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Clinics in Chest Medicine: HIV-Associated Lung Malignancies

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INTRODUCTION

With improved survival due to highly active antiretroviral therapy (HAART) ^{1–3}, HIV has transformed into a chronic disease. Growing numbers of HIV-infected persons in the U.S are surviving into older ages and a changing spectrum of diseases with reduced AIDS-defining conditions but increased non-AIDS disease is being observed ^{4–6}. Life expectancy for a newly diagnosed HIV-infected person is now approaching that of the general population ⁷. HIV-infected persons are well recognized to have a high burden cigarette smoking. With reductions in HIV-infected persons experiencing profound immunodeficiency but with prolonged survival of persons with extensive tobacco use, monitoring of the changing patterns of morbidity and mortality is needed. Temporal patterns of lung malignancies in HIV exemplify these dramatic shifts in incidence and etiology, and raise concerns regarding the future burden of disease. Understanding the epidemiology and pathogenesis of lung malignancies among HIV-infected patients can help inform approaches for improving the diagnosis, management and prevention of these malignancies in this evolving patient population.

Before the introduction of HAART, mortality among HIV-infected patients was defined largely by opportunistic infections and by AIDS-defining malignancies, particularly Kaposi's sarcoma (KS) and non-Hodgkin lymphoma (NHL) ⁸. However, with the introduction of HAART, morbidity and mortality due to opportunistic infections and AIDS-defining malignancies has declined ⁹. One recent study found that 39% of Department of Defense patients with HIV who died in the post-HAART era had a CD4 count >200 cells/mL, illustrating the lack of immunosuppression at the time of death and highlighting the changing morbidity and mortality affecting HIV-infected patients ⁸. As the incidence of KS and NHL declines, non-AIDS-defining cancers (NADC) comprise an increasing proportion of malignancies among HIV-infected patients ¹⁰. Furthermore, the incidence of non-AIDS-defining cancers is increased among HIV-infected patients when compared to the general population ^{10–11}. Engels et al reported that in the pre-HAART era, NADC comprised 31.4% of cancer diagnoses; however, the proportion of NADC then increased to 58% of cancer diagnoses during post-HAART years ¹². Primary lung cancer is the second most commonly diagnosed malignancy in the United States, with more people dying of lung cancer each year

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than any other type of cancer¹³. First recognized in the HIV setting in early 1984¹⁴, lung cancer remains the most common NADC^{9, 12, 15–18}. In light of the increasing risk of NADC, and more specifically lung cancer, among HIV-infected patients, clinicians need to better recognize, diagnose, treat and ideally prevent lung cancer in this population. In this review of lung malignancies in HIV, we briefly highlight key epidemiological and clinical features in the pulmonary involvement of AIDS-defining malignancies of KS and NHL. Then, focusing on lung cancer, we sequentially discuss the epidemiology and mechanisms, clinical presentation, pathology, treatment and outcomes, and prevention. Finally, we highlight the important knowledge gaps and future directions for research related to HIV-associated lung malignancies.

AIDS-DEFINING MALIGNANCIES OF THE LUNG: KS and NHL

KS and NHL are AIDS-defining cancers (ADC) and represent the most common malignancies that occur following the development of AIDS¹⁰. In a national AIDS and cancer registry linkage study among patients from 1980–2002 in the US, the proportion of persons diagnosed within one year of AIDS diagnosis with KS was 6.7% and NHL was 2.3%. Overall, rates of both KS and NHL significantly declined in the mid-1990s around the time of introduction of HAART (Figure 1, panel A and B); these rates have plateaued during the HAART era¹⁰. Although the lungs are not typically the primary site of disease, pulmonary involvement for both KS and NHL is relatively common.

Kaposi's Sarcoma

HIV/AIDS-associated KS most commonly occurs in homosexual or bisexual men infected with the human herpes virus-8 (HHV-8), also known as the KS-associated herpes virus (KSHV). In a review of AIDS and cancer registries from 1980–2002, 89% of KS cases occurred among men who have sex with men (MSM)¹⁰. The higher burden of KS among MSM has been attributed to differences in the seroprevalence of KSHV between HIV risk groups¹⁹. HIV/AIDS-associated KS occurs at advanced stages of immunosuppression (i.e., lower CD4 cell counts)^{20–24}, and displays a more rapid course compared to classic or endemic KS^{25–26}. While disease is rarely isolated to the lungs, pulmonary involvement occurs frequently in HIV-infected patients with extensive mucocutaneous disease. Pulmonary KS is present in approximately 30% of patients, however the rates of clinical diagnosis prior to autopsy are highly disparate²⁷. HIV-infected patients with pulmonary KS have significantly lower CD4 counts and shorter survival times than those without pulmonary manifestations of KS²⁶.

Patients generally present with vague respiratory symptoms, most commonly dyspnea and cough, and can have non-specific imaging findings – making the work-up of these symptoms in this at-risk patient population challenging^{24, 28}. In the HAART era, the current CD4 count is the patient characteristic that is most predictive of risk for KS²⁹. Imaging findings of peribronchovascular nodularity and thickening, interlobular septal thickening and fissural nodularity consistent with KS often parallel bronchoscopic findings; however, patients can present with parenchymal findings noted on computed tomography (CT) without evidence of endobronchial lesions^{30–31}. Diagnosis can be made via bronchoscopic visualization of typical KS-appearing endobronchial lesions, if present. The utility and yield of bronchoscopic evaluation is variable due to the nature of KS lesions, with intermittent presence of endobronchial lesions, unpredictable proximity to airway, irregular extension into the submucosal space and sometimes microscopic size²⁴. Pleural effusions, if present, are often related to a secondary infection; thoracentesis with pleural fluid analysis is rarely diagnostic. Gallium-thallium radionuclide imaging is helpful in distinguishing pulmonary KS from pulmonary infection because KS is thallium avid and does not uptake gallium, in contrast to infected lung³².

Despite a dramatic decrease in the prevalence of KS with the introduction of HAART, KS is associated with significant mortality burden, although it remains difficult to determine if KS represents the proximate cause of death or if KS is simply strongly associated with AIDS. A review of causes of death among HIV-infected patients from 1990–2003 found that 12.8% of patients with HIV died of KS in the post-HAART era compared to 11% in the pre-HAART era⁸. However, while the proportionate mortality due to KS has been relatively constant, survival following a KS diagnoses has improved. Two year survival of HIV/AIDS-KS patients has increased from 30% in the pre-HAART era to as high as 85% since HAART availability^{29, 33}. These changes in survival are largely due to HAART. Higher CD4 count and isolated KS as the AIDS-defining illness are associated with improved outcomes compared to poorly controlled HIV with concomitant opportunistic infections³⁴. The primary treatment for HIV/AIDS KS is reversal of immunodeficiency through use of effective ART; regression of lesions is generally observed with restoration of immune function.

Paradoxically, an immune reconstitution inflammatory syndrome (IRIS) may occasionally occur in patients with KS following ART initiation^{35–37}. In contrast to many other opportunistic infections present at ART initiation, IRIS appears to occur more commonly in patients with KS and is associated with more severe complications including death, especially in the setting of KS with pulmonary or other visceral involvement^{38–39}. Tumor-directed therapy involves combination myelosuppressive chemotherapy, with radiation therapy used in selected cases – both treatments can be challenging to tolerate in the setting of advanced AIDS.^{40–41} Cytotoxic chemotherapy also may play a role in management of KS-associated IRIS^{35, 37}. For unclear reasons, pulmonary KS portends a substantially worse prognosis, whether in the setting of simply having a KS diagnosis or if IRIS occurs. A single institution study in the HAART era reported 5-year survival of 49% in pulmonary KS compared to 82% in HIV/AIDS-KS patients without pulmonary involvement²⁶.

Non-Hodgkin Lymphoma

Severe immunosuppression is the hallmark of HIV/AIDS-associated NHL, which most commonly manifests with central nervous system (CNS) involvement in the setting of advanced HIV/AIDS disease. NHL is an ADC with risk strongly related to the degree of immunosuppression, often occurring at CD4 cell counts of <50 cells/ml. Subsequently, NHL has also demonstrated declining rates since the introduction of HAART (Figure 1)⁴².

Epstein-Barr virus (EBV) has been associated with the majority of HIV-associated NHL cases, although the degree of involvement varies in relation to the sub-type of lymphoma.^{43–44} Around 60% of AIDS-related lymphomas are diffuse large-cell lymphomas, typically presenting in the setting of advanced AIDS and at extranodal sites. Burkitt's or Burkitt's like lymphoma comprise around 40% of AIDS-related NHL, uniformly express characteristic translocations of the c-myc gene, and may occur at less degree of immunodeficiency than large-cell lymphomas.^{43, 45} Primary pulmonary lymphoma (PPL) is an infrequent causes of AIDS-related lymphoma, and is of the large-cell type with uniform EBV expression.⁴⁶ Rarely, immune compromised HIV-infected patients may manifest lymphoma of the pleura or other body cavities (primary effusion lymphoma [PEL]) which are strongly associated with KSHV infection, in addition to EBV.⁴⁷

Relative to CNS involvement, pulmonary NHL occurs infrequently in HIV-infected patients. In a retrospective review of AIDS patients undergoing autopsy at two San Francisco hospitals from 1982–1991⁴⁸, 5.8% of NHL patients experienced isolated pulmonary localization without other systemic manifestations, and the lung was the most common organ involved in those with extranodal site of disease (70%). HIV-infected patients with pulmonary NHL often present with pneumonic or pleural disease; the most common

symptoms are constitutional (95%), cough (71%), and dyspnea (63%). The majority of patients have an abnormal exam, manifest most commonly by tachypnea (74%). 97% of patients have abnormal radiographic findings with lobar consolidation (40%), nodules (40%), reticular infiltrates (24%) and masses (24%) seen on chest radiography. Thoracic lymphadenopathy may be present,^{49–50} but is thought to be uncommon. Pleural and serum lactate dehydrogenase levels are often substantially elevated, but this represents a sensitive and not specific marker of NHL. Pleural fluid analysis is typically exudative with elevated white and red blood cell counts and a low glucose level. Transbronchial biopsy specimens were diagnostic in 58% of cases in a retrospective series of patients, whereas pleural cytologic evaluation, closed needle pleural biopsy and open lung biopsy were diagnostic in 75%, 100% and 75% of cases, respectively.⁴⁸

HIV/AIDS-associated NHL demonstrates persistently elevated mortality despite HAART availability, likely related to NHL occurrence primarily at extremely advanced stages of HIV disease⁵¹. During the pre-HAART era, 80% of patients with HIV-associated NHL had advanced NHL (stage IV) at the time of diagnosis⁴⁸. In the pre-HAART era, less than 20% of persons with AIDS and non-CNS NHL survived two years; however since the introduction of HAART in 1996, two-year survival increased to 43% in these patients. Simultaneous diagnosis of non-CNS NHL and HIV appears to be associated with even better survival, likely due to the added benefit of HAART initiation³³. Though NHL rates have declined with HAART (along with overall mortality rates), the proportionate mortality due to NHL in the setting of HIV has not changed substantially^{8, 12, 52}. Treatment of NHL in HIV-infected patients has involved HAART along with administration of first line chemotherapy. In recent years, salvage high dose chemotherapy and autologous peripheral blood stem cell transplantation may also be an option for HIV-infected patients who were previously excluded from these therapies because of concern for toxicity and severe immunodeficiency⁵³.

Similar to KS, the occurrence of NHL in the period following HAART initiation has been described, although IRIS clearly is more common in relation to KS. The use of highly potent, newer HAART regimens in persons with profound immunosuppression may increase the likelihood of IRIS and NHL diagnosis⁵⁴. However, despite the risk for IRIS, HAART remains the most effective tool for reversing immune suppression and minimizing the likelihood of development of KS or NHL.

PRIMARY LUNG CANCER IN HIV

EPIDEMIOLOGY AND MECHANISMS

Below we summarize the current literature on HIV-associated lung cancer, highlighting how the epidemiological data can inform and complement mechanistic studies. As illustrated in Figure 2, as AIDS-defining cancers have declined with the advent of HAART, rates of non-AIDS defining cancers (NADC), of which lung cancer is the most common, have increased. In contrast to these data using all HIV-infected patients as the denominator, data from AIDS registries have demonstrated a substantially increasing burden of lung cancer among AIDS patients, although incidence rates appear to have stabilized or declined among this subset with an existing AIDS diagnosis (Figure 2, Panel C)⁵⁵.

HIV as an independent risk factor—The epidemiological data regarding the association of HIV with lung cancer has been recently reviewed⁹. Most epidemiologic studies report standardized incidence ratios (SIR) to compare the ratio of the observed incidence of lung cancer in clinic-based HIV-infected populations to the expected incidence in the general population⁵⁶. Depending on the population characteristics, SIRs for HIV range from 0.7 to 6.59 in the post-HAART era^{12, 18, 56–58}. In summary of these studies

(Table 1), only 1 of 22 studies reported a non-significantly decreased risk for lung cancer among HIV-infected patients compared to the general population (SIR 0.7). The remaining 21 studies all reported increased risk for lung cancer associated with HIV infection; 17 studies found a statistically significant association of HIV with lung cancer. Despite lung cancer being the most common NADC, individual studies were usually limited by small numbers of cases and the precision of the estimates was limited.

Whether HIV infection independently increases the risk of lung cancer has been debated extensively, largely because tobacco remains an important potential confounder of the HIV – lung cancer association. HIV-infected patients have substantially higher smoking prevalence with estimates ranging from 30–85% compared to the estimated 20–25% of the general population who are smokers⁹. Studies of HIV and lung cancer have therefore been challenged by the requirements of having large numbers of HIV-infected persons with individual smoking behavior data available, who are followed for prolonged periods to identify adequate lung cancer outcomes to contrast with an epidemiologically-appropriate comparison group (in contrast to simply comparing to the general population).

Several studies have had adequate design to address potential confounding of smoking (Table 2). Sigel and colleagues evaluated a cohort of demographically similar HIV-infected and uninfected patients from the Veterans Aging Cohort Study Virtual Cohort and Veterans Affairs Central Cancer Registry during the post-HAART era. HIV-infected patients were found to more likely be current smokers with a baseline history of drug abuse, alcohol abuse, HCV infection, and a history of bacterial pneumonia. After adjusting for age, gender, race/ethnicity, baseline COPD, bacterial pneumonia and smoking, they found HIV to be independently associated with lung cancer¹⁵. Among HIV-infected and uninfected injection drug users (IDUs) enrolled in the AIDS Link to the Intravenous Experience (ALIVE) Study in Baltimore, studies of lung cancer death and of incident lung cancer were performed. ALIVE has individual smoking behavior collected systematically rather than through medical records in identical fashion among HIV positive and negative IDUs. After adjusting for individual smoking and other risk factors, both studies demonstrated an independent association between HIV and lung cancer with an estimated 2–4-fold increased risk^{16, 58}. In contrast, Silverberg and colleagues reported a non-significantly increased risk for lung cancer among managed care patients with HIV compared to those without HIV after adjusting for current smoking status obtained through medical record review. Differences in these study findings could represent variability in the HIV risk groups (e.g., IDU, MSM), sociodemographic characteristics, HIV clinical status or smoking behavior of the study populations or in heterogeneity in the methods used for ascertaining smoking exposure. However, when considering all the studies, these data support the hypothesis that HIV infection plays an independent role in the increased risk for lung cancer, even after accounting for tobacco use⁹.

The role of immunosuppression—One proposed mechanism for the increased risk of lung cancer in this population is that persistent HIV-associated immunosuppression results in reduced immune surveillance and subsequent increased risk for malignancy. Epidemiological data in support of the role of immune suppression should demonstrate higher risk in persons with AIDS or advanced immunodeficiency as measured by current or nadir CD4 cell count. In data from the AIDS/Cancer Match study, a national linkage of HIV/AIDS and cancer registries, Engels and colleagues report SIRs of 4.7 (95% CI 3.0–6.9) during the post-AIDS diagnosis period compared to 2.3 (1.8–2.8) during the pre-AIDS diagnosis period. The SIRs during the pre-HAART and post-HAART time periods included in the study were equal at 2.6 (both statistically significant)¹². In further analysis from the AIDS/Cancer Match study, Frisch et al found lung cancer to be one of several non-AIDS-defining malignancies meeting all 3 of their criteria for potential association with

immunosuppression. While the authors raised concerns that potential methodological limitations and confounding by tobacco use could have influenced the findings, these data illustrate an increase in the relative risk of lung cancer with the progression of HIV to AIDS ¹¹. In a meta-analysis of NADC, Sheils et al also reported increased lung cancer among persons with AIDS ¹⁸.

At the time of lung cancer diagnosis, most HIV-infected patients have a CD4 count of >200cells/ μ L. Analysis of Parisian hospital records noted a median CD4 count of 364/mm³, while Shiels' prospective study found a median of 267 cells/mm³ ^{58–59}. Several studies have failed to demonstrate a strong association between lung cancer incidence in HIV-infected patients and CD4 count ^{16–17, 58}. In the post-HAART era, while a significantly elevated risk of lung cancer was observed as compared to the general population, incidence did not vary greatly by CD4 count ¹⁷. Engels et al. noted an inverse relationship between lung cancer incidence and HIV viral load, however no relationship was observed between lung cancer incidence and current or nadir CD4 count ⁵⁷. The ALIVE Study similarly uncovered no association between CD4 count or HIV RNA load with lung cancer mortality. The median CD4 count among HIV-infected patients with lung cancer was 260 cells/ μ L ¹⁶.

In contrast, several studies have found an association between lung cancer incidence and immunosuppression. In the Kaiser-Permanente managed care population database, the risk for lung cancer among HIV-infected patients was significant among HIV-patients with CD4 counts <200cells/ μ L, with a relative risk of 2.2 (95% CI, 1.3–3.6) compared to their non-HIV counterparts ⁶⁰. A small British study revealed no substantial change in the degree of immunosuppression between HIV-infected patients diagnosed with lung cancer in the pre- and post-HAART eras ⁶¹. In a meta-analysis including patients who were immunosuppressed either from HIV-infection or solid organ transplantation, rates of lung cancers were increased among both populations. Furthermore, among those with kidney failure, risk of lung cancer was much greater after transplantation compared to during dialysis, suggesting that immune suppression was distinctly associated with increased risk ⁶². A strong dose-response relationship was observed between increasing lung cancer risk and lower current CD4 cell counts in analysis of a large French hospital database.⁶³

Impact of HAART—Lastly, besides contributing to prolonged survival and the increased lung cancer risk associated with aging, HAART itself has been suggested to be directly oncogenic and potentially contributing to lung cancer in HIV-infected patients ⁶⁴. On the cellular level, zidovudine and didanosine have been shown to elicit mutagenic responses *in vitro*. Furthermore, zidovudine-didanosine coexposure potentiated AZT-DNA incorporation and mutagenic responses, but at concentrations 3–30 times peak plasma levels seen in patients. With the development of potent, less toxic antiretrovirals, exposure to these older medications is now relatively rare, except in resource-limited settings. It remains unclear if newer regimens have any direct mutagenic effects.

Genomic instability has been hypothesized to the increase risk of lung cancer in HIV. Microsatellite alterations, but not the loss of heterozygosity, were significantly increased in lung cancer tissue samples from HIV-infected patients compared to samples from HIV-indeterminant patients ⁶⁵. While genomic instability has been suggested as a potential mechanism in lung carcinogenesis, little is known about the putative molecular effects of these alterations.

Infections and chronic inflammation—Prior pulmonary infections have been associated with increased lung cancer risk in the general population, likely related to a chronic inflammatory process.^{66–68} Similarly, pulmonary infections have been theorized to increase the risk for lung cancer among HIV-infected patients ^{16, 69}. HIV-infected persons

are at substantially higher risk for bacterial pneumonia as well as *Pneumocystis*, mycobacterial, and viral respiratory infections. Risk for these infections appears to be further increased with immunodeficiency and with smoking. Repeated bacterial pneumonias have been associated with increased risk for lung cancer among HIV-infected persons with AIDS⁷⁰

Cancers known to be associated with HPV (anal, vaginal, penile, nasopharyngeal, laryngeal and oral) are increased in HIV-infected patients¹⁸. While HPV has been hypothesized to contribute to the increased incidence of lung cancer among HIV-infected patients, the data remain inconclusive. HPV detection in bronchial carcinoma is variable. Despite this, bronchial carcinoma induced by asbestos and radiation exposure has been studied via an HPV-18 immortalized bronchial cell line⁷¹.

CLINICAL PRESENTATION

The age at diagnosis of lung cancer has been consistently reported to be lower among HIV-infected patients compared to HIV-uninfected patients. In review of lung cancer diagnoses at Johns Hopkins Hospital from 1986–2004, HIV-infected patients were generally diagnosed between 40 and 60 years of age, rather than between 50 and 80 years of age in the HIV-indeterminate cohort. Demopoulos et al. similarly found a younger age of presentation of lung cancer in HIV-infected patients when reviewing the Cancer Registry files at Bellevue Hospital in New York. In this cohort, HIV-infected patients diagnosed with lung cancer presented at the age of 50, rather than 60⁷². In France from 1993 to 2002, the median age at diagnosis of lung cancer among HIV-infected patients was 45 years old compared to 63 years in the general population⁵⁹. Lastly, in a review of HIV-infected patients with lung cancer followed in a Baltimore clinic from 1989–2002, lung cancer incidence increased with age, however the SIR decreased with age, indicating that excess risk was greatest at younger ages⁵⁷.

However, several studies have noted that there are substantial differences in the age distribution of the HIV population compared to the general population^{72–73}. Shiels et al. adjusted for the underlying population structures (Figure 3, Panel A) and reevaluated differences in the observed age at cancer diagnosis for a variety of cancers among HIV-infected patients. They found that, for most cancers, the younger age distribution of the AIDS population compared to the general population accounted for the observed difference in age at diagnosis. For lung cancer (Figure 3, Panel B), the younger age of cancer diagnosis among HIV-infected patients persisted, though of a substantially smaller magnitude of 3–4 years rather than the previously described presentation at an age 10–20 years younger than the general population⁷⁴.

PATHOLOGY

Adenocarcinoma appears to be the most common pathologic type of lung cancer among HIV-infected patients, similar to the general population^{15, 17, 57, 73}. In contrast to these data, Hakimian et al focused on the post-HAART era in a single center retrospective analysis of 34 patients with lung cancer and HIV, where 30 (88%) were diagnosed with non-small cell lung cancer and 4 (12%) with small cell lung cancer; no adenocarcinoma cases were identified⁷⁵. In the general population, the majority of non-smokers who develop lung cancer are diagnosed with adenocarcinoma as opposed to squamous cell carcinoma, which is more commonly diagnosed among smokers. Thus, the consistently observed preponderance of adenocarcinoma among HIV-infected patients with lung cancer has led researchers to a question the relationship between tobacco use and lung cancer in these patients. However, it should be recognized that HIV-associated lung cancer has been reported almost exclusively among current or former smokers.

UNIQUE TREATMENT OUTCOMES AND CONCERNS IN HIV-LUNG CANCER

Disease Stage at Diagnosis and Survival

HIV-infected patients often present with an advanced stage of lung cancer (Table 3), although it remains unclear whether the disease stage is increased compared to HIV-uninfected lung cancer patients. In analysis of lung cancer cases in the Veterans Affairs system where similar access to care and screening patterns would be expected by HIV status, Sigel et al found that stage at diagnosis did not differ between HIV infected and uninfected patients in the post-HAART era¹⁵. However, substantial data indicate that HIV-infected lung cancer cases present at advanced disease stage. Chaturvedi's analysis of post-HAART era data indicated that >50% of HIV-infected patients diagnosed with lung cancer had distant disease at initial presentation, arguing against a strong contribution of increased surveillance in HIV positives to explain their higher cancer risk¹⁷. A French retrospective review found that >70% of patients presented with stage IIIB or stage IV disease⁵⁹. Hakimian et al. reported that 80% of NSCLC patients were diagnosed with stage IIIB/IV disease.⁷⁵ In the ALIVE study, the stage of disease at presentation was more advanced among HIV-infected compared to HIV-uninfected IDUs, each with relatively limited access to care⁵⁸. Similarly, in a large HIV-cancer registry match study from Texas, 337 HIV-infected lung cancer cases displayed more distant stage disease at presentation compared to the >156,000 HIV-uninfected lung cancer patients.⁷⁶

Following a lung cancer diagnosis, mortality appears to be higher in HIV-infected compared to uninfected patients. Conflicting evidence exists whether this simply represents more advanced disease stage at diagnosis or if there truly is lower survival with HIV. Reduced uptake, greater toxicity and more limited responses to cancer treatment have been proposed as potential mechanisms to explain poor survival in HIV-associated lung cancer. In several studies which reported clinical outcomes for HIV-associated lung cancer patients, presentation was generally advanced and survival times were dismal (Table 3). In a retrospective review of lung cancer diagnoses among HIV-infected patients at Johns Hopkins Hospital from 1986–2004, lung cancer survival was shorter among HIV-infected patients (median survival: 6.3 months vs. 9.4 months, $p=0.002$). However, after accounting for stage of cancer (HIV-infected patients: 87% stage IIIB/IV; 69% distant metastases compared to 68% and 47% in HIV-indeterminate patients, respectively), the differences in survival were attenuated⁷³. In a retrospective review of patients with HIV and lung cancer, the median survival of patients with stage IIIB or stage IV NSCLC was 5.2 months and was 7.2 months for the few patients with small cell lung cancer, all of whom had extensive disease⁷⁵. In the large study from Texas, HIV infection was associated with significantly higher lung cancer-specific mortality (hazard ratio 1.34, 95% CI, 1.15–1.56).⁷⁶ Among NSCLC patients in this study, HIV-infected patients were notably around 60% less likely to receive cancer treatment. In contrast, another large, population-based registry match study that linked cancer registry with Medicare data to ascertain HIV status among older NSCLC cancer patients (median age of 75 years for both HIV-uninfected and HIV-uninfected cases), no significant differences in survival were observed by HIV status.⁷⁷

Irrespective of how much HIV infection contributes to excess mortality in lung cancer compared to HIV-uninfected persons, mortality of persons with HIV and lung cancer appears to be primarily driven by lung cancer^{33, 78}. A French retrospective review of records at 2 hospitals from 1993–2002 found that 64% of patients did not respond to treatment with 86% of the patients dying from progressive lung cancer, rather than HIV-related complications or opportunistic infections. In this cohort, the median survival of patients with a $CD4 < 300/mm^3$ was 3 months, compared to 11 months among patients with a $CD4 \geq 300/mm^3$ ⁵⁹. ALIVE also found a high rate of mortality due to lung cancer with no

deaths due to AIDS and shorter survival time, approximately 0.39 years (IQR: 0.21–0.77), compared to HIV-uninfected lung cancer cases (0.72 years, IQR: 0.36–1.7) ⁵⁸.

Treatment of any type or stage of lung cancer among HIV-infected patients is generally the same as for non-HIV-infected patients, although several unique considerations should be evaluated prior to initiation of treatment. It is important to recognize that in the era of HAART, HIV status should not be a primary factor in the treatment decisions for lung cancer.^{77, 79} Currently, there are no HIV-specific guidelines for lung cancer treatment or for dose-adjustments of concurrently used anti-cancer and antiretroviral drugs.⁸⁰ Improved access to evidence-based, state-of-the-art cancer therapies for HIV-infected lung cancer patients should be a clinical priority.⁸¹

Prior to initiation of cancer treatment, functional status should be evaluated to help guide the timing and toxicity of the therapy to be administered. In patients with HIV, functional status assessment may assume even greater priority. If possible based on the clinical context, many clinicians would advocate for initiation of HAART to improve performance status prior to undergoing chemotherapy. In a retrospective review of a tumor registry at 2 Maryland hospitals, 20% of patients with HIV and lung cancer received these diagnoses concurrently ⁷⁵. While no guidelines currently exist for this scenario, HAART was usually started first.

Monitoring for venous thromboembolism (VTE) among HIV-associated lung cancer patients presents an equally unclear area. The increased incidence of VTE among lung cancer patients is well established, particularly related to chemotherapy, extensive cancer disease, and indwelling catheters ⁸². Substantial data also suggest that HIV-infected patients have heightened risk for VTE.^{83–84} Mechanisms remain unclear, but proposed VTE risk factors in the HIV setting include advanced HIV disease (e.g., elevated viral load, lower CD4 counts, history of opportunistic infections), injection drug use, and direct effects of antiretrovirals.^{85–89} Complicating assessment of VTE risk, HIV-infected patients often have antibodies to phospholipids, abnormal lipid profiles, and ART use ^{83, 88}. VTE prophylaxis is not currently recommended as part of routine care for HIV-infected lung cancer cases; further data is needed to clarify VTE risk and appropriate management in the setting of HIV and lung cancer.

PREVENTION

Smoking Cessation

In the current primary care guidelines for the management of HIV-infected persons by the HIV Medicine Association of the Infectious Diseases Society of America, screening for tobacco use is not explicitly recommended ⁹⁰. Smoking prevalence varies between different racial, socioeconomic, and HIV risk groups, but appears to range from 30–85%.⁹ In a cross-sectional survey of nearly 350 HIV-infected patients, 47% were current smokers and 63% were ever smokers; male gender, older age, lower educational attainment, and heavy alcohol or injection drug use were associated with being a smoker ⁹¹. In an urban IDU population, smoking was nearly ubiquitous although only moderate levels of nicotine dependence were observed; there were no substantial differences in smoking behavior (e.g., age at first smoking, pack-years, nicotine addiction) between HIV-infected compared to uninfected IDUs.⁹² Among nearly 900 HIV-infected VA patients, 63% were current smokers and 22% were former smokers. Current smokers complained of increased respiratory symptoms and reported decreased quality of life ⁹³. Among New York Medicaid patients with HIV, two-thirds were current smokers, smoking an average of 16 cigarettes/day for a mean of 23 years duration. Over 80% of the smokers with HIV were in the pre-contemplative or

contemplative stages of quitting, however nearly half of the patients (46%) expressed interested in accessing a free or low-cost smoking cessation program ⁹⁴.

Several other studies have indicated that smoking cessation is of substantial interest to HIV-infected patients; however, significant provider, insurance, financial and other barriers to utilizing evidence-based approaches to smoking cessation in HIV care persist. Further, it remains unclear whether smoking cessation programs need to be tailored to the specific needs of HIV-infected patients. Tobacco cessation should be promoted in any patient who is a smoker, however cessation is of critical importance among HIV-infected patients. In addition to tobacco-related complications common to all smokers (e.g., lung cancer, obstructive lung disease, atherosclerosis), tobacco use among HIV-infected patients is associated with increased risk for less common complications like oral candidiasis, hairy leukoplakia and bacterial pneumonia ^{93, 95–96}. These complications, along with lung cancer risk, should motivate both the patient and the primary care provider to address tobacco cessation as a priority. Smoking cessation behaviors and interventions are reviewed in further detail in the article “Tobacco use and cessation in HIV-infected individuals” by Browning et al. in this same issue of *Clinics in Chest Medicine*.

Lung Cancer Screening

IDSA guidelines for primary care do not recommend any routine screening for lung cancer. They do, however, recommend obtaining a baseline chest x-ray (CXR) in any patient with a history of positive TB screening test or with preexisting lung disease in case future abnormalities on imaging arise ⁹⁰. Findings from the National Lung Screening Trial (NLST) showed that low-dose computerized tomography (CT) scanning reduced mortality from lung cancer by 20% when compared to CXR screening among older, high-risk smokers ⁹⁷. While there is still much debate regarding the lung cancer risk posed by HIV infection, NLST recommendations for screening among older smokers may apply to HIV-infected patients as well, although the benefits and harms of screening may be different in HIV. Given the high burden of tobacco use and the concern for earlier onset of lung cancer among HIV-infected patients, growing discussions have focused on whether CT screening should be performed on HIV-infected smokers, although there exist no data in support of this approach. When considering CT imaging of the chest as part of malignancy screening in HIV-infected patients, clinicians will likely be faced with need for interpretation of an even greater number of ambiguous radiographic abnormalities. In a retrospective evaluation of 42 HIV-infected patients admitted to two Seattle hospitals between 1996 and 1998 with abnormal CXRs and an absence of pulmonary symptoms, Gold et al. found that the most frequent thoracic radiographic abnormalities were nodular disease (52%), followed by adenopathy (17%) and infiltrate (12%). The final diagnosis in these patients was most commonly tuberculosis (26%), nontuberculosis mycobacteria (24%), KS (12%), lymphoproliferative disorder (7%) and other neoplasia (6%). Nearly 40% of these diagnoses were obtained via bronchoscopy, suggesting that aggressive evaluation of radiographic abnormalities in HIV-infected patients was justified ⁹⁸. However, the role for invasive testing in the setting of CT screening is unknown. Besides pulmonary nodules, lymphadenopathy is also commonly found on thoracic imaging of HIV-infected patients. The differential diagnosis of lymphadenopathy is broad and the diagnostic approach (reviewed by Lichtenberger) may involve characterizing lymphadenopathy as low-attenuation (e.g., mycobacterial or fungal infection), or enhancing (e.g., multicentric Castleman disease, KS, or bacillary angiomatosis) ⁹⁹.

SUMMARY

HIV-associated lung malignancies contribute to substantial morbidity and mortality in the HIV-infected population. Immunosuppression is the primary risk factor for HIV/AIDS-

associated KS and NHL. Following widespread uptake of HAART, rates of KS and NHL have declined substantially. After HAART initiation, IRIS, especially in pulmonary KS, has been associated with serious clinical consequences and death. However, effective HAART remains the best strategy to lower risk for KS or NHL. Concurrent with declines in KS and NHL, non-AIDS defining cancers, of which lung cancer is the most common, have increased in incidence and importance. HIV-associated lung cancer occurs almost exclusively among smokers and generally those with significant immune deficiency. Compared to HIV-uninfected populations, the onset of lung cancer in HIV-infected individuals occurs 3–4 years earlier, generally with advanced cancer stage at diagnosis, and worse survival. Adenocarcinoma is the most frequent histological type. Despite the high smoking prevalence in HIV populations, HIV appears to increase lung cancer risk independent of smoking, though the underlying mechanisms remain unclear. Smoking cessation needs to assume greater priority in HIV primary care.

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Key Points

- Rates of KS and NHL have reduced substantially following widespread uptake of HAART, but still represent a substantial disease burden with significant mortality
- Immune reconstitution inflammatory syndrome (IRIS) infrequently occurs in KS and NHL following HAART initiation with serious clinical consequences, especially in pulmonary KS. However, HAART remains the best strategy to lower risk for KS or NHL
- Lung cancer represents the most common non-AIDS defining cancer, presenting at advanced stages with substantial mortality
- HIV appears to increase lung cancer risk independent of smoking, though the underlying mechanisms remain to be elucidated
- The prevalence of smoking among HIV-infected persons is extremely high; smoking cessation needs to assume greater priority in HIV primary care

Figure 1. Trends in cancer incidence among people living with AIDS in the United States during 1991–2005 (Adapted from Shiels et al, JNCI 2011)

Estimated counts (i.e., number of cancers) and standardized incidence rates of Kaposi sarcoma (A), non-Hodgkin lymphoma (B), and lung cancer (C). **Bars** depict the estimated counts and **points connected by lines** depict the incidence rates standardized to the 2000 US AIDS population by age group, race and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided P values were calculated using the χ^2 test.

Figure 2. Cancer incidence rates by time periods of HAART availability (Adapted from Crum-Cianflone, *AIDS* 2009)

Abbreviations: ADC; AIDS-defining cancer; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; NADC, non- AIDS-defining cancer.

(A)

(B)

Figure 3. Age at cancer diagnosis among persons with AIDS and the general population in the United States, 1996–2007 (Adapted from Shiels, *Ann Int Med* 2010)

Panel A displays the younger, more restricted age distribution of the AIDS population compared to the general population. These differences in population structure contribute to the observed younger ages of cancer diagnosis reported among persons with AIDS. To illustrate this with lung cancer, Panel B displays the younger observed age distribution of lung cancer cases in persons with AIDS (solid line) compared to the general population (dotted line). However, after standardizing the age of the general population to that of the

AIDS population, the expected age distribution in the general population (dashed line) is more similar to the AIDS population.

Table 1

Studies of lung cancer risk associated with HIV infection

Studies are listed chronologically by publication date and grouped by study design of an HIV/AIDS and cancer registry linkage or of a cohort or administrative database design. Estimates of risk for lung cancer associated with HIV are presented compared to the lung cancer cases that would have been expected in the general population with similar age and demographic characteristics. Adjustment for individual tobacco use was not possible in these studies.

Study	Publication Yr	Study Population	Yrs of Study	N HIV+ in f/u	N HIV+ LC cases	SIR (95% CI)
<i>HIV/AIDS registry linkage studies:</i>						
Parker et al [*] [100]	1998	Texas	1990–1995	26,181	36	6.5 (4.9–8.9)
Gulich et al [*] [101]	1999	NSW, Australia	1980–1993	3,616	6	3.8 (1.4–8.3)
Cooksley et al [102]	1999	Harris Co., Texas	1975–1994	14,986	18	0.7 (0.4–1.1)
Frisch et al [*] [103]	2001	U.S.	1978–1996	302,834	808	4.5 (4.2–4.8)
Gulich et al [104]	2002	Australia	1980–1999	13,067	17	1.4 (0.8–2.3)
Allardice et al [105]	2003	Scotland	1981–1996	2,574	5	4.1 (1.3–9.5)
Dal Maso et al [*] [106]	2003	Italy	1985–1998	12,104	22	2.4 (1.5–3.7)
Newnham et al [107]	2005	England	1985–2001	33,190	38	2.2 (1.6–3.1)
Engels et al [*] [10]	2006	U.S.	1980–2002	375,933	393	2.6 (2.1–3.1)
Mbulaiteye et al [108]	2006	Uganda	1989–2002	12,607	4	5.0 (1.0–15)
Galceran et al [*] [109]	2007	Catalonia, Spain	1981–1999	1,659	4	9.4 (2.4–24)
Dal Maso et al [*] [110]	2009	Italy	1986–2005	21,951	42	4.1 (2.9–5.5)
Polesel et al [*] [111]	2010	Italy	1986–2004	21,951	59	1.8 (1.0–3.2)
<i>Cohort / database studies:</i>						
Serraino et al [112]	2000	France, Italy	1982–1998	5,281	4	2.9 (0.7–7.4)
Phelps et al [113]	2001	Multi-site US	1993–2000	1,310	4	6.4 (3.7–11)
Herida et al [114]	2003	France	1992–1999	77,025	99	2.1 (1.7–2.7)
Bower et al [61]	2003	London HIV clinic	1986–2001	8,400	11	8.9 (4.9–20)
Clifford et al [115]	2005	Switzerland	1985–2003	7,304	14	3.2 (1.7–5.4)
Engels et al [57]	2006	Baltimore HIV clinic	1989–2003	5,238	33	2.5 (1.6–3.5)
Serraino et al [117]	2007	France, Italy	1985–2005	8,074	14	1.7 (0.9–2.8)
Patel et al [118]	2008	Multi-site US	1992–2003	54,780	140	3.3 (2.8–3.9)

Study	Publication Yr	Study Population	Yrs of Study	N HIV+ in f/u	N HIV+ LC cases	SIR (95% CI)
Levine et al[119]	2010	Multi-site US	1994–2004	2,651	12	3.3 (1.7–5.7)
<i>Meta-analyses:</i>						
Gulich et al[62]	2007	Multi-site	Varied	444,172	1016	2.7 (1.9–3.9)
Shiels et al[18]	2009	Multi-site	Varied	625,716	847	2.6 (2.1–3.1)

(Adapted from Kirk et al, PATS 2011).

Abbreviations: f/u, follow-up; LC, lung cancer; NSW, New South Wales; ; SIR, standardized incidence ratio; CI, confidence interval.

* Studies included only persons with AIDS diagnoses.

Table 2

Studies of lung cancer risk associated with HIV infection compared to an HIV- uninfected control group with adjustment for individual smoking exposure.

Study	Publication Yr	Population	Yrs of Study	N HIV+ in f/u	N HIV+ LC Cases	N HIV- in f/u	N HIV- LC Cases	IRR (95% CI)
Phelps et al [113]	2001	Multi-site US	1993–2000	871	4	439	1	3.3
Kirk et al [16]	2007	Baltimore IDUs	1988–2005	1,192	14	894	13	3.8 (1.6–7.9)
Shiels et al [58]	2010	Baltimore IDUs	1988–2006	1,072	13	1,423	16	2.3 (1.1–5.1)
Silverberg et al [60]	2011	California HMO patients	1996–2008	20,775	56	215,158	380	1.2 (0.9–1.6)
Sigel et al [115]	2012	U.S. Veterans	1997–2008	37,294	457	75,750	614	1.7 (1.5–1.9)

(Adapted from Kirk et al, PATS 2011).

Abbreviations: f/u, follow-up; LC, lung cancer; IRR, incidence rate ratio; CI, confidence interval; IDU, intravenous drug user; HMO, health maintenance organization.

Table 3

Overview of studies describing clinical outcomes in HIV-associated lung cancer patients

Study	Bower [61]	Brock [73]	Hakimian [75]	Shiels [58]	Siged [15]
Number of Cases	11	92	34	13	457
Type of Cohort	Hospital database (UK)	Hospital database (USA)	2 Hospital databases (USA)	IDU cohort linked to cancer registry (USA)	Veterans cohort linked to cancer registry (USA)
Years of study	1986–2001	1986–2004	1996–2003	1988–2006	1997–2008
Survival (months)	4–5 (range 2–15+)	6.3 (2.3–11.4)	8.2 (no IQR)	4.7 (2.5–9.2)	--
Age at cancer diagnosis	45*	46 (42–53)	44 (34–77)	46	51
Stage at diagnosis	4	4	4 or extensive	Distant	~70% III/IV
CD4 count at cancer diagnosis	160	305 (82–428)	> 200	267 (199–437)	286 (139–448)
Histology	Adeno 45%, Squamous 36%	Adeno 48% Squamous 10%	NSCLC 88% Squamous 12%	Adeno 8% Squamous 42%	Adeno 36% Squamous 30% Small Cell 11%
Survival (months)	4–5 (range 2–15+)	6.3 (2.3–11.4)	8.2	4.7 (2.5–9.2)	--

Abbreviations: IDU, injection drug user; Adeno, adenocarcinoma; squamous, squamous cell cancer; NSCLC, non-small cell lung cancer.

Data presented represent the median values (IQR: Interquartile range), unless otherwise indicated;

* Mean