Non–AIDS-Defining Cancers and HIV Infection

*Soon Thye Lim, MD, and Alexandra M. Levine, MD**

Address
*University of Southern California, 1441 Eastlake Avenue, Los Angeles, CA 90033, USA.
E-mail: alevine@usc.edu

Current Infectious Disease Reports 2005, **7:**227–234
Current Science Inc. ISSN 1523-3847

With fewer patients now succumbing to infectious complications of AIDS, other HIV-related morbidities such as malignancies have become increasingly important. Apart from Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer, which are considered as AIDS-defining, several additional cancers, referred to as non–AIDS-defining cancers, are also statistically increased in HIV-infected persons. These include Hodgkin's disease, anal carcinoma, lung cancer, nonmelanomatous skin cancer, and testicular germ cell tumors, among others. However, the types of cancer observed at an increased frequency and the relative risks reported vary widely among studies. Although immunosuppression is consistently associated with an increased risk of AIDS-related malignancies, the role of immunosuppression in the pathogenesis of non–AIDS-defining cancers is controversial. Although data regarding the optimal management of these cancers are lacking, current studies suggest that patients with HIV-associated malignancies should be treated with similar approaches to those of their counterparts in the general population.

Introduction

Although the use of highly active antiretroviral therapy (HAART) has decreased the mortality rate from AIDS-related deaths by approximately 70% [1], HIV continues to be a major challenge. With fewer patients now succumbing to infectious complications, other HIV-related morbidities, such as malignancies, have become increasingly important.

HIV-infected patients have a greater tendency to develop cancer, compared with the general population. Kaposi's sarcoma (KS) and aggressive non-Hodgkin's lymphoma (NHL) form the bulk of these cancers. Together with cervical cancer, they are considered as AIDS-defining conditions by the US Centers for Disease Control and Prevention. Although not considered as AIDS-defining, several additional cancers are also statistically increased in HIV-infected persons. These include Hodgkin's disease (HD), anal carcinoma, lung cancer, nonmelanomatous skin cancer, and testicular germ cell tumors (GCTs), among others.

Epidemiology of Non–AIDS-Defining Cancers

Several cohort and linkage studies have examined the association between HIV infection and the development of AIDS-defining and non–AIDS-defining cancers. Although these studies have shown a statistically significant increase in the age-standardized incidence ratio (SIR) or relative risk (RR) of several cancers, the types of cancer observed at an increased frequency and their RRs vary widely among reports (Table 1). Thus, in one large study that linked cancer registries and AIDS registries in the United States, 98,336 people with AIDS and 1,125,098 people with cancer, aged younger than 70 years in the United States and Puerto Rico, were studied by Goedert *et al.* [2], who found a significantly increased risk of HD (7.6-fold), multiple myeloma (4.5-fold), brain cancer (3.5-fold), and seminoma (2.9-fold) among HIV-infected persons. In another large epidemiologic study examining cancer patterns among adults with HIV/AIDS in 11 geographically diverse areas in the United States, Frisch *et al.* [3••] also reported an increased risk for HD (RR = 11.5), testicular seminoma (RR = 2), multiple myeloma (RR = 2.6), and brain cancer (RR = 3.5). In addition, the authors found an increased risk of penile cancer (RR = 3.9), soft tissue malignancies (RR = 3.3), and lip cancer (RR = 3.1) [3••]. Similarly, in a report from Italy published in 1998, Franceschi *et al.* [4] found the risk for HD (SIR = 8.9), testicular cancer (SIR = 2), and brain cancer (SIR = 1.1) to be increased. However, the authors found no increase in the risk of multiple myeloma, soft tissue malignancy, or lip cancers, although they did report an increased risk of lung cancer (SIR = 2.2). In contrast, in another register-based retrospective cohort study involving 3616 people with AIDS from Australia, Grulich *et al.* [5] did find an increased risk of multiple myeloma (SIR = 12.1) and lip cancer (SIR = 5.94). Although HD (SIR = 18.3), lung cancer (SIR = 3), and leukemia (SIR = 5.76) were also found to be increased, the authors did not report an increase in risk for testicular cancer [5].

Overview of Pathogenesis and Role of Immunosuppression

The pathogenesis of HIV-associated malignancies is complex and involves the interplay of multiple factors,

Table 1. Epidemiology of common non–AIDS-defining cancers and their association with chronic immunosuppression

Type of non–AIDS-defining cancer	Risk of developing non–AIDS-defining cancer	Association with chronic immunosuppression
Anal cancer	HIV-positive men and women have a 37- and 6.8-fold greater risk of developing anal cancer, respectively [23]	Current data do not prove a direct relationship between anal cancer and immunosuppression [7,23]
Seminoma	The risk of seminoma is increased 2.9- to 61.5-fold over expected [5,30]	Current data suggest a rather weak association at best between chronic immunosuppression and development of seminoma [3••]
Lung cancer	Studies have reported a three- to ninefold increase in risk of developing lung cancer in HIV-positive individuals; most affected patients smoke [3••,33,34]	The role of immunosuppression in the development of lung cancer is controversial and not universally described [3••,37–40,42] The increased risk of lung cancer is likely to be confounded by the strong history of tobacco exposure [37–39]
Hodgkin's disease	Eight- to 10-fold increased risk of developing Hodgkin's disease in HIV infection [4,48–52]	Chronic immunosuppression is likely to play an important role in the development of HIV-related Hodgkin's disease [3••,7]
Multiple myeloma	May be an increased risk, reported at 2.9- to 12.1-fold over expected in HIV [2,3••,5]	The role of immunosuppression is controversial [3••,4,7]

including immunosuppression, concomitant infection by oncogenic viruses, lifestyle factors, and the possible direct pathogenic role of HIV infection.

Although immunosuppression in the setting of HIV infection has consistently been associated with an increased risk of KS and NHL, there have been no consistent data of a similar association with non–AIDS-defining cancers, except perhaps for HD (Table 1). Several epidemiologic studies have evaluated this association with differing conclusions. Mbulaiteye *et al.* [6] examined this relationship by studying 82,217 HIV-infected adults who had a CD4 count measured at AIDS onset and who were then followed. With each decrease of 100 CD4 cells per mm^3, the risks for NHL (RR = 1.36) and KS (RR = 1.48) were increased, with the risk strongest for immunoblastic lymphoma (RR = 1.64) and central nervous system lymphoma (RR = 2.29). However, neither the combined risk nor the risk of other specific types of cancers was associated with decreasing CD4 counts. However, other studies have found HD [2,3••,7], lip cancer [3••,6], and testicular seminoma [2,3••] to be influenced by progressive immunosuppression.

Grulich *et al.* [7] compared the incidence rates of non–AIDS-defining cancers in 8351 HIV-infected individuals without AIDS with 8118 individuals with AIDS. To assess the association between cancer incidence and immune deficiency, the authors analyzed cancer risks in four periods between HIV diagnosis, AIDS, and death. The first period was defined as the period from HIV diagnosis to 5 years before the development of AIDS, the second as 5 years to 6 months before the development of AIDS, the third as 6 months before or after the diagnosis of AIDS, and the fourth as 6 months to 2 years after the diagnosis of AIDS. Although the overall risk of lip cancer, anal carcinoma, HD, myeloma, and leukemia were increased in these individuals, only cancer rates of HD and multiple myeloma showed a significant increasing trend over time, suggesting that the latter two malignancies are associated with progressive immunosuppression. In individuals who did not develop AIDS or who were evaluated more than 5 years before they developed AIDS, only anal cancer was observed at an increased rate. However, no case of anal cancer was diagnosed among patients in the period 6 months after a diagnosis of AIDS, suggesting that the development of anal cancer is not directly associated with the immediate development of immunosuppression.

Prior infections with viruses such as human herpes virus 8 (HHV8), human papillomavirus (HPV), and Epstein-Barr (EBV) virus are clearly implicated in the pathogenesis of several of these malignancies. EBV is consistently identified in the Reed-Sternberg cells of HIV-related HD and in most cases of primary central nervous system lymphoma, whereas HHV8 is now known to be the causative agent of KS and primary effusion lymphoma. Cervical cancer and anogenital cancers are closely linked to HPV. Although HIV virus is generally not considered an oncogenic virus, it may have an indirect pathogenic role in certain malignancies. For instance, aside from its ability to induce immunosuppression, the HIV *tat* gene contributes to the pathogenesis of KS by inducing the production of cytokines that mediate angiogenesis, chemotaxis, and other cellular growth processes.

Apart from immunosuppression and concomitant infection by oncogenic viruses, the role of antiretroviral agents in the pathogenesis of cancers has also been investigated. Zidovudine has been shown to induce vaginal tumors in mice and rats exposed as adults [8], and hepatic, lung, and gynecologic tumors in mice exposed in utero [9], possibly through the incorporation of zidovudine into

Table 2. Screening for common non–AIDS-defining cancers in HIV-positive individuals

Type of non–AIDS-defining cancer	Screening
Anal cancer	Although not a routine screening test, anal cytology screening has been shown to be cost effective [63,64] Anal Pap testing should be performed by clinicians who have been adequately trained Role of human papillomavirus testing is being studied
Lung cancer	There is currently no role for the routine use of chest radiography or thoracic computed tomography scan in the early detection of lung cancer
Seminoma	No routine investigations recommended Self-examination encouraged
Hodgkin's disease	No routine investigations recommended Educate about unexplained weight loss and fever
Breast, prostate, and colorectal cancer	Recommendations regarding screening of these cancers should follow those for HIV-negative individuals

cellular DNA [10]. In vitro studies have also shown that the incorporation of zidovudine into genomic DNA increases mutagenic frequencies at the X-linked hypoxanthine-guanine phosphoribosyltransferase, thymidine kinase, and adenine phosphoribosyltransferase genes in human lymphoblastoid cells [11–13]. Combining didanosine with zidovudine seems to enhance the incorporation of zidovudine into DNA and further increases the frequencies of these mutations [13]. However, the clinical significance of these in vitro and in vivo data is uncertain, and current clinical data have not convincingly shown an oncogenic effect of zidovudine or HAART in HIV-infected patients [14••]. Herida *et al*. [14••] compared the incidence of non–AIDS-defining cancers in HIV-infected persons before and during the HAART period and found no increase in the overall incidence of non–AIDS-defining cancers between the two periods. Although the incidence rates of two specific cancers, HD and lung cancer, were higher in the post-HAART era, they are more likely to be related to other factors rather than to the use of HAART per se (see discussion later).

Cancer-associated risk behaviors such as smoking, excessive alcohol consumption, and poorer eating and exercise habits provide additional factors resulting in the risk of malignancy in HIV-infected individuals.

Anal Cancer

Anal precursor lesions

Like cervical cancer, HPV has been associated with anal precursor lesions and with invasive anal carcinoma. Studies have shown that anal HPV infection is exceedingly prevalent in HIV-positive men and HIV-negative men who have sex with men (MSM). In one study, anal HPV DNA was detected in 93% of HIV-positive and 61% of HIV-negative men by polymerase chain reaction, with HPV 16 being the most common type detected [15]. To a lesser extent, this increase in the prevalence of anal HPV infection and anal precursor lesions among HIV-infected persons is also seen in the absence of anal intercourse [16].

The risk of developing anal squamous intraepithelial lesions (ASILs) and the natural history of these lesions in HIV-positive and HIV-negative MSM appear to be different, with the risk of developing ASILs greater in HIV-positive men [17]. Although the risk appears to be greatest for men with low CD4 counts, HIV-positive men with CD4 counts more than 500 per mm^3 are also at an increased risk, compared with HIV-negative men with the same demographic characteristics [17]. In addition, HIV-positive men were more likely to develop high-grade squamous intraepithelial lesions (HSILs), compared with HIV-negative MSM [17]. Progression from low-grade squamous intraepithelial lesions (LSILs) to HSILs was also more common in HIV-positive MSM [18].

Although some reports have suggested that immune reconstitution with HAART alters the course of HPV disease and cervical intraepithelial neoplasia in HIV-infected women [19], recent studies have suggested that HAART may have little effect on the incidence or progression of ASILs in HIV-infected men [20,21]. In a study evaluating the severity of ASILs in HIV-positive men before and after the initiation of HAART, 17% of study patients with normal anal cytology at diagnosis subsequently developed a precursor lesion, whereas only 4% of patients with high-grade precursor lesions regressed to normal [20]. In another study, Kiviat *et al*. [22] studied 102 HIV-infected men from Seattle and compared their outcomes in the pre- and post-HAART periods. Mean follow-up was 3.5 years, including 2.6 years after initiation of HAART. Within the cohort, as the duration of HAART increased, the prevalence of HPV infection and LSILs also decreased, suggesting that HAART may potentially be associated with a decrease in the risk of HSIL over time. Nonetheless, no decrease in the risk of high-grade anal intraepithelial lesions after initiation of HAART was observed [22]. A more recent study from Paris also suggested that HAART does not result in regression of precursor anal lesions in HIV-positive men or in the clearance of HPV infection [21]. In this cross-sectional study of 45 HIV-positive men who had taken protease inhibitor–containing HAART for a median of 32

months, abnormal anal cytology was present in 32 patients (71%), with low-grade lesions in 19 (42%) and high-grade lesions in 10 (22%), whereas HPV DNA was detected in 36 (80%) men. The presence of ASILs was not significantly different in men who had a CD4 cell count more or less than 250 cells per mm^3 at enrollment ($P = 0.7$). When stratified according to their nadir CD4 count (> or < 150 cells/mm^3, $P = 0.3$) or according to the improvement in CD4 count after initiating HAART (> or < 150 cells/mm^3, $P = 0.3$), no significant difference in the prevalence of precursor lesions or the prevalence of HPV infection was observed.

Incidence of anal cancer

The relative risk of anal cancer among HIV-infected men is approximately 37-fold greater than expected in the general population, whereas the relative risk is also increased (6.8-fold) among HIV-infected woman [23]. Compared to HIV-negative homosexual men, HIV-positive men have twice the risk of developing anal cancer [24]. Nonetheless, the role of HIV in inducing anal cancer is still not well defined. Moreover, current data do not suggest a direct relationship between anal cancer and immunosuppression [7,23].

The impact of HAART on the incidence of invasive anal cancer is also uncertain. Nonetheless, the National Cancer Institute Surveillance, Epidemiology, and End Results population-based cancer incidence data from the greater San Francisco Bay area have shown an increased incidence of anal cancer among all men and women, aged 40 to 64 years, when evaluated between 1973 and 1999. Although these data are not specific for HIV-infected individuals, they do indicate that the incidence of anal cancer continues to increase substantially, despite the high penetrance of HAART in the population of HIV-infected individuals living in the San Francisco Bay area.

Therapy for anal cancer in the setting of HIV

In the general population, treatment of anal cancer with standard combined fluorouracil/mitomycin chemoradiation is associated with a high cure rate [25,26]. Although there were initial concerns of resistance to standard chemoradiation in HIV-infected patients with anal cancer, recent data suggest that these individuals should be treated with the same approach as patients in the general population [27,28]. In a recent report of 12 HIV-positive men with anal cancer treated with 5-fluorouracil and mitomycin C, with concomitant radical radiotherapy, complete remissions were attained in nine of 11 (82%) evaluable patients [27]. At a median follow-up of 4.8 years, only two patients had died of anal cancer, whereas one died from treatment-related complications.

Germ Cell Tumor

Although several studies have documented an increased risk of seminoma in patients with HIV, the risk of developing seminoma has varied widely among published reports, ranging from an increased risk ratio of 2.9-fold in a study from the United States [2] to 61.5-fold in an earlier study from Italy [29]. The relationship between nonseminomatous germ cell tumor (GCT) and HIV is controversial. Thus, in a report involving 35 HIV-infected patients with GCT seen in six HIV-treatment centers in Europe, a higher incidence of seminoma was observed among HIV-positive patients, compared with age- and sex-matched individuals in the general population (RR = 5.45), whereas nonseminomatous GCT occurred at a similar frequency in both groups of individuals [30].

The role of immunosuppression in the development of GCT appears to be less important, as most studies have reported fairly well-preserved immunity in patients with HIV-related GCT. Powles *et al*. [30] evaluated 35 such patients, whose median CD4 cell count was 315 per mm^3, ranging from 90 to 960 per mm^3. A study from Italy [31] reported a median CD4 cell count of 325 per mm^3 (range = 65–1125/mm^3) at GCT diagnosis. However, Frisch *et al*. [3••] from the United States reported an increase in the relative risk of seminoma from 0.7 in the distant pre-AIDS period to 2 in the period after the development of AIDS ($P = 0.003$), suggesting that the risk of developing seminoma increases with progressive immunosuppression. Nonetheless, this rather weak association (RR approximately 2) suggests that chronic immunosuppression is unlikely to be a major factor in the pathogenesis of HIV-related GCT.

Although there is little information regarding the impact of HAART on the incidence of GCT, a recent study reported no significant difference in the incidence of GCT in the pre- and post-HAART eras [1].

The median age at diagnosis of GCT among patients with HIV has ranged from 28 to 34 years, and most present with early-stage disease. Thus, in one study involving 35 such patients, Powles *et al*. [30] reported stage I disease in 21 patients (60%), stage II disease in 10 (29%), and stage III disease in four (11%). In another study of 294 cases of GCT from 1980 to 1993, which also included nine HIV-infected men, there was no difference in the proportions of early-stage disease between HIV-positive versus HIV-negative men (67% vs 63%) [32].

In non–HIV-infected individuals, more than 90% of patients with newly diagnosed GCTs are cured. Recent published results have suggested that patients with HIV-related GCT have similar favorable outcomes when treated with standard therapy. Thus, Powles *et al*. [30] showed that the overall 2-year survival of 35 patients with HIV-related GCT treated with standard approaches was 94%. At a median follow-up of approximately 4.5 years, only one of the 21 patients (4%) with stage I disease had died and two of the 14 patients (14%) with stage II or III disease died from progressive disease. These results suggest that HIV-infected patients should be treated with similar strategies used for non–HIV-infected patients with GCT.

Lung Cancer

Several studies have suggested that patients with HIV infection are at an increased risk of developing lung cancer. For instance, Frisch *et al.* [3••] reported a 4.5-fold increased risk of developing lung cancer, whereas other studies have reported a threefold, 6.5-fold, and ninefold increase in risk [33,34].

However, the increased risk of lung cancer in HIV-infected individuals may be confounded by the fact that patients with HIV are more likely to be smokers, compared to the general population [35,36]. Moreover, many of the studies demonstrating an increased risk of lung cancer among HIV-infected individuals have also documented a strong history of tobacco exposure in these patients [37–39]. Considering the strong association between smoking and lung cancer, it is conceivable that the increased risk of lung cancer reported in HIV-infected persons may be attributed to the higher prevalence of smoking, rather than the effect of HIV infection per se. In a report assessing cancer risks among participants in the Women's Interagency HIV Study [40], which included 1554 HIV-infected and 391 HIV-uninfected female participants, approximately 60% of HIV-infected and HIV-uninfected women had a history of cigarette smoking. Thus, it was not surprising that the age- and race-adjusted SIRs of lung cancer in both groups of women were higher than population-based expectations, with no difference in the relative risk of lung cancer among HIV-infected women versus the HIV-negative controls [40]. Furthermore, improvement in survival among HIV-infected patients in the post-HAART period also has allowed adequate time for lung cancer to develop in smokers who were already at risk, thus increasing the frequency of this malignancy in the post-HAART era.

However, Bower and colleagues [37,41] suggested that the ninefold increase in lung cancer among HIV-infected patients in their study since the introduction of HAART could not be accounted for by the higher prevalence of smoking in these individuals, and suggested that prolonged immune suppression may be predisposing these individuals to lung cancer. Nonetheless, even in the study by Bower *et al*. [37], most HIV-infected patients with lung cancer did not have profound immune dysfunction, with median CD4 counts at diagnosis in the range of approximately 150 to 300 cells per mm^3 [38,39]. Furthermore, most HIV-infected patients with lung cancer do not have a history of an AIDS-defining diagnosis before the development of lung cancer [39]. Moreover, in considering other models of underlying immunosuppression, despite an overall increase in the incidence of malignancies in recipients of solid organ transplantation, the risk of bronchogenic carcinoma is low and occurs mainly in recipients who are smokers [42]. Thus, the role of immunosuppression in the development of lung cancer in HIV-infected individuals is uncertain.

In terms of clinical presentation, HIV-infected individuals who develop lung cancer tend to be younger compared to their counterparts in the general population, with a mean age at diagnosis of approximately 38 to 49 years [33,34,39,43]. Most of these patients present with advanced disease, and some studies have suggested that adenocarcinoma is the most common histologic subtype encountered [37,39,44,45]. However, this apparent predominance of adenocarcinoma is consistent with the recent increase in lung adenocarcinoma in the general population, even among smokers [46].

Several earlier studies have suggested that HIV-infected patients with lung cancer fared less well than their age-, stage-, and histology-matched HIV-negative controls [38,39,43]. However, recent studies that combined HAART with treatment protocols designed for non–HIV-infected patients have reported more encouraging results [47]. Although there are currently no recommendations for the management of HIV-infected patients with lung cancer, treatment of these patients should follow the same approaches recommended for patients in the general population.

Considering the high prevalence of smoking in HIV-infected individuals and their improved survival attributed to HAART, it is likely that there will be a further increase in the incidence of lung cancer in the coming years. Thus, it is of paramount importance to encourage HIV-infected smokers to stop smoking and to strengthen smoking cessation programs, which would also be expected to reduce the risk of other smoking-related ailments, such as squamous epithelial cancers of the head and neck regions in these patients.

Hodgkin's Disease

Epidemiology

Large linkage epidemiologic studies have consistently indicated that HIV-infected individuals have an eight- to 10-fold increased risk of developing HD [4,48–52]. Recent data have also suggested that chronic immunosuppression may be important in the pathogenesis of HIV-related HD. For instance, Frisch *et al.* [3••] documented a fourfold increase in the relative risk of HD when diagnosed in the period 60 to 25 months before the development of AIDS (RR = 2.6), versus the period immediately before the development of AIDS (RR = 9.8), when the degree of immunosuppression would be more profound. Others have also found a similar relationship with immunosuppression [3••,7]. It is conceivable that chronic stimulation by EBV, which can be detected in almost all cases of HIV-related HD [53,54], in the setting of an imperfectly reconstituted immune system, may be responsible for the increased risk of HD over time, even in patients with access to HAART. Furthermore, there appears to be no decrease in the incidence of HD since the introduction of HAART. The International Collaboration on HIV and Cancer reported no statistically significant change in the incidence rates for HD between the pre-HAART and the post-HARRT eras (rate ratio = 0.77; 99% confidence interval = 0.32–1.85; $P = 0.4$) [55].

Clinical presentation

HIV-related HD differs from HD in the general population (de novo HD) in several ways. In contrast with de novo HD, in which nodular sclerosis is the most common histologic subtype, mixed cellularity HD and lymphocyte depletion HD are significantly more likely to be diagnosed in HIV-infected patients [56–58]. Furthermore, compared to patients with de novo HD, patients with HIV-related HD are more likely to present with advanced stages of disease [51,57,58]. Approximately 50% present with involvement of the bone marrow, often in the setting of pancytopenia and systemic "B" symptoms, such as fever, night sweats, or weight loss.

Therapy

Treatment of HIV-related HD in the pre-HAART era with standard combination chemotherapy such as adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) was associated with poor median survival of only 12 to 18 months [59,60]. With the advent of HAART, more encouraging results have been noted [61]. Thus, Spina *et al*. [61], in a prospective study of the Stanford V regimen with HAART in 59 patients with HIV-related HD, reported an objective response rate of 89% and a complete response rate of 81%, with an estimated 3-year overall survival and disease-free survival of 51% and 68%, respectively. These results were superior to the survival rates observed in studies from the pre-HAART era [59,60]. However, outcome results are still inferior when compared to those observed in HIV-negative patients, in whom even patients with stage IV disease have a cure rate of 60% to 70%. Nonetheless, at the current time, it is reasonable to treat patients with HIV-related HD using standard regimens such as ABVD or the Stanford V regimens. More recently, investigators from Germany reported the results of a small phase II study evaluating the efficacy and safety of six cycles of a regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone at standard doses in 12 patients with HIV-related HD [62]. Although the results of this study were impressive, with all patients achieving complete disease remission and nine patients remaining in complete remission after a median follow-up of 49 months, two patients died of opportunistic infections in the treatment period. Further confirmation as to the safety and efficacy of this regimen is needed before its routine use can be recommended.

Cancer Screening and Prevention of Non–AIDS-Defining Cancers

Although screening for anal intraepithelial neoplasia (AIN) is currently not considered a routine test, studies evaluating the cost effectiveness and efficacy of periodic anal cytologic screening in HIV-positive and HIV-negative MSM suggest that anal Pap smears are comparable to other accepted prevention programs, including cervical screening using Pap smear [63,64]. Thus, although controversial, it seems reasonable to recommend anal Pap testing as screening procedure for these high-risk individuals. However, the anal Pap test should only be performed by physicians who have been adequately trained in this technique. The role of HPV testing is being studied.

Although routine screening for testicular cancer is not recommended, HIV-infected men should be instructed in self-examination. Routine use of radiologic examinations such as chest radiography and/or thoracic computed tomography scan in the screening of lung cancer cannot be recommended. Although no screening tests for the early detection of HD are available, patients should be educated about symptoms such as unexplained fever or weight loss. As for other cancers such as breast, colorectal, and prostate cancers, screening recommendations should follow those of HIV-negative patients. Table 2 summarizes the role of screening for these common non–AIDS-defining cancers in HIV-infected individuals.

Physicians caring for these patients should continue to emphasize the importance of limiting alcohol and recreational drug and tobacco use, and should encourage healthy dietary habits and regular exercise.

Conclusions

With the significant improvement in survival of HIV-infected patients, we will continue to witness an increase in the incidence of non–AIDS-defining cancers. Thus, it will be important to define optimal treatment approaches in these individuals, not only in terms of chemotherapy and radiation, but also in terms of the appropriate use of supportive measures such as growth factors and prophylactic antimicrobials during therapy. More importantly, future studies should focus on understanding the molecular and biological factors that predispose these individuals to the development of cancers, so that appropriate preventive measures can be implemented.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Palella FJ Jr, Delaney KM, Moorman AC, *et al.*: **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.** *N Engl J Med* 1998, **329:**853–860.
2. Goedert JJ, Cote TR, Virgo P, *et al.*: **Spectrum of AIDS-associated malignant disorders.** *Lancet* 1998, **351:**1833–1829.
3. •• Frisch M, Biggar RJ, Engels EA, *et al.*: **AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults.** *JAMA* 2001, **285:**1736–1745.

This large epidemiologic study examining cancer patterns among adults with HIV/AIDS reported an increased risk for HD, testicular seminoma, multiple myeloma, brain cancer, penile cancer, soft tissue malignancies, and lip cancer.

4. Franceschi S, Dal Maso L, Arniani S, *et al.*: **Risk of cancer other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. Cancer and AIDS Registry Linkage Study.** *Br J Cancer* 1998, **78:**966–970.
5. Grulich AE, Wan X, Law MG, *et al.*: **Risk of cancer in people with AIDS.** *AIDS* 1999, **13:**839–843.
6. Mbulaiteye SM, Biggar RJ, Goedert JJ, *et al.*: **Immune deficiency and risk for malignancy among persons with AIDS.** *J Acquir Immune Defic Syndr* 2003, **32:**527–533.
7. Grulich AE, Li Y, McDonald A, *et al.*: **Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis.** *AIDS* 2002, **16:**1155–1161.
8. Ayers KM, Clive D, Tucker WE Jr, *et al.*: **Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats.** *Fundam Appl Toxicol* 1996, **32:**148–158.
9. Olivero OA, Anderson LM, Diwan BA, *et al.*: **Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys.** *J Natl Cancer Inst* 1997, **89:**1602–1608.
10. **LARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Some Antiviral and Antineoplastic Drugs, and Other Pharmaceutical Agents.** Lyon, France: International Agency for Research on Cancer Scientific Publication No. 76; 2000:35–42, 73–127, 153–173.
11. Sussman HE, Olivero OA, Meng Q, *et al.*: **Genotoxicity of 3'-azido-3'-deoxythymidine in the human lymphoblastoid cell line, TK6: relationships between DNA incorporation, mutant frequency, and spectrum of deletion mutations in HPRT.** *Mutat Res* 1999, **429:**249–259.
12. Meng Q, Grosovsky AJ, Shi X, *et al.*: **Mutagenicity and loss of heterozygosity at the APRT locus in human lymphoblastoid cells exposed to 3'-azido-3'-deoxythymidine.** *Mutagenesis* 2000, **15:**405–410.
13. Meng Q, Walker DM, Olivero OA, *et al.*: **Zidovudine-didanosine coexposure potentiates DNA incorporation of zidovudine and mutagenesis in human cells.** *Proc Natl Acad Sci U S A* 2000, **97:**12667–12671.
14.•• 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* 2003, **21:**3447–3453.

This study compared the incidence of non–AIDS-defining cancers in HIV-infected persons before and during the HAART period and found no increase in the overall incidence of non–AIDS-defining cancers between the two periods.

15. Palefsky JM, Holly EA, Ralston ML, *et al.*: **Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men.** *J Infect Dis* 1998, **177:**361–367.
16. Piketty C, Darragh TM, Da Costa M, *et al.*: **High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse.** *Ann Intern Med* 2003, **138:**453–459.
17. Palefsky JM, Holly EA, Ralston ML, *et al.*: **High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men.** *AIDS* 1998, **12:**495–503.
18. Palefsky JM, Holly EA, Hogeboom CJ, *et al.*: **Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, **17:**314–319.
19. Minkoff H, Ahdieh L, Massad LS, *et al.*: **The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women.** *AIDS* 2001, **15:**2157–2164.
20. Palefsky JM, Holly EA, Ralston ML, *et al.*: **Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection.** *J Acquir Immune Defic Syndr* 2001, **28:**422–428.
21. Piketty C, Darragh TM, Heard I, *et al.*: **High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy.** *Sex Transm Dis* 2004, **31:**96–99.
22. Kiviat N, Redman MW, Hawes SE, *et al.*: **The effect HAART on detection of anal HPV and squamous intraepithelial lesions among HIV-infected homosexual men [abstract 1].** *Program and Abstracts of the 6th International Conference on Malignancies in AIDS and Other Immunodeficiencies.* Bethseda, Maryland: 2002.
23. Frisch M, Biggar RJ, Goedert JJ: **Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome.** *J Natl Cancer Inst* 2000, **92:**1500–1510.
24. Biggar RJ, Rabkin CS: **The epidemiology of AIDS-related neoplasms.** *Hematol Oncol Clin North Am* 1996, **10:**997–1010.
25. Sischy B: **The use of radiation therapy combined with chemotherapy in the management of squamous cell carcinoma of the anus and marginally resectable adenocarcinoma of the rectum.** *Int J Radiat Oncol Biol Phys* 1985, **11:**1587–1593.
26. Leichman L, Nigro N, Vaitkevicius VK, *et al.*: **Cancer of the anal canal. Model for preoperative adjuvant combined modality therapy.** *Am J Med* 1985, **78:**211–215.
27. Cleator S, Fife K, Nelson M, *et al.*: **Treatment of HIV-associated invasive anal cancer with combined chemoradiation.** *Eur J Cancer* 2000, **36:**754–758.
28. Peddada AV, Smith DE, Rao AR, *et al.*: **Chemotherapy and low-dose radiotherapy in the treatment of HIV-infected patients with carcinoma of the anal canal.** *Int J Radiat Oncol Biol Phys* 1997, **37:**1101–1105.
29. Gabutti G, Vercelli M, De Rosa MG, *et al.*: **AIDS related neoplasms in Genoa, Italy.** *Eur J Epidemiol* 1995, **11:**609–614.
30. Powles T, Bower M, Daugaard G, *et al.*: **Multicenter study of human immunodeficiency virus-related germ cell tumors.** *J Clin Oncol* 2003, **21:**1922–1927.
31. Bernardi D, Salvioni R, Vaccher E, *et al.*: **Testicular germ cell tumors and human immunodeficiency virus infection: a report of 26 cases. Italian Cooperative Group on AIDS and Tumors.** *J Clin Oncol* 1995, **13:**2705–2711.
32. Timmerman JM, Northfelt DW, Small EJ, *et al.*: **Malignant germ cell tumors in men infected with the human immunodeficiency virus: natural history and results of therapy.** *J Clin Oncol* 1995, **13:**1391–1397.
33. Ricaurte JC, Hoerman MF, Nord JA, *et al.*: **Lung cancer in HIV-infected patients: a one-year experience.** *Int J STD AIDS* 2001, **2:**100–102.
34. Parker MS, Leveno DM, Campbell TJ, *et al.*: **AIDS-related bronchogenic carcinoma. Fact or fiction?** *Chest* 1998, **113:**154.
35. Savès M, Chêne G, Ducimetière P, *et al.*: **Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population.** *Clin Infect Dis* 2003, **37:**292–298.
36. Thompson SC, Nanni C, Levine A: **The stressors and stress of being HIV-positive.** *AIDS Care* 1996, **8:**5–14.
37. Bower M, Powles T, Nelson M, *et al.*: **HIV-related lung cancer in the era of highly active antiretroviral therapy.** *AIDS* 2003, **17:**371–375.
38. Phelps RM, Smith DK, Heilig CM, *et al.*: **Cancer incidence in women with or at risk for HIV.** *Int J Cancer* 2001, **94:**753–757.
39. Tirelli U, Spina M, Sandri S, *et al.*: **Lung carcinoma in 36 patients with human immunodeficiency virus infection. The Italian Cooperative Group on AIDS and Tumors.** *Cancer* 2000, **88:**563–569.
40. **For the WIHS Collaborative Study Group. Cancer risk among participants in the Women's Interagency HIV Study.** *J Acquir Immune Defic Syndr* 2004, **36:**978–985.
41. Powles T, Bower M: **HIV and the risk of lung cancer.** *J Clin Oncol* 2004, **22:**1348–1349.
42. de Perrot M, Wigle DA, Pierre AF, *et al.*: **Bronchogenic carcinoma after solid organ transplantation.** *Ann Thorac Surg* 2003, **75:**367–371.

43. Sridhar KS, Flores MR, Raub WA Jr, *et al.*: **Lung cancer in patients with human immunodeficiency virus infection compared with historic control subjects.** *Chest* 1992, **102:**1704–1708.
44. Karp J, Profeta G, Marantz PR, *et al.*: **Lung cancer in patients with immunodeficiency syndrome.** *Chest* 1993, **103:**410–413.
45. Fraire AE, Awe RJ: **Lung cancer in association with human immunodeficiency virus infection.** *Cancer* 1992, **70:**432–436.
46. Koyi H, Hillerdal G, Branden E: **A prospective study of a total material of lung cancer from a county in Sweden 1997-1999: gender, symptoms, type, stage, and smoking habits.** *Lung Cancer* 2002, **36:**9–14.
47. Powles T, Thirwell C, Newsom-Davis T, *et al.*: **Does HIV adversely influence the outcome in advanced non-small-cell lung cancer in the era of HAART?** *Br J Cancer* 2003, **89:**457–459.
48. Ames ED, Conjalka MS, Goldberg AF, *et al.*: **Hodgkin's disease and AIDS. Twenty-three new cases and a review of the literature.** *Hematol Oncol Clin North Am* 1991, **5:**343–356.
49. Spina M, Vaccher E, Nasti G, *et al.*: **Human immunodeficiency virus-associated Hodgkin's disease.** *Semin Oncol* 2000, **27:**480–488.
50. Re A, Casari S, Cattaneo C, *et al.*: **Hodgkin disease developing in patients infected by human immunodeficiency virus results in clinical features and a prognosis similar to those in patients with human immunodeficiency virus-related non-Hodgkin lymphoma.** *Cancer* 2001, **92:**2739–2745.
51. Bellas C, Santon A, Manzanal A, *et al.*: **Pathological, immunological, and molecular features of Hodgkin's disease associated with HIV infection. Comparison with ordinary Hodgkin's disease.** *Am J Surg Pathol* 1996, **20:**1520–1524.
52. Lyter DW, Bryant J, Thackeray R, *et al.*: **Incidence of human immunodeficiency virus-related and nonrelated malignancies in a large cohort of homosexual men.** *J Clin Oncol* 1995, **13:**2540–2546.
53. Dolcetti R, Boiocchi M, Gloghini A, *et al.*: **Pathogenetic and histogenetic features of HIV-associated Hodgkin's disease.** *Eur J Cancer* 2001, **37:**1276–1287.
54. Carbone A, Gloghini A, Larocca LM, *et al.*: **Human immunodeficiency virus-associated Hodgkin's disease derives from post-germinal center B cells.** *Blood* 1999, **93:**2319–2326.
55. **International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults.** *J Natl Cancer Inst* 2000, **92:**1823–1830.
56. Monfardini S, Tirelli U, Vaccher E, *et al.*: **Hodgkin's disease in 63 intravenous drug users infected with human immunodeficiency virus. Gruppo Italiano Cooperativo AIDS & Tumori (GICAT).** *Ann Oncol* 1991, **2(Suppl 2):**201–205.
57. Andrieu JM, Roithmann S, Tourani JM, *et al.*: **Hodgkin's disease during HIV1 infection: the French registry experience. French registry of HIV-associated tumors.** *Ann Oncol* 1993, **4:**635–641.
58. Serrano M, Bellas C, Campo E, *et al.*: **Hodgkin's disease in patients with antibodies to human immunodeficiency virus. A study of 22 patients.** *Cancer* 1990, **65:**2248–2254.
59. Levine AM, Li P, Cheung T, *et al.*: **Chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease: a prospective, multi-institutional AIDS clinical trials group study (ACTG 149).** *J Acquir Immune Defic Syndr* 2000, **24:**444–450.
60. Errante D, Gabarre J, Ridolfo AL, *et al.*: **Hodgkin's disease in 35 patients with HIV infection: an experience with epirubicin, bleomycin, vinblastine and prednisone chemotherapy in combination with antiretroviral therapy and primary use of G-CSF.** *Ann Oncol* 1999, **10:**189–195.
61. Spina M, Gabarre J, Rossi G, *et al.*: **Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection.** *Blood* 2002, **100:**1984–1988.
62. Hartmann P, Rehwald U, Salzberger B, *et al.*: **BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection.** *Ann Oncol* 2003, **14:**1562–1569.
63. Goldie SJ, Kuntz KM, Weinstein MC, *et al.*: **The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men.** *JAMA* 1999, **281:**1822–1829.
64. Goldie SJ, Kuntz KM, Weinstein MC, *et al.*: **Cost-effectiveness of screening for anal squamous intraepithelial lesions.** *Am J Med* 2000, **108:**634–641.