

Epidemiology and Clinical Characteristics of Non-AIDS-Defining Malignancies

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Abstract Since the widespread introduction of HAART over 10 years ago, the epidemiology of HIV-related malignancies has been evolving. While the incidence and the mortality of AIDS-defining cancers (Kaposi sarcoma and non-Hodgkin lymphoma, in particular) have been decreasing, the incidence of and the mortality from non-AIDS-defining malignancies appear to be increasing. This chapter reviews the recent literature published on the epidemiology and clinical manifestations, including outcomes of non-AIDS-defining malignancies. Although HAART has improved survival from opportunistic infections and AIDS-defining malignancies; it appears that HIV-infected individuals on HAART still have an elevated incidence of certain non-AIDS malignancies (especially those that are mediated by viral oncogenesis, such as EBV and HPV). In addition, it is unclear if utilization of HAART during treatment results in equivalent survival compared to HIV-negative individuals. The focus of the chapter will be on the more common non-AIDS malignancies such as Hodgkin disease, SCCA, and lung cancer. However, the epidemiology of other non-AIDS-defining malignancies will also be discussed including skin cancer, head and neck cancer, conjunctival cancer, testicular cancer, leiomyosarcoma, hepatocellular carcinoma, breast cancer, multiple myeloma, leukemia, colon cancer, and prostate cancer.

Introduction

Since the advent of widely available highly active antiretroviral therapy (HAART), individuals with human immunodeficiency virus (HIV) infection have had significantly improved survival and decreased mortality from AIDS-related infections and AIDS-defining malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer (Goedert et al., 1998; Grulich et al., 1999). However, with longer

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survival, it has become evident that individuals with HIV disease are now at higher risk for other non-AIDS-defining malignancies. In addition to the three AIDS-defining malignancies, multiple recent cohort studies and linked AIDS–cancer registry studies have found that HIV-infected people are also at significantly higher risk for malignancies not included in the AIDS definition. These non-AIDS-defining cancers include squamous cell cancer of the anus (SCCA), Hodgkin lymphoma, lung cancer, head and neck cancers, testicular cancer, basal cell cancer of the skin, squamous cell cancer of the skin, and melanoma (Grulich et al., 1999; Petrukevitch et al., 1999; Serraino et al., 2000; Frisch et al., 2001; Mbulaiteye et al., 2003; Patel et al., 2004).

The non-AIDS-defining malignancies in HIV-infected patients present an evolving clinical picture. It is likely that non-AIDS-defining malignancies will become more prevalent as the HIV-positive cohort ages. However, there are many unresolved questions regarding the epidemiology, natural history, and outcomes for non-AIDS-defining malignancies. Although HIV-infected individuals are at higher risk for cancers such as squamous cell cancer of the anus (SCCA), Hodgkin disease, and lung cancer, these are still relatively rare events. Therefore, the majority of data regarding the natural history and outcomes for these cancers are based on small case series. Thus, it is difficult to answer specific questions such as whether these neoplastic processes may present at later stages and have a more aggressive course in HIV-infected patients as compared to the general non-HIV-infected population (Sridar et al., 1992; Vyzula, 1996; Powles et al., 2003b). Finally, optimal therapies, including the utilization of HAART during cancer treatment and the initiation of HAART at higher CD4 levels, also continue to evolve. This chapter focuses on the epidemiology and clinical manifestations, including outcomes of non-AIDS-defining malignancies. While the focus of the chapter will be on the more common non-AIDS malignancies such as Hodgkin disease, SCCA, and lung cancer, other non-AIDS-defining malignancies including skin cancer, head and neck cancer, conjunctival cancer, testicular cancer, leiomyosarcoma, hepatocellular carcinoma, breast cancer, multiple myeloma, leukemia, colon cancer, and prostate cancer will also be discussed.

Epidemiology

HAART has significantly changed the epidemiology of HIV disease in the United States, Europe, Australia, and other countries with widespread HAART access. Two studies have shown that the proportion of deaths due to malignancies has increased in the HAART era (Louie et al., 2002; Lewden et al., 2005). Louie et al. (2002) found that non-AIDS-defining malignancies increased as a cause of death in San Francisco County from 6.4% in 1994 to 10.9% in 1998 ($p < 0.01$). In addition, in France, Lewden et al. (2005) reported that non-AIDS-associated malignancies were the third leading cause of death and that these malignancies caused 11% of all deaths in the year 2000. Finally, a study conducted by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) evaluated factors associated with

mortality due to non-AIDS-defining malignancies (nADMs) and AIDS-defining malignancies (ADMs) in their cohort of 23,437 patients under active follow-up from December 1999 to April 2001 (Monforte et al., 2008). They found that the overall mortality rate of nADMs was higher than that of ADMs. The death rate from nADMs was 1.8 per 1,000 person-years of follow-up [95% confidence interval (CI) 1.5–2.1] compared to that from ADMs of 1.1 per 1,000 person-years of follow-up (95% CI 0.9–1.2). In addition, they found that in multivariable analysis, both low latest CD4 count and increasing age were associated with an increased risk of death from nADMs and ADMs. Other factors such as combined antiretroviral therapy (cART) utilization increased the risk of death for nADMs only. It is unlikely that cART itself increases the risk for nADMs. Rather it underscores the complex relationship between prolonged survival with HIV disease, immunosuppression, and the diagnosis of and survival from nADMs. Furthermore, several cohort studies performed in the pre-HAART era failed to convincingly show an increased risk of non-AIDS-related malignancy in HIV-infected people (Hajjar et al., 1992; Biggar et al., 1994). These studies add further evidence to support the changing epidemiology of nADMs in the HAART era.

More recent linkage analyses of data from AIDS and cancer registries have shown statistically significant increases in the age-standardized incidence ratio (SIR) or the relative risk (RR) of non-AIDS-defining malignancies for HIV-infected cohorts as compared to standardized populations (Goedert et al., 1998; Franceschi et al., 1998; Grulich et al., 1999; Serraino et al., 2000; Gallagher et al., 2001; Frisch et al., 2001; Allardice et al., 2003; Herida et al., 2003; Dal Maso et al., 2003a). Although there have been some issues with the calculation of age-standardized incidence ratios (SIRs) (Chaturvedi et al., 2008), this technique has been utilized by large AIDS–cancer match registries, the largest of which includes over 150,000 HIV-infected individuals. These studies have shown a relationship between HIV infection and a large number of cancers including Hodgkin disease (Grulich et al., 1999; Serraino et al., 2000; Frisch et al., 2001; Gallagher et al., 2001; Dal Maso et al., 2003a; Patel et al., 2008), anal cancer (Frisch et al., 2001; Gallagher et al., 2001; Grulich et al., 2002; Dal Maso et al., 2003a; Patel et al., 2008), lung cancer (Frisch et al., 2001; Gallagher et al., 2001; Allardice et al., 2003; Dal Maso et al., 2003a), testicular cancer (Frisch et al., 2001; Gallagher et al., 2001), lip cancer (Frisch et al., 2001; Grulich et al., 2002), melanoma (Frisch et al., 2001), liver cancer (Frisch et al., 2001; Allardice et al., 2003), multiple myeloma (Frisch et al., 2001; Gallagher et al., 2001; Grulich et al., 2002), brain cancer (Frisch et al., 2001; Gallagher et al., 2001; Dal Maso et al., 2003a), leukemia (Frisch et al., 2001; Grulich et al., 2002; Dal Maso et al., 2003a), and cancers of the salivary glands, skin (non-KS) (Gallagher et al., 2001; Allardice et al., 2003) and soft/connective tissue (Frisch et al., 2001; Gallagher et al., 2001; Grulich et al., 2002). None of the AIDS–cancer match studies found an increased risk of breast cancer, colon cancer, or prostate cancer. Both Frisch et al. (2001) and Gallagher et al. (2001) found a statistically significant decrease in the risk of prostate and bladder cancer, and Gallagher et al. (2001) found a statistically significantly decreased risk of esophagus and colon cancer.

Because these studies are not analyses of primary data, the relationship between HIV and certain cancers needs to be interpreted with caution due to possible detection bias and/or miscoding. For example, it is unlikely that HIV infection is associated with rare sarcomas of the soft/connective tissue. Rather, it is likely that Kaposi sarcomas were miscoded as soft/connective tissue cancers. These AIDS–cancer registry studies may also be biased because they compare cancer rates of patients with AIDS to age-matched incidence rates in the general population. However, HIV-infected individuals often have specific risk behaviors which distinguish them from the general population, such as higher rates of intravenous drug use and a larger population of men who have sex with men (MSM). Thus, higher liver cancer SIRs may be associated with an increased rate of infection with hepatitis B and C among HIV-infected individuals rather than the immunosuppression associated with HIV infection itself. Thus, prospective studies may have fewer miscoding biases, but the rate ratios or SIRs associated with comparing the rates of cancer among HIV-infected individuals compared to the general population still need to be interpreted with caution.

Studies Comparing the Pre-HAART Era and the HAART Era

Two prospective studies have been performed that included data on the development of non-AIDS-defining malignancies and included data collected after the introduction of HAART (Herida et al., 2003; Patel et al., 2008). Patel et al. (2008) evaluated 54,780 HIV-infected individuals enrolled in the Adult and Adolescent Spectrum of HIV Disease Project (ASD) and the HIV Outpatient Study (HOPS). They evaluated cancer diagnoses from 1992 to 2003 and found 708 non-AIDS-defining cancers. Among the non-AIDS-defining cancers, they found increased SIRs for anal, vaginal, liver, lung, oropharyngeal, colorectal and renal cancers, Hodgkin lymphoma, melanoma, and leukemia. They also found a significantly decreased SIR for prostate cancer. In addition, they evaluated SIRs by year of diagnosis, comparing the pre-HAART era (1992–1995), the early HAART era (1996–1999), and the late HAART era (2000–2003). They found that the incidences of anal, Hodgkin lymphoma, melanoma, colorectal, and prostate cancers all showed an increase in rates when a *p*-value was calculated for linear trend.

In addition, the authors conducted a multivariable analysis to describe factors associated with each type of cancer among HIV-infected persons. They found that antiretroviral therapy was associated with a decreased risk for AIDS-defining malignancies (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer). However, they also found that the use of antiretroviral therapy was associated with a decreased risk of breast cancer, colorectal cancer, and lung cancer. A low nadir CD4 count was associated with an increased risk of the AIDS-defining malignancies, as well as anal cancer, colorectal cancer, and lung cancer.

In France, Herida et al. (2003) performed a similar study that included 77,025 HIV-infected patients followed from 1992 to 1999. The median follow-up was 32 months. They divided the period of study enrollment into two periods: the

pre-HAART era including 1992–1995 (P1) and the post-HAART era including 1996–1999 (P2). They reported an overall increase of non-AIDS-defining malignancies among HIV-infected men but not among women during both periods of the study. Among men, they found that the incidence of Hodgkin disease was elevated in both P1 and P2. However, oral, colon, rectal and anal cancer, stomach, and CNS cancers were all statistically significantly elevated in P1, but none of these cancers showed an increased incidence in P2. Instead, only lung cancer and kidney cancer were elevated in P2. The incidence of Hodgkin disease was higher in women than in the general population during both P1 and P2 and, as in men, the incidence of lung cancer was higher during P2. Of note, the incidence of breast cancer was significantly lower in HIV-infected women than in the general French population during both P1 and P2. They hypothesized that HAART did not have a measurable impact on the incidence of non-AIDS-defining cancers (Herida et al., 2003).

Studies Linking Risk of Cancer to Level of Immunosuppression

Although using time periods to estimate HAART utilization provides some information regarding the effect of immunosuppression, several studies also attempted to use the timing of cancer diagnosis with respect to the development of an “AIDS diagnosis” as an estimate for evaluating the risk of cancer based on the level of immunosuppression (Frisch et al., 2001; Gallagher et al., 2001). Frisch et al. (2001) defined three criteria that suggested that non-AIDS-defining cancers were associated with immunosuppression: (1) the overall RR for the period from 60 months before to 27 months after AIDS was significantly elevated, (2) the RR in the early post-AIDS period was significantly elevated, and (3) there was a statistically significant increasing trend in the RRs from before to after AIDS onset. Using a test for trend, they found that Hodgkin disease, lung cancer, penile cancer, soft tissue malignancies, lip cancer, and testicular seminoma met the three criteria associated with immunosuppression (Frisch et al., 2001). Mbulaiteye et al. (2003) utilized a subset of the linked AIDS–cancer registry to evaluate the effect of decreasing CD4 count on various AIDS- and non-AIDS-related malignancies. They found that the relative risk for oropharyngeal cancer decreased with worsening immunity. Otherwise, none of the non-AIDS-defining malignancies were affected by the level of immunity (Mbulaiteye et al., 2003).

Gallagher et al. (2001) used similar criteria for defining immunosuppression-related cancers for patients diagnosed in New York state. They divided the time intervals for developing cancer into four time periods: 5–2 years prior to AIDS, 2 years–6 months prior, within 6 months before and 3 months after an AIDS diagnosis, and 3 months to 5 years after an AIDS diagnosis. Using similar criteria to those used by Frisch et al. (2001), they found that cancers of the rectum, rectosigmoid and anus, trachea, bronchus and lung, skin, and connective tissues among males were associated with increasing immunosuppression (Gallagher et al., 2001).

Again, the associations between immunosuppression approximated by time periods and cancer diagnoses need to be interpreted with caution. Because cancer often

takes 5–10 years to develop, all associations that are derived from time-based variables will likely be confounded by length of survival with HIV. Therefore, those patients who have cancer diagnosed 3 months to 5 years after an AIDS diagnosis will likely be more immunosuppressed than those diagnosed with cancer 2 years to 6 months prior to the AIDS diagnosis, but these patients will also likely have survived longer (because a diagnosis of AIDS is highly associated with mortality) (El-Sadr, Lundgren et al., 2006) and thus are inherently at higher risk for cancer. On the other hand, those studies which used temporal associations to estimate the effect of immunosuppression corroborate other studies, including Patel et al., that have specifically evaluated the effect of nadir CD4 count, a more direct measure of immunosuppression. Thus, taken together, it is likely that immunosuppression does increase the risk of several non-AIDS-defining malignancies, including anal and lung cancers.

The Effect of Interrupted Antiretroviral Therapy on the Risk of Cancers

The SMART study was a landmark study evaluating the use of episodic antiretroviral therapy guided by CD4+ count or drug conservation (DC) as compared with continuous antiretroviral therapy or viral suppression (VS). Although the authors initially hypothesized that the continuous use of combination antiretroviral therapy might be associated with adverse events, the study was prematurely terminated because there was a significant increase in all-cause mortality rates among those in the DC arm. In addition, the study showed that continuous use of antiretroviral therapy was significantly protective for not only AIDS-defining illnesses but also non-AIDS-defining illnesses. In a follow-up analysis, Kuller et al. (2008) compared biomarkers of chronic inflammation and coagulation, including high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), amyloid A, amyloid P, D-dimer, and prothrombin fragment 1+2 in the DC and VS arms of the SMART study, and also performed a nested case–control study to evaluate the relationship between these biomarkers and death. They showed that uncontrolled HIV replication was associated with increases in many markers of inflammation and coagulation, including hsCRP, IL-6, and D-dimers. Markers of chronic inflammation, such as CRP, have been associated with colon cancer (Chiu et al., 2008; Tsilidis et al., 2008).

A follow-up study evaluating all AIDS-defining and non-AIDS-defining malignancies in the SMART study found a significantly increased risk of AIDS-defining malignancies and an insignificant trend toward increased risk of non-AIDS-defining malignancies. Of a total of 5,472 participants, 70 patients developed cancer; there were 13 ADMs and 58 nADMs. The rate of all ADMs was significantly lower in the VS than in the DC arm. The rate of all nADMs was lower in the VS arm, but this difference was not statistically significant. The most common cancers were skin, lung, and prostate cancers, and the factors that predicted nADM included older age, cigarette use, and undetectable viral load at the start of the study. The authors note that because the number of cancers was small, the apparent association

with undetectable viral load may have occurred by chance; however, it is also possible that those with undetectable viral load may be long-term survivors and may have been infected with HIV for a longer time. The authors also note that because the SMART study was prematurely discontinued, it was not powered adequately to observe rare non-AIDS-defining cancers (Silverberg et al., 2007). The mean follow-up was only 16 months, which also decreased the power to detect cancers.

Meta-analysis Comparing HIV-Infected Individuals to Solid Organ Transplant Recipients

To further evaluate the relationship between immunosuppression and incidence of non-AIDS-associated cancers, Grulich et al. (2007) conducted a meta-analysis of cancer risk that pooled data from several different cohorts of HIV-infected individuals and immunosuppressed solid organ transplant recipients. They included seven HIV/AIDS studies and five transplant studies comprising a total of 444,172 individuals with HIV and 31,977 transplant recipients. In both populations, there was an increased SIR for cancers with a known infectious cause, including all three types of AIDS-defining cancer (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) and other HPV-related cancers (anal, vulvar/vaginal, and penis), as well as Hodgkin lymphoma (EBV-related), liver cancer (hepatitis B/C related), and stomach cancer (*Helicobacter pylori* related).

In addition, cancers possibly associated with HPV, such as non-melanoma skin, lip, esophageal, laryngeal, and eye cancers, were also increased. Finally, the SIRs for lung, kidney, multiple myeloma, leukemia, and melanoma were also elevated for both HIV-infected individuals and transplant recipients. However, cancers of the breast, prostate, and ovary were not elevated in either population (see Table 1). Of note, meta-analysis SIRs were elevated only among transplant recipients for bladder, thyroid, and colorectal cancers. The authors hypothesize that cancers that show elevated SIRs for both transplant recipient and HIV-infected populations share immune deficiency, a contributing factor for the increased risk observed, as opposed to other lifestyle factors. However, the results need to be interpreted with caution because the heterogeneity score for most of these analyses approached significance or was significant.

Table 1 Meta-analysis SIRs for HIV AIDS-defining and non-AIDS-defining cancers (adapted from Grulich et al.)

Type of cancer	Meta-analysis SIR (95% CI)	Observed number of cancers	Number of studies	Heterogeneity <i>p</i> -value
<i>EBV-related cancers</i>				
Hodgkin lymphoma	11.03 (8.43–14.4)	802	7	0.00
Non-Hodgkin lymphoma	76.67 (39.4–149)	5, 295	6	0.00
Nasopharyngeal cancer	2.90 (1.80–4.66)		2	Not reported

Table 1 (continued)

Type of cancer	Meta-analysis SIR (95% CI)	Observed number of cancers	Number of studies	Heterogeneity <i>p</i> -value
<i>HHV-8-related cancer</i>				
Kaposi sarcoma	3,640.0 (3,326–3,976)	494	1	Not reported
<i>HBV/HCV</i>				
Liver cancer	5.22 (3.32–8.20)	133	7	0.01
<i>H. pylori-related cancer</i>				
Stomach	1.90 (1.53–2.36)	89	7	0.49
<i>HPV-related cancers</i>				
Cervix uteri	5.82 (2.98–11.3)	104	6	0.00
Vulva and vagina	6.45 (4.07–10.2)	21	2	0.55
Penis	4.42 (2.77–7.07)	21	3	0.52
Anus	28.75 (21.6–38.3)	303	6	0.03
Oral cavity and pharynx	2.32 (1.65–3.25)	238	4	0.07
<i>Possibly HPV-related cancers</i>				
Non-melanoma skin	4.11 (1.08–16.6)	121	4	0.00
Lip	2.80 (1.91–4.11)	30	2	0.45
Esophagus	1.62 (1.20–2.19)	48	4	0.53
Larynx	2.72 (2.29–3.22)	142	4	0.55
Eye (conjunctiva)	1.98 (1.03–3.81)	11	2	0.92
<i>Non-infectious related</i>				
Breast	1.03 (0.89–1.20)	194	6	0.60
Prostate	0.70 (0.55–0.89)	202	6	0.22
Colon and rectum	0.92 (0.78–1.08)	224	5	0.34
Ovary	1.63 (0.95–2.80)	30	5	0.34
Trachea, bronchus, and lung	2.72 (1.91–3.87)	1,016	7	0.00
Brain	2.18 (1.29–3.68)	192	7	0.00
Kidney	1.50 (1.23–1.83)	93	6	0.79
Leukemia	3.20 (2.51–4.09)	235	7	0.19
Melanoma	1.24 (1.04–1.48)	200	6	0.37
Multiple myeloma	2.71 (2.13–3.44)	76	6	0.78
Testis	1.35 (1.01–1.79)	216	7	0.16227

In summary, immune suppression from HIV disease appears to increase the risk for AIDS-defining and non-AIDS-defining malignancies. The link between immunosuppression and AIDS-defining cancers appears to be more direct; however, chronic immunosuppression likely plays a role in the development of many non-AIDS-defining malignancies in HIV-infected individuals. The cancers which are associated with viral etiologies, especially Epstein–Barr virus and human papillomavirus, appear to show the strongest association between HIV-associated immunosuppression and cancer incidence. The rest of this chapter will describe

specifics of some of the most common non-AIDS-defining malignancies, including Hodgkin disease, anal, and lung cancers.

Hodgkin Disease

Hodgkin lymphoma (HL) is one of the most common non-AIDS-defining tumors in HIV-infected patients. The risk for developing HL ranged from 4 to 16 times that of the general population in several different prospective cohort and AIDS–cancer registry match studies (Frisch et al., 2001; Grulich et al., 2002; Allardice et al., 2003; Dal Maso et al., 2003a; Clifford et al., 2005; Patel et al., 2008).

HL among HIV-infected individuals appears to have a different etiology and epidemiology compared to HL among HIV-uninfected individuals. First, nearly all of AIDS-associated Hodgkin lymphomas are EBV positive, while less than 50% of HIV-uninfected cases are EBV positive (Uccini et al., 1989). Second, while the incidence of non-AIDS-associated HL has decreased over the past 30 years, the majority of recent studies show an increase in incidence of HL in HIV-infected individuals (Grulich et al., 2002) and a clear relationship between the incidence of disease and immunodeficiency. Glaser et al. (2003) reported that from 1988 to 1998 in the Greater San Francisco Bay area, incidence rates by race of HIV-associated HL were overall higher for whites (11%), blacks (22%), and Hispanics (14%) compared to those with non-HIV-associated HL. Further, data from AIDS cohort and registry matching studies showed a relative risk of HL in HIV that ranged from 2.5 to 8.5 (Franceschi et al., 1998; Spina et al., 1999a, b). Finally, in the HIV population, the HL histologic subtypes often seen are those associated with worse prognosis, including mixed cellularity and lymphocyte-depleted variant (Tirelli et al., 1995a; Glaser et al., 2003; Hoffmann et al., 2004). In a cooperative study in Spain, Rubio and colleagues reported that individuals with AIDS-associated HL showed the following distribution of histologic subtypes: mixed cellularity (41.3%), lymphoid depletion (21.7%), nodular sclerosis (21.7%), and lymphocytic predominance (4.3%) (Rubio, 1994). Biggar et al. (2006) also reported that the incidence of nodular sclerosing HL was higher among those people with AIDS (PWAs) with low CD4 counts and that HL risk significantly increased among those with intermediate CD4 counts (150–199 cells/ μ l) compared to those with low CD4 counts (<50 cells/ μ l). Thus, because the incidence of HL is significantly higher among those with higher CD4 cell counts, mixed cellularity and other histologic subtypes of HL appear to occur more frequently among PWAs.

Clinical Presentation of HL

In addition to its distinct epidemiology, HL occurring in the HIV population exhibits clinical features that are distinct from HL in the general population. HIV-infected individuals are more likely to present with advanced-stage disease, extranodal involvement, and systemic symptoms (B symptoms), including fever, night sweats,

and/or weight loss (Vaccher et al., 2001; Glaser et al., 2003; Spina et al., 2003; Doweiko et al., 2004). In the pre-HAART era, approximately 75% of patients were shown to have advanced-stage disease. Bone marrow involvement occurred in 40–50% of individuals and was the first sign of HL in 20% of cases (Ree et al., 1991; Errante et al., 1994; Rubio, 1994; Tirelli et al., 1995a, b).

Treatment of HL

Optimal regimen for HL in HIV-infected individuals has not yet been defined. Antineoplastic treatment of AIDS-associated HL presents challenges because the underlying immunodeficiency caused by HIV may be further compromised by additional chemotherapy. Further, CD4+ counts in these individuals may decrease significantly during treatment, increasing the risk of opportunistic infections (OI) (Berretta et al., 2003).

Prior to HAART, HIV-infected individuals with HL had a median survival of only 8–26 months (Berretta et al., 2003). Gerard et al. (2003) in a retrospective study over 15 years estimated that the 2-year survival probability was 45% in the pre-HAART period and 62% in the post-HAART period. HIV-infected individuals who received and responded to HAART within 2 years of their HL diagnosis were shown to have overall survival of 89% at 24 months (median survival was not reached), whereas median survival time in patients without a response to HAART was only 18.6 months (Hoffmann et al., 2004).

Chemotherapy and HAART

Although several prospective trials have now been performed using antiretroviral drugs together with different chemotherapy regimens, the standard regimen for HIV-uninfected individuals, doxorubicin (Adriamycin), bleomycin, vinblastine, and dexamethasone (ABVD), remains the most commonly used. Several other regimens have been tested, however. The combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) was tested in 12 patients of whom 5 received concurrent HAART. Complete remission (CR) was achieved in all patients. Nine of the twelve patients remained in complete remission for their individual follow-up period, which lasted a median of 49 months. The most common observed toxicity was bone marrow suppression, with grade 3/4 leukopenia in 75% (Hartmann et al., 2003).

Another prospective, non-randomized trial evaluated epirubicin, bleomycin, vinblastine, and prednisone (EBVP) administered with HAART and G-CSF (granulocyte colony-stimulating factor) in 35 previously untreated patients. The median survival was 16 months, the survival rate was 32%, and the disease-free survival was 53% at 36 months. Toxicity was moderate, with grade 3/4 leukopenia observed in 32% of patients and thrombocytopenia in 10% of patients. Forty-eight percent of patients died of HL and 9% died of OI (Errante et al., 1999).

Spina et al. (2002) tested the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone) and radiotherapy with HAART and G-CSF in a phase II prospective study in 59 HIV-infected individuals. Sixty-nine percent of patients completed treatment with no dose reduction or chemotherapy delays. Bone marrow toxicity and neurotoxicity were the most notable dose-limiting adverse effects. Complete remission was seen in 81% of patients, and 56% of patients were alive and disease-free at median follow-up of 17 months.

Finally, Berenguer et al. (2008) utilized data from the Spanish Group de Estudio del SIDA (GESIDA) clinical trials group to compare treatment and outcomes between HIV-infected HL patients who received HAART and those who did not. The median survival for the entire cohort of 104 patients was 110 months. The 5-year survival was 44% in the group that did not receive HAART and 72% in the HAART group. They found that the following factors were associated with complete remission: (1) appropriate-for-stage therapy: this group used ABVD or mechlorethamine, vincristine, procarbazine, prednisone (MOPP) followed by Adriamycin, bleomycin, vinblastine (ABV); (2) HAART utilization; and (3) CD4 count ≥ 100 .

Anal Cancer

Although squamous cell cancer of the anus (SCCA) is a relatively rare cancer in the United States, the rate in the United States is increasing. A recent US population-based analysis of Surveillance, Epidemiology and End Results (SEER) program data found that the incidence of SCCA in the United States among men increased from 1.06 per 100,000 from 1973 to 1979 to 2.04 per 100,000 from 1996 to 2004 (Johnson et al., 2004). Other recent studies have shown a steady increase in the incidence of SCCA during the past three decades (Daling et al., 1987; Melbye et al., 1994), with significant increases among never married men in the San Francisco Bay Area (Melbye et al., 1994; Cress and Holly, 2003). These data likely reflect the significant increased risk of anal cancer among men who have sex with men (MSM) and HIV-infected MSMs.

Among MSM, the incidence of anal cancer has been estimated to be 35 cases per 100,000, comparable to the incidence of cervical cancer in women prior to the introduction of routine cervical Papanicolaou (Pap) screening (Daling et al., 1987; Melbye et al., 1994; Frisch et al., 2000, 2001, 2003). The incidence of SCCA among HIV-infected populations reported from prospective cohort studies ranged from 3.9 to 92 per 100,000 and the relative risks reported ranged from 33.4 to 222 (Grulich et al., 1999; Bower et al., 2004; Clifford et al., 2005).

Clinical Features of Anal Cancer

Several studies have shown that HIV-infected patients with SCCA were younger than HIV-uninfected patients Chiao et al., (2008; Oehler-Janne et al., 2008). Using

national Veteran's Affairs data, our group found that HIV-infected individuals were more likely to be younger (median age 49 for the HIV infected compared to 63 for the HIV uninfected), male, and of African-American race compared to the HIV-uninfected individuals. We did not find a difference in the stage of the disease at presentation; in fact, the HIV-infected patients were more likely to have been diagnosed with in situ disease (Chiao et al., 2008).

Anal Cancer Treatment and Outcomes

Combined chemoradiotherapy is the primary treatment of choice, with surgical treatment reserved for relapsed disease. The 5-year survival in the general population is 70–80% (Northover, 1991; Clark et al., 2004). Only eight small case series (ranging from 4 to 26 patients) describe outcomes of HIV-associated SCCA, with 5-year survivals ranging from 47 to 60% (Doci et al., 1992; Pitcher et al., 1994; Arnott et al., 1996; Flam et al., 1996; John et al., 1996; Gerard et al., 1998; Myerson et al., 2001; Jephcott et al., 2004). The majority of cases were diagnosed at either stage 1 or stage 2 (localized tumor without lymph node invasion) and received combined chemoradiotherapy. Most series reported some toxicity associated with therapy, with one reporting up to 50% of patients unable to complete planned therapy (Bottomley et al., 1996; Hocht et al., 1997; Peddada et al., 1997; Hoffman et al., 1999; Cleator et al., 2000; Stadler et al., 2004; Blazy et al., 2005). In three studies that specifically compared survival among patients with SCCA in the pre-HAART vs. HAART eras, there was a non-significant trend toward improved survival, better tolerability of chemoradiotherapy, and improved local tumor control in the HAART era (Cleator et al., 2000; Bower et al., 2004; Stadler et al., 2004; Blazy et al., 2005). Several studies have shown that individuals with HIV infection and SCCA have similar overall survival and outcomes when compared to HIV-uninfected individuals (Chiao et al., 2008; Oehler-Janne et al., 2008). Oehler-Janne et al. (2008) found that although overall survivals of HIV-infected and HIV-uninfected patients were similar, the 5-year disease-free survival was significantly shorter (38% vs. 87%, respectively). They also found that HIV-infected patients had more acute toxicity associated with chemoradiotherapy compared to HIV-uninfected individuals, thus suggesting that although overall survival was similar in the two groups, a more tolerable chemoradiotherapy regimen will need to be explored for HIV-infected individuals (Oehler-Janne et al., 2008).

Screening for Anal Cancer

SCCA shares many biologic similarities with cervical cancer, including detectable dysplastic precursor lesions and high-risk HPV infection. Thus, the institution of annual anal Pap screening for HIV-infected patients has been recommended (Beckmann et al., 1989; Bosch et al., 1995). Anal Pap smears are obtained by randomly obtaining squamous cells from the anal canal using a Dacron swab. They are then fixed in liquid fixative medium. Similar to cervical cytology protocols,

abnormal anal cytologic findings are confirmed by high-resolution anoscopy (HRA)-directed biopsy of visualized lesions. The 2001 revised Bethesda system of cytologic classification includes a basic primer on anal cytology and uses the system of cervical cytologic classification for classifying anal cytology (Darragh et al., 2004). Anal Pap smears have a similar sensitivity and specificity to cervical Pap smears (Cocchi et al., 1997; Palefsky et al., 1997; Woodhouse et al., 1999; Stoler and Schiffman, 2001; New York State AIDS Malignancy Consortium, 2004). Although there are no definitive clinical studies showing that anal Pap smears decrease SCCA-related morbidity and mortality among HIV-infected individuals, a recent cost-effectiveness analysis found that the incremental cost-effectiveness ratio per quality-adjusted life year saved was \$16,000, which is similar to other widely accepted screening procedures (Goldie et al., 1999). Although anal Pap smears are not currently standard of care at this time, individual practitioners are offering anal Pap smear screening and follow-up HRA, but currently there is no consensus regarding the clinical utility of anal Pap smear screening (Chiao et al., 2006).

Effect of HAART on Anal Dysplasia

Like studies evaluating the effect of HAART on cervical dysplasia, studies evaluating the effect of HAART on anal dysplasia report conflicting results, likely related to the significant design and methodological differences between these studies. Palefsky et al. (2001) compared the rates of progression and regression of anal dysplasia after 6 months of HAART. They found that the likelihood of lesion progression or regression was not affected by HAART initiation, but they noted that among patients starting HAART at higher CD4 counts, the use of HAART was associated with a non-significant benefit on anal dysplasia lesions. In a subsequent study, Palefsky et al. (2002) performed a cross-sectional analysis on the prevalence of AIN 3 among a cohort of 433 HIV-positive men. They found that men on HAART had an increased risk of 12.6 (95% CI, 2.4–64) for AIN 2 or 3 after adjustment for CD4 count. In contrast, Wilkin et al. (2004) conducted a cross-sectional study evaluating anal HPV infection and anal dysplasia in 98 HIV-positive men. In a multivariate analysis they found that HAART and higher nadir CD4 count were significantly protective for anal dysplasia by histology but were not protective for anal HPV infection. Therefore, it remains unclear if HAART initiation influences the natural history of AIN in HIV-infected individuals.

Treatment outcomes for anal dysplasia have been reported only for small case series. Current treatment options are similar for HIV-positive and HIV-negative individuals. These treatments include surgical ablation, infrared coagulation, imiquimod, and topical 5-FU (Chang et al., 2002; Kreuter et al., 2004; Goldstone et al., 2005; Graham et al., 2005).

Lung Cancer

The incidence of lung cancer in the United States in the year 2000 was greater than 70 per 100,000, and approximately 160,000 new cases were diagnosed in 2000.

Lung cancer is the leading cause of cancer deaths in the United States among both men and women (American Cancer Society, 2000). Because of the increased risk associated with smoking and because individuals with HIV disease have higher smoking rates (Parker and Leveno, 1998), the incidence of lung cancer appears to be higher among HIV-infected individuals. Although Serraino et al. (2000) and Grulich et al. (1999) did not find an increased risk of lung cancer in two cohorts of HIV-infected patients from Italy and Australia, and Cooksley et al. (1999) did not find an increased risk of lung cancer in a linked AIDS–cancer registry linked study from Harris County, Texas (Cooksley et al., 1999), Frisch et al. (2001), and Gallagher et al. (2001) found an increased SIR/RR when analyzing AIDS–cancer linked registry data. Engels et al. (2001) also conducted an age-stratified analysis of the AIDS–cancer registry match and found that patients under age 50, particularly patients in the 30–49-year age group, had a significantly increased incidence of lung cancer. Also, Parker and Leveno (1998), in a retrospective analysis of the Texas Department of Health cancer and HIV registries, showed a 6.5-fold increase in the incidence of lung cancer in HIV-infected people compared to the general US population. Finally, Goedert et al. (1998) utilized the AIDS–Cancer Match Registry data to evaluate the risk of cancer incidence based on the level of immunosuppression as estimated by the time of cancer diagnosis before (or after) the onset of AIDS. They found that although lung cancer incidence did not increase with increasing immunosuppression, the risk of lung adenocarcinoma was 2.5 (1.0–5.1) in the time period 4–27 months after the diagnosis of AIDS.

Diminished tumor immune surveillance as a result of chronic HIV-related immunosuppression has been postulated as another variable accounting for the increased risk of lung cancer in this population (Vaccher et al., 2001; Engels, 2001). Wistuba et al. (1998) found microsatellite instability in a significantly higher proportion of lung tumor specimens from HIV-infected patients as compared to non-HIV-infected controls and hypothesized that immunosuppressive states may result in genomic instability, which, in turn, may play a role in tumor development. Other factors that have been linked to increased lung cancer risk in HIV-infected patients include opportunistic lung infections (Tirelli et al., 2000), intravenous drug use, and the increasing age of HIV patients in the HAART era (Engels, 2001; Herida et al., 2003).

The Effect of HAART on the Incidence of Lung Cancer

The majority of studies in the post-HAART era show an increased risk of lung cancer, and the consensus is that the incidence of the disease is stable or may be increasing since the introduction of HAART (Bower et al., 2003; Dal Maso et al., 2003b; Herida et al., 2003). In their analysis of a prospective HIV hospital cohort, Herida et al. (2003) found an increased SIR for lung cancer in the HAART period (1996–1999), but not in the pre-HAART period (1992–1995). Bower et al. (2003) analyzed a prospectively acquired database of 8,400 HIV-infected patients between

1986 and 2001. They found 11 lung cancer cases. The incidence of lung cancer increased from 0.8 per 100,000 (0.2–3.2) in the pre-HAART era to 6.7 per 100,000 (3.1–13.9) in the post-HAART era. In the post-HAART era, the relative risk of lung cancer in the HIV-infected population was comparable to that of the general population in southeast England, which was 8.93 (4.92–19.98) (Bower et al., 2003). Dal Maso et al. (2003b), using data from the Italian Cancer and AIDS Registries Study, found that HIV-infected individuals were at higher risk for lung cancer, but the risk did not change in the post-HAART era. The overall SIR was 7.4 (4.6–11.3) in the pre-HAART period and 7.9 (2.1–20.4) in the post-HAART period. A total of 21 lung cancers were identified from 1985 to 1998 (Dal Maso et al., 2003b).

Contribution of Smoking Tobacco to Risk of HIV-Related Lung Cancer

The increased risk of lung cancer seen in large epidemiologic studies has frequently been attributed to increased smoking rates in HIV-positive individuals. Serraino et al. (2000) found that the risk of lung cancer was not significantly increased in a mixed population of male HIV-positive intravenous drug users and non-intravenous drug users but was significantly elevated in a cohort of HIV-negative male intravenous drug users. Additionally, Dal Maso et al. (2003b) reported that the risk of lung cancer was significantly higher in intravenous drug users with HIV compared to other HIV exposure categories. They found that the SIR of lung cancer was 23.9 (11.9–43.0) among intravenous drug users with HIV and was 4.2 (2.0–7.7) for other HIV exposure categories (Dal Maso et al., 2003b). Both Serraino and Dal Maso suggested that intravenous drug users, regardless of HIV status, were at higher risk of lung cancer because of increased tobacco use (Serraino et al., 2000; Dal Maso et al., 2003b). Although smoking information was not specifically collected, Gallagher et al. reported that men whose HIV risk factors were either homosexual contact or intravenous drug use were all at higher risk for lung cancer. In addition, they found that women in all HIV exposure groups were at higher risk for lung cancer (Gallagher et al., 2001).

However, HIV infection may increase the risk of lung cancer independent of tobacco use. Patel et al. (2004) found an increased risk of lung cancer in a prospective cohort of HIV-infected individuals despite controlling for smoking behavior. Furthermore, a recent study by Engels et al. (2006) used an urban HIV cohort from Baltimore, Maryland, to evaluate the risk for lung cancer, specifically controlled for smoking behavior. They found 33 cancers in 5,238 patients, for an incidence of 170 per 100,000 person-years and an SIR of 4.7 (95% CI, 3.2–6.5). When they subsequently adjusted the SIR for smoking rates in the HIV-infected population and a similar urban population (Detroit, Michigan), the SIR decreased to 2.5 (95% CI, 1.6–3.5) but remained significantly elevated. This suggests that HIV infection increases the risk for lung cancer above and beyond other behavioral risks.

Clinical Characteristics of HIV-Positive Patients with Lung Cancer

As is the case for many other cancers, lung cancer in HIV-infected individuals presents differently than in HIV-uninfected individuals. Although the mean age of lung cancer patients in the general population is 68 years Kosary et al., (1995), the mean age at diagnosis in the HIV population ranged from 38 to 49 years Tirelli et al., (2000). In the majority of published series, the most common histology was adenocarcinoma. Adenocarcinoma was diagnosed in between 25 and 60% of cases, while 0–20% showed small cell histology. The authors of these series reported between 30 and 60 pack year median tobacco history. Between 13 and 57% of HIV-positive patients had a history of TB or PCP. A large proportion of cases presented with advanced-stage, unresectable disease (67–100%), and 0–26% were treated with surgery.

Patients in the pre-HAART and HAART eras appear to have similar presentations of disease. Bower et al. (2003) found that the only major difference was the median length of time from HIV diagnosis to lung cancer diagnosis, which was 2 months in the pre-HAART era and 10 months in the HAART era. Another recent HAART era study by Powles et al. (2003a) compared the presentation and outcomes of nine HIV-positive non-small cell lung cancer patients with 27 HIV-negative age- and stage-matched controls. Seven of the nine HIV-positive patients were on HAART at the start of treatment. The median age was similar in the HIV-infected patients and the HIV-uninfected controls (45 and 48 years, respectively). In this study, a similar percentage presented with adenocarcinoma, and a similar percentage presented with stage IV disease (66% of HIV-positive patients and 70% of HIV-uninfected controls). The HIV-uninfected patients had a better performance status than did the HIV-positive patients, with 52% of HIV-negative patients and 22% of the HIV-positive patients presenting with ECOG performance status less than 2.

Treatment and Outcomes of Lung Cancer in the HAART Era

Powles et al. (2003a) found that a similar percentage of the HIV-infected and uninfected lung cancer patients received chemotherapy (66% of HIV-negative patients vs. 88% of the HIV-positive patients). Overall survival was the same for HIV-positive and HIV-negative patients at 4 months ($p = 0.55$). Cancer-related death was similar in the HIV-negative patients and the HIV-positive patients (74% vs. 77%) (Powles et al., 2003a). The findings of Powles et al. (2003a) contrast with previous reports that show inferior survival for HIV-positive patients compared to HIV-negative patients (Vyzula, 1996; Tirelli et al., 2000; Sridar et al., 1992). The earlier studies hypothesized that lung cancer was a more aggressive disease in HIV-positive patients or that fewer HIV-positive than HIV-negative patients were candidates for curative surgical resection because of poor lung function as a result of multiple previous opportunistic infection. Poor performance status may have also contributed to decreased surgical resection or chemotherapy treatment.

The study by Powles et al. (2003b) was not able to address the issue of surgical resection because all the patients in the study presented with advanced-stage disease. However, they hypothesized that the poor outcomes in both the HIV-positive cases and HIV-negative controls may reflect advanced and aggressive disease behavior in young people who present with lung cancer as whole and that lung cancer does not appear to be more aggressive in HIV-positive individuals. They report that advanced non-small cell lung cancer in HIV-infected individuals treated with HAART is still associated with a poor outcome, but the outcomes are similar to HIV-negative controls matched for age and stage (Powles et al., 2003b).

It is unclear if HAART utilization improves outcomes in HIV-infected patients with lung cancer. Although there are no data that directly compare the survival between the pre-HAART era and the HAART era, pooled data from the pre-HAART era indicate that median survival was approximately 2 months (Sridar et al., 1992; Vyzula, 1996; Remick, 1996; Alshafie et al., 1997). Powles et al. (2003b) reported that the survival in the HAART era was 4 months. In addition, Hakimian et al. (2007) reported that median survival in a cohort of 30 HIV-infected individuals was approximately 5.2 months, but the majority of these patients (27/30) were diagnosed with advanced (stage 3B, 4) disease. They hypothesized that HAART may decrease HIV-related mortality and increase ability to tolerate treatment but that ultimately poor performance status and late diagnoses of cancer in HIV patients have led to poor outcomes (Hakimian et al., 2007; Powles et al., 2003b).

In the HAART era, HIV infection per se should not be a contraindication for surgical intervention or palliative therapy. The available data suggest that HIV-positive patients with lung cancer should be treated in a similar fashion to HIV-negative patients based on stage and performance status (Powles et al., 2003a). In addition, palliative chemotherapy and radiotherapy should be considered for possible improvement in quality of life. Hematopoietic growth factors may be necessary to support HIV-positive patients during treatment. Prophylaxis against opportunistic infection during chemotherapy and radiation therapy and avoidance of anemia-inducing antiretroviral medications such as zidovudine should be standard adjunctive treatment measures.

Because lung cancer has such a poor prognosis for HIV-infected individuals and the incidence appears to be stable or on the rise in the HAART era, it is important to evaluate prevention, early detection, and treatment initiatives for these patients. Because surgical resection of early stage disease is the only therapy that has been associated with long-term survival, a low threshold for early diagnostic interventions, including CT scans, to increase early diagnosis of lung cancer in patients can be recommended (White et al., 1995). Finally, smoking is also a significant risk factor for other chronic diseases besides lung cancer for which HIV-positive patients are at risk, including coronary artery disease (Friis-Moller et al., 2003), emphysema (Diaz et al., 2000), and head and neck cancers (Powles et al., 2004). A systematic approach to smoking cessation programs for HIV-positive individuals may be of great benefit in this population.

Conclusions

Antiretroviral therapy has transformed the disease trajectory of AIDS over the last 20 years. Since the widespread use of HAART over the past 10 years, AIDS is no longer an almost inevitably fatal disease and in many individuals behaves as a chronic condition (Louie et al., 2002). However, HIV-infected individuals in the HAART era develop more long-term problems, many of them being associated with chronic low-grade immunosuppression. HAART has decreased the incidence of AIDS-defining malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, and primary CNS lymphomas Eltom et al., (2002), but the influence of HAART on non-AIDS-defining malignancies is less clear. HAART was introduced less than 15 years ago, and therefore studies that attempt to compare cancer risks in the pre-HAART and post-HAART eras do not include long-term post-HAART follow-up (Herida et al., 2003; Seaberg and Kingsley, 2002; McGinnis et al., 2002). Because chronic immunosuppression may contribute to an increased risk for non-AIDS-defining malignancies in HIV-infected individuals, it will be important to closely monitor this population for emerging epidemiologic trends. The meta-analysis conducted by Grulich et al. comparing cancer incidence in HIV-infected individuals and solid organ transplant recipients underscores the similarity between these two groups and suggests that cancer screening is an important issue for both populations.

In addition, other HAART- or HIV-related adverse effects may also impact on cancer risk factors. Metabolic abnormalities associated with HAART, such as fat redistribution from the periphery to the abdomen and breast, elevated body mass indices, undesirable serum lipid levels, and elevated waist-hip ratios have been associated with breast cancer risk and survival (Agurs-Collins et al., 1998; Schreier et al., 1999; Goodwin et al., 1997). In addition, adjunctive therapies such as testosterone replacement may also be associated with increased risk for tumor growth. Finally, HAART itself has been associated with an increased incidence of cancer (Olivero et al., 2005). Thus, Clinicians need to emphasize the role of smoking cessation, patient education, and age-appropriate cancer screening recommendations in the HIV-infected population. Further studies evaluating the epidemiology, natural history, and optimal treatments for malignancies in HIV-infected individuals are needed to guide this evolving field.

References

- American Cancer Society (2000). *Cancer Facts and Figures*, (Atlanta, GA: American Cancer Society).
- Agurs-Collins, T., Kim, K. S., et al. (1998). Plasma lipid alterations in African-American women with breast cancer. *J Cancer Res Clin Oncol* 124(3-4), 186-190.
- Allardice, G. M., Hole, D. J., et al. (2003). Incidence of malignant neoplasms among HIV-infected persons in Scotland. *Br J Cancer* 89(3), 505-507.
- Alshafie, M. T., Donaldson, B., et al. (1997). Human immunodeficiency virus and lung cancer. *Br J Surg* 84(8), 1068-1071.

- Arnott, S. J., Cunningham, D., et al. (1996). Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet* 348(9034), 1049–1054.
- Beckmann, A. M., Daling, J. R., et al. (1989). Human papillomavirus infection and anal cancer. *Int J Cancer* 43(6), 1042–1049.
- Berenguer, J., Miralles, P., et al. (2008). Characteristics and outcome of AIDS-related Hodgkin lymphoma before and after the introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 47(4), 422–428.
- Berretta, M., Cinelli, R., et al. (2003). Therapeutic approaches to AIDS-related malignancies. *Oncogene* 22(42), 6646–6659.
- Biggar, R. J., Curtis, R. E., et al. (1994). Risk of other cancers following Kaposi's sarcoma: relation to acquired immunodeficiency syndrome. *Am J Epidemiol* 139(4), 362–368.
- Biggar, R. J., Jaffe, E. S., et al. (2006). Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood* 108(12), 3786–3791.
- Blazy, A., Hennequin, C., et al. (2005). Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 48(6), 1176–1181.
- Bosch, F. X., Manos, M. M., et al. (1995). Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) Study Group. *J Natl Cancer Inst* 87(11), 796–802.
- Bottomley, D. M., Aqel, N., et al. (1996). Epidermoid anal cancer in HIV infected patients. *Clin Oncol (R Coll Radiol)* 8(5), 319–322.
- Bower, M., Powles, T., Nelson, M., et al. (2003). HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS* 17, 371–375.
- Bower, M., Powles, T., et al. (2004). HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? *J Acquir Immune Defic Syndr* 37(5), 1563–1565.
- Chang, G. J., Berry, J. M., et al. (2002). Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. *Dis Colon Rectum* 45(4), 453–458.
- Chaturvedi, A. K., Mbulaiteye, S. M., et al. (2008). Underestimation of relative risks by standardized incidence ratios for AIDS-related cancers. *Ann Epidemiol* 18(3), 230–234.
- Chiao, E. Y., Giordano, T. P., et al. (2006). Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review. *Clin Infect Dis* 43(2), 223–233.
- Chiao, E. Y., Giordano, T. P., et al. (2008). Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. *J Clin Oncol* 26(3), 474–479.
- Chiu, H. M., Lin, J. T., et al. (2008). Elevation of C-reactive protein level is associated with synchronous and advanced colorectal neoplasm in men. *Am J Gastroenterol* 103(9), 2317–2325.
- Clark, M. A., Hartley, A., et al. (2004). Cancer of the anal canal. *Lancet Oncol* 5(3), 149–157.
- Cleator, S., Fife, K., et al. (2000). Treatment of HIV-associated invasive anal cancer with combined chemoradiation. *Eur J Cancer* 36(6), 754–758.
- Clifford, G. M., Polesel, J., et al. (2005). Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 97(6), 425–432.
- Cocchi, V., Carretti, D., et al. (1997). Intralaboratory quality assurance in cervical/vaginal cytology: evaluation of intercytologist diagnostic reproducibility. *Diagn Cytopathol* 16(1), 87–92.
- Cooksley, C. D., Hwang, L. Y., et al. (1999). HIV-related malignancies: community-based study using linkage of cancer registry and HIV registry data. *Int J STD AIDS* 10(12), 795–802.
- Cress, R. D., and Holly, E. A. (2003). Incidence of anal cancer in California: increased incidence among men in San Francisco, 1973–1999. *Prev Med* 36(5), 555–560.

- Dal Maso, L., Franceschi, S., et al. (2003a). Risk of cancer in persons with AIDS in Italy, 1985–1998. *Br J Cancer* 89(1), 94–100.
- Dal Maso, L., Polesel, J., et al. (2003b). Lung cancer in persons with AIDS in Italy, 1985–1998. *AIDS* 17(14), 2117–2119.
- Daling, J. R., Weiss, N. S., et al. (1987). Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med* 317(16), 973–977.
- Darragh, T., Birdson, G., et al. (2004). Chapter 8: Anal–Rectal Cytology, (New York, NY: Springer).
- Diaz, P. T., King, M. A., et al. (2000). Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 132(5), 369–372.
- Doci, R., Zucali, R., et al. (1992). Combined chemoradiation therapy for anal cancer. A report of 56 cases. *Ann Surg* 215(2), 150–156.
- Doweiko, J., Dezube, B. J., et al. (2004). Unusual sites of Hodgkin's lymphoma: CASE 1. HIV-associated Hodgkin's lymphoma of the stomach. *J Clin Oncol* 22(20), 4227–4228.
- El-Sadr, W. M., Lundgren, J. D., et al. (2006). CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 355(22), 2283–2296.
- Eltom, M. A., Jemal, A., et al. (2002). Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J Natl Cancer Inst* 94(16), 1204–1210.
- Engels, E. A. (2001). Human immunodeficiency virus infection, aging, and cancer. *J Clin Epidemiol* 54(Suppl 1), S29–S34.
- Engels, E. A., Brock, M. V., et al. (2006). Elevated incidence of lung cancer among HIV-infected individuals. *J Clin Oncol* 24(9), 1383–1388.
- Errante, D., Gabarre, J., et al. (1999). 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* 10(2), 189–195.
- Errante, D., Tirelli, U., et al. (1994). Combined antineoplastic and antiretroviral therapy for patients with Hodgkin's disease and human immunodeficiency virus infection. A prospective study of 17 patients. The Italian Cooperative Group on AIDS and Tumors (GICAT). *Cancer* 73(2), 437–444.
- Flam, M., John, M., et al. (1996). Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol* 14(9), 2527–2539.
- Franceschi, S., Dal Maso, L., et al. (1998). 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* 78(7), 966–970.
- Friis-Moller, N., Sabin, C. A., et al. (2003). Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 349(21), 1993–2003.
- Frisch, M., Biggar, R. J., et al. (2000). Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 92(18), 1500–1510.
- Frisch, M., Biggar, R., et al. (2001). Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 285(13), 1736–1745.
- Frisch, M., Smith, E., et al. (2003). Cancer in a population-based cohort of men and women in registered homosexual partnerships. *Am J Epidemiol* 157(11), 966–972.
- Gallagher, B., Zhengyan, W., et al. (2001). Cancer incidence in New York State acquired immunodeficiency syndrome patients. *Am J Epidemiol* 154, 544–556.
- Gerard, J. P., Ayzac, L., et al. (1998). Treatment of anal canal carcinoma with high dose radiation therapy and concomitant fluorouracil–cisplatin. Long-term results in 95 patients. *Radiother Oncol* 46(3), 249–256.
- Gerard, L., Galicier, L., et al. (2003). Improved survival in HIV-related Hodgkin's lymphoma since the introduction of highly active antiretroviral therapy. *AIDS* 17(1), 81–87.

- Glaser, S. L., Clarke, C. A., et al. (2003). Population-based patterns of human immunodeficiency virus-related Hodgkin lymphoma in the Greater San Francisco Bay Area, 1988–1998. *Cancer* 98(2), 300–309.
- Goedert, J. J., Cote, T. R., et al. (1998). Spectrum of AIDS-associated malignant disorders. *Lancet* 351(9119), 1833–1839.
- Goldie, S. J., Kuntz, K. M., et al. (1999). The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA* 281(19), 1822–1829.
- Goldstone, S. E., Kawalek, A. Z., et al. (2005). Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum* 48(5), 1042–1054.
- Goodwin, P. J., Boyd, N. F., et al. (1997). Elevated levels of plasma triglycerides are associated with histologically defined premenopausal breast cancer risk. *Nutr Cancer* 27(3), 284–292.
- Graham, B. D., Jetmore, A. B., et al. (2005). Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. *Dis Colon Rectum* 48(3), 444–450.
- Grulich, A. E., Li, Y., et al. (2002). Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. *AIDS* 16(8), 1155–1161.
- Grulich, A., Wan, X., et al. (1999). Risk of cancer in people with AIDS. *AIDS* 13(7), 839–843.
- Grulich, A. E., van Leeuwen, M. T., et al. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 370(9581), 59–67.
- Hajjar, M., Lacoste, D., et al. (1992). Non-acquired immune deficiency syndrome-defining malignancies in a hospital-based cohort of human immunodeficiency virus-infected patients: Bordeaux, France, 1985–1991. Groupe d'Epidemiologie clinique du SIDA en aquitaine. *J Natl Cancer Inst* 84(20), 1593–1595.
- Hakimian, R., Fang, H., et al. (2007). Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. *J Thorac Oncol* 2(4), 268–272.
- Hartmann, P., Rehwald, U., et al. (2003). BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection. *Ann Oncol* 14(10), 1562–1569.
- Herida, M., Mary-Krause, M., et al. (2003). Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol* 21(18), 3447–3453.
- Hocht, S., Wiegel, T., et al. (1997). Low acute toxicity of radiotherapy and radiochemotherapy in patients with cancer of the anal canal and HIV-infection. *Acta Oncol* 36(8), 799–802.
- Hoffman, R., Welton, M. L., et al. (1999). The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. *Int J Radiat Oncol Biol Phys* 44(1), 127–131.
- Hoffmann, C., Chow, K. U., et al. (2004). Strong impact of highly active antiretroviral therapy on survival in patients with human immunodeficiency virus-associated Hodgkin's disease. *Br J Haematol* 125(4), 455–462.
- Jephcott, C. R., Paltiel, C., et al. (2004). Quality of life after non-surgical treatment of anal carcinoma: a case control study of long-term survivors. *Clin Oncol (R Coll Radiol)* 16(8), 530–535.
- John, M., Flam, M., et al. (1996). Ten-year results of chemoradiation for anal cancer: focus on late morbidity. *Int J Radiat Oncol Biol Phys* 34(1), 65–69.
- Johnson, L. G., Madeleine, M. M., et al. (2004). Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. *Cancer* 101(2), 281–288.
- Kosary, C., Reiss, L., et al. (1995). SEER Cancer Statistics Review, 1973–1992: Tables and Graphs. (Bethesda, MD: NIH Publication, 96-2789).
- Kreuter, A., Hochdorfer, B., et al. (2004). Treatment of anal intraepithelial neoplasia in patients with acquired HIV with imiquimod 5% cream. *J Am Acad Dermatol* 50(6), 980–981.
- Kuller, L. H., Tracy, R., et al. (2008). Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 5(10), e203.

- Lewden, C., Salmon, D., et al. (2005). 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* 34(1), 121–130.
- Louie, J. K., Hsu, L. C., et al. (2002). Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. *J Infect Dis* 186(7), 1023–1027.
- Mbulaitaye, S., Biggar, R., et al. (2003). Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr* 32(5), 527–533.
- McGinnis, K., Skanderson, M., et al. (2002). Pre and post HAART cancer incidence among HIV positive veterans. *Int Conf AIDS*.
- Melbye, M., Rabkin, C., et al. (1994). Changing patterns of anal cancer incidence in the United States, 1940–1989. *Am J Epidemiol* 139(8), 772–780.
- Monforte, A., Abrams, D., et al. (2008). HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* 22(16), 2143–2153.
- Myerson, R. J., Kong, F., et al. (2001). Radiation therapy for epidermoid carcinoma of the anal canal, clinical and treatment factors associated with outcome. *Radiother Oncol* 61(1), 15–22.
- New York State AIDS Malignancy Consortium (2004). Criteria for the Medical Care of Adults with HIV Infection. pp. 1–18, (New York, NY: New York State Department of Health AIDS Institute).
- Northover, J. M. (1991). Epidermoid cancer of the anus – the surgeon retreats. *J R Soc Med* 84(7), 389–390.
- Oehler-Janne, C., Huguet, F., et al. (2008). 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* 26(15), 2550–2557.
- Olivero, O. A., Tejera, A. M., et al. (2005). Zidovudine induces S-phase arrest and cell cycle gene expression changes in human cells. *Mutagenesis* 20(2), 139–146.
- Palefsky, J. M., Holly, E. A., et al. (1997). Anal cytology as a screening tool for anal squamous intraepithelial lesions. *J Acquir Immune Defic Syndr Hum Retrovirol* 14(5), 415–422.
- Palefsky, J. M., Holly, E. A., et al. (2001). 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* 28(5), 422–428.
- Palefsky, J. M., Holly, E. A., et al. (2002). Effect of HAART on incidence of anal intraepithelial neoplasia grade 3 among HIV-positive men who have sex with men. *Proceedings of the 14th International Conference on AIDS, Barcelona, Spain*.
- Parker, M., and Leveno, D. (1998). AIDS-related bronchogenic carcinoma: factor fiction. *Chest* 113, 154–161.
- Patel, P., Hanson, D. L., et al. (2008). Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med* 148(10), 728–736.
- Patel, P., Tong, T., et al. (2004). Incidence of non-AIDS-defining malignancies in the HIV outpatient study (HOPS). *Proceedings of the 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA*.
- Peddada, A. V., Smith, D. E., et al. (1997). Chemotherapy and low-dose radiotherapy in the treatment of HIV-infected patients with carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 37(5), 1101–1105.
- Petruckevitch, A., Del Amo, J., et al. (1999). Risk of cancer in patients with HIV disease. London African HIV/AIDS Study Group. *Int J STD AIDS* 10(1), 38–42.
- Pitcher, M. E., Davidson, T. I., et al. (1994). Post irradiation sarcoma of soft tissue and bone. *Eur J Surg Oncol* 20(1), 53–56.
- Powles, T., Nelson, M., et al. (2003). HIV-related lung cancer – a growing concern? *Int J STD AIDS* 14(10), 647–651.

- Powles, T., Powles, J., et al. (2004). Head and neck cancer in patients with human immunodeficiency virus-1 infection: incidence, outcome and association with Epstein-Barr virus. *J Laryngol Otol* 118(3), 207-212.
- Powles, T., Thirwell, C., et al. (2003). Does HIV adversely influence the outcome in advanced non-small-cell lung cancer in the era of HAART? *Br J Cancer* 89(3), 457-459.
- Ree, H. J., Strauchen, J. A., et al. (1991). Human immunodeficiency virus-associated Hodgkin's disease. Clinicopathologic studies of 24 cases and preponderance of mixed cellularity type characterized by the occurrence of fibrohistiocytoid stromal cells. *Cancer* 67(6), 1614-1621.
- Remick, S. C. (1996). Non-AIDS-defining cancers. *Hematol Oncol Clin North Am* 10(5), 1203-1213.
- Rubio, R. (1994). Hodgkin's disease associated with human immunodeficiency virus infection. A clinical study of 46 cases. Cooperative study group of malignancies associated with HIV infection of Madrid. *Cancer* 73(9), 2400-2407.
- Schreier, L. E., Berg, G. A., et al. (1999). Lipoprotein alterations, abdominal fat distribution and breast cancer. *Biochem Mol Biol Int* 47(4), 681-690.
- Seaberg, E., Kingsley, L., et al. (2002). The impact of HAART on cancer incidence in the multicenter AIDS cohort study (MACS). *Int Conf AIDS*.
- Serraino, D., Boschini, A., et al. (2000). Cancer risk among men with, or at risk of, HIV infection in Southern Europe. *AIDS* 14(5), 553-559.
- Silverberg, M. J., Neuhaus, J., et al. (2007). Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS* 21(14), 1957-1963.
- Spina, M., Berretta, M., et al. (2003). Hodgkin's disease in HIV. *Hematol Oncol Clin North Am* 17(3), 843-858.
- Spina, M., Gabarre, J., et al. (2002). Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection. *Blood* 100(6), 1984-1988.
- Spina, M., Sandri, S., et al. (1999a). Hodgkin's disease in HIV-infected individuals. *Curr Opin Oncol* 11(6), 522-526.
- Spina, M., Vaccher, E., et al. (1999b). Neoplastic complications of HIV infection. *Ann Oncol* 10(11), 1271-1286.
- Sridar, S., Flores, M., et al. (1992). Lung cancer in patients with human immunodeficiency virus infection compared with historic control subjects. *Chest* 102, 1704-1708.
- Stadler, R. F., Gregorcyk, S. G., et al. (2004). Outcome of HIV-infected patients with invasive squamous-cell carcinoma of the anal canal in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 47(8), 1305-1309.
- Stoler, M. H., and Schiffman, M. (2001). Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL triage study. *JAMA* 285(11), 1500-1505.
- Tirelli, U., Errante, D., et al. (1995a). 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* 13(7), 1758-1767.
- Tirelli, U., Spina, M., et al. (2000). Lung carcinoma in 36 patients with human immunodeficiency virus infection. The Italian Cooperative Group on AIDS and Tumors. *Cancer* 88(3), 563-569.
- Tirelli, U., Vaccher, E., et al. (1995b). CD30 (Ki-1)-positive anaplastic large-cell lymphomas in 13 patients with and 27 patients without human immunodeficiency virus infection: the first comparative clinicopathologic study from a single institution that also includes 80 patients with other human immunodeficiency virus-related systemic lymphomas. *J Clin Oncol* 13(2), 373-380.
- Tsilidis, K. K., Branchini, C., et al. (2008). C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. *Int J Cancer* 123(5), 1133-1140.
- Uccini, S., Monardo, F., et al. (1989). High frequency of Epstein-Barr virus genome in HIV-positive patients with Hodgkin's disease. *Lancet* 1(8652), 1458.
- Vaccher, E., Spina, M., et al. (2001). Clinical aspects and management of Hodgkin's disease and other tumours in HIV-infected individuals. *Eur J Cancer* 37(10), 1306-1315.

- Vyzula, R. (1996). Lung cancer in patients with HIV-infection. *Lung Cancer* 15, 325–339.
- White, C. S., Haramati, L. B., et al. (1995). Carcinoma of the lung in HIV-positive patients: findings on chest radiographs and CT scans. *AJR Am J Roentgenol* 164(3), 593–597.
- Wilkin, T. J., Palmer, S., et al. (2004). Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. *J Infect Dis* 190(9), 1685–1691.
- Wistuba, I., Behrens, C., et al. (1998). Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. *JAMA* 279, 1154–1159.
- Woodhouse, S. L., Stastny, J. F., et al. (1999). Interobserver variability in subclassification of squamous intraepithelial lesions: results of the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med* 123(11), 1079–1084.

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