

## The rising challenge of Non-AIDS Defining Cancers in HIV-infected patients

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**Summary:** In the post-HAART era, HIV-infected patients are facing high rates of so-called Non-AIDS Defining Cancers. The challenge facing clinicians caring for HIV patients is how best to screen, treat, and prevent these cancers.

## **ABSTRACT**

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, anal, 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.

## **Introduction**

Since the advent of highly active combination antiretroviral therapy (HAART, or cART), patients with 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 fourfold in the post-HAART era, and the incidence of AIDS and AIDS-defining illnesses, including opportunistic infections as well as 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, anal, head and neck, and skin, as well as Hodgkin's Lymphoma, among others. Interestingly, in populations benefiting from cART, some NADCs appear to have higher relative incidence compared to 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 will highlight the epidemiology data and potential etiological causes, and then focus on means 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.[2,5,6,7,8] While the rates of AIDS-defining cancers (Non-Hodgkin's Lymphoma, Kaposi's sarcoma, and cervical cancer) declined three-fold from 1995 to 2005, the incidence of NADCs rose by more than threefold in that same time period.[2] Within the United States, national, regional, state, and local epidemiology studies have confirmed these international findings.[9,10,11,12,13,14] For example, NADCs accounted for 31% of all cancer diagnoses in

the pre-HAART era, compared to 58% of all cancers in the post-HAART era.[14] The increased rate of NADCs, measured by 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 to 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, are occurring at different rates in HIV-infected individuals compared to the general population.[7,8,9,10,13,15,16,17]

### *Epidemiology*

The increased risk for NADCs, at least in the United States, appears to be primarily among Caucasians, without an increased risk seen in African-Americans and other ethnic groups.[10] It is unclear whether these findings are due to reporting bias or whether these 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 to the overall population.[5,18,19,20]

The strongest epidemiological risk factor for developing a NADC is age. This is not surprising, since it would be expected that as patients with HIV are living longer, increased age-appropriate cancer diagnoses would be made.[21] However, NADCs are being diagnosed at a much younger age in HIV-infected patients compared to the general population, including with head and neck, anal, lung, colorectal, and liver cancers.[22,23,24,25,26,27,28,29,30,31,32] The risk of developing a NADC of any kind in an HIV-infected patient over the age of 40 years is 12 times higher compared to the general population.[10] Similarly, duration of HIV infection is also significantly associated with the risk of developing a NADC, with an increased odds ratio of 1.20 for every year of HIV-infection.[10]

While the duration of HIV-infection increases risk, the severity of HIV infection may not. This is in contrast to 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 less than 200/ $\mu$ 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 have begun to elucidate potential causes. Explanations include the HIV virus itself, co-infection with oncogenic viruses, 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.[42,43,44] Finally, HIV infection can cause endothelial abnormalities including pro-angiogenesis signaling which may enhance the development of tumor growth and metastasis.[45,46,47]

HIV-infected patients have an increased risk of exposure and subsequent infection with cancer causing viruses, including hepatitis B and C (HBV and HCV), Human Papillomavirus (HPV), and the Epstein-Barr virus.[48,49,50,51] Co-infection with HIV and these viruses continues even in the post-HAART era.[52,53,54] 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.[5,6,60,61,62] For example, while between 20 to 50 percent of Hodgkin's Disease may be caused by EBV in the general population, between 75 to 100 percent of patients with HIV have EBV-associated Hodgkin's Disease.[5,6,61,62] Local as well as systemic impairment of EBV-specific T cells 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 therapy increases, decreases, or has no effect on the risk of developing a 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 U.S. between 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 to the overall population.[65,66] Whether this higher cancer rate is due to an increased tissue sensitivity to tobacco carcinogens in the setting of HIV infection is unknown.

Unfortunately, patients with NADCs often have more aggressive cancers, and present with more advanced stage 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] While HIV patients diagnosed with early stage breast cancer have similar survival rates compared to non-HIV infected patients,[67] breast cancer in HIV-infected patients is more commonly poorly differentiated, bilateral, 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, a logical question is whether current cancer screening guidelines apply to HIV-infected patients. Should HIV infected patients be screened differently than the general population? Should HIV-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 identifying and treating pre-cancerous conditions or cancer in asymptomatic individuals will improve survival.[70] Current cancer screening guidelines vary based on the organization from which they are produced. The American Cancer Society, the National Cancer Institute, the U.S. Preventive Services Task Force (USPSTF), 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 towards the general population. However, the European AIDS Clinical Society has proposed screening recommendations in HIV-positive patients for anal, breast, cervical, colorectal, liver, and prostate cancers.[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 was significantly lower in HIV-infected women compared to 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 to 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. While there are no national or international guidelines to guide screening practice and the management of anal dysplasia in HIV infected individuals, it may be worth performing routine anal cytology screening by trained health care professionals.[74,75] Finally, a new avenue recently opened that may aid in the screening for lung cancer in at-risk individuals, including those infected with HIV. Whether the findings of the National Lung Screening Trial (NLST), which showed that screening high-risk smokers reduced lung cancer mortality by 20 percent, are adopted for the general population is not yet known.[76] If they are, then applying this screening technique to HIV-positive patients with a high-risk tobacco use history should be equally warranted.

### *Treatment*

In general, cancer therapy is determined by the primary site of disease, disease burden, and host co-morbid status. Interventions may 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, and oftentimes palliative therapy is more appropriate.

While 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 due

to the possibility of overlapping toxicities, chemotherapy effects on immune status, and potential drug-drug interactions.

A number of cART agents have toxicities which 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. While 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 greater than a 50% reduction in T-helper (CD4) cell counts during the first 3 months of chemotherapy (these counts returned to pre-treatment levels within one 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]

Drug-drug 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-patients are typically excluded from cancer clinical trials. This was likely done in the past due to 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 of performing 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 FDA-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 one of three arms: ritonavir-containing cART, NNRTI-containing cART, or other therapies. We found that patients on non-ritonavir containing cART regimens could tolerate the standard dose of sunitinib (50mg per day). However, likely due to a drug-drug interaction, patients on ritonavir should be treated at the lower dose of 37.5mg.[83] This recommendation may now be used in both outpatient treatment as well as in future cancer clinical trials using sunitinib, enabling the safe enrollment of HIV-infected patients who have a 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 clinical studies help physicians better plan concurrent cART and cancer chemotherapy, clinicians need to use their best judgment with the patients in their clinic. If the HIV disease can be well controlled, an overall guiding principle would be to provide therapy that is equivalent to that 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 to patients without HIV-infection, including in the treatment of lymphoma, anal, and lung cancers.[23,78, 84,85,86,87] . 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 [88,89] . 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 to 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, is excreted unchanged in the urine, and thus no drug-drug interaction with cART would be expected.[90] . Prevention and/or treatment for viral co-infections of Hepatitis B and 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.[91] . A companion study in women (ACTG Study A5240) has been completed with results expected. Use of the vaccine in adults is recommended by the U.S. Centers for Disease Control in all females under the age of 26, males under the age of 21, as well as in men who have sex with men and are between the ages of 22 to 26 years.[92]

### **Conclusion**

Since the advent of cART, HIV/AIDS has progressively transformed from a relatively acute terminal condition into a chronic illness. And like most chronic illnesses, it carries co-

morbidities. 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 epidemiology studies have highlighted this increased risk. While 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, policy makers 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 then 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 towards the goal of preventing these cancers -- and reversing this trend -- in the years ahead.

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**FIGURES AND TABLES**

Table 1. Standard Incidence Ratios of selected Non-AIDS Defining Cancers [refs: 2-8]

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

Table 2. HAART agents that cause common chemotherapy-related side effects [ref: 81]

<b>Adverse Reaction</b>	<b>HIV Antiretroviral Agents</b>
Myelosuppression	zidovudine
Neuropathy	didanosine, stavudine,
Nephrotoxicity	tenofovir, indinavir
Nausea/Emesis	all protease inhibitors, zidovudine, didanosine
Diarrhea	nelfinavir, lopinavir
Hepatotoxicity	all NNRTIs, all PIs, and all NRTIs

Table 3. Select metabolizing enzymes and transporters, HAART, and Chemotherapy [ref: 80-81]

<b>Enzyme</b>	<b>HAART Inhibitors</b>	<b>HAART Inducers</b>	<b>Chemotherapy</b>
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

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