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Evolving Spectrum and Incidence of Non-AIDS-Defining Malignancies

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Abstract

Purpose of review—Non-AIDS Defining Cancer (NADC) has emerged as an important cause of morbidity and mortality in the HIV-infected population. Insight into the incidence, spectrum, risk factors, management, and outcome of these cancers has continued to emerge. The recent literature on this topic is reviewed.

Recent findings—Several recent studies have explored the shifting spectrum of NADC in both developed and underdeveloped regions of the world. Investigators have shown only a minor difference in the geographic spectrum of NADC. While several NADC have continued to occur at rates significantly higher than expected, a noticeable decline was observed in other cancers despite antiretroviral therapy. Factors other than HIV and immunosuppression proved to be important in the risk, treatment response, and outcome of these neoplasms. Studies dealing with the management of several NADC were published, including the role of highly active antiretroviral therapy (HAART).

Summary—An increased overall relative risk of developing NADC continues to be reported in the HIV-infected population worldwide. The development of NADC appears to be multifactorial. While control of HIV viremia has proven to be beneficial, the impact of HAART on NADC incidence rates and survival is not uniform. Further effort is needed to resolve the direct and indirect effects of HIV on NADC in order to guide effective prevention and treatment strategies of these malignancies.

Keywords

AIDS; Cancer; HAART; HIV; Malignancy

Introduction

An increased overall risk of developing Non-AIDS Defining Cancers (NADC) has been reported in the HIV-infected population [1-2]. The pending impact of this “sleeping giant” in people with HIV infection has been realized by several authors [3]. Apart from a bona fide increased prevalence of NADC, there is greater screening, increased detection of more incidental cancers with imaging studies, augmented reporting, and improved survival in an ageing HIV-infected population. NADC include carcinomas, hematopoietic malignancies and miscellaneous neoplasms like melanoma, sarcomas other than Kaposi sarcoma, and germ cell tumors. The spectrum of NADC has expanded as the size of the HIV-positive population has increased [4]. NADC are responsible for significant morbidity and mortality in the highly

active antiretroviral therapy (HAART) era [5]. In general, patients with NADC have been reported to have an overall poor outcome manifesting with advanced cancer at presentation, rapid progression, frequent metastases, a high rate of relapse, and poor therapeutic response. Further insight into the incidence, spectrum, risk factors, management, and outcome of NADC has continued to grow. The recent literature pertaining to this topic is reviewed in this paper.

Incidence

Several studies have documented an increased incidence of NADC [6-7]. Prior investigations showed that the incidence of NADC in the United States was at least twice that of the general population [6], with a rate of 980 new NADC diagnoses per 100,000 person-years in one study [8]. A number of recent studies confirmed these findings. Investigators from the National Cancer Institute in the United States linked HIV/AIDS and cancer registries in three states where 57,350 HIV-infected persons were registered during 1991-2002 [*9]. Risk was shown to be elevated for Hodgkin lymphoma, lung cancer and hepatocellular carcinoma. In this study, NADC comprised 31% of cancers in 1991-1995 (pre-HAART) versus 58% in 1996-2002 (HAART era). Another study looking at data from 13 different cancer registries in the United States found the incidence of many NADC to be higher among HIV-infected persons than the general population from 1992 to 2003 [**4]. This particular study involved 54,780 HIV-infected persons, who contributed 157,819 person-years of follow-up (1992-2003). Specific NADC that were significantly higher in the HIV-infected population included anal, vaginal, liver, lung, oropharyngeal, colorectal, and renal cell carcinoma (RCC), as well as Hodgkin lymphoma, melanoma and leukemia. The incidence of prostate cancer in this study, however, was significantly lower among HIV-infected persons than the general population [**4]. A smaller study involving 2,566 patients in a single urban HIV clinic in the United States reported increased rates of several NADC [10]. Moreover, researchers from Spain found similar high standard incidence ratios (SIRs) for Hodgkin lymphoma (SIR 31.1), liver cancer (SIR 29.4) and lung cancer (SIR 9.4) in men [11]. Another recent study that examined linked population-based cancer and HIV/AIDS United States registry data for 268,950 men who developed AIDS in 1980 to 2003 demonstrated that seminoma risk was increased significantly with HIV/AIDS, whereas non-seminoma risk was not [12]. Extratesticular germ cell tumor risk in this paper was also increased.

In developing countries where HAART is largely unavailable, the incidence of NADC appears to have likewise advanced with the escalating HIV epidemic. The incidence and spectrum of NADC has varied only slightly in these developing regions of the world [13]. In particular, the incidence of HIV-related squamous cell carcinoma (SCC) of the conjunctiva is significantly increased in equatorial Africa [14]. In a study exploring the spectrum of HIV related cancers at the largest tertiary referral cancer center in India, the proportional incidence ratio (observed number of site-specific cancer cases divided by the expected number) was shown to be increased for anal cancer, Hodgkin lymphoma, testicular cancer, colon cancer, as well as a few head and neck cancer sites [15]. Also, a related case-control study from South Africa conducted between 1995-2004 reported significantly increased risks with HIV-associated Hodgkin lymphoma and anogenital cancer (excluding the cervix) [16].

Risk Factors

Immunodeficiency (i.e. low CD4 count) has been shown by several investigators not to be the crucial factor for the development of NADC [17,18]. However, in a recent large meta-analysis conducted by researchers from Australia that involved seven studies involving people with HIV/AIDS (n=444,172) and five with transplant recipients, the increased risk of many NADC was similar to that of transplant recipients [**19]. This strongly suggests that immunodeficiency, rather than other risk factors for cancer, is perhaps responsible for the

increased risk [**19]. Table 1 summarizes the published SIRs for several NADC from this meta-analysis. In a study evaluating the prevalence of neoplasia before and after HAART, researchers from Puerto Rico found a higher prevalence of NADC in the HAART era [20]. These findings lead these authors to suggest that factors other than severe immunosuppression may be involved in the pathogenesis of NADC.

Indeed, several other key factors probably do play a role in NADC tumorigenesis, including the duration of HIV immunosuppression, longevity (age >40 years), lifestyle habits (e.g. sexual behavior, smoking, sun exposure), coinfection with oncogenic viruses, familial cancer history, and increased genomic instability (e.g. microsatellite alterations). A recent review article on the viral etiology of AIDS-associated malignancies, including those induced by HPV (penile, anal, oral, and conjunctival cancers), pointed out that the distribution of oncogenic HPV subtypes in Africa differs from that in the United States and Europe [21]. Many HIV positive individuals have a history of cigarette smoking. Therefore, it is not surprising that in the Swiss HIV Cohort Study, no lung cancers were observed in HIV-positive persons who were non-smokers [18]. Interestingly, a recent study from the School of Public Health at Johns Hopkins University showed that their calculated risk associated with HIV-related lung cancer (hazard ratio, 3.6; 95% confidence interval, 1.6-7.9) was independent of smoking status [22]. Furthermore, preexisting lung disease, particularly noninfectious diseases and asthma, in this cohort of injection drug users was found to be associated with an increased lung cancer risk.

Haart

Longer life expectancy brought about by the introduction of HAART has, unfortunately, been met with the occurrence of certain malignancies that develop over a long latency period. An analysis of data from adults (n = 14,210) in the San Francisco AIDS surveillance registry (from 1990-2000), computer matched with the California Cancer Registry, showed that the impact of HAART on NADC (n = 482) incidence rates and survival was, in fact, not uniform [**23]. For example, the risk of anal cancer in this study increased after 1995 (relative hazard 2.9), whereas that for hepatocellular carcinoma was lower with HAART use (relative hazard = 0.32). Furthermore, lung cancer and Hodgkin lymphoma showed increased cancer survival time with HAART use, while anal cancer survival was slightly decreased.

In a recent review of the literature looking at five of the most common NADC (Hodgkin lymphoma, anal cancer, hepatocellular carcinoma, oral cancer, and lung cancer), in the pre- and post-HAART periods, the authors remained unclear whether earlier initiation (i.e. CD4+ cell count above 350 cells/mm³) of antiretroviral therapy was beneficial in preventing any of these cancers [24]. Moreover, in the SMART study that compared the rates of malignancies between patients on a CD4 T-cell-guided (interrupted) versus a continuous antiretroviral therapy strategy, the risk of AIDS-defining cancers increased with interrupted antiretrovirals while the rate for NADC was similar between the interrupted and continuous antiretroviral groups [25]. Clearly, further studies on the relationship between HAART and NADC are required.

Hodgkin Lymphoma

Hodgkin lymphoma, particularly those with unfavorable histopathology (mixed cellularity and lymphocyte depleted), is one of the most common NADC. A 3- to 18-fold increased risk of developing Hodgkin lymphoma has been reported with HIV infection [26-29]. Most cases in HIV-positive persons are EBV positive. While some studies have linked Hodgkin lymphoma to advancing HIV-related immunosuppression [30], others have shown a slightly higher risk in HIV-positive patients receiving HAART [18,31]. Prior to the introduction of HAART, patients with HIV-related Hodgkin lymphoma had a limited median survival of 1-2 years, despite chemotherapy [32]. Early chemotherapy trials were plagued by severe toxicity and

frequent deaths due to bacterial and/or opportunistic infection [33]. The use of granulocyte colony-stimulating factor did little to improve this outcome [34].

Since then, several studies have reported the benefits of combining dose-intense chemoradiotherapy regimens and HAART. Treatment with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and HAART was shown to result in a complete response rate of 100%, event/disease free survival of 83% at 2 years, and overall survival of 83% at 2 years [35]. Treatment with doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone, and involved-field radiation for initial bulky disease (Stanford V regimen) was shown to result in a complete response rate of 81%, event/disease free survival of 68% at 3 years, and overall survival of 51% at 3 years [36]. In a recent study, investigators looked at an additional regimen involving doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [37]. In this latter study, the authors reported a complete response rate of 87%, event/disease free survival of 71% at 5 years, and overall survival of 76% at 5 years.

Anal Cancer

Several studies have shown a marked increase in the incidence of both anal intraepithelial neoplasia and invasive squamous cell carcinoma (SCC) in men and women who are HIV-infected [38-41]. One of the largest studies to date, however, did not find an increase in risk [6]. Groups at risk reported by others include individuals who practice receptive anal intercourse, men who have sex with men (MSM), and those with an anal coinfection (e.g. HPV, syphilis, gonococcus, etc.). This finding was recently confirmed in a Multicenter AIDS Cohort Study from the United States that followed MSM (n=6,972) from 1984 until 2006 [42]. In this cohort, investigators reported a significantly higher incidence rate of anal cancer in HIV-positive than HIV-negative men (incidence rate = 69 vs 14 per 100,000 person-years). Among the HIV-positive men, they also found that the incidence of anal cancer was higher in the HAART era than the pre-HAART era (incidence rate = 137 vs 30 per 100,000 person-years). In multivariate analysis restricted to the HAART era, anal cancer risk increased significantly with unprotected receptive anal sex partners in HIV-positive men. Moreover, the use of HAART in this study was found not to decrease anal cancer risk.

HIV-associated invasive anal carcinoma can be treated with standard combined chemotherapy and radiation [43-45]. Chemotherapy regimens include mitomycin (or cisplatin) and 5-fluorouracil (5-FU). The response to multimodality therapy in HIV-positive patients appears to be equivalent to non-HIV patients [46]. Using a large database of United States veterans (n=1,184) diagnosed with anal SCC between 1998 and 2004, investigators reported an equivalent survival rate between HIV-positive and HIV-negative individuals in the HAART era when treated similarly [47]. The 2-year observed survival rates were 77% and 75% among HIV-positive and HIV-negative individuals, respectively. Another recent study from Switzerland compared the outcome of 40 HIV-positive patients receiving HAART to 81 HIV-negative patients treated with radiotherapy or chemoradiotherapy for anal SCC [48]. These researchers found that either form of therapy resulted in a complete response in 92% of HIV positive patients, compared to 96% in HIV negative cases. Moreover, there was very little difference in the five-year overall survival. However, five-year local disease control was 38% (95% CI, 5% to 71%) in HIV-positive and 87% (95% CI, 79% to 95%) in HIV-negative patients, compromising cancer-specific survival and sphincter preservation. Furthermore, HIV positive patients more frequently experienced acute skin and hematologic toxicity. Similar findings were recently reported in a study from St. Vincent's Cancer Care Center in New York [49], in which the outcome in 32 HIV positive patients treated with HAART and chemoradiotherapy for HIV-related anal SCC was comparable to that in patients without HIV.

Overall survival was associated with high HIV viral load and low CD4 cell count. Significant toxicity (skin, diarrhea, hematologic) was also documented with standard treatment regimens.

Lung Cancer

The incidence of lung cancer is increased several fold with HIV infection compared to age- and gender-matched populations [50-52]. This increasing incidence was recently reported in a single institution analysis at the University of Maryland in the United States [53]. Thirty of the patients in this study had non-small cell lung cancer and four had small cell carcinoma. Of the 30 patients with non-small cell lung cancer, 27 had stage IIIb/IV disease. This is in keeping with findings from other studies that HIV-related lung cancer in the majority of cases is usually diagnosed with locally advanced or metastatic disease. The patients in this Maryland study received standard chemotherapy, and their overall survival was 5.2 months [53]. Data on the efficacy and toxicity of chemotherapy and radiation therapy for HIV-related lung cancer is limited. Recently, however, researchers from Baltimore in the United States published their findings of a phase II trial of gemcitabine/carboplatin followed by paclitaxel that included only two patients with HIV infection and advanced non-small cell lung cancer [54]. Although these patient numbers are small, this is the first trial to prospectively evaluate chemotherapy for patients with HIV disease. Unfortunately, the prognosis for these patients was extremely poor despite treatment.

Breast Cancer

The link between breast cancer and HIV remains controversial [55-56]. The preponderance of evidence suggests that breast cancer incidence is not increased in people with HIV infection. Of the 1,416 HIV-infected patients seen at Ramathibodi Hospital in Thailand over a 5-year period (1999-2003), investigators recently reported 42 patients with malignancies, giving a prevalence of 3% [57]. In this study, breast cancer was the most common NADC (10%). In the last year there were a few cases reported of breast cancer in HIV infected patients [58, 59]. HIV-infected women seem to be at increased risk of presenting with advanced breast cancer, perhaps related to inadequate screening mammography because of socioeconomic disadvantages [55]. There have been very few series dealing with HIV-associated breast cancer. In one small series of HIV-infected patients who presented with early breast cancer (stage I and II), the 5-year survival rate (80%) was noted to be similar to that of an HIV-indeterminate (control) group of patients [60]. Further studies are needed.

Hepatocellular Carcinoma

There is also an increased risk of developing hepatocellular carcinoma (HCC) with HIV infection [61,62]. A recent retrospective analysis conducted by the North American Liver Cancer in HIV Study Group from 1992 to 2005, involving 63 HIV-infected HCC patients, found their HIV positive patients to be younger than controls (52 vs. 64 years of age), more commonly had chronic hepatitis B or C (97% vs. 73%), were more frequently symptomatic (51% vs. 38%), and had a higher median alpha-fetoprotein level (227 vs. 51 ng/ml), but exhibited a similar mean Child-Turcotte-Pugh score and HCC staging score [**63]. Viral hepatitis coinfection has previously been shown to result in accelerated progression to HCC, with only a short interval between viral exposure and carcinoma development. Indeed, Brau and colleagues found that HCC developed faster in HIV/HCV-coinfecting than in HCV-monoinfected patients (mean, 26 vs. 34 years after HCV infection) [**63]. The median survival in this study was similar for HIV positive and negative individuals with HCC (6.9 vs. 7.5 months). Independent factors that predicted survival in these study patients included symptomatic presentation, HCC therapy, AST/ALT ≥ 2.0 , AFP ≥ 400 ng/mL, and platelets $\geq 100,000/\text{mm}^3$, but not HIV-serostatus [**63].

Conjunctival Cancer

In HIV infected patients, the conjunctiva may develop intraepithelial dysplasia, carcinoma in situ, and/or invasive SCC. Risk factors include age >50 years, high solar ultraviolet radiation exposure, geography (sub-Saharan Africa), and possibly HPV infection [64]. In sub-Saharan Africa, several publications have reported a dramatic increased incidence of conjunctival neoplasia in concert with the HIV epidemic [65,66]. A recent epidemiologic study published by the Division of Cancer Epidemiology and Genetics at the National Cancer Institute in the United States has reported a similar increased incidence of conjunctival SCC in North America [**67]. In this study, overall SIRs were elevated for SCC of the conjunctiva (SIR, 12.2, 95% CI 6.8-20.2), primary ocular lymphoma (21.7, 95% CI 15.1-30.2) and ocular KS (109, 95% CI 63.5-175). Risk for conjunctival SCC was shown to be elevated regardless of HIV acquisition category, CD4 lymphocyte count and time relative to AIDS-onset. Relative proportions of conjunctival SCC risk were noted to be highest with age $\geq$ 50 years, Hispanic ethnicity and residence in regions with high-solar ultraviolet radiation [**67].

Prostate Cancer

Several cases of prostate carcinoma have previously been reported in HIV-positive men [68-70]. Studies reporting on the incidence of prostate cancer in the HIV positive population have been conflicting. Most large scale studies have found rates that are significantly lower than in the general population [6,19]. Risk factors for the development of HIV-related prostate cancer include increased age, black race, familial history of prostate cancer, androgen use, and possibly prostatitis. Although rare cases of aggressive HIV-related prostate cancer have been reported [71], the findings from a recent multicenter series found that in men with prostate cancer receiving HAART, their HIV status did not appear to influence their PSA levels, clinical presentation, tumor grade, stage, and management [**72]. Nor was their outcome from treated cancer affected by HIV status. The authors of this series recommended that patients with prostate cancer and well-controlled HIV viremia therefore be managed similarly to their HIV-negative counterparts [**72].

Urinary Cancer

Currently, only a few cases of bladder cancer have been reported in association with HIV infection [73-75]. Nevertheless, a meta-analysis of several studies did not find an increased incidence of bladder cancer in the HIV population [**19]. Neither did recent data from the HIV/AIDS Cancer Match Study in the United States show any increased incidence [76]. A link between HIV infection and renal cell carcinoma (RCC) has also been reported in a limited number of publications. In the HIV/AIDS Cancer Match Study, investigators identified 130 cases of RCC [76]. However, RCC risk was not significantly elevated in this study. The authors of this paper also showed that RCC risk was unaffected by race, despite higher rates of HIV-associated nephropathy in individuals of African ancestry.

Plasma Cell Neoplasia

HIV infected patients can develop paraproteinemia, plasmacytomas and multiple myeloma [77]. Recently, investigators looked at the protein electrophoresis and quantitative immunoglobulin levels in samples from 320 consecutive HIV-1-infected patients [**78]. They found that 8.1% of HIV positive individuals had subtle oligoclonal banding and that 4.4% had a low-concentration (<5% of total protein) monoclonal band. HIV-related paraproteinemia appears to be associated with younger HIV-1-infected patients, HIV viral load, a more robust immune system (i.e. higher CD4 cell count), and hepatitis B and/or C virus coinfection [**78]. These bands may be transient or persistent, and in a subset of patients may be associated with the subsequent development of myeloma, plasmacytoma, or lymphoma [79].

Gestational Trophoblastic Disease

HIV does not appear to be a risk factor for molar pregnancy [80]. Nevertheless, there have been a few case reports showing that choriocarcinoma has a dismal outcome in patients with AIDS [81-82]. Nevertheless, a recent case of a 34-year-old woman with AIDS and advanced metastatic choriocarcinoma was reported not to be fatal following appropriate chemotherapy [83].

Conclusions

Within the last year, information about the incidence and spectrum of NADC has continued to evolve, in both developed and underdeveloped regions of the world. While several NADC continue to occur at rates significantly higher than expected, no appreciable increase and even a decline was observed in other cancers. The development of NADC is probably multifactorial. Factors other than HIV and immunosuppression appear to be important in the risk, management, and outcome of these neoplasms. While control of HIV viremia is beneficial, the impact of HAART on NADC remains unclear. Recent studies have shown us that patients with NADC and well-controlled HIV viremia can be managed similarly to their HIV-negative counterparts. Further research in this emerging field is required, especially since therapy in this setting is often complicated by comorbid disease, poor performance status, additive cytotoxicity, potential drug-drug interaction, chemotherapy enhanced immunosuppression, a predilection for severe radiation adverse effects, and the fact that cancer patients with AIDS make poor surgical candidates. The need for assertive prevention strategies is also paramount. Therefore, it is encouraging to see recent publications on the subject of screening for NADC and their precursor lesions [84].

References

1. Pantanowitz L, Schlecht HP, Dezube BJ. The growing problem of Non-AIDS-defining malignancies in HIV. *Curr Opin Oncol* 2006;18:469–478. [PubMed: 16894295]
2. Laurence J. Non-AIDS-defining malignancies and HAART. *AIDS Read* 2007;17:433–434. [PubMed: 17902222]
3. Powles T, Oliver T, Bower M. Non-AIDS-defining cancers in people with HIV infection: a sleeping giant? *J HIV Ther* 2006;11:57–60. [PubMed: 17580500]
4. Patel P, Hanson DL, Sullivan PS, Novak RM. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 2008 May 20;148(10):146. ** A large prospective observational cohort study that compares cancer incidence among HIV-infected persons with incidence in the general population from 1992 to 2003 in the United States.
5. Lewden C, Salmon D, Morlat P, Bévilacqua S, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol* 2005;34:121–30. [PubMed: 15561752]
6. Engels, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. *AIDS* 2006;20:1645. [PubMed: 16868446]
7. Goedert JJ. The epidemiology of acquired immunodeficiency syndrome malignancies. *Semin Oncol* 2000;27:390. [PubMed: 10950365]
8. 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* 2005;104:1505–11. [PubMed: 16104038]
9. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008;123:187–94. [PubMed: 18435450]* In this study investigators linked HIV/AIDS and cancer registries in three US states and compared the standardized incidence ratios for cancer risk in HIV-infected persons with the general population. They identified

a shift in the spectrum of cancer among HIV-infected persons, viz. a decline in AIDS-associated cancers while the incidence of some non-AIDS-defining cancers increased.

10. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS* 2008;22:489–96. [PubMed: 18301061]
11. Galceran J, Marcos-Gragera R, Soler M, Romaguera A, et al. Cancer incidence in AIDS patients in Catalonia, Spain. *Eur J Cancer* 2007;43:1085–91. [PubMed: 17349785]
12. Goedert JJ, Purdue MP, McNeel TS, McGlynn KA, Engels EA. Risk of germ cell tumors among men with HIV/acquired immunodeficiency syndrome. *Cancer Epidemiol Biomarkers Prev* 2007;16:1266–9. [PubMed: 17548695]
13. Mbulaiteye SM, Katabira ET, Wabinga H, Parkin DM, et al. Spectrum of cancers among HIV-infected persons in Africa: The Uganda AIDS-Cancer Registry Match Study. *Int J Cancer* 2006;118:985–90. [PubMed: 16106415]
14. Newton R, Ziegler J, Ateenyi-Agaba C, et al. The epidemiology of conjunctival squamous cell carcinoma in Uganda. *Br J Cancer* 2002;87:301. [PubMed: 12177799]
15. Dhir AA, Sawant S, Dikshit RP, et al. Spectrum of HIV/AIDS related cancers in India. *Cancer Causes Control* 2008;19:147–53. [PubMed: 17992576]
16. Stein L, Urban MI, O'Connell D, et al. The spectrum of human immunodeficiency virus-associated cancers in a South African black population: results from a case-control study, 1995–2004. *Int J Cancer* 2008;122:2260–5. [PubMed: 18241034]
17. 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* 2005;104:1505–11. [PubMed: 16104038]
18. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005;97:425–32. [PubMed: 15770006]
19. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007;370:59. [PubMed: 17617273]** This is a large meta-analysis including 7 studies of people with HIV/AIDS that examined the incidence of around 30 NADCs. A similarity was identified to transplant recipients, suggesting that immune deficiency is important for the increased risk of NADC.
20. Mayor AM, Gómez MA, Ríos-Olivares E, Hunter-Mellado RF. AIDS-defining neoplasm prevalence in a cohort of HIV-infected patients, before and after highly active antiretroviral therapy. *Ethn Dis* 2008;18(Suppl 2):S2-189–94.
21. Angeletti PC, Zhang L, Wood C. The viral etiology of AIDS-associated malignancies. *Adv Pharmacol* 2008;56:509–557. [PubMed: 18086422]
22. Kirk GD, Merlo C, O' Driscoll P, Mehta SH. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007;45:103–10. [PubMed: 17554710]
23. Hessol NA, Pipkin S, Schwarcz S, et al. The impact of highly active antiretroviral therapy on Non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 2007;165:1143–53. [PubMed: 17344204]** This study from California explores the impact of HAART on AIDS-related cancer. The researchers illustrate that the impact of HAART on NADC incidence rates and survival is not uniform.
24. Cinti SK, Gandhi T, Riddell J 4th. Non-AIDS-defining cancers: should antiretroviral therapy be initiated earlier? *AIDS Read* 2008;18:30. [PubMed: 18240450]
25. Silverberg MJ, Neuhaus J, Bower M, Gey D, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS* 2007;21:1957–63. [PubMed: 17721103]
26. Hessol NA, Katz MH, Liu JY, et al. Increased incidence of Hodgkin disease in homosexual men with HIV infection. *Ann Intern Med* 1992;117:309. [PubMed: 1637026]
27. Tirelli U, Errante D, Dolcetti R, et al. Hodgkin's disease and human immunodeficiency virus infection: Clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and Tumors. *J Clin Oncol* 1995;13:1758. [PubMed: 7541452]
28. Levine AM. Hodgkin's disease in the setting of human immunodeficiency virus infection. *J Natl Cancer Inst Monogr* 1998;23:37–42. [PubMed: 9709301]

29. Engels EA, Goedert JJ. Human immunodeficiency virus/acquired immunodeficiency syndrome and cancer: past, present, and future. *J Natl Cancer Inst* 2005;97:407–9. [PubMed: 15769998]
30. Frisch M, Biggar RJ, Engels EA, Goedert JJ, et al. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736–45. [PubMed: 11277828]
31. Herida M, Mary-Krause M, Kaphan R, Cadranet J, 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;21:3447–53. [PubMed: 12972519]
32. Hartmann P, Rehwald U, Salzberger B, Franzen C, et al. Current treatment strategies for patients with Hodgkin's lymphoma and HIV infection. *Expert Rev Anticancer Ther* 2004;4:401–10. [PubMed: 15161439]
33. 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. [PubMed: 11035615]
34. 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. [PubMed: 10093688]
35. 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. [PubMed: 14504059]
36. 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. [PubMed: 12200356]
37. Xicoy B, Ribera JM, Miralles P, et al. Results of treatment with doxorubicin, bleomycin, vinblastine and dacarbazine and highly active antiretroviral therapy in advanced stage, human immunodeficiency virus-related Hodgkin's lymphoma. *Haematologica* 2007;92:191. [PubMed: 17296568]* The authors of this study analyzed the results of treating HIV-positive patients with advanced Hodgkin lymphoma using ABVD and HAART. This treatment approach was shown to be both feasible and effective.
38. Chiao EY, Krown SE, Stier EA, Schrag D. A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. *J Acquir Immune Defic Syndr* 2005;40:451–5. [PubMed: 16280701]
39. Diamond C, Taylor TH, Aboumrar T, Bringman D, et al. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sex Transm Dis* 2005;32:314–20. [PubMed: 15849533]
40. Schlecht HP, Pantanowitz L, Dezube BJ. Anal cancer in the HIV-positive patient: an escalating problem in the era of HAART. *HIV AIDS Review* 2006;5:51–56.
41. Panther LA, Schlecht HP, Dezube BJ. Spectrum of human papillomavirus-related dysplasia and carcinoma of the anus in HIV-infected patients. *AIDS Read* 2005;15:79–91. [PubMed: 15712398]
42. D'souza G, Wiley DJ, Li X, Chmiel JS, Margolick JB, et al. Incidence and Epidemiology of Anal Cancer in the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 2008;48:491–499. [PubMed: 18614927]** This study examined the incidence and risk factors for anal cancer in a multicenter cohort of HIV positive and HIV-negative men followed between 1984 and 2006. HIV-positive men were shown to have an increased risk of anal cancer, especially in the HAART era.
43. Konstantinopoulos PA, Schlecht HP, Bryan B, et al. HIV-associated anal squamous cell cancer: an otherwise preventable disease. *J Clin Oncol* 2006;24:4516–7. [PubMed: 16983122]
44. Blazy A, Hennequin C, Gornet JM, Furco A, et al. Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2005;48:1176–81. [PubMed: 15906137]
45. Kauh J, Koshy M, Gunthel C, Joyner MM, et al. Management of anal cancer in the HIV-positive population. *Oncology* 2005;19:1634–8. [PubMed: 16396154]
46. Cheung MC, Pantanowitz L, Dezube BJ. AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. *Oncologist* 2005;10:412–26. [PubMed: 15967835]
47. Chiao EY, Giordano TP, Richardson P, El-Serag HB. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. *J Clin Oncol* 2008;26:474–9. [PubMed: 18202423]* An informative study that evaluated the outcome and associated predictors of squamous cell carcinoma of the anus in the HAART era

for HIV-positive and -negative individuals using large Veterans Affairs databases in the United States.

48. Oehler-Jänne C, Hugué F, Provencher S, Seifert B, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. *J Clin Oncol* 2008;26:2550–7. [PubMed: 18427149]
**This study examined the clinical outcome after definitive chemoradiotherapy of anal carcinoma in HIV-infected patients treated with HAART. Long-term local disease control and acute toxicity were shown to represent major clinical challenges in HIV-positive patients with anal carcinoma.
49. Wexler A, Berson AM, Goldstone SE, Waltzman R, et al. Invasive anal squamous-cell carcinoma in the HIV-positive patient: outcome in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2008;51:73–81. [PubMed: 18066626]
50. Lavole A, Wislez M, Antoine M, Mayaud C, et al. Lung cancer, a new challenge in the HIV-infected population. *Lung Cancer* 2006;51:1–11. [PubMed: 16300854]
51. Spano JP, Massiani MA, Bentata M, Rixe O, et al. Lung cancer in patients with HIV Infection and review of the literature. *Med Oncol* 2004;21:109–15. [PubMed: 15299182]
52. Cadranel J, Garfield D, Lavolé A, et al. Lung cancer in HIV infected patients: facts, questions and challenges. *Thorax* 2006;61:1000–8. [PubMed: 17071836]
53. Hakimian R, Fang H, Thomas L, Edelman MJ. Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. *J Thorac Oncol* 2007;2:268–72. [PubMed: 17409796]
54. Bridges BB, Thomas L, Hausner PF, Doyle LA, et al. Phase II trial of gemcitabine/carboplatin followed by paclitaxel in patients with performance status=2,3 or other significant co-morbidity (HIV infection or s/p organ transplantation) in advanced non-small cell lung cancer. *Lung Cancer* 2008;61:61–6. [PubMed: 18201795]
55. Gewurz BE, Dezube BJ, Pantanowitz L. HIV and the breast. *AIDS Read* 2005;15:392–402. [PubMed: 16110554]
56. Pantanowitz L, Dezube BJ. Reasons for a deficit of breast cancer among HIV-infected patients. *J Clin Oncol* 2003;21:3447–53. [PubMed: 12972519]
57. Kiertiburanakul S, Likhitpongwit S, Ratanasiri S, Sungkanuparph S. Malignancies in HIV-infected Thai patients. Malignancies in HIV-infected Thai patients. *HIV Med* 2007;8:322–3. [PubMed: 17561879]
58. García-Tejedor A, Devesa NR, Suárez-Pumariiega P, del Barco S, Huerta MV. Breast cancer and HIV--the adverse effects chemotherapy. *Breast J* 2007;13:622–3. [PubMed: 17983411]
59. Ashraff Z, Nallamala S. Breast cancer in a woman with HIV/AIDS: case report and review of literature. *J HIV Ther* 2007;12:71–2. [PubMed: 17962797]
60. Oluwole SF, Ali AO, Shafae Z, DePaz HA. Breast cancer in women with HIV/AIDS: report of five cases with a review of the literature. *J Surg Oncol* 2005;89:23–7. [PubMed: 15612013]
61. Murillas J, Del Rio M, Riera M, Vaquer P, et al. Increased incidence of hepatocellular carcinoma (HCC) in HIV-1 infected patients. *Eur J Intern Med* 2005;16:113–115. [PubMed: 15833677]
62. Kramer JR, Giordano TP, Soucek J, Richardson P, et al. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. *Am J Gastroenterol* 2005;100:56–63. [PubMed: 15654781]
63. Bräu N, Fox RK, Xiao P, Marks K, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol* 2007;47:447–50. [PubMed: 17692426]** This retrospective study of 63 HIV-infected HCC patients is a valuable contribution to the literature, in which HIV patients with HCC were compared to HIV negative controls. HIV positive HCC patients were noted to be younger and more frequently symptomatic, and more likely to be infected with HCV or HBV than HIV-negative patients.
64. Ateenyi-Agaba C, Weiderpass E, Tommasino M, Smet A, et al. Papillomavirus infection in the conjunctiva of individuals with and without AIDS: An autopsy series from Uganda. *Cancer Lett* 2006;239:98–102. [PubMed: 16143449]
65. Kestelyn P, Stevens AM, Ndayambaje A, et al. HIV and conjunctival malignancies. *Lancet* 1990;336:51. [PubMed: 1973230]

66. Chisi SK, Kollmann MK, Karimurio J. Conjunctival squamous cell carcinoma in patients with human immunodeficiency virus infection seen at two hospitals in Kenya. *East Afr Med J* 2006;83:267–70. [PubMed: 16866221]
67. Guech-Ongey M, Engels EA, Goedert JJ, et al. Elevated risk for squamous cell carcinoma of the conjunctiva among adults with AIDS in the United States. *Int J Cancer* 2008;122:2590. [PubMed: 18224690]** This is an informative study from the National Cancer Institute investigating the risk for conjunctival SCC and other eye cancers in the United States. Investigators found a significantly increased incidence of conjunctival SCC among persons with HIV/AIDS, in accordance with an etiological role for ultraviolet radiation.
68. Crum NF, Spencer CR, Amling CL. Prostate carcinoma among men with human immunodeficiency virus infection. *Cancer* 2004;101:294–9. [PubMed: 15241826]
69. Levinson A, Nagler EA, Lowe FC. Approach to management of clinically localized prostate cancer in patients with human immunodeficiency virus. *Urology* 2005;65:91–4. [PubMed: 15667871]
70. O'Connor JK, Nedzi LA, Zakris EL. Prostate adenocarcinoma and human immunodeficiency virus: report of three cases and review of the literature. *Clin Genitourin Cancer* 2006;5:85–8. [PubMed: 16859585]
71. Furco A, Bani-Sadr F, Guymar S, Molina JM. Metastatic cancer of the prostate in a young 40 year-old HIV-infected male patient (article in French). *Presse Med* 2003;32:930–1. [PubMed: 12876536]
72. Pantanowitz L, Bohac G, Cooley TP, et al. Human immunodeficiency virus-associated prostate cancer: clinicopathological findings and outcome in a multi-institutional study. *BJU Int* 2008;101:1519–23. [PubMed: 18384640]** This study represents one of the largest series to date pertaining to HIV-related prostate cancer. In this retrospective, multi-institutional study investigators found that in men receiving HAART, their age, PSA levels, clinical presentation, management, and outcome from treated prostate carcinoma did not appear to be significantly altered by HIV status.
73. Al Soub H. Transitional cell carcinoma of the bladder in an HIV-infected patient. *Postgrad Med J* 1996;72:302–4. [PubMed: 8761507]
74. Clemente Ramos LM, Fernandez Fernandez E, Sanchez-Encinas M, et al. Fatal bladder carcinoma in a young man with human immunodeficiency virus. *Br J Urol* 1998;82:132–3. [PubMed: 9698677]
75. Manfredi R, Sabbatani S, Calza L, Chiodo F. Bladder carcinoma and HIV infection during the highly active antiretroviral therapy era: A rare, but intriguing association. Two case reports and literature review. *Scand J Infect Dis* 2006;38:566–70. [PubMed: 16798716]
76. Layman AB, Engels EA. Kidney and bladder cancers among people with AIDS in the United States. *J Acquir Immune Defic Syndr* 2008;48:365–7. [PubMed: 18580342]
77. Dezube BJ, Aboulafia DM, Pantanowitz L. Plasma cell disorders in HIV-infected patients: from benign gammopathy to multiple myeloma. *AIDS Read* 2004;14:372–9. [PubMed: 15282866]
78. Konstantinopoulos PA, Pantanowitz L, Dezube BJ, et al. Protein electrophoresis and immunoglobulin analysis in human immunodeficiency virus-infected patients. *Am J Clin Pathol* 2007;128:596–603. [PubMed: 17875511]* This study examined the prevalence and nature of immunoglobulin abnormalities in HIV-1-infected patients in the HAART era. The results suggest that it is younger HIV-1-infected patients with higher CD4 cell counts that are most likely to have monoclonal bands.
79. Amara S, Dezube BJ, Cooley TP, et al. HIV-associated monoclonal gammopathy: A retrospective analysis of 25 patients. *Clin Inf Dis* 2006;43:1198–1205.
80. Swapna E, Molykutty J, Rajalekshmy TN, et al. Lack of association of gestational trophoblastic diseases (GTD) with syphilis and AIDS. *Indian J Pathol Microbiol* 1998;41:277–9. [PubMed: 9805848]
81. Ojwang SB, Otieno MR, Khan KS. Human immunodeficiency virus in gestational trophoblastic neoplasias - is it a poor prognostic risk factor. *East Afr Med J* 1992;69:647–8. [PubMed: 1284342]
82. Moodley M, Moodley J. Gestational trophoblastic syndrome and human immunodeficiency virus (HIV) infection: a retrospective analysis. *Int J Gynecol Cancer* 2003;13:875–8. [PubMed: 14675327]
83. Shah AM, Tidswell M, Prefontaine M, et al. Choriocarcinoma in an AIDS patient - relapsing but not fatal. *Int J STD AIDS* 2008;19:496–8. [PubMed: 18574129]
84. Cranston RD, Hart SD, Gornbein JA, Hirschowitz SL, Cortina G, Moe AA. The prevalence, and predictive value, of abnormal anal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men. *Int J STD AIDS* 2007;18:77–80. [PubMed: 17331275]

Table 1

Summary of published standard incidence ratios (SIR) for several cancers comparing people with HIV/AIDS to transplant recipients (modified from reference **19).

CANCER	SIR in people with HIV/AIDS	SIR in transplant recipients
AIDS-Defining Cancers		
Kaposi sarcoma	3640	208
Cervical cancer	1.00-21.95	1.54-2.50
Non-Hodgkin lymphoma	22.60-353.5	5.48-9.86
Non-AIDS-Defining Cancers	1.63-2.79	2.48-4.05
Anal cancer	19.63-50.00	2.77-10.26
Bladder cancer	0.42-4.17	1.63-3.33
Breast cancer	0.68-1.43	1.00-1.45
Brain cancer	0.50-4.44	0.57-1.38
Colorectal cancer	0.90-1.41	1.35-2.14
Esophageal cancer	0.50-2.11	1.56-3.82
Eye cancer	1.72-2.00	2.00-7.56
Hodgkin lymphoma	3.57-18.00	2.20-8.00
Laryngeal cancer	0.60-2.80	1.74-2.50
Leukemia	1.82-5.33	2.27-2.46
Lip cancer	2.26-3.10	13.02-53.33
Liver cancer	1.90-22.22	1.10-3.19
Melanoma	0.20-1.34	1.35-2.53
Multiple myeloma	2.20-5.00	2.70-3.82
Oropharyngeal cancer	1.10-2.93	2.75-5.26
Ovarian cancer	0.30-4.41	1.15-2.00
Pancreatic cancer	0.70-2.86	0.90-1.21
Penile cancer	3.90-8.00	15.79
Prostate cancer	0.50-1.43	0.91-1.10
Renal cancer	0.79-2.00	4.08-7.97
Respiratory tract (lower) cancer	1.44-4.50	1.70-2.10
Skin carcinoma	1.51-19.61	10.68-56.16
Small intestine cancer	1.30-3.39	1.10-11.76
Stomach cancer	0.40-2.94	1.84-2.30
Testicular cancer	0.70-1.76	1.25-2.31
Thyroid cancer	0.40-3.00	0.91-8.09
Uterine cancer	0.50-0.90	0.90-1.74
Vulva/vaginal cancer	4.41-6.79	22.22-23.91