of course is to end the HIV/AIDS epidemic. Development of an effective HIV vaccine would help greatly, but this has so far been an elusive goal. Meanwhile, implementation of strategies including safer sex education, testing in high-risk settings and pre-exposure prophylaxis for those at risk can substantially reduce HIV transmission. Also, ensuring prompt initiation of HIV therapy and continuity of HIV care to support adherence will result in viral suppression, leading to the reduced sexual transmission of HIV. With regard to HIV-associated and other malignancies in PLWH, prevention is also essential. As noted, treatment of HIV with ART can dramatically reduce the incidence of tumors associated with profound immunosuppression. Appropriate screening for other cancers associated with advancing age and exposure to oncogenic viruses will be pivotal. Cervical cancer, caused by HPV and preceded by precancerous lesions, can be prevented by screening but this can be challenging in resource-poor regions; it will be important to optimize screening strategies in these regions and implement their use. While anal cancer is also preceded by precancerous lesions, it is unclear if treating these lesions is an effective strategy; the ANCHOR (Anal Cancer HSIL Outcomes Research Study) being conducted in the U.S. AIDS Malignancy Consortium is addressing this question. Lung cancer is now the most common cause of cancer-related death in PLWH receiving ART in the United States (*9*), and cigarette smoking prevention and cessation are among the most important prevention strategies. Studying cancer screening and prevention strategies in PLWH in other cancers increasing in incidence, such as hepatocellular carcinoma is essential. Vaccination strategies, particularly for HPV and hepatitis B, have also been shown to markedly reduce cancers caused by these viruses. The HPV vaccine has been shown to substantially reduce the incidence of cervical cancer when widely administered before sexual debut (*10*). And if effective vaccines against EBV and KSHV could be developed, we could eradicate the cancers caused by these gammaherpesviruses.

There is still much we do not know about the pathogenesis of HIV-associated cancers, and it is essential that we continue to pursue knowledge in this area through basic and translational research. This research can then inform advances in therapy of HIV-associated and other tumors developing in PLWH. While we have made great strides in the treatment of certain HIV-associated tumors, others such as primary effusion lymphoma, advanced anal carcinoma, and lung cancer, still carry a relatively poor prognosis in this population, and improved therapies are urgently needed. One promising approach is the development of specific therapies targeted at cellular mutations and/or virally-encoded genes that drive cancer development. Also, one of the most exciting advances in cancer treatment in recent years is checkpoint inhibitors and other immune therapies. We now know that checkpoint therapy is safe and can be effective in PLWH (*11*), and it will be important to continue to investigate this modality and other approaches to harness the patient's immune

system to fight HIV-associated malignancies. In this regard, PLWH are increasingly developing common tumors such as colon, breast, and prostate cancer, and it will be important to make cancer clinical trials open to PLWH whenever possible. And since the vast majority of PLWH now live in resource-limited regions, it will be important to develop treatment strategies that can be implemented in those regions.

Reflecting back after 40 years, it is remarkable how much progress has been made in HIV-associated malignancies, in part stemming from progress in HIV care and in part from progress in cancers themselves. At the same time, cancer continues to be one of the most common causes of death in PLWH, and there is much work to do.

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