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Lung Cancer in HIV-Infected Patients

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Abstract

The widespread use of HAART for persons living with HIV since 1996 has resulted in a dramatic decline in AIDS-related mortality. However, other comorbidities are increasing, such as metabolic disturbances or cancers, including solid organ malignancies. Among the latest, lung cancer, especially the adenocarcinoma subtype, is on the rise. HIV infection, even controlling for smoking, is an independent risk factor for developing lung cancer. HIV could promote lung cancers through immunosuppression, chronic inflammation, and a direct oncogenic effect.

Smoking, lung infections, and chronic pulmonary diseases are risk factors for lung cancer. All may contribute to the cumulative incidence of lung cancer in persons living with HIV. It is double that in the general population. The role of HAART in lung cancer development in persons living with HIV is not well established. Although data supporting it could be too preliminary, persons living with HIV should be considered within high-risk groups that could benefit from screening strategies with low-dose computed tomography, especially those with airway obstruction and emphysema. Current evidence suggests that quitting smoking strategies in persons living with HIV achieve abstinence rates comparable to those in healthy HIV-negative smokers. **(AIDS Rev. 2016;18:138-44)**

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Key words

HIV. PLWH. Lung cancer. Cancer screening. Smoking.

Introduction

Antiretroviral therapy (ART) has prolonged the lifespan of persons living with HIV (PLWH)[1]. However, this longer life expectancy has led to a relative increase in diseases with longer latency period such as solid organ malignancies. Cancer is increasingly common in this population[2], with a higher burden than in the general population, largely as result of impaired immune function, chronic inflammation, and higher prevalence of risk factors[3,4].

The spectrum of malignancies in PLWH has changed with the use of ART, especially following the introduction of HAART. The incidence of AIDS-defining cancers (ADC), such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer has declined markedly. In contrast, there has been a relative increase in non-AIDS-defining cancers (NADC) that surpasses rates seen in the general population[5].

Calendar trends in cancer incidence in PLWH have been recently evaluated[6]. After examination of cumulative

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cancer incidences by 75 years of age, it was found that the cumulative incidence of anal, colorectal, and liver cancer has increased significantly in PLWH. The highest cumulative incidence is seen for Kaposi's sarcoma, non-Hodgkin's lymphoma, and lung cancer. Furthermore, malignancies in PLWH are often characterized by earlier age at onset, atypical pathology (higher tumor grade), more aggressive clinical behavior, and more advanced stage at presentation[7,8]. These features have implications for treatment and contribute to poorer outcomes than in HIV-negative persons.

Magnitude of the problem

The incidence of lung cancer is increased approximately 2-4-fold in PLWH compared with age and gender matched HIV-negative populations. The incidence of lung cancer is also more than 50% higher in PLWH than expected[9]. Of note, there is a higher prevalence of cigarette smoking in this population, up to 2-3 times more than in the general population[10,11]. Tobacco smoking is probably the best-known risk factor for lung cancer. Nicotine and other components of tobacco smoke induce complex pathophysiological changes in HIV infection that seem to be different than in the general population. Thus, tobacco-related harm in the setting of HIV infection is underestimated[12]. Nevertheless, the risk of lung cancer in HIV persons remains elevated even after adjusting for smoking status. Thus, there is a need for more research to understand the mechanisms driving lung cancer risk in this population.

The main features of PLWH that develop lung cancer have been reported elsewhere[13-20]. They include important environmental and ethnic differences, suggesting that both genetics and HIV infection may contribute to lung cancer development in this population. Table 1 summarizes the main features of studies that have examined lung cancer in PLWH.

The PLWH who develop lung cancer are typically young men with a mean age of 45-50 years (compared to 62 years old in the general population) and heavy smokers. More often they are staged as CDC class C (AIDS) although they currently exhibit undetectable viral load and CD4 counts > 200 cells/ml. Resembling the general population in recent years, adenocarcinoma is the most common histological type in PLWH. Diagnosis in advanced tumor stages is more frequent in PLWH, and death is common within the first year after diagnosis.

Cancer-specific mortality is significantly higher in PLWH compared with HIV-uninfected persons for many cancers, even after adjustment for tumor treatment.

Table 1. Main studies of lung cancer in persons living with HIV

Study	Years	Patients (n)	Median age (years)	Male (%)	Smoking (%)	IDUs (%)	AdenoCa (%)	CD4 > 200 cells/µl (%)	Stage III/IV (%)	Median OS (months)
Brock, et al. 2006[13]	1986-2004	92	46	67	99	58	48	–	87	6.3
Engles, et al. 2006[60]	1989-2003	33	46	67	85	57	48	51	–	–
Chatuverdi, et al. 2007[11]	1980-2002	393	47	85	80	33	34	28	–	–
Hakimian, et al. 2007[15]	1996-2003	34	44	68	100	59	–	62	90	5.2
Lavole, et al. 2009[16]	1996-2007	49	46	67	99	17	67	–	84	8.1
D´Jaen, et al. 2010[17]	1996-2008	75	50	83	99	30	46	–	77	9.0
Pakkala, et al. 2012[18]	1995-2008	80	52	80	100	25	38	–	78	6.1
Clifford, et al. 2012[10]	1984-2010	68	50	79	76	37	–	45	–	–
Okuma, et al. 2015[19]	1988-2013	43	60	97	91	0	59	85	63	25.0
Meijide, et al. 2015[20]	1993-2013	28	49	82	85	50	50	67	78	12.3

IDU: intravenous drug user; AdenoCa: adenocarcinoma; OS: overall survival.

Coghill, et al.[21] reported a mortality adjusted hazard ratio of 1.28 (95% CI: 1.17-1.39) for lung cancer. Several classic factors are associated with poor median survival of lung cancer in PLWH, including disease stage, performance status, and histological subtype. In addition, ART use and low absolute CD4 counts contribute as well. Thus, the higher mortality rate for lung cancer seen in PLWH is further influenced by immunosuppression[22,23].

Lung tumorigenesis in HIV infection

Factors other than smoking play a role in the increased risk of lung cancer in PLWH. These include HIV-related factors and a potentially increased susceptibility to carcinogens.

Role of lung infections

Pulmonary infections, throughout producing lung inflammation and tissue damage, may be involved in the development of lung cancer. Several studies have examined the association between tuberculosis and lung cancer, with odds ratios in the range of 2-4[3,24]. The chronicity and prolonged treatment required for *Mycobacterium tuberculosis* infection induces substantial pulmonary inflammation, tumor necrosis factor (TNF) production, and pulmonary fibrosis[25].

Although pulmonary inflammation in bacterial pneumonia is shorter than in lung tuberculosis, a number of case-control studies have reported an association between bacterial or *Pneumocystis jirovecii* pneumonia and increased risk for lung cancer[3,26]. These epidemiological associations have several limitations as not all these studies strictly controlled for tobacco consumption. Smoking-induced lung disease may predispose to pulmonary infections, and tobacco is ultimately the major risk factor for lung cancer. On the other hand, the higher frequency or clinical and radiological controls in patients with lung infections may overestimate the incidence of cancer compared to uncontrolled populations and give rise to spurious associations. Nonetheless, some studies have reported associations with lung cancer for latencies over 10 years following pulmonary infections[27].

Role of HIV reservoirs

Despite the clearance of HIV in the peripheral bloodstream with suppressive HAART, low-level HIV replication persists in all infected persons. Interestingly, bronchoalveolar cells of PLWH may host at least 7.6-fold more HIV proviral DNA than cells in the peripheral blood[28]. Indeed, the lung and the intestinal tract harbor the highest levels of viremia after the lymph nodes[29]. This is largely due to its rich content in macrophages. HIV in the lung activates alveolar macrophages, leading to a marked cellular activation and accumulation of inflammatory mediators in the alveolar space[30].

Alveolar macrophages are fairly resilient to HIV in the lungs. Compared to HIV-uninfected persons, HIV-infected individuals depict a lower secretion of TNF-α and interferon-gamma (IFN-γ) in the lung[30].

Role of immunosuppression and chronic inflammation

HIV infection promotes a massive early depletion of $CD4^+$ T-cells. In contrast to other locations such as the gastrointestinal tract, the lung appears relatively resistant to the early depletion of $CD4^+$ T-cells. This has been attributed to several mechanisms, including a lesser mass of HIV-susceptible secondary lymphoid tissue, elevated presence of mucosal HIV-specific polyfunctional $CD4^+$ T-cells in the lungs, and the apparent efficacy of pulmonary HIV-specific cytotoxic T-cell responses, as reflected by intense alveolitis[31,32].

Nonetheless, human body defenses progressively deteriorate, leading to $CD4^+$ T-cell depletion and immune activation. Chronic immune activation during HIV infection results in increased production of immunosuppressive cytokines, i.e., transforming growth factor-beta 1 (TGF-β1), contributing to HIV-related immunosuppression throughout induction of FoxP3 and promotion of collagen deposition and fibrosis in secondary lymphoid tissues. TGF-β1 has also been implicated in the pathogenesis of several malignancies, including lung cancer[33,34]. Even in the context of HAART-mediated viral suppression, circulating levels of TGF-β1 remain elevated, which is consistent with the presence of ongoing chronic immune activation[35].

Chronic lung diseases such as asthma or chronic obstructive pulmonary disease (COPD) are associated with lung inflammation and may favor lung cancer independently of smoking. These lung conditions are more common in PLWH than in uninfected persons. Smoking has an immunosuppressive and proinflammatory effect similar to HIV infection. In addition, tobacco contains several carcinogenic agents. To date, the contribution of HIV infection and smoking on lung cancer development is still unclear[12].

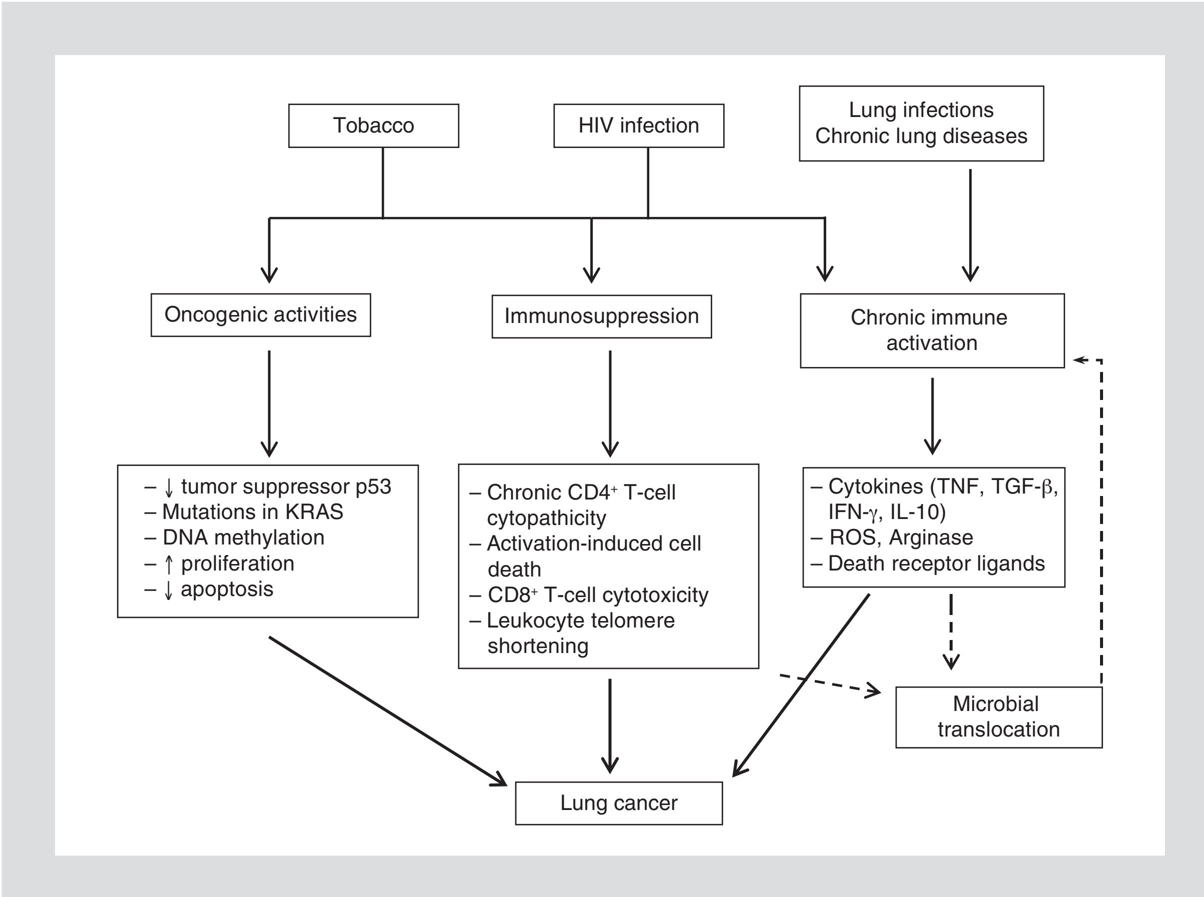

Figure 1. *Proposed mechanism by which HIV infection, tobacco, lung infections, and chronic lung diseases cause immunosuppression, chronic immune activations, and different oncogenic activities. All of them lead to the development of lung cancer in persons living with HIV. TNF: tumor necrosis factor; TGF-β: transforming growth factor beta; IFN-γ: interferon gamma; IL-10: interleukin 10; ROS: reactive oxygen species.*

In the oncology field, epidermal growth factor receptor (EGFR) mutations predispose to lung cancer development and worse prognosis. These mutations are more prevalent in Asia, but recent data have shown that the rate of these mutations in PLWH is similar to the general population, at least in Japan[19]. The role of HIV infection, tobacco, chronic lung diseases, and pulmonary infections on lung cancer development is summarized in figure 1.

Impact of antiretroviral therapy exposure

HAART has dramatically improved the morbidity/mortality of PLWH, but it does not completely restore their health. The rate of ADCs has significantly dropped in the HAART era and short and medium-term survival has extended in PLWH with cancers[35,36]. This is why first-line treatment of some ADCs, such as Kaposi's sarcoma, should include HAART, which often leads to complete resolution of the neoplasm. In contrast, NADCs have been steadily increasing in recent years.

The role of ART exposure in NADC development is not well known. On the one hand, the restoration of immunity could have a protective role, but on the other hand some studies have linked ART with some cancers, such as nonnucleoside reverse transcriptase inhibitors (NNRTI) with Hodgkin's lymphoma, or protease inhibitors (PI) with anal cancer. However, these epidemiological links come from observational retrospective studies with known limitations[37,38].

Antiretroviral therapy decreases the HIV viral load in the bronchoalveolar lavage to undetectable levels in more than 80% patients, also decreasing IFN-γ, IL-6, and $CD8^+$ T lymphocytes while increasing $CD4^+$ T-cells[39]. Glutathione and cysteine levels in the bronchoalveolar lavage are surrogate markers of oxidative stress in the lung. The PLWH without HAART show significantly decreased levels of both molecules than patients on HAART and HIV-uninfected persons, suggesting that increased oxidative stress in the lungs is an important feature of uncontrolled HIV infection[40].

The inhibition of cytochrome p450, namely CYP3A4, induced by ritonavir-boosted PI might have deleterious effects on tobacco carcinogenesis. CYP450 plays a role in the activation and metabolism of polyaromatic hydrocarbons and nitrosamines[41]. The effect of CYP450 inhibitors on the risk of lung cancer is unproven and, accordingly, recent data suggest that PI exposure is not linked to an increased risk of lung cancer in PLWH[42].

Data on HAART choice in PLWH with lung cancer are scarce. Toxicity, tolerability, and potential drug interactions between chemotherapy and HAART should be considered. Integrase inhibitors, such as raltegravir or dolutegravir, exhibit low toxicity and drug interactions and have been widely used in these patients[43]. Retrospective cohort studies have found that integrase inhibitor-based regimens are safer and more effective in maintaining viral suppression than ritonavir-boosted PI or NNRTI-based combinations in PLWH receiving chemotherapy, although those data must be assessed with caution[44].

Screening and preventive strategies

Lung cancer screening in persons living with HIV

The National Lung Screening Trial (NLST) published in 2011 was the first well-designed study able to demonstrate that lung cancer screening with low-dose computed tomography (LDCT) could allow reduction of lung cancer mortality by roughly 20% as well as all-cause mortality around 7%[45]. Lung cancer screening using LDCT is currently recommended by several guidelines[46-49] and mainly relies on the NLST inclusion criteria (age, 55-74; ≥ 30 pack-years; tobacco cessation within the previous 15 years for former smokers). However, concerns exist about the lack of sensitivity of LDCT in detecting lung cancer and therefore some authors have suggested implementing individualized risk assessment considering further considerations[50] such as the presence of airway obstruction and emphysema[51,52]. Since HIV infection could be an independent factor for lung cancer after controlling for smoking, and that the prevalence of COPD and emphysema in PLWH is higher than in the general population, PLWH could benefit from specific lung cancer screening programs.

When data from lung cancer screening trials are analyzed, information regarding HIV status is not displayed as being HIV-infected is not contraindicated for entering into the study[53]. However, age for eligibility in the trial was between 55 and 74, a range over most younger PLWH. Moreover, some questions regarding sensitivity could arise in PLWH, such as a higher frequency of nonspecific lymphadenopathy and a greater risk for bacterial infections, which could potentially interfere with likelihood of false positive computed tomography (CT) scans[54]. To date, only one trial has evaluated these questions[53]. Hulbert, et al. followed 224 PLWH and current/former smokers to assess CT detection rates of lung cancer. The study concluded that despite high rates of active smoking among HIV-infected participants, only one lung cancer was detected in 678 patient-years of examinations. The inclusion of younger patients (threshold at 25 years old) could explain these results.

Another prospective multicenter study (NCT01207986), which is still ongoing, aims to evaluate the prevalence of lung cancer detected by LDCT in HIV-infected patients. It will analyze 450 individuals with HIV infection, a nadir level of $CD4^+$ T-cells < 350/µl, ≥ 40 years old, and smoking history ≥ 20 packs a year (either active or with < 3 years of weaning). Once completed, the study will provide very valuable information on the role of LDCT screening in PLWH.

Smoking cessation in persons living with HIV

As in non-HIV-infected persons, smoking is the most important modifiable risk factor for disease and mortality in PLWH. Accordingly, smoking cessation will be the cornerstone of any preventive strategy for lung cancer (and many more diseases) in PLWH.

Smoking cessation interventions in PLWH have shown discordant results[55,56]. Most smoking cessation trials used motivational interviewing with or without nicotine replacement therapy. A recent meta-analysis[57] showed that individualized smoking cessation interventions that tailor interventions to psychosocial comorbidities and polysubstance abuse are effective in PLWH. A combination of several approaches, including counseling/education, pharmacotherapy, and self-monitoring, may lead to the greatest benefits.

Although more clinical trials testing pharmacological therapies for quitting smoking in PLWH are needed, to date those using varenicline have concluded that the percentage of adverse events (even in patients on

HAART) and abstinence rates are roughly comparable to those seen in randomized trials conducted in healthy HIV-negative smokers[58,59]. Compared to nicotine, varenicline seems to have better outcomes, with biochemically confirmed abstinence rates at three months of 26 vs. 12% in the nicotine intervention arm[59].

Conclusions

- The cumulative incidence of lung cancer in PLWH increases with age, and is overall twofold that of the general population.
- As in HIV-negative persons, smoking, lung infections, and chronic pulmonary diseases are risk factors for developing lung cancer in PLWH.
- HIV-infection, even controlling for smoking, is an independent risk factor for developing lung cancer. HIV could be carcinogenetic through immunosuppression, chronic inflammation, and direct oncogenic effects.
- The role of HAART in preventing lung cancer development in PLWH is not well established.
- Although data are scarce, PLWH would benefit from inclusion within high-risk groups to develop lung cancer and take advantage of screening strategies with low-dose CT scan, especially PLWH with airway obstruction and emphysema.
- Quitting smoking strategies in PLWH achieve abstinence rates comparable to those obtained in healthy HIV-negative smokers.

Declaration of interest

All authors declare no conflicts of interest.

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