

The Rising Challenge of Non-AIDS-Defining Cancers in HIV-Infected Patients

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Since the advent of HAART, patients with HIV infection have seen a significant improvement in their morbidity, mortality, and life expectancy. The incidence of AIDS-defining illnesses, including AIDS-defining malignancies, has been on the decline. However, deaths due to non-AIDS-defining illnesses have been on the rise. These so-called non-AIDS-defining cancers (NADCs) include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma. It is poorly understood why this higher rate of NADCs is occurring. The key challenge facing oncologists is how to administer chemotherapy effectively and safely to patients on antiretroviral therapy. The challenge to clinicians caring for HIV-infected patients is to develop and implement effective means to screen, treat, and prevent NADCs in the future. This review presents data on the epidemiology and etiology of NADCs, as well as ongoing research into this evolving aspect of the HIV epidemic.

Since the advent of highly active combination antiretroviral therapy (HAART, or cART), patients with human immunodeficiency virus (HIV) infection have seen a significant improvement in their morbidity, mortality, and life expectancy where access to cART is common [1]. The population of patients with AIDS has decreased 4-fold in the post-HAART era, and the incidence of AIDS and AIDS-defining illnesses, including opportunistic infections and AIDS-defining malignancies, have been on the decline since cART became common practice in the mid to late 1990s [2]. However, deaths due to non-AIDS-defining illnesses have been on the rise [3, 4].

Cancers not previously associated with HIV and AIDS appear to be increasing in incidence. These are

termed non-AIDS-defining cancers (NADCs) and include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma, among others. Interestingly, in populations benefiting from cART, some NADCs appear to have a higher relative incidence compared with the same cancer rates seen in the general population, even after controlling for known cancer risk factors. The reasons for these increased cancer rates are poorly understood. In this review, we highlight the epidemiology data and potential etiological causes and then focus on ways to screen, treat, and ideally prevent this growing specter of NADCs.

Incidence

In the post-HAART era, numerous international epidemiological studies, including from France, Switzerland, the United Kingdom, and the United States, have shown that rates of NADCs are on the rise [2, 5–8]. While the rates of AIDS-defining cancers (non-Hodgkin's lymphoma, Kaposi's sarcoma, and cervical cancer) declined 3-fold from 1995 to 2005, the incidence of NADCs rose by more than 3-fold in that same time period [2]. Within the United States, national,

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Table 1. Standard Incidence Ratios of Selected Non-AIDS-Defining Cancers [2, 5–8]

Non-AIDS-Defining Cancer	Cancer Risk (Standardized Incidence Ratio)
Anal	33.4–42.9
Hodgkin's Lymphoma	14.7–31.7
Liver	7.0–7.7
Skin	
Squamous cell carcinoma/Basal cell	3.2
Melanoma	1.1–2.6
Head and Neck	1.0–4.1
Lung	2.2–6.6
Leukemia	2.2–2.5
Renal	1.8–2.2

regional, state, and local epidemiological studies have confirmed these international findings [9–14]. For example, NADCs accounted for 31% of all cancer diagnoses in the pre-HAART era, compared with 58% of all cancers in the post-HAART era [14]. The increased rate of NADCs, measured using the standardized incidence ratio (SIR), in HIV-infected individuals is 2.8 (with 1.0 being the rate in the reference, or general, population) [6]. For certain cancers, the rates in HIV-infected patients are much higher compared with the general population. Table 1 shows the SIRs of selected NADCs in HIV-infected individuals from the large international studies referenced above. Conflicting evidence exists as to whether other cancers, such as colon and prostate cancers, are occurring at different rates in HIV-infected individuals compared with the general population [7–10, 13, 15–17].

Epidemiology

The increased risk for NADCs, at least in the United States, appears to be primarily among Caucasians, with no increased risk seen in African Americans and other ethnic groups [10]. It is unclear whether these findings are due to reporting bias or whether they provide important epidemiologic and biologic clues to cancer etiology. Further, the higher risk of NADCs is primarily among males, with HIV-infected women having no higher rates of NADCs compared with the overall population [5, 18–20].

The strongest epidemiological risk factor for developing an NADC is age. This is not surprising and actually would be expected because patients with HIV are living longer and increased age-appropriate cancer diagnoses are being made [21]. However, NADCs are being diagnosed at a much younger age in HIV-infected patients compared with the general population, including those with head and neck, anal, lung, colorectal, and liver cancers [22–32]. The risk of developing an NADC of any kind in an HIV-infected patient aged >40 years is 12 times higher compared with the general population [10].

Similarly, duration of HIV infection is also significantly associated with the risk of developing an NADC, with an increased odds ratio of 1.20 for every year of HIV infection [10].

Although the duration of HIV infection increases risk, the severity of HIV infection may not. This is in contrast with AIDS-defining cancers for which the degree of immune suppression (as measured by CD4 count) correlates with the risk of developing cancer [6]. For NADCs, conflicting evidence has been reported as to whether mild to moderate immune suppression correlates with cancer risk [6, 8, 10, 33, 34]. However, patients with severe and prolonged immune suppression, with CD4 counts less than 200/ μ L, show a decreased rate of NADCs, likely due to the mortality risk from AIDS-defining illnesses in this patient population [9, 10].

Etiology

Research into possible etiologies of NADCs has begun to elucidate potential causes. Explanations include the HIV virus itself, coinfection with oncogenic viruses, combination antiretroviral therapy (cART) agents, and tobacco exposure in the setting of HIV.

The HIV virus may have direct tissue, cellular, and/or genetic effects that contribute to the development of cancer, including NADCs. HIV may activate proto-oncogenes [35, 36], cause alterations in cell cycle regulation [37], inhibit tumor suppressor genes including p53 [38, 39], or cause microsatellite gene instability and genetic alterations leading to oncogenesis [40, 41]. Infected tissues may be more sensitive to the effects of carcinogens from the environment [42–44]. Finally, HIV infection can cause endothelial abnormalities including pro-angiogenesis signaling, which may enhance the development of tumor growth and metastasis [45–47].

HIV-infected patients have an increased risk of exposure and subsequent infection with cancer-causing viruses, including hepatitis B and C virus (HBV and HCV), human papillomavirus (HPV), and the Epstein-Barr virus (EBV) [48–51]. Coinfection with HIV and these viruses continues even in the post-HAART era [52–54]. HIV-infected patients have an accelerated progression of disease from viruses such as HBV and HCV disease [55, 56]. This in turn may explain higher rates of liver [13, 30, 51, 54], anal [2, 15, 57], and head and neck cancers [57, 58, 59], as well as Hodgkin's lymphoma [5, 6, 60–62]. For example, although between 20% and 50% of Hodgkin's disease may be caused by EBV in the general population, between 75% and 100% of patients with HIV have EBV-associated Hodgkin's disease [5, 6, 61, 62]. Local as well as systemic impairment of EBV-specific T-cell responses, especially CD4+ T cells, may predispose HIV patients to development of this disease [63].

Conflicting evidence has been presented as to whether—or which—antiretroviral therapies increase, decrease, or have no

effect on the risk of developing an NADC [6, 8, 10, 13], with no clear pattern emerging from these epidemiological reviews. More work needs to be done to further answer this important question.

Tobacco, the causative agent for a number of NADCs including lung and head and neck cancers, is used more commonly in HIV-infected individuals, with smoking rates among HIV-infected patients in the United States at 52%–60% and as high as 80% in some urban areas [64]. This mirrors high smoking rates seen in other countries [6]. However, after controlling for smoking status, HIV-infected individuals are still at a 2.5 to 3.6 higher risk of developing lung cancer compared with the overall population [65, 66]. It is not known whether this higher cancer rate is due to increased tissue sensitivity to tobacco carcinogens in the setting of HIV infection.

Unfortunately, patients with NADCs often have more aggressive cancers and present with more advanced stages of the disease [15, 22]. For example, HIV patients with hepatocellular carcinoma show a greater degree of infiltrative disease, with more advanced cirrhosis on presentation, and experience poorer outcomes [30]. Skin squamous cell cancers are more aggressive in HIV-infected patients, with a higher risk of local recurrence and metastasis, leading to a 50% mortality rate [32]. Although HIV patients diagnosed with early-stage breast cancer have survival rates that are similar to those in non-HIV infected patients [67], breast cancer in HIV-infected patients is more commonly poorly differentiated, bilateral, and with early metastases [68]. In Hodgkin's lymphoma, treatment outcomes may be favorable, but disease recurrence remains a problem [69].

Whatever the etiologies of these higher rates of NADCs, the central clinical questions facing primary care physicians, infectious disease specialists, and medical oncologists is how best to screen, treat, and ideally prevent these cancers in their patients.

Screening

Given these high NADC rates, logical questions to ask are: Do current cancer screening guidelines apply to HIV-infected patients? Should HIV-infected patients be screened differently than the general population? Should HIV-infected patients undergo screening at a younger age, at more frequent intervals, or with different tests than the general population? Should we be screening HIV-infected patients for cancers for which we do not screen the general population?

The tenet of cancer screening is based on the assumption that identification and treatment of precancerous conditions or cancer in asymptomatic individuals will improve survival [70]. Current cancer screening guidelines vary based on the organization that developed the guidelines. The American Cancer Society, the National Cancer Institute (NCI), the US

Preventive Services Task Force, and other organizations each publish their own recommendations for cancer screening. Currently, none of these organizations have formal screening guidelines for the most common NADCs. The only recommendations that exist for these particular cancers are geared toward the general population. However, the European AIDS Clinical Society has proposed screening recommendations for anal, breast, cervical, colorectal, liver, and prostate cancers in HIV-positive patients [71].

Clearly, clinicians caring for HIV-infected patients should be performing age-appropriate screening in their patients, including for colon, breast, and prostate cancers [2]. However, past research has found that routine screening is performed less frequently in HIV-infected subjects. For example, rates of breast cancer screening using mammography were significantly lower in HIV-infected women compared with the general population (67% vs 79%) [72]. Similarly, age-appropriate screening for colon cancer was done at a lower rate (56% vs 78%)—a difference that was statistically significant—in HIV-infected subjects compared with age- and gender-matched controls [73].

A few caveats deserve mentioning. For colon cancer screening, HIV-positive patients typically present with more advanced stage disease and more commonly have right-sided disease that would be missed by flexible sigmoidoscopy [15]. Thus, full colonoscopies should be performed. Although there are no national or international guidelines for screening practice and the management of anal dysplasia in HIV-infected individuals, it may be worth having trained healthcare professionals perform routine anal cytology screening [74, 75]. Finally, a new technique that may aid in the screening for lung cancer in at-risk individuals, including those infected with HIV, has been proposed. The National Lung Screening Trial (NLST) showed that screening with computed tomography scans in high-risk smokers reduced lung cancer mortality by 20%. Whether this will be adopted for the general population is not yet known [76]. If it is, then applying this screening technique to HIV-positive patients with a history of high-risk tobacco use should be equally warranted.

Treatment

In general, cancer therapy is determined by the primary site of disease, disease burden, and host comorbid status. Interventions often include a combination of surgery, radiation, and/or chemotherapy. Typically for early-stage disease, treatment is undertaken with a curative intent. However, patients with more advanced stage disease may not benefit from such an approach; often palliative therapy is more appropriate.

Although standard treatment should be offered to the appropriate HIV-infected patient with a newly diagnosed NADC, concerns do arise for both infectious disease physicians and medical oncologists when combining cART with chemotherapy. These concerns are well founded because there is the possibility

Table 2. Highly Active Combination Antiretroviral Therapy Agents That Cause Common Chemotherapy-Related Side Effects [81]

Adverse Reaction	Human Immunodeficiency Virus Antiretroviral Agents
Myelosuppression	Zidovudine
Neuropathy	Didanosine, stavudine
Nephrotoxicity	Tenofovir, indinavir
Nausea/Emesis	All protease inhibitors, zidovudine, didanosine
Diarrhea	Nelfinavir, lopinavir
Hepatotoxicity	All nonnucleoside reverse transcriptase inhibitors, all protease inhibitors, and all nucleoside reverse transcriptase inhibitors

of overlapping toxicities, chemotherapy effects on immune status, and potential drug–drug interactions.

A number of cART agents have toxicities that overlap those common to chemotherapy agents, such as myelosuppression, neuropathies, nausea, and diarrhea (Table 2). Concurrent cART would be expected to exacerbate side effects from chemotherapy and perhaps make cancer therapy intolerable. Although maintaining concurrent antiretroviral treatment during anticancer chemotherapy should be the goal, if an overlapping toxicity prevents combining the two, then changing the antiretroviral agent(s) or the chemotherapy drug should be considered rather than stopping cART or decreasing chemotherapy dosages.

Appropriate concern should be given to what effects chemotherapy might have on the immune parameters in HIV-infected patients. Powles et al reported that patients treated for non-Hodgkin’s lymphoma with chemotherapy while on cART experienced a >50% reduction in T-helper (CD4) cell counts during the first 3 months of chemotherapy (these counts returned to pretreatment levels within 1 month after completing chemotherapy) [77]. Thus, awareness of this

chemotherapy effect should lead practitioners to track CD4 counts and consider placing patients on opportunistic infection prophylaxis when warranted. Studies have shown that HIV viral load levels are minimally affected by the administration of chemotherapy [77, 78]. Further, there is no accelerated development of mutation-associated viral resistance during chemotherapy [79].

Interactions between cART and chemotherapy may occur and, in some cases, are likely (Table 3) [80, 81]. cART agents known to inhibit or induce key metabolizing enzymes may alter the pharmacology of common chemotherapy drugs. In most cases, these potential interactions have not been well studied, especially for newer targeted chemotherapy agents [81].

The dearth of clinical understanding of potential drug–drug interactions and chemotherapy tolerability in HIV-positive patients is in large part due to the fact that HIV-infected patients are typically excluded from cancer clinical trials. This was likely done in the past for a number of reasons, including concerns over immune suppression, drug–drug interactions, and the prognosis of patients with HIV. Those concerns are either no longer applicable or can be readily addressed in well-designed clinical studies [82].

In order to better understand potential drug–drug interactions and cart–chemotherapy tolerability, the AIDS Malignancy Consortium (AMC), an NCI-sponsored cooperative group, launched an effort in 2009 to perform a series of phase I and pharmacokinetic clinical studies in HIV-infected patients who have refractory cancers. These trials focus on new targeted chemotherapy agents. HIV-infected patients with cancer are eligible to be enrolled and are assigned to treatment based on their cART therapy. The first agent studied was sunitinib, an US Food and Drug Administration–approved drug used in the treatment of renal cell carcinoma and under active investigations to treat other malignancies. In this study (AMC-061), patients were assigned to 1 of 3 arms: ritonavir-containing cART, nonnucleoside reverse transcriptase inhibitor–containing cART, or other therapies. It was found that patients on non-

Table 3. Select Metabolizing Enzymes and Transporters, Highly Active Combination Antiretroviral Therapy, and Chemotherapy [80, 81]

Enzyme	HAART Inhibitor	HAART Inducer	Chemotherapy
CYP3A4	Delavirdine, ritonavir, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir	Nevirapine, efavirenz	Paclitaxel, docetaxel, erlotinib, sunitinib, sorafenib, etoposide, vincristine, vinblastine, vinorelbine, cyclophosphamide
CYP2C9	Efavirenz, ritonavir		Cyclophosphamide
CYP2C19	Efavirenz, amprenavir		Cyclophosphamide, ifosfamide, thalidomide
CYP2D6	Ritonavir		Tamoxifen
CYP2B6	Efavirenz, nelfinavir, ritonavir	Nevirapine	Cyclophosphamide, ifosfamide
CYP2E1	Ritonavir		Etoposide, dacarbazine
UGT1A1	Atazanavir		Irinotecan

Abbreviation: HAART, highly active combination antiretroviral therapy.

ritonavir-containing cART regimens could tolerate the standard dose of sunitinib (50 mg/d). However, likely due to a drug–drug interaction, patients on ritonavir should be treated at the lower dose of 37.5 mg [83]. This recommendation, which may now be used in both outpatient treatment as well as in future cancer clinical trials using sunitinib, enables the safe enrollment of HIV-infected patients who have an NADC. Additional drugs under investigation by the AMC include vorinostat, with further trials planned. In the coming years we will know whether these and other promising new drugs can be given safely and efficaciously to HIV-infected patients and what dose HIV patients should receive depending on their specific cART regimen.

Until studies help physicians better plan concurrent cART and cancer chemotherapy, clinicians need to use their best judgment with the patients in their clinics. If the HIV disease can be well controlled, an overall guiding principle would be to provide therapy that is equivalent to what any other patient would receive with a similar cancer diagnosis, end organ function, and performance status. Studies have suggested that equivalent treatment is feasible—and outcomes can be similar—in well-controlled HIV-infected individuals compared with patients without HIV infection, including in the treatment of lymphoma and anal and lung cancers [23, 78, 84–87]. For example, treatment for anal cancer with concurrent multidrug chemotherapy and radiation with curative intent is tolerable in HIV-positive patients, with mildly increased rates of toxicity but equivalent survival rates [85, 88]. Certain NADCs that are curable may be best approached in certain situations by suspension of antiretroviral therapy, at least during a portion of the cancer treatment. However, patients with advanced HIV disease are likely to experience worse outcomes and have a poorer tolerance for therapy compared with HIV-negative patients or those with less advanced HIV disease [11].

Prevention

Even more than screening, cancer prevention should be a key goal for practitioners caring for HIV-infected patients. This includes smoking cessation to reduce the risk of lung as well as head and neck cancers. It is worth noting that varenicline used for smoking cessation does not undergo hepatic metabolism and is excreted unchanged in the urine; thus, no drug–drug interaction with cART would be expected [89]. Prevention and/or treatment for viral coinfections of hepatitis B and hepatitis C should be routine if patients are eligible for treatment [2]. A recently completed clinical study has found that a vaccine against HPV is safe and highly immunogenic in HIV-infected men [90]. A companion study in women (ACTG Study A5240) has been completed and results are expected to be released soon. Use of the vaccine in adults is recommended by the US Centers for Disease Control and

Prevention in all females aged <26 years, males aged <21 years, as well as in men who have sex with men and are between the ages of 22 and 26 years [91].

CONCLUSION

Since the advent of cART, HIV/AIDS has progressively transformed from a relatively acute terminal condition into a chronic illness. Like most chronic illnesses, it carries comorbidities. As the incidence of AIDS-defining malignancies has declined in the post-HAART era, the aging HIV population is now known to be at an increased risk for a multitude of non-AIDS-defining malignancies. Over the past decade, large epidemiological studies have highlighted this increased risk. Although some specific rates or facts are in disagreement across these studies, the general trend of an increased cancer risk—above and beyond that seen in the general population—presents a challenge to all who care for patients infected with HIV. Clinicians and researchers, policymakers and officials, as well as patients and their advocates, must now strive to confront this challenge, as they did with access to antiretroviral treatment in the earliest stage of the HIV epidemic and with the AIDS-defining cancer challenge that surfaced soon thereafter. With the rising case load of non-AIDS-defining cancers, we must do a better job of detecting cancer as early as possible, ensuring that effective treatments are available and used in the oncology community, all while continuing to work toward the goal of preventing these cancers—and reversing this trend—in the years ahead.

Notes

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