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 as 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6,10,14,16} 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.\textsuperscript{17} Data also indicate that high-grade lymphoma is more prevalent in the HIV-positive community compared to low-grade lymphoma.\textsuperscript{14} Many agree that the risk of developing NHL, particularly PCNSL,\textsuperscript{6,18} increases with lower CD4 T cell counts\textsuperscript{6,10} and further progression of HIV infection.\textsuperscript{1} Moreover, NHL is more prevalent in HIV-positive women compared to high-risk HIV-negative women,\textsuperscript{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.\textsuperscript{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,\textsuperscript{4} and patients receiving HAART experienced a 5-fold decrease in incidence compared to treatment-naïve patients.\textsuperscript{12} However, other studies fail to show any substantial change, and even suggest modest increases in incidence.\textsuperscript{13,14} Significant decreases have been detected for immunoblastic lymphoma in some studies,\textsuperscript{4} but not others.\textsuperscript{1} Incidence of Burkitt’s lymphoma has not decreased\textsuperscript{1} and one analysis even demonstrated an increase in incidence after the introduction of HAART, but this increase was not statistically significant.\textsuperscript{4} The effect of HAART on the incidence of PEL is unknown because the disease is so rare.\textsuperscript{10} Nevertheless, studies routinely show that incidence of PCNSL has decreased considerably following the introduction of HAART.\textsuperscript{1,4,12,14} Administration of HAART has also been associated with longer survival in patients suffering from PCNSL.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16,20,21} Some analyses report no increase in incidence that is coincident with the AIDS epidemic\textsuperscript{16,20} and no correlation between immunosuppression and increased risk of developing the cancer.\textsuperscript{6,16} Indeed, HIV-positive women with ICC tend to have higher CD4 T cell counts compared to HIV-positive patients with other malignancies.\textsuperscript{20} Still, other studies report that HIV-positive women are approximately 5 to 9 times more likely to have ICC compared to seronegative women,\textsuperscript{3,6,19} and this cancer accounts for 55% of AIDS-related malignancies in some settings.\textsuperscript{22} Moreover, the clinical course becomes even more aggressive when CD4 T cell count is low.\textsuperscript{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 progression27 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-naive patients31 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 continued...
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.36,33 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. Studies assessing cancer incidence demonstrate that HIV-positive men are 1.4 to 8.2 times more likely to develop testicular cancer, though another study failed to show significantly increased incidence. 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. One large study reported a modest association between incidence of seminoma GCT and immunosuppression. However, another analysis showed that HIV-positive patients with seminoma appeared to have preserved immune systems. 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.

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. HIV-positive patients typically present with more advanced cancer at the time of diagnosis, and the average age at diagnosis is usually younger in HIV-positive patients compared to seronegative patients; this is particularly true with lung and testicular cancers.

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. 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. 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. 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.

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, 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,\textsuperscript{1,6,10} but HAART has not had a dramatic impact on NHL incidence, particularly systemic NHL.\textsuperscript{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.\textsuperscript{26} Prolonged exposure to viral oncogenes, moderate immune suppression, and genomic instability could result in impaired immune surveillance and the subsequent development of tumors.\textsuperscript{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.\textsuperscript{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,\textsuperscript{17} though others disagree.\textsuperscript{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.\textsuperscript{36,37,39} Moreover, treatment compliance tends to be poor among HIV-positive patients with cancer,\textsuperscript{26} 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\textsuperscript{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...continued on page 12...

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

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>Leukemia\textsuperscript{5,8,9}</td>
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<tr>
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<td>Skin cancer\textsuperscript{3,5,9,23}</td>
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<tr>
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<tr>
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<tr>
<td>Angiosarcoma\textsuperscript{5}</td>
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\*Associated with immunosuppression  \**Another study showed decreased incidence”
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.

**Further reading:**


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community (see Table). In contrast, the incidence rates of certain types of cancer, such as prostate, breast, and bladder cancer, 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. Surprisingly, the rates of breast cancer in men may have increased to some extent, especially in IV drug users. 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. Others hypothesize that this decrease is caused by increased AIDS-related mortality. 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. 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. 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.

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. 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.
References