HIV-Associated Lung Infections and Complications in the Era of Combination Antiretroviral Therapy

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The spectrum of lung diseases associated with HIV is broad, and many infectious and noninfectious complications of HIV infection have been recognized. The nature and prevalence of lung complications have not been fully characterized since the Pulmonary Complications of HIV Infection Study more than 15 years ago, before antiretroviral therapy (ART) increased life expectancy. Our understanding of the global epidemiology of these diseases in the current ART era is limited, and the mechanisms for the increases in the noninfectious conditions, in particular, are not well understood. The Longitudinal Studies of HIV-Associated Lung Infections and Complications (Lung HIV) Study (ClinicalTrials.gov number NCT00933595) is a collaborative multi-R01 consortium of research projects established by the National Heart, Lung, and Blood Institute to examine a diverse range of infectious and noninfectious pulmonary diseases in HIV-infected persons. This article reviews our current state of knowledge of the impact of HIV on lung health and the development of pulmonary diseases, and highlights ongoing research within the Lung HIV Study.

Keywords: HIV/AIDS; pulmonary infections; pulmonary complications; smoking

Recent global estimates indicate that approximately 33 million people are living with HIV infection (1). A disproportionate number live in low- and middle-income countries, with the highest prevalence of HIV infection reported in sub-Saharan Africa (1). Many HIV-infected persons in these resource-limited regions experience serious or fatal lung complications that are poorly characterized. HIV-associated lung complications are also frequent causes of illness and death in industrialized nations, where the greatly improved prognosis of HIV-infected patients

due to more widespread availability and access to combination antiretroviral therapy (ART) has turned HIV infection into a chronic disease. Among persons on ART, growing numbers are surviving longer and are developing comorbid diseases that significantly affect mortality, with serious “non-AIDS” conditions accounting proportionally for the majority of deaths in recent studies (2–6). This paper reviews the current state of knowledge regarding the impact of HIV on lung health, highlights ongoing research in this field, and serves as an introduction to the subsequent articles in this issue of the *Proceedings of the American Thoracic Society* that are each devoted to specific pulmonary and critical care complications of HIV infection.

IMMUNOLOGIC ABNORMALITIES ASSOCIATED WITH HIV INFECTION

HIV-infected persons experience a gradual but persistent loss of host immunity after infection that results in a syndrome of immune deregulation, dysfunction, and deficiency (Figure 1). After initial infection, HIV leads to massive depletion of CD4⁺ lymphocytes of the effector memory type from mucosal-associated lymphoid tissue (7). During the chronic phase of HIV infection, generalized immune activation occurs, and, ultimately, progressive decline in the naive and memory T-cell pool results in systemic CD4⁺ lymphocyte depletion (7, 8). As well as being decreased in number, T cells are dysfunctional and mount abnormal host responses to T-cell-dependent antigens. In addition, B-cell dysfunction results in polyclonal activation, hypergammaglobulinemia, and lack of specific antibody responses. Combined, these factors result in immune dysfunction, deregulation, and depletion of CD4⁺ lymphocytes that confer substantially increased risk for opportunistic infections and other complications over the course of HIV infection. Although immunologic abnormalities are most marked in those who do not use ART, recent data demonstrate that, although ART restores immune function, inflammation and immunodeficiency may persist, particularly in patients who initiate ART at lower CD4⁺ lymphocyte counts (9).

HIV infection is associated with changes in the cellular profile of the alveolar space of the lung (Figure 1) (10). The mucosal depletion of gut CD4⁺ T cells does not appear to occur within the lung. In contrast, bronchoalveolar lavage (BAL) fluid from HIV-infected individuals early in infection has demonstrated higher numbers of CD4⁺ T cells, which were also more polyfunctional, when compared with the terminal ileum (11). HIV-infected individuals, particularly in early- to mid-stage disease, have increased numbers of HIV-specific cytotoxic CD8⁺ T lymphocytes

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Banked biospecimens will be housed at the NHLBI Biological Specimen Repository at the completion of the Lung HIV Study and will be available upon request by qualified investigators. The Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) (www.biolincc.nhlbi.nih.gov) is the interface for applications for biospecimens, associated clinical data, or both.

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TABLE 1. SPECTRUM OF LUNG INFECTIONS AND COMPLICATIONS IN HIV

Infectious and Noninfectious Complications	
Bacteria	<i>Streptococcus pneumoniae</i> <i>Haemophilus</i> species <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> Other bacteria
Mycobacteria	<i>Mycobacterium tuberculosis</i> <i>Mycobacterium avium</i> complex <i>Mycobacterium kansasii</i> Other mycobacteria
Fungi	<i>Pneumocystis jirovecii</i> (formerly <i>P. carinii</i>) <i>Cryptococcus neoformans</i> <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i> <i>Aspergillus</i> species (most often <i>A. fumigatus</i>) <i>Blastomyces dermatitidis</i> <i>Penicillium marneffei</i> Other fungi
Viruses	Cytomegalovirus Other viruses
Parasites	<i>Toxoplasma gondii</i> Other parasites
Malignancies	Kaposi sarcoma Non-Hodgkin lymphoma Lung cancer
Other	Chronic obstructive pulmonary disease Asthma Lymphocytic interstitial pneumonitis Nonspecific interstitial pneumonitis Pulmonary arterial hypertension Sarcoidosis Immune reconstitution inflammatory syndrome

within the alveolar space (12). These cells secrete high amounts of IFN- γ (13). Lung cells that can be infected with HIV include alveolar macrophages, T cells, and fibroblasts (10). Recent evidence suggests that T cells may be a long-lived reservoir of infection within the lung (14).

HIV infection causes alteration in several lines of host defenses in the lung and respiratory tract that contribute to an increased risk for lung complications. These alterations include abnormalities in mucociliary function and soluble defense molecules, such as defensins within respiratory secretions (10). Within the lung parenchyma, innate and adaptive immune responses to pathogens may be impaired (15). For example, alveolar macrophages from HIV-infected individuals have been shown to be deficient in pathogen recognition. HIV also results in chronic stimulation and activation of inflammatory cells within the alveolar space (10).

The impact of ART on lung health of HIV-infected persons is not well understood. Systemically, treatment with ART decreases HIV replication, immune activation, and chronic inflammation and increases CD4⁺ lymphocyte counts. Within the alveolar space, ART decreases pulmonary HIV viral load and decreases pulmonary inflammatory responses (14, 16). ART results in measureable drug levels detected within the BAL fluid after initiation of therapy (17). After starting ART, the total number and percentage of BAL lymphocytes decreases due exclusively to a decrease in CD8⁺ T lymphocytes in the alveolar space (14). CD4⁺ cells in the BAL fluid reconstitute with ART, and their infection rate decreases (18).

Nonetheless, in asymptomatic HIV-infected patients, immune responses and signaling pathways may be abnormal even among those on ART (19). Risk for premature comorbidities, such as cardiovascular disease, renal, and liver disease, has been associated with residual inflammation and immunodeficiency despite treatment with ART (20). A possible association of ART with airflow obstruction has been suggested (21, 22), although ART has not been found to have direct toxic effects on the lungs. The consequences of persistently increased inflammation and the effects of ART on the pathogenesis of lung complications in HIV-infected persons are poorly understood.

SPECTRUM OF HIV-ASSOCIATED LUNG INFECTIONS AND COMPLICATIONS

The spectrum of lung complications associated with HIV is broad, and many infectious and noninfectious complications have been recognized (Table 1) (23, 24). These complications include diseases that are AIDS-defining or HIV-associated (e.g., *Pneumocystis pneumonia* [PCP], tuberculosis [TB], or bacterial pneumonia), disorders that are not classified as AIDS-defining but are more common in patients with HIV infection (e.g., lung cancer, pulmonary arterial hypertension, and chronic obstructive pulmonary disease), and conditions whose association with HIV is inconclusive or coincidental (e.g., sarcoidosis). In addition, lung complications can result from immune reconstitution inflammatory syndrome (also called immune reconstitution syndrome), which may occur after initiation of ART (25).

Throughout the HIV/AIDS epidemic, opportunistic pneumonias have been major causes of morbidity and mortality. In 1981, 15 cases of PCP heralded the onset of the HIV/AIDS epidemic, and, at its peak, more than 20,000 cases of PCP a year were reported as AIDS-defining diagnoses in the United States. Two factors—the use of combination ART and *Pneumocystis* prophylaxis—have combined to dramatically reduce the number of cases of PCP. Nevertheless, PCP continues to occur, chiefly among persons who are unaware of their HIV infection, those who fail to seek medical care, and those who fail to adhere to or respond to ART or *Pneumocystis* prophylaxis (26–28).

Approximately one third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Worldwide, TB is the major cause of mortality in persons with HIV infection, and the World Health Organization estimates that TB is the cause of death for 13% of persons who die with HIV/AIDS. In developed countries, community-acquired bacterial pneumonia is more frequent than PCP or TB. Although the rates of opportunistic pneumonias have declined markedly among HIV-infected persons on ART, the rate of bacterial pneumonia has not declined proportionately (29, 30).

Because more people are living with HIV/AIDS and are living longer, noninfectious complications and comorbid illnesses have increased in frequency (2). In addition to an increased risk for infectious pulmonary diseases, HIV-infected persons appear to have an increased risk for several noninfectious pulmonary conditions, including chronic obstructive pulmonary disease (COPD), lung cancer, and pulmonary arterial hypertension. HIV infection has been associated with several different manifestations of COPD and airway abnormalities, including features of emphysema (32), chronic bronchitis (33), nonspecific airway abnormalities, and bronchial hyperresponsiveness (34, 35). In one study of 114 HIV-infected persons compared with 44 age-, sex-, and smoking-matched HIV-uninfected control subjects, 15% of the HIV-infected persons had emphysema on CT scan, compared with only 2% of non-HIV-infected persons ($P = 0.025$) (32). Another study found that HIV infection was associated with a 50 to 60% increased odds of COPD diagnosis (36).

TABLE 2. LONGITUDINAL STUDIES OF HIV-ASSOCIATED LUNG INFECTIONS AND COMPLICATIONS (RFA: HL07-008): OVERVIEW OF PROJECTS BY CLINICAL CENTER

Clinical Center	Study	Goal/Intervention	Enrollment Sites; Date Enrollment Began	Affiliated Cohort Study	Patient Population
1	Longitudinal Evaluation of Lung Health in a Soweto Cohort of HIV-infected Adults (PI, Richard Chaisson; co-PI, Neil Martinson)	1. Establish a database and tissue repository from a clinical cohort of HIV-infected South Africans. 2. Assess the epidemiology, natural history, and clinical course of AIDS-associated lung diseases longitudinally.	South Africa; 11/2008	HIV Wellness Cohort, Soweto; Novel TB preventive Therapy Study Cohort (44, 45)	1,000 HIV+ adults from Soweto, South Africa: 500 from previous RCT of TB preventive therapy regimens, 500 from HIV Wellness Clinics
2	Study of HIV Infection in the Etiology of Lung Disease (SHIELD) (PI, Gregory Kirk)	1. Investigate the prevalence or incidence and risk factors for noninfectious lung disease, including COPD, lung cancer, and pulmonary arterial hypertension.	USA; 12/2008	Three affiliated HIV cohort studies in Baltimore: AIDS Linked to the IntraVenous Experience (ALIVE), Johns Hopkins HIV Clinical Cohort (JHCC), Study to Help the AIDS Research Effort (SHARE) (46–48)	Approximately 3,500 HIV+ outpatients enrolled in parent cohort studies; 450 of these enrolled in focused COPD and 750 in PAH studies
3	Longitudinal Studies of HIV-Associated Bacterial Pneumonia (PI, William Rom)	1. Follow 400 HIV+ subjects for bacterial pneumonia. 2. Evaluate BAL and peripheral blood specimens for differences in cytokines, cell surface molecules, and HIV replication and mutations.	USA and South Africa; 10/2008	N/A	400 HIV+ subjects enrolled. Bacterial pneumonia diagnosed in ~36 patients at each site lavaged for mechanistic studies focused on HIV and bacterial pneumonia. Two control HIV+ patients lavaged at the same time for studies on lung HIV, neutrophils, and alveolar macrophages.
4	Smoking Cessation and the Natural History of HIV-associated Emphysema (PI, Philip Diaz)	1. Examine the effects of smoking cessation on respiratory symptoms, pulmonary function and alveolar macrophage biology in a cohort of HIV+ smokers.	USA; 9/2008	N/A	365 HIV+ current smokers
5	International HIV-associated Opportunistic Pneumonias (IHOP) Study (PI, Laurence Huang)	1. Determine the frequency and mortality of HIV-associated opportunistic pneumonias. 2. Evaluate the sensitivity and specificity of molecular tools for PCP and pulmonary TB diagnosis. 3. Determine the frequency of <i>Pneumocystis</i> dihydropteroate synthase (DHPS) gene mutations and study putative mechanisms for trimethoprim-sulfamethoxazole drug resistance.	USA, Uganda; 10/2008	N/A	2,400–3,000 HIV+ inpatients with suspected pneumonia
6	Longitudinal Studies of HIV-1 Nef in Pulmonary Hypertension (PI, Sonia Flores)	1. Determine if particular HIV Nef signature sequences are associated with and predict HIV-related pulmonary hypertension.	France, USA; 12/2008	N/A	80 HIV+ patients with PAH and 60 HIV+ patients without PAH
7	Prevalence & Pathogenesis of Pulmonary Disease in a Large Multicenter HIV Cohort (PI, Alison Morris)	1. Describe epidemiology and risk factors for pulmonary disease in the current era. 2. Determine if COPD is more prevalent and progresses more quickly in those with HIV infection compared with control subjects. 3. Evaluate the role of infections in HIV-associated COPD.	USA; 8/2008	Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) cohorts (48, 49)	4000 HIV+ and HIV– outpatients enrolled in MACS and WIHS, with 600 of these enrolled in emphysema studies

(Continued)

TABLE 2. (CONTINUED)

Clinical Center	Study	Goal/Intervention	Enrollment Sites; Date Enrollment Began	Affiliated Cohort Study	Patient Population
8	Investigations in HIV Associated Lung Events (INHALE) and Examinations of HIV Associated Lung Emphysema (EXHALE) Studies (PI, Kristina Crothers)	1. Understand the epidemiology of lung diseases in HIV, and smoking as a risk factor 2. Compare clinical and pathophysiologic differences in COPD and decline in pulmonary function between HIV+ and HIV- patients	USA;12/2008	Veterans Aging Cohort Study (VACS) (50)	Approximately 3,500 HIV+ and 3,500 HIV- veterans enrolled in VACS for INHALE; with 180 HIV+ and 180 HIV- participants with or at risk for COPD prospectively enrolled in EXHALE; those with lung diseases other than COPD are excluded from EXHALE.

Definition of abbreviations: BAL = bronchoalveolar lavage; COPD = chronic obstructive pulmonary disease; HIV+ = HIV-infected; HIV- = HIV-uninfected; PAH = pulmonary arterial hypertension; PCP = *Pneumocystis pneumonia*; PI = principal investigator; RCT = randomized controlled trial; TB = tuberculosis.

Rates of lung cancer have been reported to be substantially increased among HIV-infected persons, even after controlling for the higher prevalence of smoking in this population. In one study, HIV infection was independently associated with a hazard ratio of 3.6 for lung cancer (95% confidence interval, 1.6–7.9) (37). Similarly, in another study, HIV infection was associated with a standardized incidence ratio of 2.5 (95% confidence interval, 1.6–3.5) for lung cancer, adjusting for estimates of smoking prevalence (38).

Numerous studies have reported an increased frequency of pulmonary arterial hypertension in the HIV-infected population. Prevalence is estimated at approximately 1 case per 200 (0.5%) among HIV-infected persons, compared with 1 to 2 cases per million in the non-HIV-infected population (39). Advancing age, a high prevalence of cigarette smoking, and an independent risk from HIV infection all likely contribute, particularly to increases in COPD and lung cancer.

Wide gaps in our understanding of the pulmonary complications of HIV exist, particularly in the modern era of combination ART. The nature and prevalence of lung complications was characterized by the Pulmonary Complications of HIV Infection Study (40) more than 15 years ago, before ART increased life expectancy. Although studies in the combination ART era have reported changes in pulmonary complications (29, 30, 41, 42), HIV-related lung complications have not been systematically

reassessed in multisite cohorts or compared among international sites with wide variations in ART use.

Although HIV infection continues to confer an increased risk for opportunistic pneumonias, including bacterial pneumonia, TB, and PCP, our understanding of the global epidemiology of these diseases in the current ART era is limited. Numerous questions need to be answered to improve our understanding and management of HIV-associated lung infections. For example, strategies to improve the diagnosis and management of TB, particularly multidrug resistant and extremely drug resistant TB, in populations with HIV infection are urgently needed. How additional risk factors, such as body mass index and ART-induced diabetes, influence risk for TB in HIV-infected patients requires investigation. The optimal timing for initiation of ART in the setting of lung infections associated with respiratory failure and critical illness is uncertain. Whether *Pneumocystis* is developing drug resistance to sulfa-containing medications remains unclear. Reasons for the persistently elevated rates of bacterial pneumonia are not fully understood, although the high prevalence of cigarette smoking among many HIV-infected populations is one important risk factor (31). Whether bacterial pneumonia, like TB, influences HIV viral replication is unknown (43).

Our understanding of the prevalence, consequences, and mechanisms that account for the increased risk of noninfectious pulmonary conditions associated with HIV infection are not well

Figure 1. Systemic and lung alterations in T lymphocytes with HIV infection and initiation of antiretroviral therapy (ART) after initial HIV infection. CD4⁺ lymphocytes of the effector memory type are depleted from mucosal-associated lymphoid tissue; the CD4⁺ cells within the alveolar space appear to be spared but gradually decrease over time with progressive, untreated HIV. During the chronic phase of HIV infection, there is progressive decline in the systemic CD4⁺ cell count due to decreased naïve and memory T cells. Within the alveolar space, HIV-specific cytotoxic CD8⁺ T lymphocytes predominate, although in late-stage disease these are replaced with CD8⁺ suppressor lymphocytes. HIV infection is also associated with abnormal function of T cells, B-cell dysfunction, and, within the lung, abnormalities in several other lines of host defense. With initiation of ART, CD4⁺ cell counts increase both systemically and in the lung.

Figure 2. Common data elements collected at clinical centers that comprise the Lung HIV Common Database.

understood. For example, studies have not addressed the role of screening (e.g., with pulmonary function testing to detect COPD or chest imaging to detect lung cancer), nor have they assessed treatment of these diseases in the setting of HIV. Little is known regarding the impact of chronic lung diseases on morbidity, including risk for lung infections and cardiac disease, as well as mortality and patient-centered outcomes such as quality of life. Effective methods to decrease smoking prevalence among HIV-infected populations are needed. It also remains unclear whether noninfectious pulmonary diseases have synergistic or additive effects to influence HIV viral replication or compartmentalization of HIV within the lung. The subsequent articles in this issue of the *Proceedings of the American Thoracic Society* review the major HIV-associated pulmonary diseases as well as critical illness among HIV-infected persons and highlight ongoing research in each of these areas.

NEW INSIGHTS INTO HIV AND LUNG DISEASE IN THE ART ERA: THE LUNG HIV STUDY

The ongoing Lung HIV Study, sponsored by the National Heart, Lung, and Blood Institute, is a collaborative multi-R01 consortium designed to address gaps in our knowledge of HIV-associated pulmonary diseases. The Lung HIV Study, which began enrolling participants in studies in 2008, includes a broad range of pulmonary topics in persons with HIV infection. Studies are focused on infectious and noninfectious lung complications and encompass United States and international populations, thereby providing researchers with the opportunity to study these diseases in multiple settings.

Eight Clinical Center principal investigators and their collaborators conduct their own separate research studies but also join under the stewardship of the National Heart, Lung, and Blood Institute and a Data Coordinating Center run by the Clinical Trials and Surveys Corp to conduct multisite and group-level collaborative studies. The program is structured to facilitate the completion of all eight individual projects, the development of shared resources, and the generation of biospecimens and accompanying clinical data for future mechanistic studies (Figure 1). As individually funded R01 projects, each of the eight Clinical Centers of the Lung HIV Study has its own unique cohort and study design (Table 2). However, the Lung HIV investigators have also created a collection of shared clinical datasets and biological specimens for use during their individual-, multisite-, and group-level projects and for future investigations (Figure 2). Collaborative efforts have enabled harmonized clinical data and specimen collection. Clinical Centers administer surveys that include items

from a standardized core set of data elements and use common definitions for prevalence and incidence of pulmonary diseases, and several perform standardized pulmonary function testing and chest CT scans. Clinical Centers also bank peripheral blood and BAL specimens at a central repository for future research studies by these investigators and the entire scientific community.

The common Lung HIV Study dataset offers numerous opportunities and strengths for studying HIV-related pulmonary diseases, including diversity in geographic locations, age, gender, racial and ethnic backgrounds, risk factors for HIV infection, stage and severity of HIV disease, and use of ART. Standardized data definitions facilitate streamlined data management and analyses. The broad range of data collected will facilitate a better understanding of the prevalence and incidence of pulmonary diseases across these populations and will allow for comparisons of risk factors, respiratory symptoms, medication use, disease control, and progression over time. With biologic specimens paired to refined clinical phenotypes, insights can be gained into the underlying mechanisms of lung diseases in HIV-infected patients. The Lung HIV common dataset offers the opportunity to advance our scientific knowledge of HIV-associated lung diseases in the modern ART era because it will support investigations of HIV-related lung diseases with greater breadth and power than the individual projects could achieve.

CONCLUSIONS

Lung diseases are a significant cause of morbidity and mortality in HIV-infected individuals, and the lung infections and complications associated with HIV infection are broad. The impact of ART and chronic infection with HIV on lung health are unknown. Ongoing research within the Lung HIV Study seeks to characterize the lung complications occurring in HIV-infected individuals in diverse geographic regions, with and without ART, and to provide insights into pathogenesis of these complications.

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