DEAR READER

Cancer has been associated with AIDS before the human immunodeficiency virus was even identified. The telltale purple-brown lesions of Kaposi's sarcoma (KS) were one of the characteristic signs of an epidemic coming into its own. In the very early days of AIDS, many patients with nowhere to turn were being referred to cancer centers for care only to find out that (as with the rest of the general medical community) there was great fear, and many clinicians were reluctant to go anywhere near them. As an understanding of HIV and AIDS grew, so did the realization that a weakened immune system allowed opportunistic infections to take over, eventually leading to death.

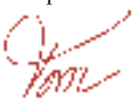
But why cancer? Until AIDS came on the scene, KS was a relatively rare cancer that was endemic in certain populations, such as older men of Mediterranean descent. Indeed, a great deal of interest was generated in finding out why this particular cancer was associated with AIDS in many patients. In the mid-1990s, the discovery of Kaposi's sarcoma-associated herpesvirus (or human herpesvirus 8) in patients with AIDS provided an answer. That virus, normally suppressed by a healthy immune system, can be sexually transmitted and can cause cancer under biological conditions of immunosuppression. This scenario is similar to what happens with invasive cervical cancer, another AIDS-defining cancer, with the viral agent being human papillomavirus. (Of course, cervical cancer is a risk for all women, but even more so for women with HIV infection.) Another example is non-Hodgkin's lymphoma, which is associated with Epstein-Barr virus (the virus that causes mononucleosis or the "kissing disease"). In fact, all AIDS-defining cancers are caused by or strongly associated with viruses.

The connection between viruses, the immune system, and cancer has been better explored and defined since the discovery of HIV. But improved understanding of immunity and virology has led to even more questions. In addition, antiretroviral therapy has changed the landscape of HIV and cancer: severe immunosuppression is not necessarily the only key factor that allows AIDS-defining cancers to emerge. The risks of cancer transcend whether or not a patient has a certain number of CD4 T cells. People living with HIV are surviving on treatment, but getting a wider variety of cancers at different rates than in the uninfected population. Lung, testicular, and anal cancers are some of the new malignancies being seen in the HIV-infected population with growing frequency. Is this a product of survival with incomplete immune restoration? If so, what can be done to improve therapy for HIV? In the meantime, how are such cancers best treated in the context of HIV? Only time and fervent research will provide answers.

This issue of RI*TA!* explores the latest epidemiological data on HIV/AIDS and cancer, the mechanisms of pathogenesis behind some of these malignancies, current philosophies of treatment, and available resources for research. But there are growing challenges in this important area of HIV research and treatment. In the current economy, with spending cuts in research as well as in public dollars to fund medications and treatment for those in need, a crisis is looming. Because immune dysfunction is a common thread between HIV and cancer, research on HIV-associated malignancies must remain a priority.

Cancer is a devastating disease that has plagued humankind for far longer than HIV/AIDS. Yet, where these diseases overlap has remained a fruitful field of endeavor for basic science and clinical research. May cures be found on the fronts of both diseases in the years to come.

Very truly yours,
The Center for AIDS:
Hope & Remembrance Project



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Cancer in the HIV-infected population

By Jennifer Newcomb-Fernandez, PhD

Cancer is a significant cause of mortality and morbidity in people infected with HIV;[1] in fact 30% to 40% will develop a malignancy during their lifetime.[2] The majority of cancers affecting HIV-positive people are those established as AIDS-defining: Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer.[3,4] However, other types of cancer also appear to be more common among those infected with HIV. While not classified as AIDS-defining, these malignancies are affecting the HIV/AIDS community greatly and have been referred to as "AIDS-associated malignancies"[1,5] or "opportunistic" cancers.[2] Analyses have revealed a 2- to 3-fold increase in overall risk of developing these cancers.[3,5,6] The introduction of highly active antiretroviral therapy (HAART) has resulted in decreased mortality and morbidity,[7] and the majority of people in developed countries infected with HIV are living with only mild to moderate immunosuppression because of wide access to antiretroviral therapy.[8] However, has the widespread use of these medications altered the incidence of cancer or perhaps even increased the prevalence of some types of cancer in this population? This article will present an overview of AIDS-defining malignancies and other malignancies that are prevalent in the HIV-positive population. In addition, the effect of HAART on the incidence of these malignancies will be discussed.

AIDS-DEFINING CANCERS

Kaposi's sarcoma

In the HIV-negative population, Kaposi's sarcoma (KS) is a rare, typically indolent cancer that affects older people or those receiving immunosuppressants following an organ transplant.[2] People infected with HIV are 100 to 300 times more likely to have KS.[3,5,6,9] In the presence of HIV, KS is associated with human herpesvirus 8 (HHV-8, also referred to KSHV for KS-associated herpesvirus). While there is a strong correlation between seropositivity for HHV-8 and the populations likely to develop KS, there is no definitive proof that HHV-8 causes KS. The exact cause of AIDS-related KS is presently unknown and causes appear to be multiple.[2,10] The risk and severity of KS increase in the presence of low CD4 T cell counts,[6] and people with intact immune systems tend not to develop KS when infected with HHV-8.[10]

Studies have unequivocally demonstrated significant declines in the incidence of KS following the introduction of HAART.[1,2,4,11] Prior to the widespread use of HAART, KS was the most common malignancy in HIV-positive patients. In the early 1980's, KS was the AIDS-defining illness in approximately 30% of infected individuals; a value which later dropped to 10% to 15% in the late 1990s.[10] Furthermore, the incidence rates for KS are 5 times lower in HIV-positive patients who have received HAART compared to those patients who have not.[12] In San Francisco, deaths from KS significantly decreased from 15.6% of total AIDS deaths in 1994 to 7.1% in 1998.[13] A recent study demonstrated that HAART regimens containing protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI) are equally protective against developing KS. Presently, most patients who develop KS while taking HAART show evidence of virologic treatment failure.[11] Importantly, HAART may also have a pos-

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itive effect on treating established KS, especially in patients without visceral disease.[10]

Non-Hodgkin's lymphoma

The risk of non-Hodgkin's lymphoma (NHL, also referred to as AIDS-related lymphoma) is substantially increased in the HIV-infected population, with risks ranging from approximately 40 to 400 times that of the general population, depending on the specific study and the type of NHL, though most studies report rates of 100 to 200 fold.[2,3,5,6,9,14,15] NHL encompasses several types of lymphoma, including systemic NHL, primary central nervous system NHL (PCNSL, also referred to as primary brain lymphoma or cerebral lymphoma), and primary effusion lymphoma (PEL) or body cavity-based lymphoma, a rare and aggressive form of NHL.[10,14,16] Between 1982 and 1990, NHL incidence rates increased approximately 800% among men between the ages of 20 and 59 years old in San Francisco county.[17] Data also indicate that high-grade lymphoma is more prevalent in the HIV-positive community compared to low-grade lymphoma.[14] Many agree that the risk of developing NHL, particularly PCNSL,[6,18] increases with lower CD4 T cell counts[6,10] and further progression of HIV infection.[1] Moreover, NHL is more prevalent in HIV-positive women compared to high-risk HIV-negative women,[19] indicating that immunosuppression, rather than other risk factors, is associated with the increased incidence of NHL in the HIV-positive community.

No definitive conclusions can be drawn regarding the effect of HAART on the incidence of NHL; though it continues to be one of the most common malignancies afflicting those with HIV infection.[1,10,17] Some studies have demonstrated significant decreases in incidence of NHL following the introduction of HAART, whereby incidence rates decreased by almost half,[4] and patients receiving HAART experienced a 5-fold decrease in incidence compared to treatment-naïve patients.[12] However, other studies fail to show any substantial change, and even suggest modest increases in incidence.[13,14] Significant decreases have been detected for immunoblastic lymphoma in some studies,[4] but not others.[1] Incidence of Burkitt's lymphoma has not decreased[1] and one analysis even demonstrated an increase in incidence after the introduction of HAART, but this increase was not statistically significant.[4] The effect of HAART on the incidence of PEL is unknown because the disease is so rare.[16] Nevertheless, studies routinely show that incidence of PCNSL has decreased considerably following the introduction of HAART.[1,4,12,14] Administration of HAART has also been associated with longer survival in patients suffering from PCNSL.[18] Interestingly, patients with systemic NHL who received and responded to HAART were significantly more likely to achieve a complete response, suggesting that a patient's response to HAART may provide insight into their cancer prognosis.[15] Regardless, unlike for KS, there has not been a dramatic decrease in the number of cases of AIDS-related lymphoma following the introduction of HAART.

Invasive cervical cancer

Though invasive cervical cancer (ICC) is considered an AIDS-defining condition, the association between HIV and cervical cancer is somewhat inconsistent.[16,20,21] Some analyses report no increase in incidence that is coincident with the AIDS epidemic[16,20] and no correlation between immunosuppression and increased risk of developing the cancer.[6,16] Indeed, HIV-positive women with ICC tend to have higher CD4 T cell counts compared to HIV-positive patients with other malignancies.[20] Still, other studies report that HIV-positive women are approximately 5 to 9 times more likely to have ICC compared to seronegative women,[3,6,19] and this cancer accounts for 55% of AIDS-related malignancies in some settings.[22] Moreover, the clinical course becomes even more aggressive when CD4 T cell count is low.[23]

Human papillomavirus (HPV) is involved in almost all cases of cervical cancer, regardless of HIV status, and is strongly associated with cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesions (SIL), which are precursors to ICC.[20,24] Women infected with HIV are more likely to be co-infected with HPV,[25] possibly because of similar risk profiles and mode of transmission,[20] as well as interactions that could putatively result in immune dysfunction and abnormal cytokine expression and growth factor production.[16] Decreased CD4 T cell counts are associated with increased risk of acquiring HPV.[26,27] Further, HPV infection may predispose a person to HIV infection and facilitate progression of HIV.[20] Interestingly, level of viremia has not been associated with persistence of HPV.[27] While the relationship between HIV and ICC is not definitive, this is not the case for CIN and SIL. In fact, immunosuppression may more associated with cervical dysplasia.[24,27] In contrast to seronegative individuals whose low-grade lesions typically resolve without treatment,[28] lesions are more likely to progress and to recur after treatment in HIV-positive women.[20,21]

Most studies have assessed the impact of HAART on incidence and progression of precancerous cervical lesions. However, one large study reported no significant changes in incidence of ICC when rates were compared during the pre-HAART and post-HAART eras.[4] Data conflict regarding incidence of SIL and CIN, and HAART has not consistently been associated with improvement. Some studies have shown increased cytologic regression and decreased cytologic progression of these lesions,[29,30] while others have reported increased progression[27] or inconclusive results.[24] Moreover, HAART was not associated with decreased prevalence or persistence of HPV infection, but a significant reduction in the incidence of new cases of HPV-16 and HPV-18 (oncogenic types of HPV) was detected in HAART-treated women, suggesting that HAART may have an effect on acute HPV infection, but not on advanced infection.[27] Of note, women taking HAART who experienced disease regression had higher CD4 T cell counts, suggesting some level of immune restoration.[30]

NON-AIDS-DEFINING MALIGNANCIES

Hodgkin's disease

Currently, Hodgkin's disease (HD) is not considered an AIDS-defining cancer. However, those infected with HIV are 7.6 to 11.5 times more likely to have HD compared to the general population.[3,5,6,8,9,14] Some report that HD is the most common non-AIDS-defining malignancy among HIV-positive people;[2] however, other studies cite lung cancer as the most common.[6,13,19] Some researchers feel strongly that HD should be considered an AIDS-defining condition,[3] though this issue is controversial. While analyses have routinely demonstrated increased risk of HD in those infected with HIV,[3,5,6,8,9,14] an actual causal link between HIV and HD has not been established and studies assessing the effect of immunosuppression on incidence of HD are conflicting. A positive correlation between immunosuppression and increased incidence of HD has been demonstrated in some analyses,[3,8,9] but not others.[6] Additional evidence indicates that HD tends to occur early in HIV infection when CD4 T cell counts are higher and immune competence is still intact,[2] indicating that HD is not a critical event in the development of AIDS.

Few studies have looked at the effect of HAART on incidence of HD. However, those that have assessed this relationship reported no difference in rates either when comparing patients who had received HAART with treatment-naïve patients[31] or when comparing HD rates during the pre-HAART and post-HAART eras.[4]

Anal cancer

Similar to cervical cancer, anal cancer is strongly associated with HPV infection and the presence of precancerous anal lesions, which are referred to as squamous intraepithelial lesions (SIL) and anal intraepithelial neoplasia (AIN).[21,26] High-grade

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forms of these lesions tend to contain the oncogenic types of HPV, specifically HPV-16 and HPV-18.[23] Most studies demonstrate that those infected with HIV are 30 to 50 times more likely to have anal cancer,[3,5,6,8] with rates as high as 60 fold in HIV-positive men who are bisexual or homosexual.[32] Progression to high-grade dysplasia is increased in the presence of HIV infection,[16] and anal HPV infection and high-grade SIL (HSIL) are extremely common in bisexual and homosexual men, regardless of HIV serostatus.[26,33] Until recently, anal sex was assumed to be the mode of acquisition for anal HPV infection. However, when rates of HPV infection and SILs were compared in HIV-positive men with or without a history of bisexual or homosexual behavior, rates were high even in those men with no history of anal sex who contracted HIV through IV drug use.[32] These data suggest that anal HPV infection can be acquired through means other than anal intercourse in HIV-positive men. Moreover, 76% of HIV-positive women and 42% of high-risk HIV-negative women tested positive for anal HPV DNA.[25]

Presently, it is unclear whether prevalent risk factors, such as anal intercourse, a history of sexually transmitted diseases, or even heavy tobacco use are responsible for the increased incidence of anal cancer in the HIV-positive population. An alternative hypothesis is that HIV-induced immunosuppression results in the development of anal neoplasia and, consequently, anal cancer. Incidence of anal SIL is highest among the most immunosuppressed HIV-positive men.[26] Moreover, regression of lesions is associated with high CD4 T cell counts at the time of HAART initiation, and HIV-positive men who progress have the lowest CD4 T cell counts.[26] However, other analyses have failed to show a clear relationship between CD4 T cell counts and incidence of anal cancer.[6] In addition, one study revealed that incidence was significantly increased even during early HIV infection, suggesting that severe immunosuppression is not necessary for the development of anal cancer.[8]

The possible benefits of HAART on the incidence of anal cancer and precancerous lesions have not been conclusively demonstrated. The few studies that have examined this relationship suggest that HAART has not decreased the incidence or increased the regression of these lesions.[21,26] When rates during the pre-HAART and post-HAART eras were compared, no significant change in incidence of anal cancer was observed; however, researchers pointed out that there were too few cases from which to draw definitive conclusions.[4]

Lung cancer

People infected with HIV are 2.5 to 7.5 times more likely to develop lung cancer compared to HIV-negative people.[3,5,6,9] In fact, lung cancer was the most frequently observed non-AIDS-defining malignancy in several studies.[6,13,19] Lung cancer was the most common cause of death from a non-AIDS-defining malignancy in persons with AIDS in San Francisco between 1994 and 1998.[13] However, another study failed to demonstrate a significant increase in lung cancer incidence in the HIV-positive population.[8] Several studies have reported a positive correlation between rates of lung cancer and immune suppression.[3,9] Analyses of risk behavior have reported conflicting data: one study showed that HIV-positive patients with lung cancer smoked twice as many cigarettes as HIV-negative patients with lung cancer,[34] while another study that compared HIV-positive women to HIV-negative women with similar smoking histories showed a 2-fold increased incidence in the HIV-positive women.[19] Long-term cigarette exposure is typically lower in HIV-positive patients because they are usually diagnosed with lung cancer at an earlier age.[35] Before the introduction of HAART, rates of lung cancer were low, perhaps on account of early AIDS-related mortality. A recent analysis showed an almost 9-fold increase in lung cancer incidence following the introduction of HAART.[35]

Testicular germ cell tumors

Testicular cancer (also referred to as testicular germ cell tumors or GCTs) is the most common solid malignancy in men between the ages of 15 and 34 years in the general population.[36] Studies assessing cancer incidence demonstrate that HIV-positive men are 1.4 to 8.2 times more likely to develop testicular cancer,[3,5,6,9,23,37] though another study failed to show significantly increased incidence.[8] While no viral oncogene has been implicated in HIV-associated testicular cancer, viruses such as mumps orchitis, HPV, Epstein-Barr virus (EBV), and human endogenous retrovirus K10 are associated with testicular cancer in HIV-negative men and may be involved in development of testicular cancer in the HIV-positive population.[36,37] One large study reported a modest association between incidence of seminoma GCT and immunosuppression.[3] However, another analysis showed that HIV-positive patients with seminoma appeared to have preserved immune systems.[37] The effect of HAART on incidence rates has not been analyzed thoroughly, but one report showed no difference in incidence rates when comparing the pre-HAART and post-HAART eras.[37]

DISCUSSION

The cancer prognosis for people infected with HIV tends to be worse compared to seronegative cancer patients, regardless of the type of malignancy. Perhaps because of a suppressed immune system and impaired immune surveillance, malignancies take a more aggressive clinical course in those infected with HIV.[10,19,23,34] HIV-positive patients typically present with more advanced cancer at the time of diagnosis,[34] and the average age at diagnosis is usually younger in HIV-positive patients compared to seronegative patients;[38] this is particularly true with lung and testicular cancers.[34,37]

Potential causes of cancer in HIV/AIDS. Although it remains unclear whether HIV functions directly as an oncogenic agent, it putatively contributes to the development of malignancies through several mechanisms. Impaired immune surveillance, dysregulation of cytokine pathways and growth factor production, inability to combat genomic instability, chronic B cell stimulation, and imbalance between cellular proliferation and differentiation may all contribute to the prevalence of HIV/AIDS-associated malignancies.[2,6,10,13,14] AIDS-defining malignancies are associated with oncogenic viruses (EBV, HHV-8, and HPV). Uncontrolled viral infection may also play a causative role in many HIV/AIDS-associated cancers. Some researchers hypothesize that repeated exposure to viruses or other infectious organisms may be responsible for cancer development. Indeed, many of the malignancies prevalent in the HIV-positive community affect sites that are in contact with the outside environment (eg, cervix, lung, oral cavity, skin, and anus). The increased density of immune cells and coincident elevated concentration of HIV at these sites could lead to local compromised immune defenses and the subsequent development of malignancies at these sites.[38] Alternatively, risk factors present in the HIV-positive community, including multiple sexual partners, illicit drug use, and increased alcohol consumption and cigarette smoking, could account for the increased rates of these cancers. For example, compared to HIV-negative patients with cancer, more HIV-positive patients with cancer have a history of cigarette smoking and illicit drug use.[34,38] However, in one study assessing incidence of cancer in HIV-positive women and HIV-negative women with acknowledged HIV risk behavior, cancer was still significantly more prevalent in the HIV-positive women.[19]

The impact of HAART. Preliminary data suggest that with the exception of KS, HAART has not had a significant impact on cancer incidence in the HIV-positive population, though it may be premature to draw any definitive conclusions at this time. Widespread availability of HAART has only occurred within the last decade and many of the malignancies discussed require several years to develop. Because of HAART's effect on the incidence of KS,[1,2,4,11] one would expect malignancies that are associated with immunosuppression to

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undergo a robust decline in incidence following the widespread availability of HAART. Potentially, if immunosuppression is a key factor in the development of these tumors, immune restoration associated with HAART would slow tumor progression. Unfortunately, this has not been the case. For example, evidence suggests that NHL occurs more frequently in immunocompromised patients,[1,6,10] but HAART has not had a dramatic impact on NHL incidence, particularly systemic NHL.[1,4,12-14]

Some researchers have speculated that the extended survival afforded by HAART, in conjunction with incomplete immune restoration, may actually increase the incidence of some cancers.[26] Prolonged exposure to viral oncogenes, moderate immune suppression, and genomic instability could result in impaired immune surveillance and the subsequent development of tumors.[26,35,37] Given that scenario, the incidence of tumors associated with chronic moderate immune suppression would be expected to increase. In fact, the incidence of lung cancer appears to be increasing.[35] Another explanation could be that prior to the introduction of HAART, patients typically died of opportunistic infections or other HIV-related complications prior to developing a malignancy, some of which take years to develop. Presently, it is unclear whether HAART will ever provide full immune recovery in HIV-positive patients, a situation that may be necessary in order to decrease cancer incidence as a whole in this population. Many researchers speculate that cancer rates, specifically of lymphoma, will rise in areas with widespread availability to HAART,[17] though others disagree.[4] In summary, many of the large retrospective studies included in this overview used data from the late 1990s and early 2000s, and it will be interesting to see what future studies conclude.

Regardless of whether these cancers are directly related to HIV-induced immunosuppression, treating cancer in HIV-positive patients remains a challenge because of drug interactions, compounded side effects, and the potential effect of chemotherapy on CD4 T cell count and viral load.[36,37,39] Moreover, treatment compliance tends to be poor among HIV-positive patients with cancer,[36] perhaps because of the increased responsibility of taking drugs for both diseases. The question of whether to suspend HAART during chemotherapy depends on several factors, particularly the type and stage of malignancy and the status of HIV infection[40] (see page 19 in this issue for a complete discussion).

Other malignancies in the HIV-positive community. In addition to the cancers discussed in this article, the risk of developing a multitude of other cancers appears to be slightly increased in the HIV-positive

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Table. Other non-AIDS-defining cancers with increased incidence in the HIV-infected population

Leukemia[3,8,9]	Pharynx[3,9]	Pancreas[3]
*Multiple myeloma[3,5,8,9]	Esophagus[3,9]	Liver[1,3,8]
Skin cancer[3,5,9,23]	*Lip[3,8]	Kidney[3]
*Penile[3]	Tongue[9]	**Colorectal[9]
Vulva/Vagina[3]	Stomach[3,9]	Brain and CNS[3,5,9]
Leiomyosarcoma[3,23]	Larynx[3,9]	Heart[3]
		Angiosarcoma[5]

*associated with immunosuppression

** another study showed decreased incidence[8]

IMMUNE EVASION AND MODULATION: key strategies for viral persistence

Common sense tells us that viruses should be cleared from our bodies just like any other invading pathogen. However, many are not cleared entirely and are able to persist by establishing latent infection. In many cases, virus-host interactions have evolved over the millennia such that viruses reproduce, remain viable, and are transmitted, while host immune systems can contain infections and prevent severe illness or death. Examples of such viruses include herpesviruses and papillomaviruses. Herpesviruses that can establish latent and long-term infection in host humans include cytomegalovirus (CMV) or human herpesvirus 5 (HHV-5), Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8), and Epstein-Barr virus (EBV). The latter two viruses, along with certain forms of the human papillomavirus (HPV), are associated with the development of AIDS-defining cancers. These viruses avoid immune clearance using strategies such as modulating the expression and activity of major histocompatibility complex (MHC) proteins (which are involved in antigen presentation), preventing apoptosis of virally infected cells, suppressing the antiviral activity of host interferon, and interfering with cytotoxic lymphocytes (CTLs).

Many of the above activities are mediated by special viral proteins produced in infected cells. In some cases, viral proteins play other roles such as enabling viral genes to attach to cellular chromosomes during mitosis or inducing angiogenesis to ensure an enhanced blood supply to developing tumors. The possibility even exists that the immunomodulatory mechanisms used by one type of virus may actually enhance or benefit the activity or replication of other viruses. Many of these viruses (for example, HPV, CMV, and EBV) are quite common in the human population but do not always lead to the development of malignancies. Certainly, infection with HIV changes the playing field and an environment of immunosuppression may eventually tip the scale in favor of these other viruses, leading to an increased risk of cancer.

Of course, in theory, HIV is relatively new to the human immune system and a virus-host balance (such as that seen with, for example, a normal herpes infection in an otherwise healthy individual) has yet to evolve. This scenario would be difficult to envision for HIV (given the primary target of viral infection, the CD4 T cell) were it not for the insights afforded by studying long-term nonprogressors and others who have staved off disease progression in the absence of anti-HIV therapy. Nonetheless, research has shown that there is more to HIV than its ability to wipe out T cells and that HIV is associated with the development of a variety of malignancies, as discussed in this current issue. HIV has shown itself to be an elusive target, and it accomplishes this feat by using a variety of immune evasion and manipulation strategies, including several similar to those employed by other viruses as described above.

The more we come to understand viral mechanisms of immune evasion and manipulation, the better we will be able to treat the maladies and malignancies associated with chronic viral infections.

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community (see Table). In contrast, the incidence rates of certain types of cancer, such as prostate,[6,9] breast,[3,6,9] and bladder cancer,[9] appear to be decreased in the HIV-infected community, though a small case study reported a modestly increased incidence of prostate cancer in HIV-positive men.[41] Surprisingly, the rates of breast cancer in men may have increased to some extent, especially in IV drug users.[3] Reasons for the general decline in incidence of these specific cancers are not clear, but some speculate that immune suppression may reduce risk of these cancers.[3] Others hypothesize that this decrease is caused by increased AIDS-related mortality.[39] In particular, prostate cancer tends to affect older men.

Limitations of these analyses. The topic of AIDS-defining and HIV/AIDS-associated malignancies has been extensively investigated, and these studies have provided critical data. However, there are several limitations to these analyses. Many of the large retrospective studies rely on two distinct databases, cancer registries and AIDS registries, and the potential for incomplete data collection exists.[14,17] In addition, only the initial AIDS-defining illness is routinely included in HIV/AIDS registries, so subsequent malignancies may not be reported. Cancers that were previously not thought to be associated with HIV/AIDS may not have been recorded at the time of death (eg, HD or lung cancer). Moreover, since much information is collected via AIDS registries and death certificates, this data source will continue to dwindle as the use of HAART decreases disease progression to AIDS and deaths from AIDS.[17] Further, when studying rates of cancer in the HIV-positive population, many studies examine surrogate groups, such as unmarried men in San Francisco, assuming these men are homosexual. As a result, compiled relative risks could be underestimated since many of these men may not be HIV-positive.[14]

When studying the effects of HAART, many studies divide the data into cases from the pre-HAART and post-HAART eras, a method that may be flawed because some patients in the post-HAART era may not be taking HAART and others may not have responded to treatment. In fact, only 71% of patients diagnosed with AIDS-defining NHL in the post-HAART era actually received HAART.[15] Studies that assess cancer incidence in patients with or without a history of HAART administration may provide more accurate data, though a potential drawback would be the difficulty in extracting such information from large cohorts of HIV-positive people, which are necessary to draw any definitive conclusions.

As discussed in this overview, cancers not officially considered AIDS-defining are occurring with greater frequency in people with HIV, and evidence suggests that the clinical course of these cancers is more aggressive. Patients and doctors must be aware of this threat, the shift in the age group affected, and the very rapid progression that can occur. Finally, it is imperative that oncologists and HIV-treating physicians work together to effectively manage cancer, HIV infection, and any opportunistic infections.

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An overview of the biology and viral pathogenesis of lymphoproliferative disorders in HIV-infected patients

By Regis A. Vilchez, MD, and Janet S. Butel, PhD

Introduction

Immunodeficiency (whether congenital, iatrogenic, or caused by infection) increases the risk of some types of cancer, especially malignancies etiologically linked to DNA tumor viruses, such as herpesviruses and polyomavirus.[1-4] Indeed, immunosuppression associated with HIV infection substantially increases the risk of developing Kaposi's sarcoma and non-Hodgkin's lymphoma. These two malignancies and invasive cervical carcinoma are the only recognized AIDS-defining cancers.[5] Hodgkin's lymphoma was not included as an AIDS-defining illness by the Center for Disease Control and Prevention HIV classification system,[5] but data from several studies suggest that the risk of Hodgkin's lymphoma in persons with HIV infection is increased.[6-9]

The introduction of highly active antiretroviral therapy (HAART) and prophylaxis against opportunistic diseases has significantly improved the survival of patients with HIV infection.[10,11] HAART can cause a significant and sustained decrease in peripheral blood HIV RNA levels, as well as an increase in CD4 T cells.[12-15] However, the influence of this therapy on AIDS-related lymphoproliferative disorders is less clear.[16,17] Recent data from the United States and Western Europe have shown no significant decrease in the incidence of non-Hodgkin's and Hodgkin's lymphomas, in contrast to dramatic reductions in Kaposi's sarcoma among patients treated with HAART.[11,18-26] A meta-analysis of the incidence of cancers from selected cohorts[27] of HIV-infected patients from the periods of 1992 to 1996 and 1997 to 1999 by the International Collaboration on HIV and Cancer suggested a small decrease in systemic diffuse large cell lymphoma but no decreases in other types of non-Hodgkin's lymphoma. However, the analysis of lymphomas is limited by the lack of specific pathology information from some of the cohorts included in the meta-analysis.

While the goal of antiretroviral therapy is the suppression of HIV replication,[28,29] failure to accomplish this objective is common in clinical practice, occurring at a rate of 40% to 70%.[30-32] Also, data suggest that the continuing efficacy of present antiretroviral therapy may allow more HIV-infected patients to survive with long-term mild to moderate immunosuppression, thereby placing such patients at risk for the development of lymphoproliferative disorders such as Hodgkin's and non-Hodgkin's lymphomas. Indeed, recent data suggest that 23% to 50% of patients receiving HAART developed Hodgkin's and non-Hodgkin's lymphomas despite effective HIV suppression and high CD4 T cell counts.[25,26,33-36] These results substantiate that the development of lymphomas in HIV-infected individuals is a complex process not determined by HIV replication. In this review, we examine advances in understanding the biology and viral pathogenesis of lymphoproliferative disorders among HIV-infected patients.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is a common malignancy in HIV-infected patients and its incidence in that population may be increased up to 300 times.[9,12,13] NHL incidence increases markedly with progression of HIV infection, although association with the level of CD4 lymphopenia is less pronounced than with other opportunistic infections. All populations at risk for HIV are also at risk for

the development of lymphoma, in contrast to Kaposi's sarcoma, which is diagnosed primarily in homosexual or bisexual men. The NHL that occurs in HIV-infected patients can be divided into two categories: systemic and primary central nervous system lymphoma (see Table). The genetic alterations of systemic NHL among HIV-infected patients include activation of oncogenes by chromosomal translocations (ie, *c-myc* and *bcl-2*) and/or inactivation of tumor suppressor genes (ie, p53).[37] A recent analysis showed that, compared to HIV-negative cases, NHL among HIV-infected patients was more likely to be highly proliferative and to express p53.[36] These data suggest a different pathogenesis of NHL among HIV-infected patients as compared to uninfected patients.

Some NHL in HIV-infected patients has been attributed to deficient immune surveillance of oncogenic herpesviruses, such as Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8), or perhaps to chronic antigenic stimulation and defective immune regulation.[1,38] EBV is suspected of playing a major causative role in primary central nervous system (CNS) NHL in HIV-infected patients, as most of those tumors contain EBV DNA, but it is detected less frequently (<40%) in systemic NHL in HIV-infected patients[38] (see Table). EBV is found even less commonly in NHL from HIV-negative patients. HHV-8 is specifically associated with multicentric Castleman's disease and primary effusion lymphoma, which often occurs in a setting of profound immunosuppression.[38]

As EBV and HHV-8 are absent from many forms of NHL, other viral agents such as polyomavirus simian virus 40 (SV40) have been investigated. Early studies reported the detection of polyomavirus SV40 DNA sequences in NHL from HIV-infected and non-HIV-infected patients, but the small size of the study populations, the lack of screening for other tumor viruses, and the limited confirmation of the detected viral sequences made it difficult to assess whether SV40 was associated with NHL.[39,40] However, recent large and controlled studies demonstrated that SV40 tumor antigen (T-ag) DNA sequences were significantly associated with NHL in both HIV-infected and non-HIV-infected patients.[3,4,41] In addition, EBV was found to be associated with 39% of systemic NHL from HIV-infected patients and with only 15% from the HIV-negative group,[3] similar to rates reported previously.[38] Importantly, the observation of minimal instances of co-infection with SV40 and EBV and the lack of detection of SV40 in nonmalignant lymphoid samples and cancer control specimens suggest that SV40 may be contributing to the development of some NHL among HIV-infected patients.[3]

The lymphomagenic capacity of SV40 is well-established in laboratory animal models. In hamsters inoculated intravenously with SV40, lymphomas developed among 72% of the animals, compared to none in the control group.[42] The lymphomas were of B cell origin as they expressed cell surface antigen and their histology was consistent with diffuse large cell type.[43] An etiologic role for the virus in the development of lymphomas was supported because SV40 T-ag was expressed in all tumor cells, animals with tumors developed antibody against SV40 T-ag, and neutralization of SV40 with specific antibody before virus inoculation prevented lymphoma development.[42] SV40 oncogenesis is mediated in large part by the viral oncoprotein, T-ag, as a result of its binding and inactivation of tumor suppressor proteins in the p53 and pRb families.[1] The functional inactivation of these two important cell cycle control proteins stimulates host cells to proliferate. Other cellular effects may be mediated by SV40 in human B cells as well.[44,45] Further studies are needed to define the mechanisms of SV40 interactions with human lymphocytes.

Hodgkin's lymphoma

The association between HIV infection and the development of Hodgkin's lymphoma, which typically occurs in the age groups of patients most affected by HIV, has been slowly established because this

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malignancy is an uncommon cancer. An analysis[7] of AIDS and cancer registry data from diverse regions of the United States conducted between 1978 and 1996 showed that Hodgkin's lymphoma occurred in a statistically significant excess in HIV-infected patients (relative risk [RR] 11.5; 95% confidence interval [95% CI], 10.6–12.5). More importantly, that analysis indicated a particular association with Hodgkin's lymphoma subtypes of mixed cellularity (RR, 18.3; 95% CI, 15.9–20.9) and lymphocyte depletion (RR, 35.3; 95% CI, 24.7–48.8).

There are very few studies that have analyzed Hodgkin's lymphoma during the HAART era,[10,20,24] so assessing the incidence of this malignancy in HIV-infected patients since the introduction of HAART has been difficult. However, a recent investigation[26] showed that Hodgkin's lymphoma has a low incidence in HIV-infected patients receiving HAART (6.5 per 1,000 patients) and that no significant difference in the incidence of this malignancy was observed between patients receiving HAART and those naïve to antiretroviral therapy. The results further suggested that Hodgkin's lymphoma is an aggressive disease with unfavorable clinical outcome in HIV-infected patients.[26] Reports prior to the introduction of HAART described HIV-related Hodgkin's lymphoma as an atypical and more aggressive form of disease with unusual presentation and worse outcome compared with Hodgkin's lymphoma in patients with HIV-negative status.[6-9,12] Hodgkin's lymphoma in persons with HIV infection presented at an advanced stage, and commonly at extranodal sites. Mixed cellularity and lymphocyte depletion subtypes accounted for a greater proportion of the cases, and nodular sclerosing subtype for a lower proportion of cases, than in persons without HIV infection.[6-9,12] Recent data indicate that mixed cellularity and lymphocyte depletion subtypes continue to be the most frequent types of Hodgkin's lymphoma and that diffuse disease remains a common feature of this malignancy in the HAART era.[26] These clinical and histopathologic features of Hodgkin's lymphoma among HIV-infected patients may be the result of the alterations of CD4 T cells in this patient population.

In non-HIV-infected patients with Hodgkin's lymphoma, CD4 T cells predominate in the tumor microenvironment and may contribute, at least in part, to the modulation of the Hodgkin's lymphoma phenotype[46] and eventually to its clinical behavior.[47,48] In contrast, among patients with HIV infection, the tumor microenvironment reportedly lacks the typical high proportion of CD4 T cells that may keep tumor cells and tissues under control and is characterized by an unusually high proportion of malignant cells.[12,49] Indeed, studies both prior to the introduction of HAART and in patients receiving HAART indicate that Hodgkin's lymphoma tends to develop in patients with a median CD4 T cell count of 200 cells/mm^3.[6-9,12,26]

Immunodeficiency can play a negative role both in the clinical presentation and the outcome of HIV-infected patients with lymphoma.[26] A recent study compared the clinical features and prognosis of Hodgkin's lymphoma and NHL among HIV-infected patients.[50] The clinical presentation of these two lymphoproliferative disorders was similar, except for the decreased frequency of extranodal disease that was seen in patients with Hodgkin's lymphoma as compared to NHL (56% vs. 82%, $p=0.02$) and the increased frequency of bone marrow involvement in patients with Hodgkin's lymphoma as compared to NHL (50% vs. 20%, $p=0.01$). Complete remission and overall survival rates did not differ significantly, with estimated overall survival at 5 years of 24% in HIV-infected patients with Hodgkin's lymphoma and 23% in patients with NHL.

Data indicate that 50% of the patients with Hodgkin's lymphoma who were receiving HAART had detectable HIV RNA viral loads.[26] These findings support the hypothesis that factors promoting the development of lymphomas may not be related

to immune dysfunction or may be associated with processes not affected by HAART. Indeed, EBV is suspected of playing a causative role in Hodgkin's lymphoma: as many as 70% of Reed-Sternberg cells are EBV-positive in HIV-infected patients, whereas only about one-third of these malignancies in the general population are EBV-positive[26] (see Table). The precise role of EBV in Hodgkin's lymphoma among HIV-infected patients, however, requires further investigation.

Conclusion

Recent investigations suggest that Hodgkin's lymphoma and systemic NHL are significant causes of mortality among HIV-infected patients during the HAART era. As antiretroviral therapies improve the survival of HIV-infected patients, the risk of developing or dying from cancer may increase. Large and well-designed population-based studies will be needed to better define the spectrum of malignancies and the most effective strategies for screening and treatment in HIV-infected patients. In addition, further research is essential to define the role of DNA tumor viruses in the genesis of lymphoproliferative disorders among these patients.

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Table. Characteristics of non-Hodgkin's and Hodgkin's lymphoma in patients with HIV infection during the HAART era.

Characteristics	Systemic-NHL	Primary CNS-NHL	Hodgkin's Lymphoma	Other
Histology	Diffuse large B-cell and Burkitt's	Diffuse large B-cell		–
Median CD4 T cell count	~200 cells/mm^3	<50 cells/mm^3	~200 cells/mm^3	–
Incidence (per 1000 patients)	3.6 – 17	ND	6.5	–
EBV DNA in tumors	< 40%	~100%	~70%	–
SV40 DNA in tumors	0% – 40%	ND	< 10%	–
HHV-8 DNA in tumors	< 5%	0	0	Primary effusion lymphoma (100%) Castleman's disease (100%)

Abbreviations: NHL, non-Hodgkin's lymphoma; CNS, central nervous system; HAART, highly active antiretroviral therapy; EBV, Epstein-Barr virus; SV40, simian virus 40; HHV-8, human herpesvirus 8; ND, not determined.

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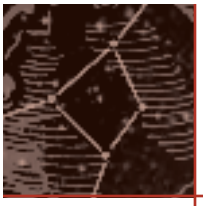

The use of antiretroviral therapy in patients undergoing treatment for HIV-related neoplastic disease

By Richard F. Little, MD, and Robert Yarchoan, MD

Introduction

Individuals with HIV infection and cancer are faced with two complex life-threatening diseases. Treatment of such complex illnesses is more straight-forward for the clinician when adequate evidence-based clinical guidelines are available. However, for many patients with AIDS-related (or "AIDS-defining") malignancies, there are no such guidelines and there is in fact little actual clinical science upon which to base dogmatic recommendations. Several important issues remain inadequately studied in this population. Two such issues are whether or not anti-HIV therapy should be administered during anti-neoplastic therapy, and whether anti-neoplastic chemotherapy should be dose-reduced in the setting of HIV-infection. A one-size fits all solution to this dilemma will neither serve the patient well nor promote clinical studies that will be useful in defining the issues. In the absence of evidence-based medicine, various disease elements and biologic principles must be carefully weighed in terms of the realistic therapeutic goals relevant to the affected individual. In this article, we will focus on the first of these issues—the use of HAART during the treatment of AIDS-related malignancies.

Patients with AIDS-related malignancies often present a substantial challenge for the clinical care team because the development of optimal treatment goals and strategies requires a thorough understanding of both HIV and the specific malignancy. The most common tumors that occur in AIDS, AIDS-related Kaposi's sarcoma (KS) and AIDS-related non-Hodgkin's lymphoma (ARL), provide models that illustrate the various issues and highlight the available clinical science findings on which to base a treatment plan for individuals with cancer and HIV/AIDS.

A first step toward developing an appropriate treatment plan is to assess the status of underlying HIV infection and the nature of the tumor. A patient with advanced HIV disease, multidrug-resistant virus, and a tumor that does not respond well to anti-neoplastic therapy clearly presents a separate set of challenges than a patient with well-preserved immune function whose tumor can be easily treated with limited oncologic intervention. Also, a patient with a life-threatening tumor that has some potential to be cured is very different from a patient whose tumor requires long-term palliation. Available clinical data from experiences in KS and ARL are useful for helping consider reasonable approaches, but strict conformity to any given approach is unlikely to be best for all patients. Thus, in the absence of evidence-based practice guidelines, it may be useful to examine the various approaches and to consider the assumptions and data that have been used to support the different approaches. In this way, difficult decisions may at least be made with an understanding of what is known and the relevant biologic principles. Even so, there may be many patients for whom it is hard to identify an optimal approach.

Since the advent of highly active antiretroviral therapy (HAART) for HIV infection, the clinical outcomes for persons living with AIDS have improved substantially, and this includes those affected by neoplastic disease. Drawing on this observation, it has generally been thought that HAART should be used as part of the treatment for all patients with AIDS-related malignancies. However, whether this is correct or not is unclear; in fact, the treatment guidelines for HIV disease provide room for individualiz-

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ing therapy based on consideration of these complex issues. The Department of Health and Human Services guidelines for treatment of HIV infection[1] recommend that patients with symptomatic HIV infection be treated with anti-HIV therapy, but that the physician should consider clinical problems such as drug toxicity, ability to adhere to treatment regimens, and drug interactions when determining the time to initiate antiretroviral therapy. The guidelines further note that patients with advanced disease should be maintained on antiretroviral therapy unless drug toxicity, intolerance, or drug interactions are of concern. Many patients with an AIDS-related malignancy do, in fact, have problems with overlapping drug toxicity, drug interactions, and difficulty adhering to drug regimens. Thus, there is no clear answer provided as how to best apply such guidelines in the patient with an AIDS-related malignancy. Also, the guidelines do allow for interruption of antiretroviral therapy in certain situations. With this overview in mind, we will discuss concepts of antiretroviral therapy and anti-neoplastic therapy in KS and ARL as models for principles and practice in AIDS-related malignancies.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is a multicentric, angioproliferative disorder primarily affecting the skin, but also with a predilection for the lungs and gastrointestinal tract. KS can also involve other visceral organs. This disease is caused by a gammaherpesvirus called either Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8). KS is not curable, but advances in the treatment of KS have included the development of several mono-chemotherapy agents as well as advances in the treatment of HIV (for HIV-associated KS). Also, a number of novel pathogenesis-based therapies are currently in development, including those based on inhibition of angiogenesis. Clearly, many cases of KS improve substantially in patients with initiation of HAART alone. This is most likely the case if there is a significant virologic and immunologic response to HAART. Patients with greatest benefit are usually those with relatively low tumor burden who are naïve to antiretroviral therapy and KS therapy in whom HIV viral load decreases to undetectable levels and CD4 T cells increase by 150 cells/mm^3 or more above pretreatment levels.[2] In further support of the protective and therapeutic effect of HAART in KS is the marked decrease in KS incidence since the advent of HAART.[3]

The positive clinical benefit and epidemiologic observation that HAART is active in KS have a sound biologic basis. KSHV encodes for a major immunoreactive latency-associated nuclear antigen (LANA-1), analogous to the Epstein-Barr virus latency-associated nuclear antigens.[4] KSHV evades immune responses in part through its intrinsic ability to downregulate major histocompatibility complex (MHC)-1 surface molecules, an effect that may be decreased if T-helper depletion is prevented or restored with HAART.[5] Evidence exists that HIV-encoded or -induced proteins can activate KSHV and can promote KS growth.[6] KSHV viral load, response to HAART, and KS clinical course are all strongly related, suggesting that the immunologic and virologic features of HIV are important in KS.[7] Also, there is no evidence that either KS or the underlying KSHV infection is curable—rather, oncologic therapy is considered palliative and frequently must be continued for a long period of time (although some patients can later be maintained on HAART alone). These clinical and biologic observations have established HAART as part of the fundamental oncologic therapy in KS.[8] Because treatment advances for KS have included a variety of well-tolerated mono-chemotherapy drugs, combining HAART with anti-KS chemotherapy is relatively straightforward.

Clinicians should be aware that the 3 approved mono-chemotherapy agents for KS (2 liposomal anthracyclines and paclitaxel) have predictable overlapping toxicities with the various antiretroviral drugs. The liposomal anthracyclines (liposomal daunorubicin and pegylated liposomal doxorubicin) have mild myelotoxicity at the doses used in KS, and

in general can be used even with myelotoxic antiretroviral drugs such a zidovudine, when necessary. Bone-marrow stimulating agents such as filgrastim and erythropoietin are often effective in overcoming treatment-related myelotoxicity, and can be used in conjunction with HAART and chemotherapy when needed. Overlapping neurotoxicity between agents such as stavudine, didanosine, zalcitabine, and paclitaxel can at times become problematic, but in general, neurotoxicity is relatively mild in the short run and usually reversible when paclitaxel is suspended. Pharmacokinetic interactions may be somewhat unpredictable, and increases in the plasma levels of these cytotoxic drugs may occur, particularly with inhibition of cytochrome P450 enzymes from antiretroviral drugs such a ritonavir. Generally, in clinical practice this does not seem to be a major issue.[9] Moreover, because the goal of KS treatment is palliative and not curative, optimization of the antitumor and antiretroviral therapies is likely to provide for the best longer-term palliation and quality of life for affected persons. Experience has demonstrated, both anecdotally and in clinical trials work, that this approach represents a valuable advance in AIDS-related KS.[10]

AIDS-related lymphoma (ARL)

ARLs are a heterogeneous group of aggressive non-Hodgkin's lymphomas occurring overall 60 fold more frequently in HIV-infected individuals than expected, compared to the non-HIV-infected population.[11] ARL foreshortens life more than any other commonly occurring malignancy in HIV infection.[12] Some changes in the epidemiology and outcome of ARL have been documented since the advent of HAART. These changes vary among the various forms of ARL. The epidemiology for systemic ARL, however, is extraordinary for what it potentially may be teaching us. While the incidence of ARL in HIV infection has decreased overall since the advent of HAART, there has been no change within any patient grouping defined by CD4 T cell counts.[13] As has been recognized since the beginning of the AIDS epidemic, the risk of lymphoma increases with decreasing CD4 T cell counts,[11] and this has remained a constant finding since HAART.[13] Thus, the changes in the incidence of ARL since the advent of HAART can be explained by the overall increase in CD4 T cell counts in the HIV-infected population brought about by HAART.

Also a consistent finding since the beginning of the AIDS epidemic is a correlation with the histologic lymphoma subtype, prognosis, and CD4 T cells.[11,13] Patients with low CD4 T cells are more likely to develop treatment-refractory immunoblastic lymphomas expressing the anti-apoptosis protein Bcl-2, whereas patients with higher CD4 T cells are more likely to develop treatment-sensitive Burkitt's or centroblastic tumors.[14] Since HAART, there has been a relative decrease in the occurrence of the immunoblastic tumors, with the more favorable Burkitt's and centroblastic tumors representing a relatively larger proportion of lymphomas. Recent DNA microarray analysis has demonstrated that gene expression profiles predict treatment outcome. For example, the poor outcome marker Bcl-2 more likely segregates with immunoblastic tumors of post-germinal center origin and predicts poor prognosis compared to the Burkitt's and centroblastic tumors, both of which are more likely associated with germinal center histogenesis and a better prognosis.[15,16] Thus, although there has been a modest improvement in ARL survival from approximately 11 to 22 months since the advent of HAART, this effect is most likely because of a change in tumor biology resulting from immune preservation that gives rise to an environment in which lymphomas develop from a germinal center origin with greater treatment sensitivity.[13,14] The available data do not document any additional specific treatment effects of HAART plus anti-lymphoma therapy administered with curative intent in patients with systemic ARL.

Multiple studies have shown that combination anti-lymphoma therapy can be safely combined with HAART, but there are no clinical data that have demonstrated an improvement in treatment outcome achieved by combining HAART with chemotherapy. A Phase 2 study by Ratner *et al.* combined either low or standard-dose CHOP

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(cyclophosphamide, doxorubicin, vincristine, and prednisone) with stavudine, lamivudine, and indinavir.[17] Although neither designed nor powered to detect a difference, there was a trend for better outcome among those treated with standard-dose CHOP. This finding in itself was important. In NHL developing outside the setting of HIV infection, adequate doses of chemotherapy are associated with the curative potential of the regimen,[18] and the study by Ratner *et al*. was among the first to suggest that low-dose chemotherapy may not necessarily be the best treatment in all ARL cases. Pharmacokinetic studies suggested a significant decrease in cyclophosphamide clearance, but no obvious affects on the other drugs. The toxicity data should be interpreted with an awareness that there was not a control arm. Also, the study was not designed to assess the effect of HAART on lymphoma outcome. However, the study is important in showing full or standard-dose CHOP could be safely administered with HAART and that standard-dose CHOP may yield a better outcome than low-dose CHOP in this context.

A retrospective analysis of patients treated with CHOP or CHOP-like regimens in the pre-HAART era compared to those in whom the chemotherapy was combined with HAART in the post-HAART era documented considerably more cases of grade 3 or 4 neurotoxicity (17% versus 0%) and anemia (33% versus 7%) in the combined therapy group as compared to the no-HAART group.[19] Opportunistic infections were decreased in the combined therapy group (18%) compared to the no-HAART group (52%). However, this finding may have been linked to the relative CD4 T cells at lymphoma diagnosis and changes in prophylaxis practices, since the two groups were treated at substantially different periods of the AIDS epidemic.

A separate study that analyzed a subset of patients defined as long-term HAART responders compared to HAART-naïve patients and patients failing HAART reported improved lymphoma outcomes in the HAART responders.[20] The overall response rate was 52%, consistent with expected response rates to CHOP and CHOP-like regimens. Among the patients responding to HAART, the response rate to CHOP was 71%, compared to 30% in those who did not have a virologic response to HAART. The use of HAART during therapy for lymphoma has been assumed by some to account for the results. However, another interpretation is that the results are because of an uncontrolled variable (such as more advanced HIV disease, poor compliance, or hindered access to medical care) that led to both HAART failure and poor lymphoma outcome. The study does suggest that individuals who develop lymphoma when their HIV viral load is well controlled are more likely to develop treatment-sensitive tumors, and that administration of concomitant HAART with CHOP or CHOP-like chemotherapy regimens is feasible. Nonetheless, as suggested above, tumor biology is associated with immune status, and this provides a more biologically plausible explanation for the reported findings of this retrospective analysis. Such data do not address the role of concomitant HAART and chemotherapy as beneficially affecting therapy, but rather suggest that it does not substantially adversely affect the outcome.

Early results of a Phase 2 study examining HAART combined with 96-hour infusional CDE (cyclophosphamide, doxorubicin, and etoposide) plus a monoclonal antibody directed against the CD20 antigen suggest that this combination of therapy is feasible and effective. At a short follow-up time of 9 months, the median overall survival had not been reached.[21] The high complete response rate of 86% in this trial is noteworthy.[21] However, it is not clear to what extent the prior HAART, as opposed to the simultaneous use of HAART, may have contributed to these results, and this issue bears further study. In considering this question, it is worth keeping in mind that recent studies of a variety of regimens have shown improving response to ARL and that adding therapeutic agents (such as HAART) to a regimen has the possibility of increasing toxicity. In a recently completed, large, randomized study of CHOP plus HAART, given with or without ritux-

imab, the response rates on the 2 arms (50% and 58% respectively) were similar, but there was an excess of deaths from toxicity in the group randomized to also receive rituximab.[22] Even so, these response rates of 50% and 58% in this large, prospective, randomized trial are typical of what is expected with CHOP and do not demonstrate that HAART added to treatment efficacy in ARL.

Taking a somewhat different approach to this question of whether to combine HAART with therapy for ARL, our group at the National Cancer Institute has explored the use of infusional dose-adjusted EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone) chemotherapy in ARL with HAART temporarily withheld during the period of EPOCH treatment.[14] In considering whether to use HAART during the period of EPOCH therapy, we were concerned that overlapping toxicities and unpredictable pharmacokinetic interactions could lead to impaired curative potential of the EPOCH regimen. In this regard, it is important to keep in mind that unlike the case with KS, chemotherapy for ARL is administered with curative intent and that a number of studies have suggested that failure to achieve a durable complete response with the first regimen portends a poor overall prognosis. Additionally, we were concerned that HAART adherence would be challenged by potential EPOCH side effects such as nausea, vomiting, mucositis, or diarrhea, thus increasing the risk of drug-resistant HIV developing in the setting of suboptimal antiretroviral therapy adherence or absorption. Also, even with very high HIV viral loads during the 15 weeks required to administer 6 cycles of EPOCH, at most approximately 20 CD4 T cells/mm^3 would be lost secondarily to HIV,[23] whereas EPOCH would be expected to profoundly deplete the CD4 T cells whether HAART was present or not.

Thus, we designed the protocol so that antiretroviral therapy was not administered until all cycles of chemotherapy were completed. HIV viral loads increased modestly during chemotherapy, and as expected, CD4 T cells dropped substantially during treatment. Virologic response to subsequent HAART was similar to what is expected in uncomplicated HIV disease, and the time for CD4 T cell recovery to pretreatment levels was similar to that seen in non-HIV-infected individuals receiving similar chemotherapy.[24,25] In fact, the magnitude of the CD4 T cell loss during chemotherapy was clearly in excess of what would be expected from the immune-destructive effects of HIV, but entirely consistent with the effects predicted from lymphocytotoxic chemotherapy.[23,24] HAART would not be expected to prevent the lympholytic effects of chemotherapy, and if it did, would raise concern that it was also protecting against lymphosis of the malignant cells. Thus, there was no evidence that transiently withholding HAART during the period of lymphoma treatment with curative intent compromised HIV disease status or long-term HIV control. Of note, there was no control arm with simultaneous HAART.

The complete response rate of 74% (87% for those with greater than 100 CD4 T cells/mm^3) and the disease-free survival of 92% at 52 months of follow-up demonstrated that a desirable outcome in the therapy of ARL is not dependent on concomitant HAART administration during chemotherapy. Furthermore, intensive study of pathobiologic markers provided evidence that the tumor biology was related to outcome. This is important in that, as mentioned above, HAART may affect tumor biology through its effects on the immune environment at the time the lymphoma is developing, but would be irrelevant to tumor biology once the tumor has already developed.

The comments above apply to systemic ARL in which therapy is administered for curative intent. In such cases, it is reasonable to consider that the immediate threat to prolonged survival is the lymphoma and that the primary focus of initial therapy should be achieving cure of the lymphoma. For patients with primary central nervous system lymphoma, a different set of principles may apply—such patients often die of complications of AIDS and administering HAART during lymphoma therapy would seem to be a higher priority. Also, for patients

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whose lymphoma is not likely to be curable and who are receiving palliative therapy, consideration of clinical principles would indicate co-administering HAART if at all possible.

Conclusion

HAART represents a major treatment advance for HIV disease and has affected the bio-epidemiology of certain AIDS-related malignancies, most notably KS and ARL. Through biologically plausible mechanisms, HAART has decreased the incidence of KS and exerts a beneficial treatment effect in KS. HAART should be considered a fundamental component of the oncologic armamentarium in AIDS-related KS. Only in exceptional circumstances should it be omitted from the therapy of AIDS-related KS. HAART should be used either as the only component of anti-tumor therapy or in combination with additional specific anti-KS therapy depending on the extent and aggressiveness of the KS.

HAART has also affected the bio-epidemiology of ARL, though in ways that do not parallel its effect in KS. HAART has not been shown to affect the CD4 T cell count-specific incidence of ARL. However, the histologic subtypes of ARL have shifted, coincident with HAART-related immune preservation or restoration. This shift in histologic types toward more treatment-sensitive tumors is the likely explanation for the modestly improved overall survival in ARL since HAART. Unlike the case with KS, chemotherapy of ARL is undertaken with curative intent and the best chance of cure comes by optimizing the first anti-lymphoma regimen. There are no data proving that concomitant administration of HAART with lymphoma therapy leads to better treatment outcome and no prospective randomized trials specifically addressing this point. Certain regimens for ARL can be safely given with certain HAART regimens, although there are mixed data as to whether the strategy of combining HAART with chemotherapy results in additional toxicity or not. This issue is to some extent dependent on the particular drugs being used. For certain patients or patient populations, optimal treatment may consist of the combined use of HAART plus anti-lymphoma therapy. However, as has been pointed out, the continuously expanding assortment of antiretroviral drugs has created an environment that makes methodical examination of HAART and chemotherapy difficult at best.[26]

In our opinion, the current state of the literature does not provide clear guidance on what approach in systemic lymphoma is best. The appropriate trials have not been conducted, and may be difficult to design. However, in developing a therapeutic plan for a curable tumor (such as lymphoma or germ cell tumors) consideration of whether HAART is to be included should at least include an examination of the potential for increased complications created by overlapping toxicities and potential pharmacokinetic interactions.

In the individual case, the principles of oncology and antiretroviral therapy can be used to help make the decision of whether or not to include HAART during anti-neoplastic therapy. Thus, it is useful to consider the expected effects of chemotherapy on the immune system, whether HAART is likely to protect against such effects, whether HAART has any oncologic role in the specific tumor, and whether HAART may compromise the anti-tumor therapy. The biologic plausibility of any assumed benefits of HAART should be considered. If there is evidence that HAART has specific anti-tumor effects for the tumor under consideration or can provide immune-protection without compromising the oncologic therapy, it may be important to include HAART in the treatment. These considerations must be made in the context of individualizing therapy to tumor type and therapeutic goals.

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Cancer and AIDS: National Cancer Institute's investment in research

By Ellen G. Feigal, MD, and Jodi B. Black, PhD

Research on AIDS-associated malignancies has focused on the interplay of immunity and viral infections and has increased our understanding of cancer pathogenesis. But what have we learned, and how can we build upon our knowledge to develop improved preventive and therapeutic interventions? This article outlines resources available from the National Cancer Institute (NCI) to stimulate research and to increase our knowledge of the underlying pathophysiology of HIV/AIDS-associated malignancies and the development of more effective interventions.

The role of viruses and immunity

By now, we know that viruses clearly play a major role in the development of cancer in HIV-infected individuals. Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), anogenital dysplasia, and cervical cancer feature specific infectious agents in their etiology. These infectious agents are human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus (HHV-8/KSHV) in Kaposi's sarcoma; Epstein-Barr virus (EBV) in primary central nervous system lymphoma (PCNSL) and a subset of systemic B cell NHL and pediatric leiomyosarcomas; and human papillomavirus (HPV) in anogenital dysplasia and cervical cancer. Immunity has a critical function in the development of cancers, both in HIV-infected individuals as well as in those individuals with depressed immune systems caused by congenital conditions or iatrogenically induced in the transplant setting. Infection with HIV alters the immunologic landscape, most markedly noted in impaired quality and insufficient quantity of CD4 helper T cells, and dysregulated cytokine expression resulting from persistent antigen stimulation.

The changing face of HIV/AIDS and cancer

While the widespread use of highly active antiretroviral therapy (HAART) has led to a rapid decline of incidence in certain cancers (see article on page 5), the types of cancers associated with AIDS have not substantially changed since the beginning of the AIDS epidemic. So why the decrease in some cancers but not others? The dramatic effect of HAART on KS and PCNSL incidence is postulated to result from partial reconstitution of immunity and enhanced responses to viral and other tumor antigens. However, other plausible explanations that are likely to be concomitantly involved include: 1) inhibition of the broad spectrum HIV trans-activating protein Tat, 2) decreased expression of growth factors and cytokines contributing to cancer development and maintenance, 3) direct antitumor effects of protease inhibitors, and 4) direct effects of HAART on HHV-8 or EBV. But how these mechanisms contribute on an individual patient basis and the differences in their effects or apparent lack of effect are not understood.

The longer life expectancy of HIV-positive people with access to HAART may actually increase the cumulative risk of developing cancer. This, coupled with HAART class switching because of HIV drug resistance, may lead to an increase in the incidence of non-AIDS-defining cancers, including Hodgkin's disease (HD) and lung cancer. HD is currently the most frequently diagnosed non-AIDS-defining cancer that is related to immunosuppression. Lung cancer risk is increased in the HIV-positive population, occurring at a younger age and more frequently in the HAART era. The outcome of these patients remains poor despite HAART. In addition, there are

reports of increased risk of several rare malignancies and proliferative lesions, including Merkel cell carcinoma, squamous cell carcinoma of the conjunctiva, and multicentric Castleman's disease. As HAART becomes available in developing countries, the resulting longer life expectancy combined with the endemic viruses associated with cancer portend an increase in AIDS malignancies in these regions.

Current activities towards developing more effective treatment strategies for HIV/AIDS-related malignancies include: 1) targeting molecules in the angiogenesis and apoptotic pathways; 2) fortifying the immune system using immunomodulatory molecules, vaccines designed to increase the cell-mediated immune responses to viral antigens, and monoclonal antibodies to eliminate cancer cells; 3) targeting EBV or KSHV to disrupt the viral life cycle; 4) investigating low morbidity anal lesion ablation techniques, and 5) combining standard chemotherapy regimens with biologic therapies.

Gaps in our knowledge

What is needed is a better understanding of the pathways to cancer development: whether they are similar in HIV-positive versus HIV-negative individuals and whether we can extrapolate treatment modalities used in the immunocompetent population or need to develop new treatment regimens. Also, we need a better understanding of the roles of HIV viral loads and CD4 T cell counts, immune cell function, and HAART in cancer pathogenesis, treatment, and control. The association of viruses with the AIDS-defining malignancies suggests differential involvement of immune function and viral gene expression in tumor development. Additional research into the precise interactions of viral gene expression and impaired or dysregulated immunity in cancer development and maintenance are required.

NCI resources

In cooperation with other divisions at the National Institutes of Health (NIH), NCI developed a multicomponent AIDS Malignancy Program to stimulate and facilitate the integration of the biology and epidemiology of AIDS malignancies with the development of treatment strategies. The AIDS Malignancy Program was designed to assist the research community in studying the interplay of viruses, immune dysfunction, aberrant growth factor expression, and the development of cancer in AIDS patients, with the goal of creating more effective treatment regimens. A description of the pertinent components follows.

Bringing more effective treatments to the clinic. The Inter-Institute Program (IIP) for the Development of AIDS-related Therapeutics is a joint effort between the National Institute of Allergy and Infectious Diseases (NIAID) and NCI. The program aims to promote the preclinical development of microbicides as well as therapies for treating HIV disease, AIDS-associated malignancies, and opportunistic infections associated with AIDS including tuberculosis. The program assists investigators from academic institutions, nonprofit research institutions, and biotechnology and small pharmaceutical companies by providing access to NIH contract resources for therapeutics development. Services include high-throughput screening, studies in animal models, formulation, pharmacology and toxicology studies, and bulk substances acquisition. Additional information and application receipt dates can be found at ***dtp.nci.nih.gov/docs/dart/dart.html***

Clinical trials. The AIDS Malignancy Consortium (AMC) was developed in 1995 to expedite the rapid evaluation of hypothesis-driven Phase I, II, and III multicenter clinical trials that utilize the expertise of both NCI- and NIAID-sponsored scientists. Their charge is to identify therapeutic approaches for the treatment of malignancies in AIDS (also see page 30). These approaches include biologic therapy using interleukin (IL)-2, IL-12, interferon-alpha, monoclonal antibodies directed against B cell targets, cytotoxic T lymphocytes directed against viral targets, immune-based therapy, stem cell reconstitution, angiogenesis inhibitors, therapeutic vaccines, and traditional cytotoxic chemotherapy regimens (often in combination with a biologic or immuno-

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logic approach). In addition to assessing potential antitumor activity and drug-drug interactions, the AMC also evaluates the impact of therapy on viral load and underlying immune function. Additional information about the AMC can be obtained at ***www.amc.uab.edu***

Training. The AIDS Oncology Clinical Scientist Training Program was developed in response to the important need for trained AIDS-oncology specialists. The program was developed to exploit research opportunities, conduct patient-oriented research, and provide the clinical management skills necessary for the advancement of this field. A cadre of clinicians was trained with the highly specialized skills necessary to address the clinical and research problems associated with AIDS-related malignancies.

Access to biospecimens. The AIDS and Cancer Specimen Resource (ACSR) is the nation's leading multisite resource for tissues, fluids, and clinical data collected from HIV-positive patients with cancer. The ACSR was established in 1994 to identify and to improve access to well-characterized tissues, fluids, and associated demographic and clinical data collected from HIV-positive patients and HIV-negative controls. The ACSR contains over 100,000 specimens collected from cohort studies, clinical trials, and other research sources (including international research). Information on available specimen types and how to obtain them is available at ***acsb.ucsf.edu.***

Setting the research agenda. The AIDS Malignancies Working Group (AMWG) was established in 1996 and is charged with identifying the major research priorities in AIDS malignancies. This multidisciplinary group includes members from both the intramural and extramural components of NIH, researchers outside of NIH, and community representatives. The group meets yearly to discuss the biomedical research opportunities for AIDS malignancies, the clinical gaps in our knowledge, and mechanisms to move the research forward and address specific issues. Summaries from recent AMWG meetings are available at ***deainfo.nci.nih.gov/ADVISORY/pog/other_wg/index.htm***.

Fostering scientific exchange and international collaboration. The International Conference on Malignancies in AIDS and Other Immunodeficiencies (ICMAOI) is a forum for the presentation of basic, epidemiologic, and clinical aspects of research on malignancies in HIV-infected and other immunosuppressed individuals. The objective is to facilitate information exchange between investigators from laboratory and clinical settings to decrease the interval between basic discovery and clinical application. The scope of the conference includes basic and clinical research on viral oncology, immunology, genetics, epidemiology, pathogenesis, drug discovery, and early diagnosis of malignant diseases in AIDS and other immunodeficient states including organ transplantation. Additional information about the international conference is available at ***www3.cancer.gov/dctd/aids/conference/index.html.***

NCI investment in AIDS oncology. The *AIDS Oncology Resource Handbook* provides a comprehensive listing of the clinical and laboratory research resources that receive NCI funding. A brief synopsis of the research studies and recent accomplishments is provided, as well as personnel contact information. The Handbook can be viewed in its entirety at ***ctep.cancer.gov/resources/aids.html***.

NCI partners in AIDS oncology research. NCI partners with other National Institutes and Centers to promote epidemiology and natural history studies, infrastructure, training, and international capacity-building for research on cancer in HIV-positive individuals. NCI co-sponsors the Centers for AIDS Research (CFAR) program, which provides administrative and shared research support to synergistically enhance and coordinate high-quality AIDS research projects. CFARs accomplish this through core facilities that provide expertise, resources, and

services not otherwise readily obtained through more traditional funding mechanisms. There are 19 CFAR sites across the US. Additional information about the CFAR program and a site map is available at ***www.niaid.nih.gov/research/cfar/***

NCI participates in the Multicenter AIDS Cohort Study or MACS (***statepi.jhsph.edu/macs/macs.html***) and the Women's Interagency HIV Study or WIHS (***statepiaps.jhsph.edu/wihs***). The MACS, which began in 1984, is an ongoing, multicenter, prospective study of the natural and treated histories of HIV infection in homosexual and bisexual men. The WIHS is a multicenter, prospective study established in 1993 to carry out comprehensive investigations of the impact of HIV infection in women. Both cohorts monitor changes in the natural history of HIV and associated conditions occurring as a result of treatment advances and longer survival.

Rates of HIV/AIDS-associated malignancies have increased in developing countries as a result of the HIV epidemic, thus NCI is helping to strengthen research on such malignancies in these geographic areas. For its international research agenda, NCI partners with the Fogarty International Center to build capacity for basic and clinical studies in resource-poor countries with significant HIV/AIDS incidence and prevalence via their AIDS International Training and Research Program (AITRP) and the International Clinical, Operational, and Health Services Research Training Award (ICOHRTA). Both AITRP and ICORHTA are training programs designed to enhance basic, clinical, and health services research on AIDS and co-morbid conditions (including cancer) in resource-poor areas. Information about both programs is available at ***www.fic.nih.gov/programs/aitrp/aitrp.html*** and ***www.fic.nih.gov/programs/ICOHRTA-AIDS-TB/ICOHRTA-AIDS-TB.html***.

Conclusion

Current advances in research technology allow the identification of complex interactions between viruses, immune dysregulation, and genetic mutations to better understand their roles in cancer etiology and to develop targeted treatment strategies at an accelerated pace. This, coupled with decreased morbidity from cancer therapies in HAART-treated, HIV-positive patients, provides impetus for the development of more targeted or aggressive regimens that will lengthen patient survival. NCI has critical infrastructures and initiatives in place to further our understanding of both HIV/AIDS and cancer and to allow testing of novel therapeutic strategies. These challenges and opportunities will continue to evolve with the worldwide HIV epidemic as well as new advances in technology.

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The rise and fall of the AIDS Malignancy Consortium

By Jeffrey Schouten, MD, JD

The AIDS Malignancy Consortium (AMC) is a National Cancer Institute (NCI)-supported clinical trials group, founded in 1995 to support innovative trials for AIDS-associated malignancies. The AMC is composed of 15 main Clinical Trials Sites and their affiliates, and an Operations and Statistical Center. The AMC has three disease-focused working groups: Kaposi's sarcoma (KS), lymphoma, and human papillomavirus (HPV) working groups. They are responsible for developing and implementing therapeutic protocols for these diseases.

Before 1995, primarily the Adult AIDS Clinical Trials Group (AACTG) conducted multicenter AIDS-related cancer trials. In the mid to late 1990's, there were large numbers of people with KS as well as lymphoma. However, with the success of antiretroviral regimens following the approval of protease inhibitors, the incidence of KS and some other cancers declined dramatically, and the health and quality of life of many HIV-positive people improved substantially. Thus, shortly after the creation and funding of the AMC by the NCI, enrolling large numbers of people in HIV-related cancer trials became difficult. Consequently, the last few years have seen declining numbers of people entering AMC trials. While the cause of this trend is great news for people living with HIV, it has impeded the progress of this important research. From a basic science perspective, research into the relationship between cancers and viral infections could lead to developments benefiting many people. For instance, research has clearly shown that KS is associated with infection with a virus from the herpes family, the KS-associated herpes virus (KSHV), also known as human herpesvirus 8 (HHV-8).

As a result of a combination of factors, probably including low study enrollment, problems with tracking samples (particularly pathology specimens), inadequate funding for a centralized data collection and management system, and lack of referrals from community oncologists, the NCI has decided not to continue funding the AMC in its current configuration when the grant expires next year. The NCI is only allowing the AMC to conduct a few trials that may fully enroll within a year, but otherwise no new trials will be developed. This is particularly disappointing because no other funded multicenter network is conducting research for these still very important problems. There remains a need for less toxic initial therapy for KS, as well as therapy for people who fail to obtain good control with the firstline KS treatment options currently available. Also, the field of angiogenesis (new blood vessel growth) inhibition is quite new and, because KS is essentially a cancerous proliferation of blood vessels, opportunities exist to find drugs that inhibit blood vessel growth to treat KS and many other cancers.

The optimal treatment of HIV-associated lymphomas is still unknown. Only about half of people with HIV-associated non-Hodgkin's lymphoma (NHL) achieve long-term remission with initial therapy. Also, a greater proportion of people with HIV are developing Hodgkin's disease (HD). The treatment outcome of HD is generally much better than NHL, but whether this is the case for HIV-positive

people is unknown. The treatment outcome of primary brain (CNS) lymphoma is still very poor for most people. For people with relapsed lymphoma, bone marrow transplantation may be an option but many questions remain about the efficacy and safety of this treatment in the HIV-infected population.

As several studies have shown, the safety and efficacy of treatment for HIV-associated lymphomas cannot be assumed the same as for similar types of lymphomas in HIV-negative people. Several years ago, research showed that the higher doses of chemotherapy used in HIV-negative people did not increase cure rates in HIV-positive people and were associated with higher rates of serious side effects. More recently, the AMC trial 010 was unable to show that HIV-positive people benefited from the addition of Rituximab (a monoclonal antibody that attacks cancerous lymphoma cells) to a standard chemotherapy regimen. Also, there was a higher rate of infections observed in the people who received Rituximab than expected. The AMC has recently begun a trial, AMC 034, to see if the outcomes observed using infusional chemotherapy regimens in HIV-negative people with lymphoma will be achieved in HIV-positive people as well.

Thus, much research in these areas is still needed. With the NCI not renewing the AMC, where and how will this research be conducted? As attention shifts to the international arena for the treatment of HIV, consideration must be given to the very high incidence of KSHV in Africa. There remain many questions about the association of KSHV and HIV in Africa and what optimal therapy can be effectively implemented in resource-poor settings. The NCI should consider creating a new cooperative network with maximal flexibility for the effective use of funding and for conducting quality research. Alternatively, the AACTG may need to consider re-entering HIV-associated cancer research and adding this area to its scientific agenda.

Lastly, the human papillomavirus (HPV) working group is a relatively new addition to the AMC, and has initiated the development of several protocols under the leadership of Joel Palefsky. However, only part of the research agenda for HPV is focused on cancer development and treatment. Many questions about HPV infection in HIV-positive people must still be answered, including whether to monitor men and women with routine anal pap smears, what is the natural history of precancerous changes from HPV after effective antiretroviral therapy, and what is the best treatment for precancerous and cancerous changes in the peri-anal area. There is a great need for a national HPV cooperative trials network for gathering the data necessary to address these very important issues.

Jeffrey Schouten *is an HIV/AIDS activist and a Community Representative for the AIDS Malignancy Consortium.*

AIDS and cancer: one patient's story

By L. Joel Martinez

I have always had a distaste for writing autobiographically when I write for this publication. It stems from a personal belief in and conviction for the so-called "scientific method"—an early indoctrination that disease could and would be conquered. AIDS has been the great curve ball. Still, in my heart I have always had this deep-seated sentiment that what HIV/AIDS research and medicine lack most is the scientific authority that comes from sufficient process and analytical thinking.

Having been diagnosed with HIV around 1986 and involved in some form of advocacy and information dissemination since that time (sometimes loosely, other times in a more structured setting), much of the information I have written about has been "light" on the science and "strong" on the proverbial "this worked for me; maybe it will work for you."

The anecdote, or as we jokingly refer to it here at The Center for AIDS (CFA): "the N=1," has been an integral part of the AIDS battle. Anecdotal information has often been best simply because sometimes it has been the only information available. This has not been helped by the epidemic's history of hurried, sloppy, and huge mood swings regarding treatment guidelines.

So I begin this strange story of my HIV disease with an admission of guilt: to write anecdotally goes wholly against my grain. Striking my computer keys to record these words keeps me on the verge of upchucking at times. Still, in some strange way I hope this story is useful to someone, maybe only because it reflects the unusual nature of HIV disease and the true lack of knowledge of the body's immune system, and because it may sadly illustrate how clinical defeat is possible despite "HIV surrogate number" success.

As with most persons diagnosed in the mid-1980s, I too clung to the mystic of bloodwork—the numbers, the markers we later learned to identify more accurately as surrogates for other, more important clinical events such as opportunistic infections (OIs) or death. As with many early patients, I lived for the numbers, anxiously and impatiently knowing that they "must" be imbued with the magic of continuous health or decline. These were numbers whose minute fluctuations could as easily drive me to ecstasy as to fantastic depression.

I remember my first T cell count as a nice round 350 cells; at that time the number had no realistic point of reference, except that it looked better than my friends' lower numbers and worse than those with higher, more robust numbers. I could start to see in my friends with lower numbers the more frequents bouts of fatigue, the increase in hospitalizations, and the plain deterioration that had been predicted by my doctor.

From the beginning, except for some minor white markings on my tongue that my doctor identified as "oral hairy leukoplakia," I seemed to be lacking any of the classic signs of HIV disease. I could work a full day, I could party, I could carry on my life as usual. Still, the underlying strain of knowing I had this "terminal" disease had its own debilitating effects. And I was not one to live comfortably in denial. If I could nip this disease in the bud, I was going to do it and I was willing to take the chances of doing myself more harm than good.

I remember sitting in my doctor's office while he held up a chart of the stages of AIDS as he knew them then. In his usual, somber way he explained the correlation between T cell decline and health

problems. Psychologically, it was a harrowing experience (although I tried my best to be stoical about it). Having someone explain the likely course of the rest of my possibly short life, its probable medical deterioration, and its possible end, in a small half-poster was unexpected to say the least. The last line of the chart's simple algorithm showed a path that diverged to either "death" (strangely marked in red) or what seemed like an errant "?" (equally strangely marked in blue). I knew in the balance of things, that death carried more weight even in my doctor's desperate reach for optimism. And I was not immune from the onslaught of the media's overblown take on the great pandemic.

My symptoms of HIV never seemed to follow the predicted course for the epidemic. Still, I took AZT monotherapy shortly after its approval and after a short stint of crossing into Mexico to carry over boxes and boxes of Ribiviran. Despite the steady decline in my T cells, I never developed PCP, fevers, or long bouts of fatigue. Then in December of 1989, I had approximately 5 seizures that quickly depleted my platelets to dangerously life-threatening levels and hospitalized me for a week. This was my first real encounter with the word "idiopathic." Idiopathic: of unknown origin or cause. Idiopathic: also signaling the end of some form of clinical invincibility.

Soon after my seizures, I began to develop some small tumors I suspected to be Kaposi's sarcoma (KS). Of course, the physical manifestations were not typical either, since the tumors, while raised, never turned purple. I could see them tracing the veins in my left leg and along my upper arms. My doctors ordered biopsies and the diagnosis of KS was confirmed. Luckily for me, one of my doctors was a lead researcher for Doxil and I was able to enroll in the protocol almost immediately. My response was quick and definite, and the twice-monthly infusions seemed to keep the KS from progressing.

As time passed, I began to develop more classic signs of AIDS: fatigue, fever, and exhaustion, which accompanied the decline in my T cells to single digits. By the mid-1990s, I had a T cell count of 1, but continued to live a fairly active life, volunteering in treatment information and then being instrumental in starting The CFA. Protease inhibitors were around the corner and the advent of viral load tests promised to be a boon for those with immune systems that were still "salvageable."

I remember my doctor saying wisely, "even if I could kill every HIV particle in your body, I would still need a way to restore your immune system." In retrospect this seems like an unusually prescient prediction. Still, when the early results of Crixivan and Norvir studies began to be made public, it seemed that the body could perhaps mount its own robust recovery that, while not complete, could ward off many of the OIs that had terrified most of us as patients. Having participated in a series of monotherapies and dual therapies by the time highly active antiretroviral therapy (HAART) came around, my underlying viral resistance was sufficient that HAART had only temporary and minor successes in my immune reconstitution.

In 1997, my treatments with Doxil suddenly stopped working, and what I had gotten accustomed to in terms of "melting tumors" changed to more numerous tumors that started affecting other parts of my body. A change to Daunaxome as a treatment for KS had no effect. Then after a few weeks of struggling and further biopsies, I was told that I had large B-cell, non-Hodgkin's AIDS-associated lymphoma. At the time, I still had a T cell count of 1 and my treatment with HAART seemed ineffective.

After 7 grueling rounds of chemotherapy, I achieved partial remission of my NHL, but it soon started recurring, mostly around my lower limbs. During this time, I had several intestinal CMV lesions, which responded to therapy. However, the recurring NHL had to take priority and I received radiation therapy to large sections of my legs.

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After many rounds of radiation, my tumors kept returning and I was given the choice of more radiation (with the risk of developing continuously weeping and open sores) or to retry chemotherapy. I spent several weeks in Colorado reviewing my options and returned to Houston to further stage my tumors before making a decision on how to proceed. During a thorough and confusing sonogram, the technician informed my doctor that I had no tumors to be found. Nothing in my immune status had changed dramatically; I still had remarkably low T cell numbers and no other signs of obvious immune reconstitution, but something in my body had changed to eliminate the NHL.

This change in my body's response to NHL continues to be a mystery to all involved, even baffling my family, with its strong belief in "gift-granting" miracles. The recovery from NHL finally gave me sufficient time for 3 new antiretrovirals to come to market. This was the first time in my disease history that I was able to start multiple antivirals without having some underlying resistance. The results were remarkable and soon I was flaunting T cell counts of 600 and viral loads that came extremely close to being undetectable.

This unexpected flourishing of health lasted about a year before I noticed that my T cell numbers were rising too rapidly and too robustly. When my T cell numbers started to climb into the 900s, I began to suspect something was wrong. After more tests, it was determined that the sudden increase in T cell numbers was accompanied by a huge increase in my white cell count without any signs of infection. Then came the determination that I had developed chronic myelogenous leukemia (CML). As in some prophetic pronouncement, the FDA announced the approval of a drug to treat CML just a few months before my diagnosis. The drug, known as Gleevec, was highly selective and effective at treating CML. Before starting this promising therapy, I encountered a slight medical detour in that I suffered a heart attack that required me to have open heart surgery with a triple bypass. As with other things, this too passed and soon I was on an effective dose of Gleevec that has kept my CML at bay.

With my HIV and CML under some form of control, what else could go wrong? In January 2002, I developed squamous cell carcinoma of the tonsil without really having any of the major risk factors for this type of cancer. The carcinoma has spread to both sides of my neck and I have endured and survived both radiation and chemotherapy, but I still have a persistent mass.

As with the 3 other major cancer events in my life, the development of this cancer has been accompanied by the recent approval of a new drug called Iressa that, while not specifically indicated for head and neck cancers, appears to have some activity against them. The Iressa seems to have the short-term effect of forestalling the progression of the squamous cell carcinoma. Still, its long-term effects are much in question.

So once again, I find myself in a strange stage of limbo, knowing finally all the names (trademark and generic) of my biggest friends: HIV drugs, and now having to learn a completely new language having to do with cancer. In the end, I cannot help but wonder that this is all connected with prolonged immunodeficiency (naturally occurring because of a virus and perhaps also induced by therapy). The question remains whether increased immunosurveillance of my HIV with the help of HAART will help or whether further treatment of the squamous cell carcinoma will have any effect at all. For now, I have decided that there must be something else for me to accomplish on this earth. Why else am I here? I am constantly thinking it over and searching for a way to clear this latest hurdle.

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