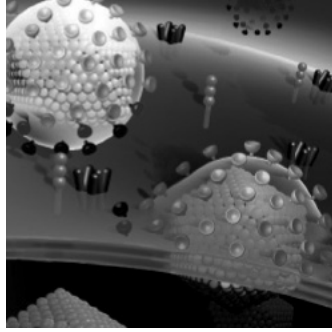
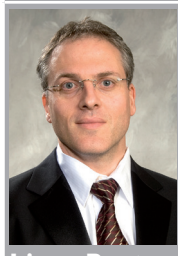


Future treatment for non-AIDS-defining cancers in HIV-infected patients

"The incidence of NADCs has increased more than threefold in the last decade and now surpasses that of AIDS-defining malignancies in HIV-infected individuals."

John F Deeken
Author for correspondence:
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA
Tel.: +1 202 444 3958;
Fax: +1 202 444 9429;
deekenj@georgetown.edu



Liron Pantanowitz
Department of Pathology, Tufts University School of Medicine, Springfield, MA, USA

Bruce J Dezube
Department of Medicine, Harvard Medical School, Boston, MA, USA

HAART has dramatically changed the prognosis of treated patients diagnosed with HIV infection. In many ways, we have been able to turn HIV from a fatal to a chronic disease. Unfortunately, as patients infected with HIV have begun to live longer in a state of chronic immune suppression, illnesses that are no longer soley associated with AIDS are becoming more prevalent, including non-AIDS-defining cancers (NADCs).

The incidence of NADCs has increased more than threefold in the last decade and now surpasses that of AIDS-defining malignancies in HIV-infected individuals [1]. Epidemiology studies from the USA, France, Switzerland and most recently the UK have all confirmed this growing cancer risk in HIV-infected patients [2–5]. These studies have demonstrated that NADCs, including Hodgkin's lymphoma, testicular germ-cell neoplasms and specific carcinomas (anal, hepatocellular, conjunctival and aerodigestive malignancies, such as head and neck, lung and esophageal cancers) all have higher incidence rates in HIV-positive patients compared with the general (HIV negative) population.

Not only are these malignancies being diagnosed at higher rates, but unfortunately, NADCs in HIV-positive patients tend to have more aggressive features compared with similar cancers in the general population. These malignancies are occurring at younger ages (typically showing atypical pathology and a higher tumor grade), are being diagnosed at more advanced stages and, unfortunately, follow a more aggressive disease course, with higher rates of relapse and poor outcomes [6].

Risk factors

The risk factors for HIV-positive patients developing NADCs are beginning to be elucidated. These include advancing age, duration of HIV infection and ethnicity. Caucasians appear to be at higher risk for some cancers compared with African–Americans and patients of other ethnic groups [7]. Additional risk factors include behavioral aspects, such as an increased use of tobacco and alcohol in patients with HIV [8].

Research has demonstrated that HIV itself may have direct effects that contribute to the development of NADC. For example, the HIV Tat protein may cause transactivation of proto-oncogenes [9]. Other genes within the HIV virus may inhibit tumor suppressor genes, including *p53*. HIV infection may cause microsatellite gene instability and genetic alterations leading towards oncogenesis. Tissue infection with HIV may make these tissues more sensitive to the effects of carcinogens from the environment. Finally, HIV infection can cause endothelial abnormalities including proangiogenesis, which may enhance the development of tumor growth and metastasis [1].

There have been conflicting data regarding whether HAART is associated with the risk of developing NADCs. Some studies have demonstrated a decreased risk of developing a NADC while patients are on HAART, compared with patients who are not receiving antiretroviral therapy or are only on single agent or dual agent antiretroviral therapy [7]. Other studies have demonstrated a possible increased risk if patients are on HAART [4], and specifically if they are on a non-nucleoside reverse transcriptase inhibitor-based therapy [5]. A concerning, recent finding in the large Phase III trial that led to the approval of raltegravir (an integrase inhibitor also known as Isentress® [Merck] and MK-0518) was that during the period of the study, patients on raltegravir had a higher risk of developing a NADC compared with those taking placebo [10]. Clearly more research is needed to elucidate the role of antiretroviral therapy, immune reconstitution and the relative risk of developing NADCs.

part of future medicine fsg

Additional contributing factors for the development of specific NADCs include coinfection with oncogenic viruses. Patients with HIV are 13–31-times more likely to develop Hodgkin's lymphoma compared with the general population. This could be attributed to coinfection with Epstein–Barr virus, since HIV-positive patients have been found to be coinfected with Epstein–Barr virus at a much higher rate than HIV-negative patients who also have Hodgkin's lymphoma [3,4,11,12]. Patients with HIV have a seven times higher rate of developing hepatocellular carcinoma. This is likely to be due to coinfection with the HBV and/or HCV. In fact, coinfection with HCV and HIV increases the risk of developing liver cancer by more than fivefold [13–16]. HIV-positive patients have a higher risk of developing malignancies known to be caused by the human papillomavirus, including anal carcinoma as well as cancer of the head and neck [17].

Patients with HIV have twice the incidence of kidney cancer while those with AIDS have an almost six times higher risk of getting kidney cancer compared with the general population, for reasons that are not fully understood. Perhaps the immune dysregulation caused by HIV infection may play some role in tumorigenesis. Another hypothesis is that chronic, subclinical renal irritation from antiretroviral therapy may predispose HIV-positive patients to kidney cancer [2,18].

HIV-positive patients have more than a twofold increased risk for developing colorectal cancer, again for reasons that are poorly understood. Colorectal cancer in HIV-positive patients is known to be diagnosed at a younger age, with a mean age of 41 years found in one series [19,20]. Interestingly, patients who are infected with HIV have higher rates of precursor colon cancer lesions (e.g., adenomas). In fact, HIV-positive patients more often have larger adenomas with concerning histology (villous architecture and high-grade dysplasia) compared with HIV-negative patients.

"Patients with HIV and breast cancer tend to have higher rates of bilateral disease, tumors that are poorly differentiated and manifest with metastases early in their disease course."

While not all cancers appear to be diagnosed at a higher rate in HIV-positive patients, some NADCs that occur infrequently in patients with HIV infection, such as breast carcinoma, nevertheless still exhibit a more virulent course with a poorer prognosis in HIV-positive patients. Patients with HIV and breast cancer tend to have higher rates of bilateral disease, tumors that are poorly differentiated and manifest with metastases early in their disease course [21,22].

Detection & screening

Given the emerging increased rates of NADCs, the key challenges facing those who care for HIV-positive patients are how better to detect, treat and ideally, prevent such cancers in the first place.

In terms of early detection, standard screening procedures must be actively pursued in patients infected with HIV. Such screening measures should include Pap tests for anogenetial (cervicovaginal and anal) cancer. Colonoscopy of the entire colon and mammography need to be performed, as often as is recommended for the general population, and perhaps at an earlier age. In addition, given the high rates of skin cancers (including Kaposi's sarcoma, melanoma, Merkel cell carcinoma, bacal cell carcinoma and squamous cell carcinoma) in HIV-positive patients, aggressive use of sun screen and annual physical examinations are needed, which must include a thorough skin exam with early referral to a dermatologist if concerning lesions are detected.

For additional cancer-specific screening, further research is needed. This includes determining whether screening for human papillomavirus in the squamous epithelium of the oral cavity, as well as in the anus, would help detect early premalignant changes. Experimental head and neck cancer screening techniques, such as saliva rinses, should be explored in HIV-positive patients given their higher rates of this disease. The use of CT scans has not yet been found to affect the prognosis for patients who are eventually diagnosed with lung cancer. However, perhaps this screening tool might be of benefit to patients with HIV.

An additional complication facing medical oncologists is how best to treat NADC in HIV-positive patients who are on HAART. Antiretroviral agents are notorious for causing significant drug–drug interactions through the inhibition or induction of enzymes and transporters that are central to the pharmacokinetics of many drugs, including chemotherapy. For example, ritonavir is known to significantly inhibit the CYP3A4 enzyme in the liver, causing increased levels of coadministered drugs, which are also metabolized by this crucial enzyme. When treating HIV, we have used this fact to our benefit by coadministering other antiretroviral therapies with ritonavir in order to 'boost' antiretroviral drug levels. This same beneficial 'boosting' of coadministered antiretroviral agents could cause significant complications in patients treated with chemotherapy for

NADCs. Over half of all chemotherapy drugs are metabolized by CYP3A4. The inhibition of this enzyme by ritonavir and other HAART agents could significantly increase chemotherapy drug levels, leading to more severe, and even life-threatening toxicities. Other HAART agents can induce the activity of metabolizing enzymes in the liver. Enzyme induction may lead to more rapid metabolism and elimination of chemotherapy drugs, in turn, lowering their efficacy.

Unfortunately, and for too long, patients infected with HIV have been excluded from chemotherapy trials. This exclusion has occurred both in pharmaceutical-sponsored trials as well as government-funded cooperative group trials. However, this is beginning to change through a new effort by the National Cancer Institute (NCI) of the NIH. Leaders at the NCI are pursuing a multipronged strategy to overcome this deficit in clinical experience. New cooperative group trials will be encouraged to enrol HIV-positive patients and perform a subset analysis of these patients in terms of treatment toxicity, efficacy and HIV-related complications. In addition, a new series of pharmacokinetic studies will be pursued to study how patients with HIV on HAART tolerate new targeted chemotherapy drugs. We are the national co-chairs for the first such trial, sponsored by the NCI and the AIDS Malignancy Consortium, which will study the use of sunitinib (Sutent®, Pfizer) in HIV patients on HAART who also have cancer.

Clearly, all of these issues and complications would be avoided if patients infected with HIV could be prevented from developing cancer in the first place. Thus, prevention strategies need to be front and center, and pursued by all physicians caring for HIV patients. Aggressive smoking cessation programs can dramatically affect the incidence of head and neck, lung and other malignancies. Vaccinations against viral coinfections including HBV and HCV, as well as human papillomavirus, could be beneficial in lowering the risks of viral-mediated cancers.

Conclusion

The development of HAART has dramatically improved the prognosis of patients diagnosed with HIV infection, both in the USA and around the world. Unfortunately, a burgeoning epidemic of NADCs in patients with HIV now requires a concerted clinical research effort in order to better determine its etiology, biology, prevention and treatment. Fortunately, leaders within the AIDS research community, as well as at the NIH and other public health agencies, have recognized this growing public health threat and have begun to address it. Much clinical research will be necessary.

Those involved in the care of HIV-positive patients need to be aware of this growing threat to their patients and address the issues of risk reduction and prevention in their clinics. Hopefully, in the years ahead we will have the same success in treating this growing epidemic of NADCs as we did over the past decade with the diagnosis and treatment of AIDS-defining malignancies.

"Over half of all chemotherapy drugs are metabolized by CYP3A4. The inhibition of this enzyme by ritonavir and other HAART agents could significantly increase chemotherapy drug levels, leading to more severe, and even life-threatening toxicities."

Financial & competing interests disclosure

John Deeken and Bruce Dezube are supported in part by the AIDS Malignancy Consortium of the NCI/NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Mitsuyasu R: Non-AIDS defining malignancies in HIV. *Top. HIV Med.* 16, 117–121 (2008).

2 Engels EA, Pfeiffer RM, Goedert JJ *et al.*; for the HIV/AIDS cancer match study: Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS* 20(12), 1645–1654 (2006).

3 Herida M, Mary-Krause M, Kaphan R *et al.*: Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J. Clin. Oncol.* 21(18), 3447–3453 (2003).

4 Clifford GM, Polesel J, Rickenbach M *et al.*: Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J. Natl Cancer Inst.* 97(6), 425–432 (2005).

5 Powles T, Robinson D, Stebbing J *et al.*: Highly active antiretroviral therapy and the incidence of non-AIDS defining cancers in people with HIV infection. *J. Clin. Oncol.* 27(6), 884–890 (2009).

6 Pantanowitz L, Dezube BJ: Evolving spectrum and incidence of non-AIDS-defining malignancies. *Curr. Opin. HIV AIDS* 4(1), 27–34 (2009).

7 Burgi A, Brodine S, Wegner S *et al.*: Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. *Cancer* 104(7), 1505–1511 (2005).

8 Stall RD, Greenwood GL, Acree M, Paul J, Coates TJ: Cigarette smoking among gay and bisexual men. *Am. J. Public Health* 89(12), 1875–1878 (1999).

9 Wright S, Lu X, Peterlin BM: Human immunodeficiency virus type 1 tat directs transcription through attenuation sites within the mouse *c-myc* gene. *J. Mol. Biol.* 243(4), 568–573 (1994).

10 Steigbigel RT, Cooper DA, Kumar PN *et al.*: Raltegravir with optimized background therapy for resistant HIV-1 infection. *N. Engl. J. Med.* 359, 339–354 (2008).

11 Thompson LD, Fisher SI, Chu WS, Nelson A, Abbondanzo SL: HIV-associated Hodgkin lymphoma: a clinicopathologic and immunophenotypic study of 45 cases. *Am. J. Clin. Pathol.* 121(5), 727–738 (2004).

12 Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D: AIDS-related malignancies: state of the art and therapeutic challenges. *J. Clin. Oncol.* 26(29), 4834–4842 (2008).

13 Murillas J, Del Río M, Riera M *et al.*: Increased incidence of hepatocellular carcinoma (HCC) in HIV-1 infected patients. *Eur. J. Intern. Med.* 16(2), 113–115 (2005).

14 Kramer JR, Giordano TP, Souchek J, El-Serag HB: Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era. *J. Hepatol.* 42(3), 309–314 (2005).

15 Puoti M, Bruno R, Soriano V *et al.*; HIV HCC Cooperative Italian–Spanish Group: Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 18(17), 2285–2293 (2004).

16 Hessol NA, Kalinowski A, Benning L *et al.*: Mortality among participants in the multicenter AIDS cohort study and the women's interagency HIV study. *Clin. Infect. Dis.* 44(2), 287–294 (2007).

17 Palefsky J: Human papillomavirus-related disease in people with HIV. *Curr. Opin. HIV AIDS* 4(1), 52–56 (2009).

18 Layman AB, Engels EA: Kidney and bladder cancers among people with AIDS in the United States. *J. Acquir. Immune Defic. Syndr.* 48(3), 365–367 (2008).

19 Yegüez JF, Martinez SA, Sands DR, Sands LR, Hellinger MD. Colorectal malignancies in HIV-positive patients. *Am. Surg.* 69(11), 981–987 (2003).

20 Bini EJ, Green B, Poles M: Screening colonoscopy for the detection of neoplastic lesions in asymptomatic HIV-infected subjects. *Gut* (2009) (Epub ahead of print).

21 Pantanowitz L, Dezube BJ: Breast cancer in HIV positive women: a report of four cases and review of the literature. *Cancer Invest.* 21(4), 665 (2003).

22 Gewurz BE, Dezube BJ, Pantanowitz L: HIV and the breast. *AIDS Read.* 15(8), 392–396, 399–402 (2005).