

A Glass Half Full: Cancer Risk for People Living with HIV

Cancer cannot be mentioned without arousing anxiety. But there is reason to believe the glass is at least half full when it comes to people with HIV and their risk for cancer.

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A review of cancers among people with HIV before and since the mid-1990s advent of HAART (highly active anti-retroviral therapy) quickly reveals a “before” and “after” experience. Before HAART made it possible to suppress HIV replication to a low or even undetectable level, certain cancers were fairly common in this population.

These “AIDS-defining cancers” (ADCs) are Kaposi’s sarcoma (KS, seen mainly in men), non-Hodgkin lymphoma (NHL), and invasive cervical cancer (caused by certain types of human papillomavirus, or HPV). Having one of them while infected with HIV constitutes an AIDS diagnosis. Although anal cancer is caused by the same HPV types and has the same clinical course as cervical cancer, it is not classified as an AIDS-defining cancer.

HAART greatly reduces the risk for both ADCs and the various non-AIDS-defining cancers (NADCs) seen disproportionately in people with HIV. It strengthens the immune system’s ability to keep in check such potentially cancer-causing viruses as HPV, hepatitis B virus (HBV), and hepatitis C virus (HCV), as well as the other opportunistic infections that prey on a weakened immune system.

In resource-limited countries, cancer has been blamed for fewer HIV-related deaths. But some experts suggest this is either due to the lack of recognition and recording of malignancies, or because HIV positive people are still dying from AIDS-related causes before they have lived long enough

**ABBREVIATIONS USED
FREQUENTLY IN THIS ARTICLE**

- ADC: AIDS-defining cancer
- EBV: Epstein-Barr virus
- CNS: central nervous system
- HAART: highly active antiretroviral therapy
- HBV: hepatitis B virus
- HCV: hepatitis C virus
- HPV: human papillomavirus
- KS: Kaposi's sarcoma
- NADC: non-AIDS-defining cancer
- NHL: non-Hodgkin lymphoma

to develop cancers, which often take years to emerge.

In major United States cities such as San Francisco, an HIV/AIDS epicenter since the start of the epidemic, the picture of cancer risk among long-term HIV survivors is very different than in less wealthy regions. Here, most people who know they have HIV are managing the disease with HAART, and doctors predict that many are likely to have a more normal lifespan.

But even in San Francisco, HIV physician Christopher Hall, MD, observed that managing cancers, particularly KS and squamous cell carcinoma of the anus and rectum, “is becoming a bigger part of what we do.” He added, “we’ve become closer to our oncology colleagues and get them involved in cases.”

As we age, our immune systems weaken and make us more susceptible to cancers of various sorts, regardless of HIV status. People with HIV are at greater risk than their HIV negative age peers because their immune systems are already challenged. Chronic

inflammation and simply living longer with other potentially harmful viral infections increases the risk of cancer developing over time.

While HAART can strengthen the immune system and weaken the effects of HIV, it cannot make us choose to eat nutritious food, moderate alcohol intake, exercise regularly, reduce our number of sexual partners and use condoms, quit smoking, or get the recommended screenings, vaccines, and treatments needed to avoid complications from other infections.

Today, HIV positive people who are on HAART and receiving regular medical care have a number of tools to minimize the risk for cancer—tools that were unavailable in the epidemic’s early years.

A Dividing Line: Before and After HAART

The beginning of the HAART era in 1996 marks a dividing line in the rates and types of cancers affecting people with HIV.

Antiretroviral therapy has greatly reduced HIV positive people’s risk for AIDS-defining cancers, according to a review of cancer occurrence in the HAART era by Michael J. Silverberg, PhD, a cancer researcher with Kaiser Permanente Northern California, and longtime HIV and cancer expert Donald Abrams, MD, of the University of California, San Francisco (UCSF).

For example, a U.S. military study of 4,500 people with HIV looked at rates of cancer between 1984 and 2007—that is, 12 years before HAART was introduced until 11 years after it became available. Before HAART became the standard of care for HIV disease,

80% of cancers in people with HIV were AIDS-defining. Five years later, 71% of cancers seen in HIV positive people were deemed unrelated to AIDS.

Apples to Apples

Most studies of HIV positive people’s cancer risk have examined whether HAART has lowered that risk. But Silverberg said that comparing the experience of people with HIV before (or still not on) HAART to today “is comparing apples and oranges.”

Silverberg and his colleagues examined the histories of 20,277 HIV patients at Kaiser Permanente Northern California, who were unusual in that they all had health insurance. This means they were, more or less, on a level playing field as far as their ability to access medical care. They could presumably get annual Pap smears, colonoscopies (for those over 50 without a family history of colon cancer), mammograms, and other screenings that could detect anything unusual—a precancerous lesion, for example—well before it progressed to cancer.

The researchers looked at the histories of these Kaiser members from 1996—the first year HAART was available—to 2007. Participants were 90% male, 55% white, 19% black, and 21% Latino. Of the men, 74% were infected with HIV through sexual contact with another man, 16% through sexual contact with a woman, and 8% through injection drug use.

Among the men, at some point 552 had an ADC, 221 had an infection-related NADC, and 388 had an NADC unrelated to another infection. A majority of cancers (67%) seen in HIV positive members were related to an

Certain viruses have been linked with specific cancers; however, this does not mean that cancer is infectious and can be “caught” like a virus.

Rather, *oncogenic* viruses—that is, viruses that play a role in the formation of tumors—can cause genetic changes in cells that make them more likely to become cancerous. Oncogenic viruses and the cancers linked to them are discussed in greater detail on page 34.

infectious cause, compared with only 12% in HIV negative people of similar sex and age. The HIV positive participants also had a 30% increased risk of NADCs not caused by other infectious agents, compared with their HIV negative counterparts.

The researchers noted in the journal *AIDS* that almost 70% of cancers in HIV positive people were either AIDS-defining or related to infections—mainly human herpesvirus 8 (the cause of KS), HPV, and hepatitis B and C (which can cause liver cancer). They suggested that immunodeficiency reduces the body's ability to suppress oncogenic viruses.

The Kaiser study was limited in that it did not account for cancer risk factors such as smoking—which is well known to cause lung cancer and can amplify the effects of HPV. The study also did not examine alcohol use, which is linked to cancers of the larynx and liver. Given the high rates of smoking and alcohol use among people with HIV, these omissions represent serious limitations.

Nevertheless, this study is notable for its long follow-up period, given the fact that most earlier research compared rates and risks of cancer among HIV positive people before and only shortly after the start of the HAART era. In spite of its limitations, the Kaiser study may give a more accurate snapshot of today's cancer risk for people with HIV in the U.S.—at least men who have access to HAART and private health insurance. (Editor's note: See "New Briefs" on page 12 for an overview of several recent studies of cancer in people with HIV.)

AIDS-Defining Cancers

The Early Years: Kaposi's Sarcoma

The reddish-purple, slightly raised skin lesions of Kaposi's sarcoma were among the first warning signs that a frightening new epidemic was underway in the early 1980s.

The disease was known for years as a condition that mainly affected elderly men of Eastern European or Mediterranean ancestry, as well as people with suppressed immune systems, such as transplant recipients.

Men are eight times more likely than women to have KS. This malignancy is caused by human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus, which is easily transmitted through unprotected anal or vaginal sex. Although it usually appears on the skin, KS can also spread to other parts of the body—most seriously to the lungs, where it can lead to shortness of breath or even a fatal accumulation of fluid.

In a review of the histories of 375,933 people with AIDS between 1980 and 2002, Eric Engels, MD, MPH, and his colleagues at the National Cancer Institute found that HAART has led to dramatic declines in KS and non-Hodgkin lymphoma, the two most common AIDS-defining cancers.

They found that KS declined 84% by 2002, with a "discrete fall in risk" in 1996, when HAART became widely available. They point out, however, that those with AIDS—that is, a CD4 cell count below 200 cells/mm³—"remain at marked risk."

HAART is the single best treatment for active KS. As effective therapy suppresses HIV and raises CD4 cell counts, it can literally stop the growth of, and even clear up, skin lesions. There are several ways to directly treat skin lesions, including freezing them with liquid nitrogen, removing them surgically, or treating them with radiation. For KS that has spread to internal organs, systemic chemotherapy is used. If HAART does not work by itself, the anti-cancer drugs doxorubicin (Doxil), paclitaxel (Taxol), or daunorubicin (DaunoXome) may be added.

Non-Hodgkin Lymphoma

The second most commonly diagnosed AIDS-defining cancer in the

pre-HAART era was non-Hodgkin lymphoma. Engels and his research partners found declines in NHL rates that mirrored those of KS.

NHL is a group of nearly 40 types of cancer that originate in the lymphatic system—the lymph nodes, vessels, and organs that produce infection-fighting and tumor-fighting cells and carry them throughout the body. Though they are all cancers of white blood cells known as lymphocytes, they behave differently and may have different treatment options and outcomes.

NHL often affects people with suppressed immune systems. For people living with HIV, however, the risk is heightened by coinfection with HCV and Epstein-Barr virus (EBV)—both of which can be sexually transmitted.

The symptoms of NHL are what might be termed "classic" symptoms of AIDS: swollen lymph nodes in the neck, armpit, or groin; abdominal pain or swelling; chest pain, coughing, or trouble breathing; fatigue; fever; night sweats; and weight loss.

Before HAART, people living with HIV/AIDS had an unusually high incidence of NHL of the central nervous system (CNS), a rare form of the cancer. More than a quarter (28%) of NHL in people with AIDS pre-HAART was in the brain or spinal cord. CNS lymphoma tends to be aggressive and deadly. Fortunately, the risk for CNS NHL fell 79% by 2002, when Engels and colleagues examined their data.

NHL is treated with chemotherapy, radiation, and steroids. In people with AIDS, options may be more limited. But even aggressive CNS NHL is being treated with greater success using advanced chemotherapies that are able to target the brain. Survival measured in years is not unusual today, compared with mere months not too long ago.

Cervical Cancer

Worldwide, cervical cancer kills 275,000 women every year. It is the leading cause of years of life lost to

cancer in poorer countries. In the U.S., cervical cancer has become less common, mainly because more women get regular Pap smears to look for precancerous cell changes and tests for cancer-causing HPV. Still, the National Cancer Institute estimates that 12,200 American women will be diagnosed with cervical cancer this year, and 4,210 women will die from the disease.

“Rates for HPV-related cancers haven’t come down the same ways as for KS,” said Joel Palefsky, MD, professor of medicine at UCSF.

“The prevalence is not going down at all,” concurred Erna Kojic, MD, assistant professor of medicine and an expert on HPV infection in women at Brown University.

This seems surprising, given the powerful effects of HAART on other viral coinfections. “There is some synergism between the two viruses,” Kojic explained. “So even if we’re treating HIV, we’re not getting rid of HPV.”

Kojic noted that HIV positive women and men have a higher than usual prevalence of HPV, including types such as 16 and 18 that are responsible for cervical and anal cancer.

HIV positive women not only have higher rates of HPV infection, but having HIV seems to make it harder for the immune system to clear HPV from the body, even for women on HAART. If infected with the cancer-causing HPV types, they also have more frequent progression to early-stage lesions that can progress to cancer if untreated. Thanks to screening, however, most studies suggest that HIV positive women do not have a higher risk of death due to invasive cervical cancer, the most advanced stage of the disease.

HPV infection itself cannot be cured, but its effects can be mitigated with regular monitoring, particularly regular Pap smears, and prompt treatment of any abnormalities. Abnormal precancerous tissue (dysplasia or neoplasia) can be destroyed or removed by freezing, burning, or surgical excision.

The New Frontier: Non-AIDS-Defining Cancers

“Now that we have effective HIV therapy,” said Eric Engels in an interview, “the risk of the two major AIDS-defining cancers [KS and NHL] has dropped. But we are seeing a continuing high risk for the non-AIDS-defining cancers.”

Cancer researchers seem to agree that the best way for HIV positive people to reduce cancer risk is by starting HAART as soon as possible after HIV diagnosis. HAART has made a tremendous difference in reducing classic ADCs, though it alone cannot protect against every type of cancer.

In fact, as Engels pointed out in *AIDS*, while HAART has dramatically reduced the risk for ADCs, cancer overall affects people with HIV at a steady rate. NADCs now account for more illness and death than the three ADCs. Traditional cancer risk factors—including older age, smoking, and coinfections with other viruses—play a significant role in HIV positive people’s increased risk for NADCs.

In addition, “HIV positive people are living longer,” said Engels, “which could be related to the types of cancers” now seen in this population.

Cancer prognosis also tends to be poorer for people with HIV. Engels said this could be because: (1) people with lung and liver cancer may be delaying care until the disease is at a more advanced stage, likely because of poor access to medical care; (2) many HIV positive people have a higher prevalence of known cancer risk factors (such as smoking); (3) HIV itself may affect cancer progression; or (4) HIV may interact with and exacerbate the effects of known risk factors.

Generally speaking, the number-one NADC is lung cancer (due mainly to the unusually high number of HIV positive people who smoke cigarettes), followed in terms of incidence by Hodgkin’s lymphoma, anal cancer, and liver cancer. Engels called these four the “important cancers” for people with HIV today. In contrast, people with HIV do not appear to be at higher risk for breast and prostate cancer compared with the general population.

Lung Cancer

Two words frequently come up in interviews with and articles by cancer researchers looking at the links between HIV and lung cancer: “Not surprising.”

“We know lung cancer is the most common non-AIDS cancer” among people with HIV, said Gregory Kirk, MD, PhD, MPH, associate professor of medicine and an expert on HIV and hepatitis at Johns Hopkins. “But it’s not surprising, because HIV positive patients as a whole smoke more than the general population.” Studies find that upwards of 80% of HIV positive people smoke cigarettes—and virtually all lung cancer occurs in smokers.

Studies also indicate that smoking is a particularly serious risk for HIV positive women. According to a *Journal of Clinical Oncology* report, a study of 3,549 women with a history of smoking (2,651 of them HIV positive) found that for women with HIV, smoking was the sole risk factor for developing lung cancer. Of the 14 cases of lung cancer that developed, 12 were in women with HIV. (It is important to point out that at the time of their lung cancer diagnosis, only two of these 12 were on HAART.)

Lung cancer incidence among people with HIV has not declined noticeably as HAART has become widely available—again, most likely due to

For more information on HIV and smoking—and how to kick the habit—see “Smoking and Your Health: How to Quit (and Why You Should)” in the Winter 2008 issue of *BETA*.

the population's unusually high rate of smoking.

Smoking has also been implicated in higher HPV viral load and higher rates of anal and cervical cancer. Researchers have found that many carcinogenic compounds from tobacco smoke accumulate in the mucosal tissue of the genitals, which may explain this connection.

Hodgkin's Lymphoma

Incidence of the second most common NADC, Hodgkin's lymphoma, actually increased substantially after HAART was introduced. Engels and colleagues found in their large retrospective study that as the incidence of ADCs declined thanks to HAART, the incidence of Hodgkin's lymphoma increased by a startling 68%.

Hodgkin's lymphoma, like the more common NHL, begins in the lymphatic system and eventually undermines the body's infection-fighting abilities. Fortunately, according to the Mayo Clinic, advances in diagnosis and treatment of Hodgkin's lymphoma have helped to make this once uniformly fatal disease highly treatable, with the potential for full recovery. The prognosis continues to improve for people with Hodgkin's lymphoma.

Epstein-Barr virus is almost always present in immunocompromised individuals with Hodgkin's lymphoma. EBV, a type of herpesvirus, occurs globally, and most people become infected with it at some point in their lives. In the U.S., as many as 95% of adults between 35 and 40 years of age have been infected.

Engels and colleagues suggested the apparently increased risk of Hodgkin's lymphoma could be due to the immune-modulating effects of HAART. But they also emphasized that Hodgkin's lymphoma is rare among people

on antiretroviral treatment. "Although Hodgkin's lymphoma risk has risen," they wrote in *AIDS*, "this malignancy is still less common than non-Hodgkin's lymphoma among people with AIDS."

Oncogenic Viruses

Human papillomavirus

Human papillomavirus is the most common sexually transmitted virus and one of the most easily transmitted viruses. There are more than 100 identified types of HPV. Some, including types 6 and 11, cause common skin warts and genital warts.

High-risk, potentially oncogenic HPV types—especially 16 and 18—can cause cancer of the anogenital area, including the cervix and anus. HIV positive people coinfecting with HPV are more likely than HIV negative individuals to carry more than one type of HPV.

HIV negative people typically develop antibodies to HPV within six to nine months after infection, and then clear the infection from the body. This is not always the case for people with HIV, whose immune systems may not be able to mount the response needed to eliminate the virus.

Joel Palefsky pointed out that, unlike most sexually transmitted infections, HPV can spread easily in the genital and anal area regardless of condom use—including via "auto-inoculation," or transfer of the virus from one area to another on the same person. In addition, infants born to HPV-infected mothers may contract HPV during delivery.

HIV positive women, especially those with advanced disease, tend to have more persistent HPV and are more likely to develop dysplasia (abnormal cell changes), progress faster to cancer, and experience recurrence after treatment.

Women with HIV in wealthier countries do not appear to be at higher risk for invasive cancer (typically a marker of advanced infection) because most of them receive regular Pap smears to check for early precancerous cell changes.

An analysis of 20 studies including nearly 5,600 individuals worldwide found that 41% of HIV positive women with high-grade precancerous lesions had more than one type of HPV, compared with 7% of women in the general population. The women with HIV were less likely to have oncogenic HPV type 16, but more likely to have other high-risk types such as 18, 51, 52, and 58.

The annual incidence of anal cancer among people with HIV has continued to increase in the HAART era, now standing at 128 cases per 100,000, or one case per 784 people. This is nearly 100 times the rate in the general population.

HIV positive men are 13 times more likely than HIV negative men of similar age to develop anal cancer. Men who have sex with men are more likely to have anal dysplasia and have a rate of anal cancer 35 times greater than that of the general population. In a study by Palefsky and colleagues, 95% of male participants who had sex with men had anal HPV infection, and 52% had precancerous abnormalities in anal skin cells.

It is important to emphasize that men who have sex with men are not the only people at risk for anal cancer. "Studies of women," said Palefsky, "show very high rates of anal HPV infection. It's clear that anal intercourse is a risk [factor] for many."

Erna Kojic said she sees women with anal HPV as often as cervical HPV. "We don't ask women about anal sex," she said, adding that although her own study has not found a link between anal sex and HPV in women, "I don't think we know enough."

Men also can be at risk for anal HPV even if they do not engage in

To learn more about HPV prevention, screening, and treatment (for women *and* men), see "Women and HIV: Human Papillomavirus" in the Summer 2007 issue of *BETA*.

anal sex. For men, explained Palefsky, “anal HPV may [result] from some form of sexual play around the anal canal from a woman or another man; it doesn’t require the insertion of a penis into the anus.”

Palefsky said the important message is that anal HPV infection is far more ubiquitous in men and women than previously thought. Regular anal Pap smears and HPV tests are not considered part of the standard of care for HIV positive people, but Palefsky and other experts think they should be.

Hepatitis B and C

“Liver cancer needs to be part of any discussion of cancer for people with HIV,” said Lynn Taylor, MD, assistant professor of medicine at Brown University and an expert on HIV and viral hepatitis.

Liver cancer is deadly. “Average survival is seven months,” said Taylor. But, she emphasized, many risk factors are modifiable.

Over years or decades, HBV and HCV can cause severe liver disease, including cirrhosis (scarring) and a type of cancer known as hepatocellular carcinoma. HIV speeds up the course of both HBV and HCV disease, according to Taylor.

Hepatitis B and C are the leading causes of liver cancer overall, seven times more so for people with HIV; men, especially African American men, are at higher risk. “This cancer has a predilection for men,” said Taylor. (There is evidence, in fact, that the hormone estrogen helps protect women from developing liver cancer.)

Taylor recommends that all HIV positive people should know their HBV and HCV status. This will enable them to seek appropriate treatment and modify risk behaviors that can contribute to disease progression and possible liver cancer.

Taylor described HBV and HCV as “sneakier than HIV because they’re silent much longer.” She explained, “With HIV, we may get other infec-

tions and say, ‘Something is wrong, I better get a test.’ Hepatitis B and C are sneaky. For years and years, people don’t have symptoms.”

She noted that people infected with HBV may become sick soon afterward. Most adults clear the virus and develop antibodies that will protect them against future exposure. But 10% of infected adults (and 90% of babies infected at birth) do not clear the virus and become chronic carriers. This means they are able to transmit the virus to others and are at increased risk for developing cirrhosis or liver cancer.

For HIV positive people who are not already coinfecting with HBV, a highly effective hepatitis B vaccine has been available since the late 1970s. Said Taylor, “no one who is HIV positive who doesn’t have hepatitis B should be unvaccinated for hepatitis B. It is a cancer-preventing vaccine.”

For chronic HBV carriers, Taylor said the antiviral medications used to manage HBV are some of the “safest and best tolerated” meds, and some are also active against HIV. These include tenofovir and emtricitabine (the drugs in Truvada), and lamivudine (3TC, Epivir).

U.S. antiretroviral treatment guidelines state that regimens for HIV/HBV coinfecting people should include drugs active against both viruses. Nearly a third of people with HIV in the U.S., and upwards of five million worldwide, are coinfecting with hepatitis C—comprising what Taylor calls “the global HIV/HCV epidemic.”

“Alcohol used to be the leading cause of liver cancer,” said Taylor. “Now it’s hepatitis C.”

HCV has typically been more common among injection drug users who share needles. But Taylor said there is an “alarming rise” in sexually transmitted HCV infection among HIV positive men who do not inject drugs but do engage in “rough” sexual activities with other men (which may damage rectal tissue enough to permit

HCV entry) and have other sexually transmitted infections.

HAART slows liver disease progression in coinfecting individuals, though this group faces a greater risk of liver toxicity from antiretroviral drugs than someone infected with HIV alone. Taylor recommends that HIV positive people who are coinfecting with HBV or HCV begin HAART early. “Control of HIV is the foundation of care for people with both [hepatitis] B and C,” she said.

The current standard of care for chronic hepatitis C is pegylated interferon alpha-2a (Pegasys) or pegylated interferon alpha-2b (PegIntron) plus weight-adjusted ribavirin. The usual duration is 48 weeks for people with hard-to-treat HCV genotype 1, and 24 weeks for those with genotypes 2 or 3, but many experts recommend that all HIV/HCV coinfecting people receive the longer course.

Not everyone with hepatitis C experiences serious liver disease progression. Traditionally, treatment has been recommended for people with advancing fibrosis, as determined by a liver biopsy, but some experts recommend that coinfecting people should be treated sooner.

Taylor acknowledges that current interferon-based treatment has “a lot of limitations and problems.” She said, “There can be terrible side effects, including fever, headache, weight loss, and depression.” But, she added, “We never know who’s going to feel something or not. I’ve seen people on interferon run marathons.”

Taylor said a “whole host” of new meds that directly target HCV (including protease and polymerase inhibitors) are in development; the first two, telaprevir and boceprevir, are expected to become available within the next year. These drugs will still have to be taken with interferon and/or ribavirin, but will likely shorten the duration of treatment and improve response rates.

In the meantime, Taylor said those facing the dilemma of whether to risk

**SKIN CANCER:
ANOTHER NADC OF NOTE**

People with HIV, especially those with lighter skin, seem to be at higher risk for various types of skin cancers. Basal cell and squamous cell carcinomas are the most common subtypes of skin cancer that can affect this population. They are also at higher risk for melanoma, the deadliest skin cancer, possibly because of immune suppression.

Although the actual relationship between HIV-related immune suppression and skin cancer is still unclear, we do know that chronic exposure to the sun's ultraviolet rays is probably the leading risk factor for all skin cancers. Using sunscreen and avoiding prolonged exposure to the sun are widely considered the best preventive measures.

a difficult reaction to interferon might want to ask themselves: Should I take these meds and maybe benefit, get cured, and then stop the meds, or do I do nothing and risk progression to cirrhosis and liver cancer? It's a bit of a gamble not knowing how one will tolerate the current treatment. But on the positive side, Taylor said, HCV meds can potentially eliminate the virus altogether—what is called sustained virological response—unlike the lifelong therapy needed for HIV.

"It's their choice," Taylor concluded. "As long as people understand there are consequences of not being treated." But clearly, she added, "the treatments are much more effective" if HCV is detected early.

The Role of Immune Health

The relevant question, as Eric Engels put it in his 2009 editorial in *AIDS*, is whether HIV amplifies the effects of known carcinogens (including other viruses) to promote the development of cancer. He pointed out that the most obvious way HIV could facilitate the development of these malignancies is by disturbing the immune system.

Another relevant question in the age of HAART is: Can antiretroviral treatment sufficiently suppress HIV and restore the immune system so

as to reduce the potentially cancer-causing effects of viruses and other microbes that otherwise take advantage of weakened immunity?

Because good medical care, self-care, and HAART can keep people with HIV alive and well for many years—possibly a normal lifespan—there is also the question of whether aging HIV positive people are simply at higher risk for cancer because they are getting older. Aging is a cancer risk factor for all people, regardless of HIV status.

Aging and Inflammation

Seeing more cancer among HIV positive people, even those on HAART, does not surprise Johns Hopkins' Gregory Kirk. "People are living longer, and as people age they are just going to be at risk for these other types of cancer we didn't see earlier in the epidemic."

There has been much discussion of the role of chronic immune activation and inflammation in the pathogenesis of HIV disease, and their link to non-AIDS conditions such as cardiovascular disease and cancer. Are people with HIV, even those on HAART, experiencing what some call "accelerated aging" as their immune systems show characteristics typical of older people—including a lack of immune cell regeneration and accumulation of aging T-cells? (See "Inflamma-

tion, Immune Activation, and HIV" in the Winter/Spring 2010 issue of *BETA*.)

How will aging itself contribute to risk for "age-related" cancers? Until relatively recently, these cancers weren't investigated in people with HIV, simply because they died from AIDS-related causes before they could age. (See "Aging & HIV: Emerging Issues in Research, Treatment, and Care" on page 42.)

Writing in the *Journal of the National Cancer Institute*, Engels and James Goedert noted that HAART is increasing the size of the HIV positive population, "and their long-term cancer risks are undefined." They cite a Swiss study that found the risk for KS and NHL was still 20 times greater among HAART-treated HIV positive individuals than for the general population. Did this mean antiretroviral treatment had failed? Or were other mechanisms involved?

Engels and Goedert also pointed out that no one knows "the types and magnitude of cancer risk after 10–20 years with partial immune reconstitution with HAART." Some models suggest that aging and prolonged mild immunosuppression could interact—particularly if there are other cancer risk factors—to magnify the incidence of tumors currently deemed unrelated to AIDS.

"Inflammation could play a role in the development of those cancers, particularly lung cancer," said Engels. He said inflammation in the lungs could act in concert with cigarette smoke to cause lung damage. He also noted that HIV positive people have a higher rate of emphysema, which could be related to inflammation or HIV itself. But Engels does not see evidence that people with HIV age faster. "It may be true for other conditions," he said, "but at least where cancer goes, it doesn't seem to be accelerated."

Another piece of evidence that works against the assumption that HIV alone accelerates the cancer risk associated with aging is that HIV

positive children and adolescents do not develop cancers at rates comparable to adults. Three-quarters of the cancers found among children with HIV are malignancies of the lymph nodes. Given this difference between younger and older people with HIV, it is possible that different cancer rates may be due to different modes of HIV transmission, age-related factors, and coinfection with other viruses more commonly found among sexually active adults.

Researchers increasingly believe that “duration”—the length of time one lives with HIV infection or with other coinfections—has at least as much to do with cancer risk as inflammation or aging.

“Cancer development can occur over 20 to 30 years,” said Michael Silverberg. “I don’t think it’s known at this point where, with HIV or the inflammatory state, the hits to the immune system occur.”

Proxies of Immunity

For people with HIV, the development of most ADCs and NADCs is tied to their CD4 cell count and HIV viral load. Those on HAART typically have relatively high (or even near-normal) CD4 counts and low or undetectable viral load.

CD4 cell count. Having a more compromised immune system, as indicated by CD4 cell count, is the biggest risk factor for both ADCs and NADCs. Silverberg has found low current CD4 count and high viral load to be risk factors for cervical cancer, KS, and NHL—the three ADCs common in the pre-HAART era. Anal cancer risk is also increased in people with a long-term low CD4 count. Other researchers have found current CD4 count predictive of lung and liver cancer.

“If you look at how long the CD4 count is suppressed,” said Gregory Kirk, “it’s more what the CD4 count was just before the cancer diagnosis.”

People with HIV and transplant recipients—who receive immune-

suppressing drugs to prevent organ rejection—are at particular risk for cancers caused by oncogenic viruses, such as anal, cervical, and liver cancer. As the CD4 count drops, the immune system is less able to clear HPV or the hepatitis viruses.

Engels has pointed out that the immune restoration that results from HAART may actually trigger development of Hodgkin’s lymphoma. “Partial restoration of immunity allows recruitment of surrounding immune cells and manifestation of the tumor,” he wrote in *AIDS*.

The lowest-ever or “nadir” CD4 count plays a role. Even after achieving good CD4 cell recovery on HAART, people who previously had a low level—especially those who qualified for an AIDS diagnosis (less than 200 cells/mm³)—continue to have a higher risk for a variety of conditions compared with HIV negative people.

A 2009 study of 52,278 HIV positive people reported in *The Lancet Oncology* by Marguerite Guiguet and colleagues found that those diagnosed with KS and NHL—two classic ADCs—had low nadir CD4 counts (as low as 68 cells/mm³) and current CD4 counts (below 200 cells/mm³). Two-thirds of those with NADCs also had low CD4 counts. These individuals had been living with HIV for a long time and had spent an average of two years with a CD4 count below 200 cells/mm³ and a year with a viral load above 100,000 copies/mL.

Engels pointed out in his 2009 *AIDS* review that low CD4 counts are strongly associated with the early stages of HPV-induced anal cancer. Merely finding HPV at all, and possibly precancerous lesions, is evidence that an individual’s immune system is compromised—so a corresponding low CD4 count is not surprising.

But the low CD4 count did not seem to be as strongly associated with risk of anal cancer itself. HAART may appear to be associated with higher rates of anal cancer because HIV positive people coinfecting with anal HPV

live longer with HPV infection—and so need to be monitored regularly to treat and prevent escalation to anal cancer.

Viral load. Michael Silverberg noted that, although we do not know exactly what factors may trigger malignancy (low CD4 count? inflammation?), we do have viral load as a proxy for immune status. In general, a higher viral load corresponds with a weakened immune system.

Speaking at the 2008 Conference on Retroviruses and Opportunistic Infections in Boston, Alexander Zoufaly of the University Medical Centre Hamburg-Eppendorf said that age, latest CD4 count, and cumulative viral load were strong predictors for development of AIDS-related lymphoma.

Zoufaly recommended optimizing HAART for maximum HIV suppression to help reduce the incidence of AIDS-related lymphoma. Similarly, an earlier Swiss study found that HAART cut the risk of NHL by half within five months, and kept it extremely low even after ten years.

In Guiguet’s study, a high viral load (above 100,000 copies/mL) was associated with an increased risk of ADC. HAART protected against cancer, reducing the risk of cervical cancer alone by 50%. A higher CD4 count also significantly reduced the risk of this particular malignancy.

Prevention

As Guiguet and others have noted, HAART is the key to reducing HIV positive people’s risk of cancer. Early HAART that maintains the CD4 count above 500 cells/mm³ will go far toward protecting against a range of cancers, especially KS and NHL.

There are other ways people with HIV can reduce their risk for cancer of all sorts. Receiving appropriate screenings, treatment for viral coinfections, and vaccines as needed—as well as making behavior changes like smoking cessation—can contribute substantially to lower cancer risk and improved overall health.

HAART as Cancer Prevention and Treatment

Silverberg and colleagues Chun Chao and Donald Abrams have noted evidence that beginning HAART early sustains immune function, improves HIV-related outcomes, and also reduces the risk of cardiovascular, kidney, and liver disease. They suggest these findings also support earlier initiation of HAART to reduce the risk of non-AIDS cancers. They further suggest that the association of NADCs with recent CD4 count means HAART might make it possible to reverse the risk of NADCs.

Silverberg has found that protease inhibitors are particularly beneficial in preventing and treating KS. HIV positive people taking protease inhibitors also appear to have fewer cases of prostate cancer. “We’re seeing a decreased risk [of prostate cancer] compared to the general population,” Silverberg said. “It’s currently not clear why. It could be a hormonal deficiency—decreased testosterone.”

Or, as Silverberg and Abrams suggested in *Current Opinion in Oncology*, the protease inhibitors often used in HAART may be demonstrating the kind of anti-cancer effect seen with other natural protease inhibitors such as rice, seeds, and legumes (e.g., beans, soy beans, and chickpeas).

Silverberg, like others, points out that HAART has been implicated as a possible contributor to increased risk of Hodgkin’s lymphoma as part of immune reconstitution inflammatory syndrome (IRIS), which some HIV positive individuals temporarily experience as their immune systems recover with antiretroviral treatment.

Although some antiretroviral drugs can cause liver toxicity, Engels has noted that HAART use may actually decrease liver cancer risk—perhaps by improving immune control of viral hepatitis. For people with HIV who are being treated for any type of cancer, Silverberg said, “discontinuing

antiretrovirals with chemo[therapy] is not advised” because it will raise viral load.

HAART’s ability to raise CD4 cell counts makes it an essential part of cancer prevention and treatment for HIV positive people. “The immune system is very closely linked to cancer risk,” said Silverberg, “so a low CD4 count is associated with cancers.”

Regular Screenings

All sexually active people, regardless of HIV status, are advised to be tested on a regular basis for the presence of any new microbes that may have taken up residence in their body since their last test. This means annual cervical or anal Pap smears for everyone. Joel Palefsky pointed out that rates of anal cancer are increasing, and regular testing could virtually eliminate this cancer.

“It is not the standard of care yet,” he lamented. “Even in San Francisco,” he said, “with all the work we do, we only see a tiny fraction of people at risk.” Palefsky said it is incumbent upon men and women with HIV to be proactive and informed, and to request—even insist upon, if necessary—yearly anal Pap smears.

As people with HIV get older, they—like all aging people—are advised to have regular screening tests that are proven to reduce cancer risk.

The National Cancer Institute advises women over 40 to have annual mammograms. Everyone over 50 is advised to have a colonoscopy every five years; the procedure is the single-most effective measure available for detecting, preventing progression of, and treating abnormalities in the colon and rectum that can be precursors to cancer.

The American Urological Association recommends that men receive a first-time prostate test at age 40, with follow-up testing to be determined on an individual basis. Typically, men are advised to receive annual prostate exams starting at age 50. African American men or men with a family history

of prostate cancer are typically advised to start screening earlier.

Annual skin exams are recommended given the higher risk for skin cancers among HIV positive people, particularly those with fair complexions. Examination, often performed during a routine annual checkup, can look for anything unusual and also determine whether naturally occurring moles or blemishes look different or have changed enough to warrant follow-up.

Hepatitis B and C Testing and Treatment

In 2010, the U.S. Food and Drug Administration (FDA) approved the Ora-Sure rapid hepatitis C test. Lynn Taylor said the test will be even more useful and widely available once it doesn’t require blood drawn from a vein and can be done either by a fingerstick blood test or, easier still, an oral swab.

For chronic HBV carriers, antiviral medication will suppress the virus and thereby reduce its ability to cause disease progression to cirrhosis or cancer. “We have very manageable treatment,” Taylor said. HIV/HBV coinfecting people are advised to use drugs such as lamivudine and tenofovir that are active against both viruses. However, HAART regimens must be carefully reviewed to avoid drug-drug interactions or intensified side effects when combined with hepatitis B treatment.

As discussed above, interferon-based chronic hepatitis C treatment remains challenging, but new oral drugs are coming that will reduce treatment duration and increase response rates.

Taylor recommends that people with chronic hepatitis B or C receive a liver ultrasound exam every six months to detect liver tumors at an early stage. “Not everyone with HIV needs to be screened” via ultrasound, she stressed. “It’s only for HIV positive people who have chronic hep B or C, or cirrhosis. Once scarring of the

liver sets in, you have to have [regular] screening.”

Vaccines

“Hepatitis B is preventable” by vaccination, Taylor said. “It is a very safe, much-studied vaccine.” The ability to prevent HBV infection makes it literally a cancer-preventing vaccine, because the one in ten people who become chronically infected are at greater risk for cirrhosis and liver cancer.

For young women and men, HPV vaccines prevent infection or disease progression. Studies with young women have shown that Gardasil and Cervarix are highly effective at preventing precancerous and cancerous cervical cell changes caused by HPV. Gardasil protects against HPV types 6, 11, 16, and 18. Cervarix protects against types 16 and 18.

“The effectiveness is greatest in women who have no HPV types,” said

Erna Kojic. She pointed out that the vaccines’ protection is “totally type-dependent”—which means, “theoretically, if you have HPV 53, you get the vaccine and should still be protected for 6, 11, 18, 16, etc.”

In November, an FDA advisory panel recommended that the indication for Gardasil be expanded to include prevention of anal cancer and precancerous cell changes in men and women age 9–26 years.

Presenting at the February 2010 Conference on Retroviruses and Opportunistic Infections, Palefsky reported that Gardasil was highly effective at preventing precancerous anal lesions in younger gay men. At the International AIDS Conference in July 2010, researchers presented data showing that Gardasil reduced external genital lesions in men. The vaccine also appeared to help prevent precancerous anal lesions in a sample

of gay men in the study, and there were no cases of anal cancer seen in these participants.

Behavior Change

For some people with HIV, changing behavior may mean establishing better exercise habits, improving adherence to an antiretroviral treatment regimen, or simply finding a way to access medical care.

For HIV positive individuals on HAART who are still at higher risk for cancer because of immune deficiency or viral coinfections, there are other important opportunities to change behaviors that are counterproductive to living well with HIV.

Reducing the number of sex partners and using condoms are ways to limit exposure to new infections that could potentially lead to cancer, including HPV, HBV, and HCV.

Smoking cessation is the most important preventive measure for avoiding lung cancer and lowering the risk of HPV-related anal and cervical cancer. Giving up smoking, said Palefsky, is one of the things “patients can do for themselves when they ask how to reduce risk for cancer.”

Moderating alcohol use is also important, especially for people with chronic hepatitis B or C (since alcohol can accelerate liver disease progression), and for those on HAART, as hepatitis and antiretroviral drugs both tax the liver. “Alcohol is the most modifiable risk [factor] of all,” said Taylor. She noted that medications such as bupropion (Wellbutrin, Luvox), naltrexone (Depade, ReVia), and opioid antagonists can help reduce alcohol intake, acknowledging that “not everyone can say through force of will, ‘I will shut down alcohol use.’”

Next Steps

Like other researchers looking at the connections between HIV and cancer, Eric Engels predicts that incidence of NADCs will continue to increase among people with HIV.

GARDASIL AND ADVERSE EVENTS

No discussion of Gardasil can be complete without mentioning that serious adverse events—including blood clots and deaths—have been documented via the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program of the U.S. Centers for Disease Control and Prevention (CDC) and the FDA.

However, as Barbara Slade of the CDC and colleagues noted in a review article, “VAERS data need to be interpreted with caution, because not all reported events are systematically validated, and many may have only coincidentally followed vaccination.” For example, nearly half the reports of deaths following vaccination lacked a patient name or contact information, so the deaths could not be confirmed—and a direct link between vaccination and death has not been established for any of the deaths that were confirmed.

Slade and colleagues’ review did find that syncope (fainting) and venous thromboembolic events, such as blood clots and strokes, were reported more frequently with Gardasil than with other vaccines. Again, not all of these reports could be confirmed, and some were linked to other risk factors (including smoking, family history, and one case of “trauma from surfing”). The authors concluded that “ongoing monitoring will help assess whether the serious reports to VAERS . . . require further evaluation.”

Individuals considering Gardasil (or any other vaccine) would be wise to thoroughly discuss their health and family medical history with their clinician. For more on Gardasil safety surveillance, visit www.cdc.gov/vaccinesafety/vaccines/hpv/gardasil.html.

As he explained in *AIDS*, two ADCs already have increased among people on HAART: Hodgkin's lymphoma because of immune reconstitution syndrome, and anal cancer due to prolonged exposure to HPV. HAART is helping HIV positive people live longer, which means they will be at greater risk for cancer as they age, like the general population. And longer survival will increase the number of observed cases.

"Thus," wrote Engels, "the rising number of cases of non-AIDS-defining cancers will make prevention and treatment of these malignancies an increasing priority in HIV care."

Further Research Needed

In a study of trends in cancer risk among people with HIV in the U.S. from 1980 to 2002, Engels and colleagues said that more data are needed to address the concern that cancer incidence, which generally increases with age, "will rise dramatically as people with advanced HIV infection survive longer."

Michael Silverberg and Donald Abrams have pointed out that future studies are needed to characterize the epidemiology of NADCs in HIV positive people in the HAART era—including changes in risk factors, coinfections, and screening practices.

They noted that more research is needed on the relationship between immunodeficiency and cancer risk because earlier studies did not consider such factors as current or nadir CD4 cell counts or viral load for individual NADCs, or immunological changes over time due to HAART. They added that studies have not determined whether immune function is associated with cancer risk independent of cigarette use, coinfections, or other known risk factors.

Reducing Cancer Risk

The glass is at least half full when it comes to the variety of ways people with HIV and their physicians can

reduce—sometimes dramatically—the risk of developing cancer.

Based on what is currently known, HAART is the best overall method of cancer prevention and risk reduction. Maintaining immune system health is the key to good health in general, and to reducing cancer risk in particular. ADCs can be almost entirely prevented by keeping CD4 counts above 500 cells/mm³ and viral load as low as possible, ideally undetectable.

The leading NADC, lung cancer, can be virtually eliminated by not smoking cigarettes. "We need to be much more aggressive in identifying and developing programs for smoking cessation in our HIV-infected populations," said Gregory Kirk. "We need to educate patients and providers more about the risk of smoking." He recommended evidence-based strategies such as nicotine patches and gum to help people with HIV quit smoking.

Preventing Anal and Cervical Cancer

For HIV positive people coinfecting with HPV, cervical and anal cancer can be virtually eliminated by regular Pap smears (cervical for women, anal for women and all men), with follow-up treatment of any lesions or other abnormalities that may be discovered.

To enjoy the protective benefits offered by Pap smears, people with HIV must actually receive them. A 2009 *AIDS* article reported that nearly one in four HIV positive women had not received an annual Pap smear in the previous year.

Worldwide, the Pap test is not used as widely as it is in the U.S. and other industrialized countries. But even a simple program—such as one used to screen 21,000 women (6,572 of them HIV positive) in Zambia—can detect risk for cervical cancer and get women who need it into treatment.

The program used a basic method of screening: cotton wool soaked in vinegar and applied to the cervix for three minutes, long enough to ensure

that any abnormalities would show up as white or red marks. The screening detected abnormal results in 54% of the HIV positive women.

Clearly, even in a resource-constrained setting, regular Pap smears would prevent a great deal of cervical cancer caused by HPV. The researchers estimated that their program prevented one death from cervical cancer for every 32 women screened.

At the 2009 International AIDS Society Conference, a report from the Veterans Administration health care system suggested that up to 89% of men with HIV could potentially derive at least some benefit from one of the two currently licensed HPV vaccines.

Although this study found that the vaccines were not as effective in older men as they are in younger people prior to HPV exposure, the findings warrant further research on the effectiveness of vaccines for those already infected with HPV.

Preventing Liver Cancer

It is imperative to educate all people with HIV about hepatitis B vaccination to prevent infection and medical management of HBV for those already living with it. Chronic hepatitis B carriers can greatly reduce their risk for liver cancer by taking antiviral medication to keep the virus suppressed.

Injection drug users have historically been at greatest risk for liver cancer, at least partly because of their greater incidence of hepatitis B and C. But reports of clusters of sexually transmitted acute hepatitis C infection among men who have sex with men in the U.S., Europe, and Australia have led to calls for regular screening of all at-risk individuals, including people with HIV.

At Brown University, Lynn Taylor and her Miriam Hospital colleague Kenneth Mayer are studying a low-cost screening strategy to identify acute HCV with routine blood tests at an HIV clinic. "People don't know what risk factors lead to hep C because they

aren't asked respectfully—doctors don't know *how* to ask—or they have no symptoms,” said Taylor.

She advocates that the guidelines now used in Europe—which recommend annual hepatitis C testing for people with HIV—should become the standard of care in the U.S., as well. “We need to adopt the European guidelines that everyone with HIV gets an annual hep C test,” said Taylor. “It would mean the sneaky, silent infection is picked up.” It would also mean “people would have a lot more they can do—such as cut down on alcohol and [begin] treatment.”

While there is currently no vaccine to prevent HCV infection, new drugs are nearing approval that, when used with interferon, will shorten treatment time and improve the likelihood of sustained response. Taylor added, “I tell my hep C patients, ‘The rest of your life, see a hep C doctor; go every six months.’”

Closing Note

One goal of HIV care is empowering people to live well with the virus. When it comes to the risk of developing most of the cancers described in this article, HIV positive people have a great deal of power to determine the outcome.

People living with HIV today have a variety of tools for cancer prevention, including antiretroviral therapy, regular health screenings, changing

smoking habits and alcohol use, and learning about cancer and its risk factors. Making these changes may not be easy, but they can empower HIV positive people to take control of their health and protect themselves from cancer.

John-Manuel Andriote recently updated and expanded his 1999 book, *Victory Deferred: How AIDS Changed Gay Life in America*, for a new paperback edition. He has been living well with HIV since 2005.

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