

Cancer in HIV and Aging

- As part of general health maintenance practices, cancer screening in clinically stable HIV-infected patients 50 years and older should be in accordance with current guidelines for the general population.
- For cervical cancer, anal cancer, and liver cancer where HIV-specific recommendations exist, these guidelines should be followed.
- For all patients, providers should take into consideration functional status and life expectancy in applying these screening strategies.

Non-AIDS Cancers Increasing as Cause of Mortality Among HIV-Infected Persons

Several lines of evidence indicate that cancer, especially non-AIDS-defining cancers (NADCs), has become an increasing cause of mortality in the HAART era. The risk of a particular cancer varies widely by HIV status.

The HIV Outpatient Study, a prospective, multicenter, observational cohort study of subjects treated from 1996 through 2004, showed all-cause mortality among HIV-infected persons in the United States decreasing by almost 80%. Deaths due exclusively to non-AIDS-defining illnesses (NADIs) rose from 13.1% to 42.5% in 2004. In the study, the most common causes of NADIs were cardiovascular disease (CVD), hepatic disease, pulmonary disease, and non-AIDS malignancies at 23.5% each [1].

A more recent retrospective review as conducted of all causes of mortality in HIV-infected individuals in Europe and North

America from 1996 through 2006 in 13 HIV-1 cohorts participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC). This study found that of 1,597 deaths among 39,272 patients studied and 154,667 person-years (PY) of follow-up, 49.5% were due to AIDS and 50.5% were due to non-AIDS-associated causes. The most frequent non-AIDS causes of death were non-AIDS malignancy (11.8%), followed by non-AIDS infection (8.2%), cardiovascular disease (7.9%), violence (7.8%), and liver disease (7.1%). The proportion of deaths due to AIDS-defining cancers (ADCs) decreased from 20.5% to 12.5%, while that due to NADCs increased from 7.3% to 15.4% over the study periods [2].

Similarly, the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group observed 2,482 deaths in 180,176 PY on 33,308 individuals and found that, among primary causes of death, NADIs were more common than AIDS-related causes (n=916 vs. 743) [3]. The main non-AIDS-related causes

were liver-related (n=341), CVD-related (n=289), and non-AIDS malignancy (n=286).

Increasing Incidence of Cancer Among HIV-Infected Persons Compared to HIV-Uninfected

Data on increased incidence of NADCs in HIV-infected individuals in the HAART era compared with HIV-uninfected persons has been mixed, but increasingly supportive that this number is going up.

A review of the literature shows a statistically significant increase in the age standardized incidence ratio (SIR) of several non-AIDS-defining malignancies for HIV-infected persons compared with HIV-uninfected cohorts [4]. In particular, Hodgkin's lymphoma, anal cancer, soft tissue cancer, and multiple myeloma were found to have statistically significant increased SIRs in five large published studies that were reviewed [5-9].

No studies found significant increases in breast cancer, colon cancer, or prostate cancer. In addition, some studies have suggested a higher incidence of invasive cervical cancer in HIV-infected women compared with HIV-uninfected women [6, 10], although this may have diminished in the HAART era and with aggressive cancer screening.

More recently, a meta-analysis of the incidence of NADCs in HIV-infected individuals, in which 4,797 non-AIDS cancers occurred among 625,716 HIV-infected individuals, demonstrated that HIV-infected persons were twice as likely to develop a NADC as the general population [11].

A recent U.S. study, the HIV/AIDS Cancer Match study, showed that anal, liver, and prostate cancers rates increased between 1996 and 2010, while rates of Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and cervical and lung cancer decreased in HIV-infected adults. This study examined the contribution of changing demographics (including aging) over time, trends in rates of cancer in the general population, and HIV-associated relative risks

for cancers. Changing demographics, including aging, helped explain changing rates for Kaposi's sarcoma and breast, colorectal, liver, lung, and prostate cancers [12].

Most Frequent Sites of Non-AIDS Malignancies

In the meta-analysis by Shiels [11], HIV-infected individuals were found to be particularly at risk for cancers associated with infections (including anal, vaginal, penile, nasopharyngeal, laryngeal, and oral cancers related to human papilloma virus; liver cancer from the hepatitis B and C viruses; and nasopharyngeal cancer and Hodgkin's lymphoma associated with Epstein-Barr virus) and those associated with smoking (including lung, kidney, stomach, laryngeal, and oral cancers). Prostate and breast cancer were less common in HIV-infected persons [11]. A listing of the relative SIRs for HIV-infected persons compared with the general population is shown in Table 1.

Findings were similar in a retrospective cohort study of HIV-infected and matched HIV-uninfected members of Kaiser Permanente followed between 1996 and 2007 for the incidence of ADCs and NADCs. This study found that, rates for most individual infection-related NADCs were significantly higher in HIV-infected group, including anal squamous cell, vagina/vulva, Hodgkin's lymphoma, penis, liver, and HPV-related oral squamous cell cancers [13].

Infection-unrelated NADCs with increased rates among HIV-infected persons were other anal, non-melanoma skin, other head and neck, and lung cancers and melanoma. Infection-related cancers (ADC and infection-related NADC combined) made up almost 70% of all cancers in HIV-infected persons. HIV-infected persons had more than a nine fold increased risk of infection-related NADC compared with HIV-uninfected persons, mainly in the risk of anal squamous cell cancer and Hodgkin's lymphoma. HIV-infected persons also had a modest 30% increased risk of infection-unrelated NADC,

including a higher risk of other anal, skin, other head and neck, and lung cancers, but lower risk of prostate cancer.

Others have also found that lung cancer was a major NADC early in the HAART era. It was the most common non-AIDS cancer and the third most common cancer among HIV-infected individuals in the U.S.A. behind

	Studies	Cases	SIR	95% CL
Lung	13	847	2.6	2.1 to 3.1
Hodgkin lymphoma	13	643	11	8.8 to 15
Anus	8	253	28	21 to 35
Colorectal	4	174	1.1	0.69 to 1.7
Liver	11	171	5.6	4.0 to 7.7
Melanoma	10	161	1.2	0.88 to 1.6
Skin cancer	7	160	3.5	1.8 to 6.8
Prostate	9	159	0.69	0.55 to 0.86
Female breast	11	142	0.74	0.56 to 0.97
Kidney	9	109	1.7	1.3 to 2.2
Oropharynx	3	108	1.9	1.4 to 2.6
Leukemia	10	102	2.6	1.9 to 3.5
Stomach	11	96	1.7	1.2 to 2.5
Testis	8	96	1.4	1.1 to 1.9
Lip, oral, and pharynx	2	84	2.2	1.0 to 4.7
Brain	9	75	1.8	1.2 to 2.7
Multiple myeloma	9	72	2.6	1.5 to 4.5
Larynx	5	62	1.5	1.1 to 2.0
Esophagus	8	51	1.5	0.99 to 2.3
Bladder	9	48	1.1	0.72 to 1.7
Head and neck	4	42	2.0	1.1 to 3.6
Pancreas	9	39	1.0	0.74 to 1.4
Colon	4	26	0.81	0.48 to 1.4
Vagina	4	25	9.4	4.9 to 18
Thyroid	6	24	1.1	0.56 to 2.3
Penis	4	16	6.8	4.2 to 11
Rectum	2	16	1.5	0.54 to 4.2
Ovary	6	14	1.4	0.78 to 2.4
Uterus	4	14	1.5	0.68 to 3.4
Small intestine	3	10	2.2	1.4 to 3.3
Bone	5	7	2.6	1.3 to 5.0
Eye	2	7	3.1	1.6 to 5.9
Nasopharynx	2	7	4.1	2.1 to 7.9
Gall bladder	2	3	2.6	1.1 to 6.4
All non-AIDS cancers	9	3513	2.0	1.8 to 2.2

Table 1: From Shiels MS. A Meta-Analysis of the Incidence of Non-AIDS Cancers in HIV-Infected individuals. JAIDS:52(5):611-622 by Lippincott Williams & Wilkins. Reproduced with permission of Lippincott Williams & Wilkins in the format Journal via Copyright Clearance Center.

the most frequent sites for non-AIDS malignancies were respiratory tract or intrathoracic organs (36.7%); digestive organs and peritoneum (28.7%); lip, oral cavity, and pharynx (6.0%); and skin (4.7%) [2]. A recent study of skin cancer, however, suggested that the higher rate of melanoma for HIV-infected persons was more likely due to confounding by sun exposure or perhaps increased medical surveillance than as a

result of immunosuppression [15], and other recent studies found no increased risk [16].

Increased Virulence of Cancers Among HIV-Infected Persons

A 2003 study [4] noted that some malignancies tend to be of higher grade and present with a more aggressive clinical course in HIV-infected patients compared with HIV-uninfected patients. Some studies have shown that HIV-infected women with invasive cervical cancer are more likely to present with advanced clinical disease and to have persistent or recurrent disease at follow-up, a shorter time to recurrence, and a shorter survival time after diagnosis, and are more likely to die of cervical cancer [6, 17, 18] than their HIV-negative sisters.

A study in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) demonstrated that HIV-infected women were more likely to have invasive cervical cancer than HIV-uninfected women, although a response to this article points out that some of the results may have been influenced by screening and monitoring, that in HIV-infected women who were appropriately monitored, increased invasive disease was not seen [19, 20].

Other studies have shown that HIV-seropositive individuals with hepatocellular carcinoma are younger and more frequently symptomatic and infected with HCV or HBV than HIV-uninfected persons, although tumor staging and survival were similar [21].

As discussed by Shiels [22] HIV-infected individuals may have more virulent cancers because: 1) their depressed immune system is less able to fight oncogenic insults, and/or 2) behaviors of HIV-infected individuals expose them to higher levels of carcinogens, e.g., higher levels of exposure to tobacco smoke, HPV, and others.

Finally, a recent report from Italy showed that from 1999 through 2006 the risk of death from NADCs was 6.6-fold higher among Italian people with AIDS than in the general population particularly for virus-related cancers [23].

Role of Increasing Age in Cancer Risks Among HIV-Infected Persons

As with the general population, older age has been associated with increased risks of NADCs in HIV-infected individuals. In the ART-CC study, older age was strongly associated with increased rates of non-AIDS malignancy (HR per 10 years, 2.32) [2].

Similarly, in the D:A:D study, older age was associated with an increased risk of death from all causes considered, with the strongest associations for deaths due to non-AIDS malignancies and CVD-related causes [3].

In an analysis of the SMART study, cancer rates were compared between the subjects continuously taking HAART and those that intermittently took HAART. ADC rates were higher in the latter group, while NADCs were similar between groups. In this study, age was also a predictor of NADCs, with an HR of 2.2 per 10 years older [24].

Disparities in Cancer Screening and Treatment

A possible explanation for increased rates of cancer related mortality among HIV-infected adults compared with HIV-uninfected adults may also be explained by differing treatments; a study that looked at cancer registries in three U.S. states showed that higher proportions of HIV-infected adults did not receive treatment for cancers that included lung, prostate, and colorectal cancers, as well as diffuse B cell and Hodgkin's lymphomas. Higher degree of immunosuppression, age, race, male sex, and use of injection drugs were some of the factors associated with lack of treatment [25].

Other studies have shown that, despite increased risk, screening rates are lower in HIV-infected adults for particular cancers [18, 26].

Current Cancer Screening Guidelines for HIV-Seropositive Patients

Given the higher rate and virulence of some cancers among HIV-infected individuals, consideration must be given to distinct cancer screening guidelines for HIV-positive individuals. These guidelines should be individualized for patients, since life expectancy rather than strict age cutoffs are better determinants of the usefulness of cancer screenings [27].

A 2011 review outlines the current evidence base for benefits and harms of screening in HIV-infected adults and suggests a framework for approaching screening [28].

Cervical Cancer

The U.S. Preventive Services Task Force (USPSTF), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association (HIVMA) of the Infectious Disease Society of America (IDSA) recommend that HIV-infected women should receive Pap smears upon starting care and again in six months; if both tests are unremarkable, then the woman needs to be screened only annually thereafter [29]. Women with atypical squamous cells; atypical glandular cells; low-grade or high-grade squamous intraepithelial lesion; or squamous carcinoma noted by Pap testing should undergo colposcopy and directed biopsy, with further treatment as indicated by the results of the evaluation [29].

Despite these recommendations and the increased risk of cervical cancer, about 20% of HIV-seropositive women don't receive Pap smears within the first year of diagnosis [13, 18, 30], and up to 25% do not receive annual screening [31]. Higher age was a risk factor for not getting a Pap smear. Nevertheless, among women with HIV in a prospective study that incorporated cervical cancer prevention measures, including biannual Pap smears, the incidence of invasive cervical cancer (ICC) was not significantly higher than that in a comparison group of HIV-negative women [32].

Colorectal Cancer

While there is no clear evidence that the incidence of colorectal cancer is significantly higher in HIV-infected persons compared with the HIV-uninfected population, it is the second leading cause of cancer-related death in the U.S.A. As people with HIV live longer, however, the incidence of colon cancer has been rising [48]. Nevertheless, HIV-infected individuals are significantly less likely to have ever had one or more colorectal cancer screening tests or for that testing to be up to date [26].

Current guidelines from multiple sources recommend colorectal cancer screening starting at 50 years of age for all persons at average risk for the disease. In the 2009 update, the USPSTF recommended that adults aged 50 to 74 years (older on case-by-case basis) be screened in one of the following ways: every year with high-sensitivity fecal occult blood testing (FOBT); every ten years with colonoscopy; or every five years with flexible sigmoidoscopy plus interval high-sensitivity FOBT.

The American College of Gastroenterology also recently updated its guidelines with specific recommendations [33]. The 2013 IDSA Primary Care Guidelines for the Management of Persons infected with HIV included colorectal screening as part of routine health for people age 50 or older, with earlier or more frequent screening for those with a family history of cancer or personal history of polyps consistent with other guidelines for HIV-negative persons [29].

Anal Cancer

The risk of anal cancer is significantly higher in HIV-infected than in HIV-uninfected individuals, with the relative risk for developing anal cancer among HIV-infected men 37 times higher than in the general population; furthermore, the risk is 60 times higher in HIV-seropositive men who had sex with men (MSM) [6].

Despite this significantly higher risk, there are currently no national recommendations on screening for anal cancer, although the New York State Department of Health does recommend screening of HIV-infected individuals. But anal cancer screening has been shown to be cost effective in certain models [34]. Some specialists advocate screening similar to that for cervical cancer, with annual screening using the Thinprep solution, especially for patients with ongoing sexual partners.

The IDSA guidelines suggest consideration of screening for MSM, HIV-infected women with abnormal cervical cytology, and HIV-infected adults with genital warts [29]. A recent review summarizes current evidence for screening and notes that additional studies are warranted as anal cancer screening is adopted more widely, even in the absence of official recommendations [35].

Liver Cancer

Studies have found that HIV-infected individuals develop hepatic cancer at approximately seven times the rate of non-HIV-infected individuals [21, 36]. Screening for hepatic cancer is currently recommended only in patients with cirrhosis, although screening may also be warranted in HBV carriers over 40 years of age with persistent or intermittent ALT elevation and/or HBV DNA level >2000 [37, 38]. This screening involves hepatic ultrasound at six- to twelve-month intervals [39, 40]. Alpha-fetoprotein (AFP) has poor specificity and sensitivity, and its use is currently optional, with abnormalities confirmed by liver imaging studies [41].

Breast Cancer

Risk does not appear to be elevated in HIV. Screening as outlined in the HIVMA/IDSA recommendations and others include annual mammograms in all women over 50 years old (every one to two years if lifetime risk is <20%). For women 40 to 49 years old, providers should periodically perform

individualized assessments of risk for breast cancer and discuss pros and cons of earlier screening [29].

Lung Cancer

Lung cancer is the leading cause of cancer-related death in the U.S.A. and significantly higher in HIV-infected patients, possibly because of the high rate of smoking in this population. Recent guidelines have been created after results from the National Lung Screening Trial (NLST), showed 20% fewer lung cancer deaths among heavy smokers screened with low-dose helical CT compared to standard chest X-ray.

The USPSTF recommends annual screening with low dose CT for adults age 55 to 80 with at least a 30 pack/year history and who are either current smokers or have quit within the preceding 15 years. A single study has examined these screening guidelines in HIV-infected adults, given the concern of possible increased false positive findings in HIV-infected adults, and did not find increased risk of abnormal findings on CT or follow-up testing, suggesting a favorable balance of harms and benefits in HIV-infected adults [42]. More data will be needed to understand the role of these new screening guidelines in HIV-infected adults.

Lymphoma and Multiple Myeloma

Non-Hodgkin's lymphoma has consistently been found to be an important non-AIDS malignancy in HIV-infected patients. There are currently no screening recommendations for asymptomatic individuals. Multiple myeloma is rare in HIV but significantly higher in comparison with the general population. There are no official recommendations for screening asymptomatic individuals.

Prostate Cancer

Risk does not appear to be elevated in HIV-infected men, and a recent study in Northern California demonstrated a lower incidence rate of prostate cancer in HIV-positive compared to HIV-negative men that did not

appear to be explained by risk factors or screening rates [43]. The increased rate of prostate cancer over time seen in the U.S. HIV/AIDS Cancer Match study was influenced primarily by increasing age [12].

Screening recommendations are controversial and include annual digital rectal exams and PSA levels in men over 50 years of age, and earlier for certain high-risk groups such as African-Americans. Some guidelines recommend that screenings stop at age 75 or if the patient has less than an expected 10 year survival.

Primary CNS Lymphoma (PCNSL)

The incidence of non-Hodgkin's lymphoma is greatly increased in HIV-infected persons. The vast majority are clinically aggressive B cell-derived tumors.

The diagnosis of PCNSL is based upon the presence of malignant lymphocytes within the CNS (typically by biopsy) and by exclusion of systemic disease. PCNSL makes up 15% of non-Hodgkin's lymphoma in HIV, as compared to less than 1% in the general population [44]. It is important to conduct an aggressive screening for systemic disease, as it has been documented that cases initially presenting as PCNSL may actually be systemic lymphomas when screened more thoroughly [45].

AIDS is the most common disease associated with this tumor. Virtually all PCNSLs in patients with AIDS express EBV-related genomic markers. PCNSL has been reported in 6 to 20% of patients infected with HIV, and the incidence is expected to rise as patients with low CD4 cell counts survive longer [46].

Generally, relatively younger age has been associated with the incidence of PCNSL [47], with most patients reported as being in their fourth decade. Now, however, the incidence appears to be increasing across a wider age range. Older age is associated with decreased survival time in PCNSL.

Recently, PCNSL has been shown to respond at a high rate to a combination of radiotherapy and chemotherapy in younger

patients. This gain has not been generalized to older patient, since they are unlikely candidates for combined chemotherapy and radiation therapy treatment because of its toxicity. Hence, older HIV-infected patients with suspected PCNSL should be considered earlier for brain biopsy, rather than after empirical treatment for CNS toxoplasmosis for proof of diagnosis.

Conclusion

HIV-infected individuals may be at increased risk of infection-related NADCs, especially anal, cervical, vaginal, penile, nasopharyngeal, laryngeal, and oral cancers related to HPV; liver cancer from the HBV and HCV; and nasopharyngeal cancer and Hodgkin's lymphoma related to EBV. Patients may also be at risk for smoking-related NADCs, especially non-melanoma skin, other head and neck, lung, and less likely melanoma.

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