Lung Malignancies in HIV Infection

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Abstract

Pulmonary malignancies are a major source of morbidity and mortality in HIV-infected persons. Non-AIDS defining lung cancers (mostly non-small cell lung cancers) are now a leading cause of cancer death. HIV-associated factors appear to affect the risk of lung cancer and may adversely impact cancer treatment and outcomes. HIV infection also may modify the potential harms and benefits of lung cancer screening with computed tomography. AIDS-defining lung malignancies include pulmonary Kaposi sarcoma and pulmonary lymphoma, both of which are less prevalent with widespread adoption of antiretroviral therapy.

Key Words (MeSH terms)

HIV; Lung neoplasms; Carcinoma, non-small cell lung; AIDS-related Kaposi sarcoma; Lymphoma, Non-Hodgkin

Overview

Malignancies of the lung are a major source of morbidity and mortality in persons with HIV infection.[1] In the pre-antiretroviral (ART) era, AIDS-defining cancers (ADCs) were prominent, and pulmonary involvement of Kaposi Sarcoma (KS) and non-Hodgkin lymphoma (NHL) were the most common lung tumors from this group.[2,3] As AIDS-related morbidity and mortality have declined with widespread ART use, non-AIDS-defining cancers (NADCs) have become a leading cause of death in HIV-infected persons. Lung malignancies, particularly non-small cell lung cancer (NSCLC), are now a major source of disease in HIV-infected persons. Recent estimates have also suggested that lung cancer is the leading cause of cancer death among HIV-infected persons, similar to the general population. This review will provide an update summarizing the existing epidemiologic and clinical literature regarding NADC lung cancers and ADCs that affect the lung.

Non-AIDS Defining Cancers of the Lung

NADCs of the lung are mostly comprised of non-small cell lung cancer (NSCLC), followed by small cell lung cancer (SCLC). Some epidemiologic studies of lung cancer in HIV-

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infected persons also include less common lung cancer morphologies such as lung sarcomas and neuroendocrine tumors in this group.

Epidemiology of Lung Cancer in HIV

Lung Cancer Incidence: Lung cancer incidence estimates from the pre-ART era were significantly elevated compared to expected rates in the general population despite marked competing risks of AIDS-related mortality.[4] The incidence of lung cancer in HIV-infected persons in the ART era still appears to exceed general population rates, with estimates ranging from 80–170 cases per 100,000 person-years.[5,6] Nearly all studies of lung cancer risk in HIV-infected persons have found increased risk compared to uninfected persons, with relative risks ranging from 2.2 to 4.7.[5,7–10] Several studies accounting for factors potentially confounding the observed increased risk of lung cancer in HIV-infected persons have found an independent relationship between HIV infection and increased lung cancer incidence.[8,10,11] It is unclear if lung cancer rates are increasing among HIV-infected persons. Studies of lung cancer incidence trends in HIV-infected persons during the ART era have shown conflicting results; some have demonstrated continued increases in incidence, [12] others a flat trend.[5,6]

Lung Cancer Risk Factors in HIV

Established Risk Factors: Established lung cancer risk factors such as age and tobacco smoking are important lung cancer risk factors in HIV-infected persons. Several studies have suggested that lung cancer may develop in HIV-infected persons at earlier ages than in uninfected persons.[8,11] Individuals with HIV have greater smoking prevalence than uninfected persons, and therefore smoking is an important risk factor and a source of some of the excess lung cancer seen in this group.[8,13–15] There are limited data regarding differential effects of smoking exposure on lung cancer risk in HIV-infected persons; however in one study, HIV-infected persons developed lung cancer with fewer pack-years of cigarette smoking compared to uninfected persons.[10]

Chronic obstructive pulmonary disease (COPD) is an independent lung cancer risk factor in uninfected persons[16,17] and also appears to be an independent risk factor in HIV-infected persons as well.[11] HIV-infected persons are at greater risk of developing COPD compared to uninfected persons.[18] The increased risk may be due to increased cigarette smoking, [13] propensity for lung inflammation due to unregulated or overactive CD8 activity[19,20] (as COPD severity is directly correlated to the degree of CD8 infiltration in the lungs),[21] or the damaging effects of recurrent or chronic lung infections.[22–24] There are no data regarding differences in COPD as a lung cancer risk factor for HIV-infected persons versus uninfected persons, but pro-inflammatory markers of monocyte activation (sCD14) are higher in HIV-infected COPD patients compared to uninfected COPD patients. [25] Increased sCD14 has also been found in HIV-infected individuals with lung nodules [26] COPD may therefore represent a more intense "inflammatory" state in HIV-infected persons, which may have implications for lung cancer risk, but these potential associations require further study.

Lung Infections: The inflammatory response to serious lung infections, such as bacterial pneumonia, has been proposed as a potential stimulus for lung cancer.[27] In epidemiologic studies of uninfected persons, prior lung disease and infections, particularly bacterial pneumonia and tuberculosis, have been associated with risk for subsequent lung cancer.[28–32] As these pulmonary infections are increased in HIV infection,[18] they may result in recurrent inflammatory injury contributing to the causal pathways responsible for the excess lung cancer risk observed in HIV-infected persons.[33] Furthermore, inflammatory damage from lung infections may be more prominent in the setting of HIV as dysfunctional immune activation may lead to a more deleterious inflammatory reponse.[34,35] Previous studies have linked prior pneumonia episodes to increased subsequent risk of lung cancer in HIV-infected persons.[33,36] Chronic colonization with *Pneumocystis jirovecii* has been associated with the development of COPD in both HIV-infected humans as well as in simian immunodeficiency virus primate models, also demonstrating a potential link between lung infections and a lung cancer precursor state.[37]

Immunosuppression: Increased overall risk of NADC has been associated with HIV-related immunosuppression as measured by CD4 count.[38,39] Studies investigating lung cancer risk and severity of HIV-related immunosuppression, however, have shown mixed results. Several analyses have found an association between lung cancer incidence and increased immunosuppression[40–42], while others have found no relationship.[5,8,9,14,43] Longitudinal studies using time-updated CD4 count data from larger, ART-era cohort studies such as the French Hospital Database on HIV cohort and the Veterans Aging Cohort Study (VACS) have demonstrated associations between low CD4 counts and increased lung cancer after adjustment for potential confounders.[44,45]

ART Toxicity: There are studies supporting theoretical associations between ART and cancer risk. Azidothymidine (AZT) and 3TC (lamivudine) have been shown to have mutagenic effects in animal models[46] and evidence of genotoxicity has been demonstrated in neonates exposed to AZT and tenofovir *in utero*.[47,48] There is no direct evidence of increased lung cancer risk (or any other type of cancer) associated with these drugs in humans, however. The relationship between protease inhibitor (PI) use and lung cancer risk in HIV-infected smokers has also been evaluated, as PI-mediated cytochrome P450 inhibition may enhance the carcinogenicity of tobacco-related metabolites, but a large case control study found no increase in lung cancer risk associated with this drug class.[49]

Inflammation: Pro-inflammatory states and subsequent chronic inflammation have been associated with lung cancer in uninfected persons.[27] HIV is associated with an increased prevalence of numerous pro-inflammatory processes including abnormal immune activation, diabetes and metabolic syndromes, and chronic infections.[50,51] Chronic HIV infection is also associated with a process termed "inflammaging" where chronic inflammation has been linked to an increase in diseases associated with aging.[51] Limited data exist linking evidence of HIV-related chronic inflammation and lung cancer risk; however, one prospective study of more than 5,000 HIV-infected individuals with baseline biomarker data found an association between elevated baseline interleukin (IL)-6 (an inflammatory cytokine) and subsequent lung cancer incidence.[52]

Oncoviruses: *In vitro* data have suggested oncogenic potential for HIV-related proteins Tat[53] and Gag p17[54], however a recent investigation using an HIV transgenic mouse model failed to find an association between HIV proteins and lung cancer risk.[55] Other malignancies that are found at higher than expected rates in HIV-infected persons have been associated with viral co-factors, such as squamous cell carcinoma of the anus (with human papilloma virus) and hepatocellular carcinoma (with hepatitis B and C viruses), but no viral co-factor has been identified to explain the excess of lung cancer in HIV-infected persons. In uninfected persons, epidemiologic data have implicated viral co-infections such as human papilloma virus with increased lung cancer risk, especially in non-smokers, but these associations are controversial.[56,57]

Clinical Characteristics of Lung Cancer in HIV

Cancer Stage and Morphology at Diagnosis: Pre-ART lung cancer series found that HIV-infected patients were more likely to present with advanced stage disease[9,58] and with more frequent adenocarcinomatous histologic subtypes than expected.[59] Larger ART-era studies have generally found that HIV-infected patients with lung cancer appear to have a similar stage at diagnosis and tumor morphologic distribution compared to uninfected patients.[11,60,61]

Molecular characteristics: There are limited data regarding unique molecular characteristics of lung cancer in HIV-infected persons. A study of cancer DNA including a small number of tumors from the pre-ART era found that lung cancers from HIV-infected patients were more likely to demonstrate microsatellite instability.[62] Studies evaluating the prevalence of clinically relevant oncogenic mutations have not found any differences in the occurrence of epidermal growth factor receptor mutations, *KRAS* (Kristen rat sarcoma), or *ALK* (anaplastic lymphoma kinase) rearrangements in NSCLCs from HIV-infected patients compared to uninfected patients.[63,64]

Lung cancer outcomes in HIV-infected patients—As with uninfected persons, the majority of HIV-infected patients with lung cancer are diagnosed at advanced stages.[11] Advanced lung cancer in uninfected persons carries a poor prognosis, with 5-year survival rates less than 15%.[65] HIV-infected individuals may have an even worse prognosis. Studies from the pre-ART era reported very poor survival rates (less than 10% 5-year survival) in HIV-infected lung cancer patients.[66,67] Studies from the ART era have shown improvements in lung cancer outcomes for HIV-infected persons, but survival still appears to lag compared to uninfected persons. Hakimian et al reported outcomes for 34 lung cancer patients from the early ART era and found survival rates that appeared to be worse than expected. Two larger studies utilizing population-based data found that lung cancer-specific survival was worse for HIV-infected lung cancer patients even after adjustment for potential confounding factors such as cancer treatment and competing risks of death.[61,68]

Worse lung cancer survival in HIV-infected patients in ART era studies has been explained by several factors including cancer treatment disparities, more aggressive tumor behavior in the setting of HIV, and worse overall survival due to AIDS or HIV-related complications. Of these factors, aggressive tumor behavior in the setting of HIV infection is the most difficult

to prove, but is an intriguing and plausible explanation. An interaction between the immune system and cancer is suggested by accelerated progression of other diverse NADCs in HIV-infected patients including hepatocellular carcinoma, melanoma, and Hodgkin's lymphoma[69–71], though it is remains unclear whether lung cancer is truly more aggressive in the setting of HIV-related immunosuppression.

Lung cancer treatment in HIV-infected patients—Disparities in lung cancer treatment in HIV-infected patients compared to uninfected patients may be partly due to real or perceived treatment intolerance in this population. A study of post-operative outcomes for NSCLC treatment found that HIV-infected patients had increased perioperative complications and increased frequency of disease progression after surgical resection (Table 1).[72] A study of chemotherapy toxicity in HIV-infected patients found that patients on protease inhibitors were significantly more likely to experience grade 4 hematologic complications.[73] Harms and benefits associated with lung cancer treatment in HIV-infected persons may differ from uninfected persons; however, there are currently no guidelines specific to the management of lung cancer in HIV-infected persons. There are also no HIV-specific data regarding quality of life for lung cancer patients with HIV. Further research is needed in these areas to improve the quality of lung cancer care for HIV-infected persons.

Lung Cancer Prevention and Screening

Smoking Prevalence and Cessation: Tobacco smoking is responsible for much of the lung cancer risk in the HIV-infected population, and rates of smoking exceed those in uninfected persons.[13,74] Smoking cessation should be emphasized as an important measure for lung cancer prevention in high-risk HIV-infected persons. Several different strategies for supporting smoking cessation, including nicotine replacement, pharmacotherapy, and internet-based tobacco treatment have demonstrated efficacy and safety in the HIV-infected population.[75–77]

Computed Tomography Screening: The National Lung Cancer Screening Trial (NLST) demonstrated a lung cancer mortality benefit associated with computed tomographic (CT) screening in uninfected smokers (former and current smokers, more than 55 years of age, with at least 30 pack-years of smoking exposure). The NLST protocol used a baseline screening low dose CT scan (LDCT) and two annual follow-up scans and was stopped early because of the benefit of this regimen. As a result, the National Comprehensive Cancer Network and other national organizations have published guidelines recommending LDCT screening in patients meeting NLST inclusion criteria[78–80] and screening coverage has been adopted by private health insurers and Medicare.

The harms and benefits of lung cancer screening in HIV-infected persons are still unclear. Although there is an increased burden of lung cancer in HIV-infected smokers compared to uninfected smokers, there may be factors that limit the benefits or increase the harms associated with screening in this population. First, although there have been major life expectancy gains in HIV-infected persons associated with ART use, survival still is less than uninfected persons for some groups of HIV-infected persons,[81] which may diminish the

benefits of lung cancer screening. Second, clinical evaluation of false positive lung cancer screens may lead to a number of harms including unnecessary procedures (needle biopsies, surgical resections, imaging procedures, or bronchoscopies) with potential complications and mortality.[82] The risks of these adverse events may be increased in HIV-infected persons as abnormal findings are more common on chest imaging due to prior pulmonary infections and higher rates of granulomatous lung disease.[83,84] Furthermore, clinicians caring for HIV-infected patients may be aware of the higher risk of lung cancer and other malignant and non-malignant lung diseases and as a consequence may be more likely to aggressively evaluate abnormal imaging findings.[85] Moreover, the morbidity associated with diagnostic tests for lung nodules may be higher in HIV-infected patients.[72] The rate of false-positive screens and their subsequent clinical consequences is one of the most important factors in determining the cost-effectiveness of lung cancer screening.[86,87] Other factors that may affect the harms and benefits of lung cancer screening in HIV-infected persons include more potentially more aggressive lung cancer behavior[61] and modification of smoking behavior in the setting of lung cancer screening.[88]

To address these issues, several studies have reported the results of lung cancer screening in HIV-infected cohorts or have analyzed the results of chest CTs performed in asymptomatic HIV-infected persons (Table 2). Two studies reported the results of research chest CTs from cohorts of HIV-infected persons at elevated risk of lung disease. Both studies reported rates of baseline suspicious nodules that were not elevated compared to rates from the NLST. [89,90] The results of the first lung cancer screening trial conducted in 224 HIV-infected persons were reported by Hulbert et al; screening revealed a low proportion of lung cancers (0.4%) but also a low rate of screen positivity, likely due to the younger age and lesser smoking quantity in the cohort.[91] In contrast, a large lung cancer screening study of HIV-infected smokers from France found a greater number of lung cancers in an older group with a history of severe immunosuppression.[92]

Antiretroviral Therapy: There are limited data regarding ART use as a preventive measure to decrease lung cancer risk. The French Hospital Database cohort compared HIV-infected individuals with CD4 cell recovery to >500 cells/mm^3 after ART initiation to those with slower CD4 recoveries and found a lower risk of lung cancer with recovery to >500 cells/mm^3.[44]

AIDS-Defining Cancers of the Lung

Pulmonary Kaposi Sarcoma—Kaposi sarcoma (KS) is an ADC that can occur in the lung, but is rarely confined to the lung. The development of KS is associated with the presence of Human Herpes Virus-8 (HHV-8) co-infection.[93,94] KS is not a true sarcoma; it is thought to originate from lymphatic endothelial cells.

Epidemiology and Risk Factors for Pulmonary Kaposi Sarcoma: KS was the most common tumor in HIV-infected persons during the pre-ART era with an incidence of 1500–2500 cases per 100,000 person-years.[93,95] Incidence has declined significantly to <500 cases per 100,000 person-years with the adoption of ART.[95] The Westminster HIV cohort described the pulmonary KS cases from their cohort in the early ART era; 8% of the 305 KS

cases during this period had pulmonary involvement.[96] Patients with pulmonary KS had lower CD4 cell counts and were more likely to be of African origin. Other studies have suggested that pulmonary KS is more likely to present in patients with extensive cutaneous disease, although 15% of patients with pulmonary KS have no mucocutaneous involvement. [97] KS may also present in patients as part of the immune reconstitution inflammatory syndrome (IRIS). IRIS-associated KS flares have been reported with pulmonary involvement.[98] Of note, increasing recognition of KS cases emerging in patients with viral suppression and/or higher CD4 counts has occurred. These KS cases suggest that aging, virally suppressed HIV-infected patients may continue to be at risk for KS.[99] KS lesions are associated with significant local inflammation,[100] and preceding systemic inflammation may also be associated with KS risk.[101] Systemic IL-6 levels (a pro-inflammatory cytokine) may be associated with subsequent KS risk in HIV-infected patients[102] and HIV-infected patients with HHV-8 infection have higher markers of systemic inflammation.[103]

Clinical Presentation, Treatment and Outcomes: Patients with pulmonary KS are often symptomatic and present with dyspnea, cough and sometimes fever.[97] Patients will typically have evidence of KS at other sites (skin, mucous membranes). Radiographically, pulmonary KS most frequently manifests as multiple nodules, also potentially with bronchial wall thickening, and less frequently with bilateral pleural effusions.[104] Characteristic "flame-shaped" infiltrates have also been described on lung CT images from patients with pulmonary KS.[105] The bronchoscopic appearance of pulmonary KS is similar to the appearance at other sites; the lesions are red or purple macules that often appear at airway bifurcations.[106]

Use of ART is a key component of the treatment of KS in HIV-infected patients[107]; lesion regression is noted in patients on ART. Use of chemotherapy should be considered for patients with severe or progressive KS (which would likely include patients with pulmonary KS). A recent Cochrane review (summarizing the results of six randomized trials and three observational studies) concluded that chemotherapy is beneficial in HIV-infected KS patients and that there was no clear difference in outcomes with liposomal doxorubicin, liposomal daunorubicin or paclitaxel.[108] Pulmonary KS is a severe manifestation of KS disease and has been associated with poor outcomes despite treatment. Median survival estimates from the ART-era in the Westminster HIV cohort were 19 months.[96]

Pulmonary Lymphoma—Non-Hodgkin lymphoma (NHL) was a leading ADC in the pre-ART era that has decreased in incidence during the ART era, but is still a prominent source of morbidity in HIV-infected persons.[4] NHL is seen in the lungs of HIV-infected patients as a secondary entity (an extension of NHL originating outside the lungs) or as an uncommon form, primary pulmonary NHL.[109] Primary pulmonary NHL is defined as lymphomatous parenchymal involvement exclusive to pulmonary sites noted at diagnosis and/or during the following 3 months.[110] Whereas most primary pulmonary lymphomas in uninfected persons tend to be low-grade B-cell lymphomas, HIV-infected persons are at greater risk for high grade B-cell lymphomas of the lung, and thus poorer outcomes. [111,112]

Epidemiology and Risk Factors: Primary pulmonary lymphoma is rare in both immunocompetent and HIV-infected persons and incidence rates specifically in persons infected with HIV are not known. NHL of all sites was a leading ADC in the pre-ART era with an incidence rate of 1066 cases per 100,000 person-years.[113] In the ART era this rate has declined significantly, much like KS, to 390 cases per 100,000 person-years.[113] Epstein Barr Virus (EBV) infection has an established role in HIV-infected patients diagnosed with NHL, as latent EBV infection of tumor cells has been persistently demonstrated in case series.[109,114] Several HIV-associated processes have also been linked to increased risk of NHL including: 1) immunosuppression (i.e. low CD4 count), [113] 2) evidence of increased gut microbial translocation as measured by lipopolysaccharide levels, and 3) increased levels of the proinflammatory markers, such as sCD14, released by both hepatocytes and peripheral macrophages in response to LPS exposure.[115] Interestingly, HIV-infected patients with the CCR5-32 deletion tend to have a both favorable prognosis with respect to HIV infection and reduced risk to develop lymphomas.[116,117]

Clinical Presentation, Treatment and Outcomes: Although primary pulmonary NHL is often asymptomatic in uninfected persons[111], persons with HIV infection may present with cough, dyspnea and B-symptoms. Lung CTs of HIV-infected patients with primary pulmonary lymphoma have typically shown multiple peripheral nodules, tending towards the lung bases.[110] It is also notable that in one published series of seven cases, there was no hilar or mediastinal adenopathy reported.[110]

In the pre-ART era NHL was associated with worse outcomes in HIV-infected compared to uninfected persons, but ART appears to have decreased both NHL incidence and improved treatment outcomes to levels comparable to uninfected persons.[97,118–120] The use of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab (R-CHOP), in addition to etoposide (EPOCH-R), is standard of care for NHL in non-immunosuppressed patients. The recombinant anti-CD20 antibody rituximab has improved survival for CD20-positive lymphomas in uninfected patients, but use in HIV-infected NHL patients has been somewhat controversial because of concerns over excessive toxicity. Several prospective studies have evaluated rituximab use in HIV-infected persons with B-cell lymphoma. These studies found no signs of excess toxicity, even in patients with low CD4 counts[121,122] although a phase III trial comparing CHOP to R-CHOP did find a significant increase in death due to infection in the rituximab arm.[123] The phase III trial also did not find any improvement in treatment outcomes associated with rituximab use. Nonetheless, efficacy of chemotherapy in the ART-era for HIV-infected patients with NHL appears to be broadly similar to uninfected patients: in results pooled from three phase II trials using rituximab plus infusional CDE (cyclophosphamide, doxorubicin, etoposide) in 74 patients with AIDS-related lymphoma, complete remission was demonstrated in over two thirds of patients, with overall survival of 64 percent.[124]

There are very limited data to evaluate survival specific to primary pulmonary lymphoma, and larger series suggest similar outcomes to other types of NHL.[125] Overall survival rates from the ART-era in HIV-infected patients with NHL range from 56% to 67%.[121,126]

References

1. Hakimian R, Fang H, Thomas L, et al. Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. J Thorac Oncol. 2007; 2:268–272. [PubMed: 17409796]

2. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS. 2006; 20:1645–1654. [PubMed: 16868446]

3. Levine AM. Non-Hodgkin's lymphomas and other malignancies in the acquired immune deficiency syndrome. Semin Oncol. 1987; 14:34–39.

4. Shiels MS, Cole SR, Kirk GD, et al. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009; 52:611–622. [PubMed: 19770804]

5. Engels EA, Brock MV, Chen J, et al. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol. 2006; 24:1383–1388. [PubMed: 16549832]

6. Worm SW, Bower M, Reiss P, et al. Non-AIDS defining cancers in the D:A:D Study--time trends and predictors of survival: a cohort study. BMC Infect Dis. 2013; 13:471. [PubMed: 24106926]

7. Phelps RM, Smith DK, Heilig CM, et al. Cancer incidence in women with or at risk for HIV. Int J Cancer. 2001; 94:753–757. [PubMed: 11745473]

8. Kirk GD, Merlo C, POD, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis. 2007; 45:103–110. [PubMed: 17554710]

9. Chaturvedi AK, Pfeiffer RM, Chang L, et al. Elevated risk of lung cancer among people with AIDS. AIDS. 2007; 21:207–213. [PubMed: 17197812]

10. Shiels MS, Cole SR, Mehta SH, et al. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. J Acquir Immune Defic Syndr. 2010; 55:510–515. [PubMed: 20838223]

11. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. AIDS. 2012; 26:1017–1025. [PubMed: 22382152]

12. Hessol NA, Seaberg EC, Preston-Martin S, et al. Cancer risk among participants in the women's interagency HIV study. J Acquir Immune Defic Syndr. 2004; 36:978–985. [PubMed: 15220706]

13. Crothers K, Goulet JL, Rodriguez-Barradas MC, et al. Impact of cigarette smoking on mortality in HIV-positive and HIV-negative veterans. AIDS Educ Prev. 2009; 21:40–53. [PubMed: 19537953]

14. Clifford GM, Lise M, Franceschi S, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J Cancer. 2012; 106:447–452. [PubMed: 22240797]

15. Lifson AR, Neuhaus J, Arribas JR, et al. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. Am J Public Health. 2010; 100:1896–1903. [PubMed: 20724677]

16. Koshiol J, Rotunno M, Consonni D, et al. Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. PLoS One. 2009; 4:e7380. [PubMed: 19812684]

17. Agusti A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One. 2012; 7:e37483. [PubMed: 22624038]

18. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit Care Med. 2011; 183:388–395. [PubMed: 20851926]

19. Diaz PT, King MA, Pacht ER, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. Ann Intern Med. 2000; 132:369–372. [PubMed: 10691587]

20. Twigg HL, Soliman DM, Day RB, et al. Lymphocytic alveolitis, bronchoalveolar lavage viral load, and outcome in human immunodeficiency virus infection. Am J Respir Crit Care Med. 1999; 159:1439–1444. [PubMed: 10228108]

21. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. NEJM. 2009; 360:2445–2454. [PubMed: 19494220]

22. Morris AM, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of

HIV Infection Study Group. Am J Respir Crit Care Med. 2000; 162:612–616. [PubMed: 10934095]

23. Morris A, Alexander T, Radhi S, et al. Airway obstruction is increased in pneumocystis-colonized human immunodeficiency virus-infected outpatients. J Clin Microbiol. 2009; 47:3773–3776. [PubMed: 19759224]

24. Christensen PJ, Preston AM, Ling T, et al. Pneumocystis murina infection and cigarette smoke exposure interact to cause increased organism burden, development of airspace enlargement, and pulmonary inflammation in mice. Infect Immun. 2008; 76:3481–3490. [PubMed: 18490462]

25. Attia EF, Akgun KM, Wongtrakool C, et al. Increased risk of radiographic emphysema in HIV is associated with elevated soluble CD14 and nadir CD4. Chest. 2014; 146:1543–1553. [PubMed: 25080158]

26. Crothers, K.; Sigel, K.; Wisnivesky, J., et al. Inflammatory Biomarkers and CT-Detected Lung Nodules: Potential Implications for Lung Cancer Screening in HIV-Infected Patients. International Conference on Malignancies in AIDS and Other Immunodeficiencies; 2013; Bethesda, MD.

27. Cho WC, Kwan CK, Yau S, et al. The role of inflammation in the pathogenesis of lung cancer. Expert Opin Ther Tar. 2011; 15:1127–1137.

28. Wu AH, Fontham ET, Reynolds P, et al. Previous lung disease and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol. 1995; 141:1023–1032. [PubMed: 7771438]

29. Liang HY, Li XL, Yu XS, et al. Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. Int J Cancer. 2009; 125:2936–2944. [PubMed: 19521963]

30. Mayne ST, Buenconsejo J, Janerich DT. Previous lung disease and risk of lung cancer among men and women nonsmokers. Am J Epidemiol. 1999; 149:13–20. [PubMed: 9883789]

31. Littman AJ, Thornquist MD, White E, et al. Prior lung disease and risk of lung cancer in a large prospective study. Cancer Cause Control. 2004; 15:819–827.

32. Ramanakumar AV, Parent ME, Menzies D, et al. Risk of lung cancer following nonmalignant respiratory conditions: evidence from two case-control studies in Montreal, Canada. Lung Cancer. 2006; 53:5–12. [PubMed: 16733074]

33. Shebl FM, Engels EA, Goedert JJ, et al. Pulmonary infections and risk of lung cancer among persons with AIDS. J Acquir Immune Defic Syndr. 2010; 55:375–379. [PubMed: 20736841]

34. Bordon J, Aliberti S, Fernandez-Botran R, et al. Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. Int J Infect Dis. 2013; 17:e76–83. [PubMed: 23069683]

35. Rubbo PA, Tuaillon E, Bollore K, et al. The potential impact of CD4+ T cell activation and enhanced Th1/Th2 cytokine ratio on HIV-1 secretion in the lungs of individuals with advanced AIDS and active pulmonary infection. Clin Immunol. 2011; 139:142–154. [PubMed: 21345739]

36. Hessol NA, Martinez-Maza O, Levine AM, et al. Lung cancer incidence and survival among HIV-infected and uninfected women and men. AIDS. 2015; 29:1183–1193. [PubMed: 25888645]

37. Norris KA, Morris A. Pneumocystis infection and the pathogenesis of chronic obstructive pulmonary disease. Immunol Res. 2011; 50:175–180. [PubMed: 21717077]

38. Dubrow R, Silverberg MJ, Park LS, et al. HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol. 2012; 24:506–516. [PubMed: 22759737]

39. Yanik EL, Napravnik S, Cole SR, et al. Relationship of immunologic response to antiretroviral therapy with non-AIDS defining cancer incidence. AIDS. 2014; 28:979–987. [PubMed: 24681415]

40. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20:2551–2559. [PubMed: 22109347]

41. Guiguet M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009; 10:1152–1159. [PubMed: 19818686]

42. Reekie J, Kosa C, Engsig F, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer. 2010; 116:5306–5315. [PubMed: 20661911]

43. Kesselring A, Gras L, Smit C, et al. Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. Clin Infect Dis. 2011; 52:1458–1465. [PubMed: 21628488]

44. Hleyhel M, Hleyhel M, Bouvier AM, et al. Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort. AIDS. 2014; 28:2109–2118. [PubMed: 25265077]

45. Sigel, K.; Crothers, K.; Gordon, K., et al. CD4 Measures as Predictors of Lung Cancer Risk and Prognosis in HIV Infection. Conference on Retroviruses and Opportunistic Infections; 2015; Seattle, WA.

46. Poirier MC, Olivero OA, Walker DM, et al. Perinatal genotoxicity and carcinogenicity of anti-retroviral nucleoside analog drugs. Toxicol Appl Pharmacol. 2004; 199:151–161. [PubMed: 15313587]

47. Vivanti A, Soheili TS, Cuccuini W, et al. Comparing genotoxic signatures in cord blood cells from neonates exposed in utero to zidovudine or tenofovir. AIDS. 2015; 29:1319–1324. [PubMed: 25513819]

48. Andre-Schmutz I, Dal-Cortivo L, Six E, et al. Genotoxic signature in cord blood cells of newborns exposed in utero to a Zidovudine-based antiretroviral combination. J Infect Dis. 2013; 208:235–243. [PubMed: 23559464]

49. Bruyand M, Le Marec F, Lavole A, et al. Protease inhibitors exposure is not related to lung cancer risk in HIV smoker patients: a nested case-control study. AIDS. 2015; 29:1105–1109. [PubMed: 26125142]

50. Beltran LM, Rubio-Navarro A, Amaro-Villalobos JM, et al. Influence of immune activation and inflammatory response on cardiovascular risk associated with the human immunodeficiency virus. Vasc Health Risk Manag. 2015; 11:35–48. [PubMed: 25609975]

51. Lu W, Mehraj V, Vyboh K, et al. CD4:CD8 ratio as a frontier marker for clinical outcome, immune dysfunction and viral reservoir size in virologically suppressed HIV-positive patients. J Int AIDS Soc. 2015; 18:20052. [PubMed: 26130226]

52. Borges AH, Silverberg MJ, Wentworth D, et al. Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers. AIDS. 2013; 27:1433–1441. [PubMed: 23945504]

53. Altavilla G, Caputo A, Lanfredi M, et al. Enhancement of chemical hepatocarcinogenesis by the HIV-1 tat gene. Am J Pathol. 2000; 157:1081–1089. [PubMed: 11021811]

54. Giagulli C, Marsico S, Magiera AK, et al. Opposite effects of HIV-1 p17 variants on PTEN activation and cell growth in B cells. PLoS One. 2011; 6:e17831. [PubMed: 21423810]

55. Kawabata S, Heredia A, Gills J, et al. Impact of HIV on lung tumorigenesis in an animal model. AIDS. 2015; 29:633–635. [PubMed: 25611150]

56. Hasegawa Y, Ando M, Kubo A, et al. Human papilloma virus in non-small cell lung cancer in never smokers: a systematic review of the literature. Lung Cancer. 2014; 83:8–13. [PubMed: 24252423]

57. De Paoli P, Carbone A. Carcinogenic viruses and solid cancers without sufficient evidence of causal association. Int J Cancer. 2013; 133:1517–1529. [PubMed: 23280523]

58. Brock MV, Hooker CM, Engels EA, et al. Delayed diagnosis and elevated mortality in an urban population with HIV and lung cancer: implications for patient care. J Acquir Immune Defic Syndr. 2006; 43:47–55. [PubMed: 16936558]

59. Vyzula R, Remick SC. Lung cancer in patients with HIV-infection. Lung Cancer. 1996; 15:325–339. [PubMed: 8959678]

60. D'Jaen GA, Pantanowitz L, Bower M, et al. Human immunodeficiency virus-associated primary lung cancer in the era of highly active antiretroviral therapy: a multi-institutional collaboration. Clin Lung Cancer. 2010; 11:396–404. [PubMed: 21062730]

61. Sigel K, Crothers K, Dubrow R, et al. Prognosis in HIV-infected patients with non-small cell lung cancer. Br J Cancer. 2013; 109:1974–1980. [PubMed: 24022194]

62. Wistuba II, Behrens C, Milchgrub S, et al. Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. JAMA. 1998; 279:1554–1559. [PubMed: 9605900]

63. Okuma Y, Tanuma J, Kamiryo H, et al. A multi-institutional study of clinicopathological features and molecular epidemiology of epidermal growth factor receptor mutations in lung cancer patients living with human immunodeficiency virus infection. J Cancer Res Clin Oncol. 2015; 141:1669–1678. [PubMed: 25800620]

64. Sigel, K.; Sigel, C.; Wisnivesky, J., et al. Rates of Cancer Mutations in HIV Infected Non-Small Cell Lung Cancer Patients. 14th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiences; 2013; Bethesda, MD.

65. Howlader, NNA.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W.; Altekruse, SF.; Kosary, CL.; Ruhl, J.; Tatalovich, Z.; Cho, H.; Mariotto, A.; Eisner, MP.; Lewis, DR.; Chen, HS.; Feuer, EJ.; Cronin, KA.; Edwards, BK., editors. SEER Cancer Statistics Review 1975–2008. Bethesda, MD: National Cancer Institute; 2011.

66. Tirelli U, Spina M, Sandri S, et al. Lung carcinoma in 36 patients with human immunodeficiency virus infection. The Italian Cooperative Group on AIDS and Tumors. Cancer. 2000; 88:563–569. [PubMed: 10649248]

67. Biggar RJ, Engels EA, Ly S, et al. Survival after cancer diagnosis in persons with AIDS. J Acquir Immune Defic Syndr. 2005; 39:293–299. [PubMed: 15980688]

68. Suneja G, Shiels MS, Melville SK, et al. Disparities in the treatment and outcomes of lung cancer among HIV-infected people in Texas. AIDS. 2012; doi: 10.1097/QAD.0b013e32835ad56e:

69. Poluri A, Shah KG, Carew JF, et al. Hodgkin's disease of the head and neck in human immunodeficiency virus-infected patients. Am J Otolaryngol. 2002; 23:12–16. [PubMed: 11791243]

70. Bourcier V, Winnock M, Ait Ahmed M, et al. Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection. A prospective study (ANRS CO13 Hepavih and CO12 Cirvir). Clin Res Hepatol Gastroenterol. 2012; 36:214–221. [PubMed: 22189509]

71. Rodrigues LK, Klencke BJ, Vin-Christian K, et al. Altered clinical course of malignant melanoma in HIV-positive patients. Arch Dermatol. 2002; 138:765–770. [PubMed: 12056957]

72. Hooker CM, Meguid RA, Hulbert A, et al. Human immunodeficiency virus infection as a prognostic factor in surgical patients with non-small cell lung cancer. Ann Thorac Surg. 2012; 93:405–412. [PubMed: 22269705]

73. Makinson A, Tenon JC, Eymard-Duvernay S, et al. Human immunodeficiency virus infection and non-small cell lung cancer: survival and toxicity of antineoplastic chemotherapy in a cohort study. J Thorac Oncol. 2011; 6:1022–1029. [PubMed: 21512403]

74. Clifford GM, Lise M, Franceschi S, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Brit J Cancer. 2012; 106:447–452. [PubMed: 22240797]

75. Ferketich AK, Diaz P, Browning KK, et al. Safety of varenicline among smokers enrolled in the lung HIV study. Nicotine Tob Res. 2013; 15:247–254. [PubMed: 22589421]

76. Lloyd-Richardson EE, Stanton CA, Papandonatos GD, et al. Motivation and patch treatment for HIV+ smokers: a randomized controlled trial. Addiction. 2009; 104:1891–1900. [PubMed: 19719796]

77. Shuter J, Morales DA, Considine-Dunn SE, et al. Feasibility and preliminary efficacy of a web-based smoking cessation intervention for HIV-infected smokers: a randomized controlled trial. J Acquir Immune Defic Syndr. 2014; 67:59–66. [PubMed: 25118794]

78. Jaklitsch MT, Jacobson FL, Austin JH, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012; 144:33–38. [PubMed: 22710039]

79. Network NCC. Lung Cancer Screening Guidelines. 2011.

80. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012; 307:2418–2429. [PubMed: 22610500]

81. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. Curr Opin Infect Dis. 2013; 26:17–25. [PubMed: 23221765]

82. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. NEJM. 2011; 365:395–409. [PubMed: 21714641]

83. Crum-Cianflone N, Stepenosky J, Medina S, et al. Clinically significant incidental findings among human immunodeficiency virus-infected men during computed tomography for determination of coronary artery calcium. Am J Cardiol. 2011; 107:633–637. [PubMed: 21195379]

84. Crothers K, Thompson BW, Burkhardt K, et al. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. Proc Am Thorac Soc. 2010; 8:275–281.

85. Cohen, JV.; Stern, J.; Henry, D. Correlating age-at-diagnosis of lung cancer in the HIV/AIDS population (Abstract #437). 49th Infectious Diseases Society of America Conference; 2011; Boston.

86. Black C, Bagust A, Boland A, et al. The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews. Health Technol Assess. 2006; 10:iii–iv. ix–x, 1–90.

87. Goulart BH, Bensink ME, Mummy DG, et al. Lung cancer screening with low-dose computed tomography: costs, national expenditures, and cost-effectiveness. J Natl Compr Canc Netw. 2012; 10:267–275. [PubMed: 22308519]

88. Poghosyan H, Kennedy Sheldon L, Cooley ME. The impact of computed tomography screening for lung cancer on smoking behaviors: a teachable moment? Cancer nursing. 2012; 35:446–475. [PubMed: 22209869]

89. Sigel K, Wisnivesky J, Shahrir S, et al. Findings in asymptomatic HIV-infected patients undergoing chest computed tomography testing: implications for lung cancer screening. AIDS. 2014; 28:1007–1014. [PubMed: 24401647]

90. Clausen E, Wittman C, Gingo M, et al. Chest computed tomography findings in HIV-infected individuals in the era of antiretroviral therapy. PLoS One. 2014; 9:e112237. [PubMed: 25409510]

91. Hulbert A, Hooker CM, Keruly JC, et al. Prospective CT screening for lung cancer in a high-risk population: HIV-positive smokers. J Thorac Oncol. 2014; 9:752–759. [PubMed: 24828660]

92. Makinson, A.; Eymard-Duvernay, S.; Raffi, F., et al. High Frequency of Early Lung Cancer Diagnosis with Chest CT in HIV Infected Smokers. Conference on Retroviruses and Opportunistic Infections; 2015; Seattle, WA. 2015.

93. International Collaboration on HIV, Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. J Natl Cancer Inst. 2000; 92:1823–1830. [PubMed: 11078759]

94. Gramolelli S, Schulz TF. The role of Kaposi sarcoma-associated herpesvirus in the pathogenesis of Kaposi sarcoma. J Pathol. 2015; 235:368–380. [PubMed: 25212381]

95. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103:753–762. [PubMed: 21483021]

96. Palmieri C, Dhillon T, Thirlwell C, et al. Pulmonary Kaposi sarcoma in the era of highly active antiretroviral therapy. HIV Med. 2006; 7:291–293. [PubMed: 16945073]

97. Pinzone MR, Berretta M, Cacopardo B, et al. Epstein-barr virus- and Kaposi sarcoma-associated herpesvirus-related malignancies in the setting of human immunodeficiency virus infection. Sem Oncol. 2015; 42:258–271.

98. Leidner RS, Aboulafia DM. Recrudescent Kaposi's sarcoma after initiation of HAART: a manifestation of immune reconstitution syndrome. AIDS Patient Care STDs. 2005; 19:635–644. [PubMed: 16232048]

99. Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. NEJM. 2007; 357:1352–1353. [PubMed: 17898112]

100. Ensoli B, Sturzl M. Kaposi's sarcoma: a result of the interplay among inflammatory cytokines, angiogenic factors and viral agents. Cytokine Growth Factor. 1998; 9:63–83.

101. Aka PV, Kemp TJ, Rabkin CS, et al. A multiplex panel of plasma markers of immunity and inflammation in classical kaposi sarcoma. J Infect Dis. 2015; 211:226–229. [PubMed: 25149762]

102. Foster CB, Lehrnbecher T, Samuels S, et al. An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in men infected with human immunodeficiency virus. Blood. 2000; 96:2562–2567. [PubMed: 11001912]

103. Masia M, Robledano C, Ortiz de la Tabla V, et al. Coinfection with human herpesvirus 8 is associated with persistent inflammation and immune activation in virologically suppressed HIV-infected patients. PLoS One. 2014; 9:e105442. [PubMed: 25133669]

104. Khalil AM, Carette MF, Cadranel JL, et al. Intrathoracic Kaposi's sarcoma. CT findings. Chest. 1995; 108:1622–1626. [PubMed: 7497772]

105. Hoskote SS, Patel VP. Pulmonary Kaposi sarcoma in AIDS. Mayo Clin Proc. 2012; 87:e77. [PubMed: 23036685]

106. Hamm PG, Judson MA, Aranda CP. Diagnosis of pulmonary Kaposi's sarcoma with fiberoptic bronchoscopy and endobronchial biopsy. A report of five cases. Cancer. 1987; 59:807–810. [PubMed: 3802039]

107. Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol. 2004; 22:399–402. [PubMed: 14752065]

108. Gbabe OF, Okwundu CI, Dedicoat M, et al. Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults. The Cochrane database of systematic reviews. 2014; 8:CD003256.

109. Ray P, Antoine M, Mary-Krause M, et al. AIDS-related primary pulmonary lymphoma. Am J Respir Crit Care Med. 1998; 158:1221–1229. [PubMed: 9769285]

110. Bazot M, Cadranel J, Benayoun S, et al. Primary pulmonary AIDS-related lymphoma: radiographic and CT findings. Chest. 1999; 116:1282–1286. [PubMed: 10559088]

111. Cadranel J, Wislez M, Antoine M. Primary pulmonary lymphoma. Eur Resp J. 2002; 20:750–762.

112. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. Lancet. 1984; 1:583–587. [PubMed: 6142304]

113. Biggar RJ, Chaturvedi AK, Goedert JJ, et al. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst. 2007; 99:962–972. [PubMed: 17565153]

114. Cadranel J, Naccache J, Wislez M, et al. Pulmonary malignancies in the immunocompromised patient. Respiration. 1999; 66:289–309. [PubMed: 10461078]

115. Marks MA, Rabkin CS, Engels EA, et al. Markers of microbial translocation and risk of AIDS-related lymphoma. AIDS. 2013; 27:469–474. [PubMed: 23169327]

116. Dean M, Jacobson LP, McFarlane G, et al. Reduced risk of AIDS lymphoma in individuals heterozygous for the CCR5-delta32 mutation. Cancer Res. 1999; 59:3561–3564. [PubMed: 10446961]

117. Rabkin CS, Yang Q, Goedert JJ, et al. Chemokine and chemokine receptor gene variants and risk of non-Hodgkin's lymphoma in human immunodeficiency virus-1-infected individuals. Blood. 1999; 93:1838–1842. [PubMed: 10068655]

118. Spina M, Carbone A, Vaccher E, et al. Outcome in patients with non-hodgkin lymphoma and with or without human immunodeficiency virus infection. Clin Infect Dis. 2004; 38:142–144. [PubMed: 14679461]

119. Navarro JT, Lloveras N, Ribera JM, et al. The prognosis of HIV-infected patients with diffuse large B-cell lymphoma treated with chemotherapy and highly active antiretroviral therapy is similar to that of HIV-negative patients receiving chemotherapy. Haematologica. 2005; 90:704–706. [PubMed: 15921395]

120. Diamond C, Taylor TH, Im T, et al. Presentation and outcomes of systemic non-Hodgkin's lymphoma: a comparison between patients with acquired immunodeficiency syndrome (AIDS) treated with highly active antiretroviral therapy and patients without AIDS. Leuk Lymphoma. 2006; 47:1822–1829. [PubMed: 17064995]

121. Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol. 2008; 140:411–419. [PubMed: 18162120]

122. Barta SK, Xue X, Wang D, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. Blood. 2013; 122:3251–3262. [PubMed: 24014242]

123. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated

non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood. 2005; 106:1538–1543. [PubMed: 15914552]

124. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood. 2005; 105:1891–1897. [PubMed: 15550484]

125. Cooksley N, Judge DJ, Brown J. Primary pulmonary Hodgkin's lymphoma and a review of the literature since 2006. BMJ Case Rep. 2014

126. Barta SK, Samuel MS, Xue X, et al. Changes in the influence of lymphoma- and HIV-specific factors on outcomes in AIDS-related non-Hodgkin lymphoma. Ann Oncol. 2015; 26:958–966. [PubMed: 25632071]

127. Massera F, Rocco G, Rossi G, et al. Pulmonary resection for lung cancer in HIV-positive patients with low (<200 lymphocytes/mm(3)) CD4(+) count. Lung Cancer. 2000; 29:147–149. [PubMed: 10963845]

128. Bearz A, Vaccher E, Martellotta F, et al. Lung cancer in HIV positive patients: the GICAT experience. Eur Rev Med Pharmacol Sci. 2014; 18:500–508. [PubMed: 24610616]

129. Powles T, Thirwell C, Newsom-Davis T, et al. Does HIV adversely influence the outcome in advanced non-small-cell lung cancer in the era of HAART? Br J Cancer. 2003; 89:457–459. [PubMed: 12888811]

130. Lavole A, Chouaid C, Baudrin L, et al. Effect of highly active antiretroviral therapy on survival of HIV infected patients with non-small-cell lung cancer. Lung Cancer. 2009; 65:345–350. [PubMed: 19135758]

Table 1

Studies With Data Regarding Safety of Lung Cancer Treatments in HIV-infected Patients.

Study	Number of Lung Cancer Subjects	Lung Cancer Treatment	Outcomes	
Massera et al. 2000[127]	2 HIV+ (both CD4<200 cells/mm^3)	Surgical resection	•	No perioperative complications, 100% 30 day survival
Hooker et al. 2012[72]	22 HIV+ 66 HIV unspecified	Surgical resection	•	Increased perioperative complications in HIV+
			•	Increased length of stay in HIV+
			•	Similar 30 day survival
			•	Increased short-term surgical complications in HIV+ subjects
Hakimian et al. 2007[1]	34 HIV+	Chemotherapy (n=19) Radiotherapy (n=7)	•	No evidence of poor treatment tolerance
Bearz et al. 2014[128]	68 HIV+	Surgical Resection (n=4) Chemotherapy (n=42) Radiotherapy (n=22)	•	Median 3 cycles of chemotherapy administered, no major complications
Makinson et al. 2011[73]	52 HIV+	Chemotherapy (n=42)	•	6 deaths due to grade 4 hematologic toxicity; protease inhibitor use associated with grade 4 toxicity
Powles et al. 2003[129]	9 HIV+ 27 HIV uninfected	Chemotherapy (n=8)	•	HIV+ received same number of chemotherapy cycles as uninfected; 50% with grade 3–4 toxicity
Lavole et al. 2009[130]	49 HIV+	Surgical Resection (n=12) Chemotherapy (n=34) Radiotherapy (n=5)	•	1 post-operative death and one serious post-operative complication in surgical patients
			•	Chemotherapy patients received a median of 3 cycles; one death related to chemotherapy and one death from combined CRT toxicity

Table 2

Results of studies of reporting lung computed tomography results in asymptomatic HIV infected persons and National Lung Screening Trial for comparison.

Study	Number of Participants	Inclusion Criteria	Imaging Procedure	Median Age	Positive Baseline Tests (%)	Lung Cancers (%)
Makinson et al. 2015[92]	442 HIV+	• Age ≥ 40 years • Smoking ≥ 20 pack years • Nadir CD4 < 350 cells/mm³ • Recent CD4 > 100 cells/mm³	One time LDCT	50	94 (21)	8 (1.8)
Hulbert et al. 2014[91]	224 HIV+	• Age ≥ 25 years • Smoking ≥ 20 pack-years	LDCT repeated annually up to 4 times	48	10 (5)	1 (0.4)
Clausen et al. 2014[90]	121 HIV+	• Age ≥ 18 years	One time research non-contrast CT	45	20 (17)*	1 (0.8)
Sigel et al. 2014[89]	139 HIV+	• Age ≥ 18 years • Veterans	One time research non-contrast CT	55	33 (24)	3 (2)
National Lung Screening Trial[82]	26,715 participants (presumed uninfected; HIV status was not ascertained)	• Age 55–74 years • Smoking ≥ 30 pack-years	LDCT repeated annually up to 3 times	62	7,191 (27)	292 (1.1)

*
Proportion with baseline nodule; study did not define test "positivity"

LDCT Low dose computed tomography