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An Official ATS Workshop Report: Emerging Issues and Current Controversies in HIV-Associated Pulmonary Diseases

Alison Morris, Kristina Crothers, James M. Beck, and Laurence Huang, on behalf of the American Thoracic Society Committee on HIV Pulmonary Disease

CONTENTS

Pulmonary diseases are major causes of morbidity and death in persons with HIV infection. Millions of people with HIV/AIDS throughout the world are at risk of opportunistic pneumonias such as tuberculosis, bacterial pneumonia, and *Pneumocystis* pneumonia. However, the availability of combination antiretroviral therapy has turned HIV into a chronic disease, and noninfectious lung diseases such as lung cancer, chronic obstructive pulmonary disease, and pulmonary arterial hypertension are also emerging as important causes of illness. Despite the importance of these diseases and the rapidly evolving understanding of their pathogenesis and epidemiology, few avenues exist for the discussion and dissemination of new clinical and basic insights. In May of 2008, the American Thoracic Society sponsored a 1-day workshop, "Emerging Issues and Current Controversies in HIV-Associated Pulmonary Diseases," which brought together basic and clinical researchers in HIV-associated pulmonary disease. A review of the literature was performed by workshop participants, and the workshop included 18 presentations on diverse topics summarized in this article.

Keywords: human immunodeficiency virus; lung; antiretroviral therapy

INTRODUCTION

Since its unforeseen onset in the early 1980s, the scourge of human immunodeficiency virus (HIV) infection has spread rapidly throughout the world and caused an estimated 25 million deaths (1). In 2008, according to the United Nations Program on HIV/AIDS (UNAIDS), 33.4 million people worldwide were living with HIV, the majority of these in resource-poor nations (1). In 2007 to 2008, the Centers for Disease Control and Prevention estimated that more than 800,000 people were living with HIV infection in the United States and over 40,000 were newly infected each year (2).

Historically, pulmonary diseases have accounted for a large percentage of both infectious and noninfectious complications of HIV. Since the advent of effective combination antiretroviral therapy (ART), the epidemiology of HIV-associated lung disease has changed dramatically in those countries where treatment is available. In the early (pre-ART) years of the epidemic, pulmonary infections such as *Pneumocystis* pneumonia (PCP), tuberculosis (TB), and bacterial pneumonia were the most frequent complications. Currently, infectious diseases are less common, although still prevalent, and diseases such as emphysema, pulmonary arterial hypertension (PAH), and lung cancer appear to be increasing; moreover, new syndromes associated with ART have also become important. In contrast, HIV-infected patients without access to ART still suffer from opportunistic pulmonary infections such as TB in low-income and middle-income countries where TB is endemic, and from PCP and bacterial pneumonia in the U.S. and Western Europe. Our understanding of the pulmonary immune response in HIV-infected people has also greatly improved over the past several years and now offers new possiblities for treatment and prevention of pulmonary disease.

Because of the importance of HIV-associated pulmonary diseases and the rapidly evolving knowledge about their pathogenesis and epidemiology, the American Thoracic Society convened a workshop to discuss current trends and emerging issues. A review of the literature was performed by workshop participants. Search strategies included electronic searches of Medline and PubMed, manually searching journals, and a review of published HIV guidelines. Inclusion of references was limited to articles written in English. Final decisions for inclusion of references were made by consensus among members of the Writing Committee. Each member of the Writing Committee has declared any conflict of interest. The workshop was funded by the American Thoracic Society, and discussions from the workshop are summarized in the following report.

EPIDEMIOLOGY OF HIV-ASSOCIATED LUNG DISEASES

Pulmonary Complications in Low-Income and Middle-Income Countries

According to UNAIDS, more than 7,400 new cases of HIV infection occurred each day in 2008 (1). More than 97% of new cases were in low- and middle-income countries that were already overburdening insufficient resources. Sub-Saharan Africa is the most heavily affected region in the world, accounting for 67% of all people living with HIV and for 70% of acquired immunodeficiency syndrome (AIDS) deaths in 2008 (1). Because of limited diagnostic resources and empirical treatment of many illnesses and varying indigenous microorganisms, precise epidemiologic information is lacking for many African countries. Nevertheless, it is clear that many HIV-associated pneumonias, especially TB, are extremely prevalent. In contrast to many other regions, PCP appears to be infrequent in sub-Saharan Africa (3, 4). Asia and Latin America are also increasingly affected by HIV. As in sub-Saharan Africa, *M. tuberculosis* is the most common pathogen in these regions; but in contrast, PCP occurs in many areas (5). In Asia, patients may also present with *Penicillium marneffei* infection (6).

The threat of TB in low- and middle-income countries antedates the arrival of HIV, but the problem has been enormously enhanced by HIV, which increases the incidence rate 20-fold compared with persons who are not HIV-infected (7). Tuberculosis results in significant morbidity and mortality in low- and middle-income countries and poses a threat to the non–HIV-infected population. Among the 9.27 million incident cases of TB worldwide in 2007, 1.37 million (14.8%) were co-infected with HIV: of these, 79% were in sub-Saharan Africa and 11% were in Southeast Asia (7). TB was also the largest single cause of mortality in people with HIV infection worldwide. Treatment with ART has decreased TB incidence in South Africa but is not widely available in other countries (8). Major clinical and programmatic challenges also complicate the combining of ART with TB treatment. Now the problem is worsened by the increasing incidence of multidrug-resistant and extensively drug-resistant TB (9). To combat TB in low- and middle-income nations, efforts are urgently needed to reduce nosocomial transmission, to test health care workers and patients with TB for HIV, to search for TB in people with HIV, to integrate TB and HIV programs, and to improve laboratory infrastructure and drug susceptibility testing.

Pulmonary Complications in the United States and Europe

The HIV epidemic in the United States and Western Europe has changed enormously with the introduction of combination ART, and with these changes, the epidemiology of pulmonary disease has also shifted. Two historically important causes of morbidity and mortality, PCP and TB, have decreased as shown by data from the Adult/Adolescent Spectrum of HIV disease cohort (10). Two major HIV centers, San Francisco General Hospital and the University College of London, have also seen decreasing numbers of cases of PCP and TB in recent years. Invasive pneumococcal disease also decreased in the HIV-infected population after the introduction of the pneumococcal vaccine (11). Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is one disease that has become more common, and it is debated whether MRSA infection should be considered as another opportunistic infection. Although there is no evidence that MRSA is more common or more severe in HIV, there have been community outbreaks of MRSA among men who have sex with men, and nasal carriage of MRSA is more common in HIV-infected persons and is related to CD4 cell counts (12).

Emerging or increasing pulmonary diseases in the current HIV era include immune reconstitution syndromes directed against pulmonary pathogens, obstructive lung disease, and PAH, as discussed later in this review. Despite the availability of ART for almost 15 years, little is known about the impact of ART or long-term HIV on the incidence of noninfectious pulmonary disorders. Large-scale cohort studies are needed to track HIV-associated pulmonary diseases in the current era.

HIV and Critical Care

Rates of ICU admission and ICU-related mortality for HIV-infected patients have shifted multiple times during the AIDS epidemic, depending on changes in the demographics of the HIV epidemic, evolving treatment interventions for both opportunistic infections and HIV, and changes in physicians' and patients' attitudes toward ICU care. University College of London and San Francisco General Hospital have tracked trends in ICU epidemiology and outcomes over the course of the AIDS epidemic (13–17). As with changes in the epidemic overall, and depending on the type and location of the clinical center, patients with HIV risk factors of intravenous drug use or heterosexual contact comprise an increasing number of ICU patients (15, 17). Approximately one-third of patients are diagnosed with HIV infection during or just prior to ICU admission. At San Francisco General Hospital, respiratory failure is still the most common admission diagnosis in the ART era, but this diagnosis has decreased from previous levels while admissions for conditions such as sepsis and cardiac disease have increased (18). In London, admissions for non-PCP pneumonia, neurological disorders, and postcardiac arrest have increased over time (17). Survival subsequent to hospital discharge among HIV-infected patients in London during the post-ART era is almost 70%, which is similar to that of the general medical population and has improved compared with the pre-ART era. Low hemoglobin, high APACHE score, and need for mechanical ventilation continue to be predictors of higher mortality (17, 18).

Two developments in HIV and general ICU care are important to consider in the care of HIV-infected critical care patients. First, ART has altered the spectrum of ICU admission diagnoses, but its effect on survival to hospital discharge is less clear. In an observational study, the San Francisco group reported that mortality for subjects with PCP who received ART in the ICU was 25% compared with 63% for those who did not receive ART ($P = 0.03$) (19). The London group found a low mortality for severe PCP during the combination ART era, despite the fact that none of their patients received ART regimens, suggesting that the association of ART and survival found in the San Francisco General Hospital cohort may not have been causal (20). Low tidal volume ventilation might instead have contributed to recent improvements observed in ICU outcomes both for patients with PCP and for those with other causes of acute lung injury. A study from San Francisco General Hospital that specifically examined the relationship of survival to ventilatory strategy in patients infected with HIV found that lower tidal volumes were independently associated with mortality reduction (odds ratio = 0.76 per 1 ml/kg decrease) (21). As HIV and ICU treatments continue to evolve, it will be important to evaluate the impact of new interventions on ICU mortality.

PULMONARY IMMUNITY IN HIV

Replication of HIV in the Lung

The epidemic spread of HIV infection and identification of the virus was closely followed by a massive research effort focused on the biology of HIV replication in the human host. In addressing

HIV replication in the lung, at least two major issues require further study: the compartmentalized kinetics of lung HIV replication and the importance of lung-specific HIV reservoirs.

Studies in primates infected with the simian immunodeficiency virus (SIV) demonstrate that acute infection results in a rapid increase, and then a reduction, of SIV RNA expression in the lung. The lung replication, however, is significantly compartmentalized, as plasma viral levels do not correlate with bronchoalveolar lavage (BAL) levels (22). In humans, comparisons of HIV replication in serum and in alveolar lining fluid indicate that there is little HIV replication in the lung when individuals are asymptomatic, but there is a significant increase in lung HIV replication when individuals develop pulmonary disease; in some instances lung HIV replication exceeds that in serum (23). Other investigations confirm that viral levels in BAL and plasma are not correlative, nor do they vary consistently with clinical status (24). Lung memory CD4$^+$ T cells are not infected by HIV as extensively as those in the gut, and alveolar macrophages have lower infection rates than macrophages obtained from other compartments (24).

Differential regulation of HIV infection in the lung also produces unique reservoirs of infection. In comparison to other compartments, the lung is continually exposed to aerosolized antigens and microorganisms, and there is significant potential for oxidative stress. Investigations have focused on the role of *M. tuberculosis* in modulation of HIV replication in alveolar macrophages, specifically control of replication by the CCAAT/ enhancer binding protein (C/EBP) (25). These studies demonstrate that HIV replication in the lung increases during *M. tuberculosis* infection, and that *M. tuberculosis* induces an isoform of C/EBP that results in enhanced HIV replication. Similarly, redox regulation of HIV replication may differ significantly in the lung and in other compartments, with oxidative stress leading to viral replication.

Lung Innate Immunity

Although much clinical and scientific attention has focused on adaptive immunity in HIV infection, HIV infection also has significant modulatory effects on innate immunity. HIV influences both the humoral and cellular components of innate immunity; these alterations are specific and are evident even with relatively preserved CD4$^+$ T cell counts and undetectable viral loads. Impaired innate immune function, particularly in the setting of CD4$^+$ T cell depletion, may contribute to the pathogenesis of opportunistic lung infections. Altered innate immunity in early clinical stages of HIV infection contributes to increased risk of *M. tuberculosis* infection and bacterial pneumonia. Finally, modulation of lung innate immune components may provide a therapeutic strategy as adjunctive treatment for pulmonary infections in HIV-infected individuals.

Studies examining responses to bacterial pathogens identify significant defects in innate immune responses during HIV infection. Phagocytosis of bacteria by human alveolar macrophages does not appear to be influenced by HIV infection (26), and thus other mechanisms must be important. Considerable interest has focused on signaling through toll-like receptors (TLRs), as deficiencies in signaling have been associated with a variety of infections. TLR5 polymorphisms are associated with susceptibility to *Legionella pneumophila* infections (27), TLR4 polymorphisms are associated with a trend toward increased mortality in the systemic inflammatory response syndrome (28), and interleukin-1 receptor-associated kinase (IRAK)-4 deficiency is associated with recurrent pyogenic infections (29). In considering HIV, activation of HIV-infected human macrophages by TLR4 results in impaired TNF-α release compared with release from uninfected macrophages (30); this effect is relatively specific as IL-10 release is not impaired (31).

Mechanisms of *Mycobacterium tuberculosis* Susceptibility in HIV

Although infection with *M. tuberculosis* remains a worldwide problem fueled by the HIV epidemic, significant issues remain unresolved regarding the pathogenesis of TB in HIV-infected individuals. Some of these issues include understanding the effect of declining CD4$^+$ T cells in the periphery and the mucosa, evaluating the importance of alveolar macrophage responses, and addressing the importance of *M. tuberculosis*-HIV co-infections.

M. tuberculosis infection clearly impacts HIV progression and mortality (32), and disease from *M. tuberculosis* increases in HIV-infected patients as CD4$^+$ T cell counts decline. Less well-appreciated are the qualitative defects that occur in immune cells from HIV-infected individuals. For example, peripheral blood mononuclear cells from individuals co-infected with *M. tuberculosis* and HIV secrete less IFN-γ than cells from non-HIV-infected individuals with *M. tuberculosis* infection (33). Furthermore, the frequency of *M. tuberculosis*-specific CD4$^+$ T cells that secrete IL-2 decreases with increasing HIV viral loads (34).

The alveolar macrophage's role in host defense against *M. tuberculosis* remains an area of active investigation. Once *M. tuberculosis* is phagocytosed by alveolar macrophages, phagosome maturation and acidification is required for effective killing. In HIV-infected individuals, it appears that phagosomes do not acidify adequately and so organisms persist (35). This may be one mechanism by which alveolar macrophages from HIV-infected individuals do not limit growth of *M. tuberculosis* despite increased phagocytosis (36). There are also significant defects in cytokine production, including decreased production of macrophage inflammatory protein-1β (37). Research demonstrates that HIV infection impairs *M. tuberculosis*-mediated apoptosis of alveolar macrophages (38); this defect likely impairs effective antigen presentation in the lung.

Although significant progress in our understanding has been made, there are several important issues that need to be addressed in this field. An improved understanding of T-cell, particularly of lung T-cell, responses to *M. tuberculosis* in persons with latent TB infection (LTBI) is needed. Further exploration of effector functions required for protection against primary infection and reactivation is also needed. The mechanisms for impaired alveolar macrophage function during HIV infection require additional investigation, including whether these effects result directly or indirectly from HIV infection of these cells. Finally, an improved understanding of antigen presentation during HIV infection could lead to more effective prophylactic and therapeutic approaches.

Effects of HIV Therapy on Pulmonary Immunity

As successive generations of antiretroviral medications have become available, control of HIV replication has become a more realistic goal, at least in populations for whom the drugs are accessible and affordable. Immune responses after ART initiation are not as well understood as the changes in immune function during untreated HIV infection. Previous work has demonstrated that initiation of ART decreases the detection of HIV in BAL, compared with lavages obtained from individuals not receiving ART (39), but immunologic correlates of this observation require further study. To address this question, a prospective study was conducted under the auspices of the Adult AIDS Clinical Trials Group in which blood and BAL were obtained from HIV-infected subjects starting ART and again after 4 weeks, 24 weeks,

and 52 weeks (optional) (40). ART was associated with a delayed but significant decrease in absolute number and percentage of alveolar lymphocytes. This decline was due exclusively to decreased absolute numbers of CD8^{+} lymphocytes in the alveolar space. ART also resulted in decreased activated lung CD8^{+} T cells, primarily in those individuals who had good pulmonary virologic responses to ART. Furthermore, ART was associated with increases in CD8^{+} naive and central memory cells and decreases in CD8^{+} effector memory cells in the lung, suggesting the lung was repopulating its CD8^{+} lymphocyte pool from the peripheral circulation. CD4^{+} lung lymphocytes were not changed, suggesting that longer therapy courses may be necessary to affect changes in this population.

ART also induced a significant decline in BAL concentrations of proinflammatory cytokines and chemokines. Despite these decreases, both IFN-γ and the IFN-γ inducible chemokines (inducible protein [IP]-10, monokine induced by IFN-γ [MIG]) remained easily detectable in both HIV-infected subjects and normal volunteers. These chemokines contribute to the recruitment of memory cells to the lung (41). Furthermore, there was a correlation between the number of lymphocytes in the alveolar space and the concentration of IP-10 and MIG, but not other chemokines such as IL-8 or RANTES. This correlation was weak in untreated subjects, but strengthened markedly with time on ART.

Based on these findings, one can propose a model wherein untreated patients have unchecked HIV in the lung leading to generalized cellular activation and augmented cytokine and chemokine secretion (Figure 1). This activation promotes a nonspecific influx of inflammatory cells to the alveolar space. The large amount of nonspecific cytokine and chemokine secretion leads to a relatively poor correlation between lung lymphocyte numbers and chemokine concentrations. With ART, pulmonary viral load and cellular activation decreases, and nonspecific cytokine secretion resolves. Low-level IFN-γ production from resident memory cells remains (42), which maintains BAL concentration of IFN-γ inducible chemokines leading to normal trafficking of these cells into the lung and a tighter relationship between BAL chemokine concentrations and lung lymphocyte numbers. ART may also alter signaling through toll-like receptors, as TLR2-mediated mononuclear cell chemokine production may be decreased by ART (43).

Animal Models in Investigation of Lung Host Defense

As detailed above, there are multiple mechanisms by which HIV infection alters pulmonary host defense mechanisms (44). Because of the inherent difficulties present in studying pulmonary host defense in HIV-infected humans, animal models have been important in the delineation and modulation of these defects. A primary experimental barrier is the strict tropism of HIV for human cells, making direct use of HIV in animal models problematic. These models are summarized in Table 1, including a brief discussion of their advantages, disadvantages, and utility for the study of pulmonary host defense.

OPPORTUNISTIC INFECTIONS

Bacterial Pneumonia

Respiratory tract infections remain a major cause of morbidity and mortality among HIV-infected persons. Following the introduction of ART, the incidence of HIV-associated pneumonias has decreased, and bacterial pneumonia has replaced PCP as the most frequent HIV-associated pneumonia in the United States. Although the relative proportion of pneumonias secondary to bacterial pneumonia has increased, ART has been related to
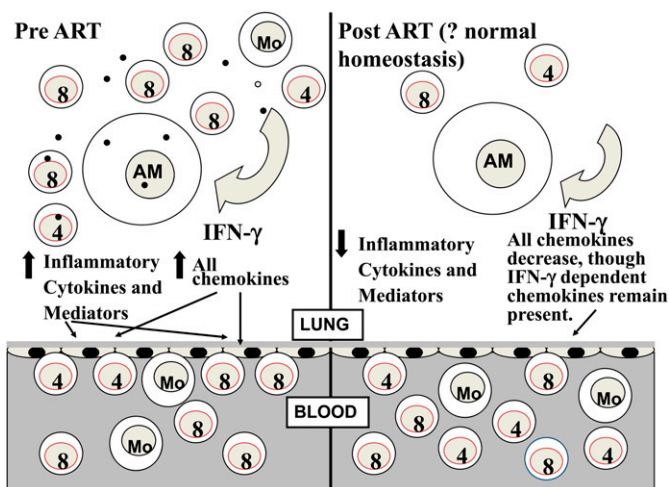

Figure 1. Model of HIV and lung immune response before and after antiretroviral treatment. AM, alveolar macrophage; ART, antiretroviral therapy; MO, monocyte; 4, CD4 T cell; 8, CD8 T cell.

a significant decrease in the absolute incidence of bacterial pneumonia (45, 46). ART and trimethoprim-sulfamethoxazole used for PCP prophylaxis have been associated with decreases in risk of bacterial pneumonia, whereas lower CD4^{+} T cell count and cigarette smoking have been associated with increases (47). The prevalence of cigarette smoking among HIV-infected persons is high, with many smoking more than 1 pack per day (48). Cigarette smoking appears to attenuate the immunological and virological responses to ART (48). *S. pneumoniae* is the most frequently identified etiology of HIV-associated bacterial pneumonia and incidence of bacteremia is increased in HIV-infected persons. Among persons with bacteremic pneumococcal pneumonia, HIV infection is associated with an increased mortality (49). Current guidelines recommend the 23-valent polysaccharide pneumococcal vaccine for HIV-infected persons, especially in persons with CD4^{+} cell counts greater than 200 cells/μl in whom the development of protective antibodies may be more likely (50).

Tuberculosis

Worldwide, TB is the dominant HIV-associated pneumonia, and it is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*. HIV-infected persons with a positive test for LTBI and/or symptoms or signs of TB should be ruled out for active disease (50). IFN-γ release assays (IGRAs) such as the QuantiFERON-TB Gold and T-Spot.TB tests, are more sensitive and specific than tuberculin skin tests (TST) for detecting LTBI, and IGRA results are less affected by low CD4^{+} T cell counts than TST. Treatment of LTBI in HIV-infected individuals is strongly recommended given the high rate of progression from latent to active TB (50). The preferred treatment regimen is 9 months of isoniazid and pyridoxine (50).

The treatment of TB in HIV-infected patients is the same as in HIV-uninfected patients, except that a once-weekly rifapentine regimen is not recommended, and twice-weekly rifampin or rifabutin are not recommended in the subset of persons with a CD4^{+} T cell count less than 100 cells/μl (50). Ensuring completion of treatment is essential and directly observed therapy is highly recommended. In those receiving ART, clinicians must be alert for drug–drug interactions and the immune reconstitution inflammatory syndrome (IRIS).

TABLE 1. COMPARISON OF VARIOUS ANIMAL MODELS OF HIV

Model	Host	Advantages	Disadvantages	Utility for Host Defense Investigation
SIV	Macaques	• Uses HIV-related lentivirus • Intravenous inoculation of virus results in disseminated tissue infection after 14 days (40) • Most CD4$^+$ memory cells are eliminated within days of infection, and subclinical opportunistic infections appear after several weeks	• Clinical disease progression is quite slow (approximately 1 year after infection) • Expense • Restricted availability of animals • Need for a primate center • Evolution of the virus over time	• SIV-infected macaques become colonized and infected with *Pneumocystis*, with BAL demonstrating increased numbers of neutrophils and lymphocytes (41) • Longitudinal studies have demonstrated that inoculation with *Pneumocystis* results in prolonged increases in peripheral blood CD8$^+$ T cells with profound depletion of CD4$^+$ T cells (42)
SHIV	Primates	• Aggressive viruses with progression to AIDS and eventual animal death after about 4 months	• Most experimentation has been focused on vaccine studies • Short interval between infection and death has limited use	• Plasma antibody responses to *Pneumocystis* inoculation can be followed over a period of weeks as SHIV infection progresses (44)
MAIDS (murine AIDS)	Rodents	• Leukemia virus that produces lymphoproliferative disease and immunosuppression (45)	• Nonselective CD4$^+$ T cell depletion • Functions as a superantigen, inducing polyclonal T and B cell proliferation • Marked differences in viral structure compared with HIV • Only some mouse strains are susceptible	• Limited because of non-selective immunosuppression
SCID-hu	SCID mice	• Transfer of fetal human liver and thymus cells into SCID mice (46)	• Can only be used to study primary immune responses to HIV • Uses tissues of fetal origin	• Limited because of primary immune responses
Hu-PBL-SCID	SCID mice	• Utilizes transfer of human peripheral blood mononuclear cells into SCID mice	• No primary immune response to HIV • T cells are anergic	• Limited because of model
Trimera	Mice	• Normal mice are irradiated, reconstituted with SCID bone marrow, and then reconstituted with human peripheral blood lymphocytes (47) • Allows study of primary and secondary immune responses	• Engraftment is transient	• Complexity presents considerable barriers to study of pulmonary host defense
AIDS-like immunosuppression	Various mammals	• Corticosteroid treatment (48) • Depletion of CD4$^+$ T cells with monoclonal antibodies • CD4-knockout mice • Selective reconstitution of SCID mice with CD4-depleted cell populations • Less expensive • Use variety of mouse strains and transgenics	• Models necessarily reductionist as do not use retroviral infections	• Applicable for testing hypotheses using specific hosts and organisms

Definition of abbreviations: SCID, severe combined immunodeficiency; SHIV, simian-human immunodeficiency chimeric virus; SIV, simian immunodeficiency virus.

Nontuberculous Mycobacterial Disease

Non tuberculous mycobacteria (NTM) most often cause disseminated disease in HIV-infected persons, with *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* accounting for the majority of disseminated NTM cases. HIV-infected persons with disseminated MAC typically present with fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain and may have lymphadenopathy, hepatomegaly, and/or splenomegaly. The diagnosis of disseminated MAC requires isolation of the organism from blood, lymph node, bone marrow, or other sterile sites.

IRIS (discussed subsequently in this review) occurs commonly in patients with mycobacterial infections (*M. tuberculosis* and MAC). MAC-IRIS most frequently presents with focal lymphadenitis, but pneumonitis, pericarditis, osteomyelitis, skin and soft tissue abscesses, and central nervous system (CNS) involvement also occur. There is often an absence of mycobacteremia. Treatment options for MAC-IRIS include nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone for moderate to severe cases; occasionally surgical drainage of affected nodes is needed.

M. kansasii is less common than TB or MAC. Pulmonary disease is more common than extrapulmonary/disseminated disease. Presenting symptoms include fever, cough, dyspnea, and weight loss. Radiographic findings include alveolar and interstitial infiltrates, thin-walled cavities, nodules, pleural effusions, and lymphadenopathy (51).

Fungal Pneumonias

Fungi remain an important cause of HIV-associated pneumonia. *Pneumocystis, Cryptococcus*, *Histoplasma*, and *Coccidioides* are the most frequent etiologies but *Blastomyces, Aspergillus*, and *Penicillium* also occur. Cryptococcosis occurs at advanced stages of HIV infection. *Cryptococcus neoformans* is the usual pathogenic species in the U.S. HIV-infected patients with cryptococcal disease most often present with meningitis with fever, weight loss, headache, and confusion. Pneumonia is less frequent. Serum cryptococcal antigen tests can be useful in diagnosis and the organism is readily cultured from respiratory secretions, blood, and cerebrospinal fluid. Fluconazole or itraconazole are recommended for initial treatment of mild pneumonia, and amphoter-

icin B plus flucytosine is recommended for severe pneumonia, meningitis, or disseminated disease (50).

Histoplasmosis occurs in persons with CD4+ T cell counts less than 50 cells/μl. *Histoplasma capsulatum* var. *capsulatum* predominates. HIV-infected persons with histoplasmosis usually present with disseminated disease with fever, weight loss, and respiratory symptoms. The chest radiograph often reveals diffuse reticulonodular infiltrates. The urine *Histoplasma* antigen test and microscopic examination of stained respiratory specimens are the mainstays of diagnosis. Amphotericin B (and liposomal amphotericin for those with renal insufficiency) is recommended for initial treatment (50).

Coccidioidomycosis occurs at advanced stages of HIV infection. *Coccidioides immitis* and *C. posadasii* are the main pathogenic species. HIV-infected persons often present with pneumonia or disseminated disease. Chest radiography typically reveals bilateral nodular or reticulonodular infiltrates. Diagnosis is usually established by microscopy or culture. Fluconazole or itraconazole are recommended for initial treatment of focal or cavitary pneumonia, and amphotericin B is recommended for severe, diffuse pneumonia (50).

Pneumocystis Pneumonia

Although its incidence has declined in the ART era, PCP remains a frequent AIDS-defining diagnosis. PCP mortality has improved over the course of the AIDS epidemic (52). Bronchoscopy with BAL remains the gold standard procedure for PCP diagnosis, but noninvasive tests using oropharyngeal washes combined with polymerase chain reaction (PCR) and plasma S-adenosylmethionine measurements appear to be both sensitive and specific tests for PCP (53, 54). Unfortunately, neither of these tests is widely available clinically.

Trimethoprim-sulfamethoxazole is the first-line recommended treatment for PCP (50), and one systematic review reports that clindamycin plus primaquine is an effective second-line regimen (55). Concern has been raised over potential development of trimethoprim-sulfamethoxazole drug resistance in the form of non-synonymous mutations in the human *Pneumocystis* dihydropteroate synthase (DHPS) gene, the enzymatic target of sulfamethoxazole and dapsone, a sulfone (56). These mutations have only been observed in human *Pneumocystis* (57) and not in *Pneumocystis* isolated from non-human mammals.

Multiple studies report that *Pneumocystis* or *Pneumocystis* DNA can be detected in respiratory specimens from a host of populations in the absence of PCP (58). These individuals are considered to be colonized with *Pneumocystis*. In young children, *Pneumocystis* colonization is associated with upper respiratory tract illness (59, 60). In adults, colonization has been associated with smoking and chronic obstructive pulmonary disease (COPD) (61, 62). Animal models also suggest an association with development of COPD (63, 64).

Empiric Therapy versus Definitive Diagnosis of HIV-Associated Pneumonias

Each of the HIV-associated pneumonias has a characteristic clinical and radiographic presentation, and an empiric approach in these cases may be justified. Many of the arguments for and against empiric therapy of HIV-associated pneumonia have involved PCP insofar as *Pneumocystis*, unlike the other significant respiratory pathogens, cannot be cultured, and the gold standard diagnosis of PCP relies on bronchoscopy, an invasive and expensive procedure. There is no universal agreement on the best approach to managing suspected PCP, with some advocating definitive diagnosis and others arguing for empiric therapy (65, 66).

NONINFECTIOUS COMPLICATIONS

Lung Cancer

HIV-infected patients have an increased rate of non–small cell lung cancer, but whether this increased risk is solely due to heavier smoking in HIV-infected patients has been controversial. In a study by Kirk and colleagues, HIV infection was associated with a hazard ratio of 3.6 for lung cancer (95% confidence interval [CI], 1.6–7.9) after controlling for smoking status as well as for age, sex, and calendar period (67). Similarly, in a study by Engels and colleagues, HIV infection was associated with a standardized incidence ratio of 2.5 (95% CI, 1.6–3.5) for lung cancer, adjusting for estimates of smoking prevalence (68). These studies support that hypothesis that HIV is an independent risk factor for lung cancer, even in the current ART era.

The clinical presentation of lung cancer in HIV-infected patients is similar to that in HIV-uninfected patients. Most HIV-infected patients who develop lung cancer are cigarette smokers. Lung cancer occurs at a wide range of CD4+ T cell counts with no apparent relationship between CD4+ T cell count, plasma HIV viral levels, and use of ART with lung cancer risk (67). HIV-infected patients may present with lung cancer at a younger age than those without HIV. Although all pathologic types are seen, adenocarcinoma and squamous cell carcinoma are the most frequently reported (68, 69).

Mechanisms to explain the increased risk of lung cancer in HIV are not fully understood, and whether HIV plays an oncogenic role in the development of lung cancer is not clear. Microsatellite alterations have been identified in tissue samples of lung cancer in HIV-infected patients at a greater rate than in tumors of HIV-uninfected patients (70). Although no association with lung cancer risk and systemic CD4+ cell counts or plasma HIV viral levels have been identified, decreased immune surveillance or impaired immune function are possible contributing factors. Cigarette smoking has been associated with decreased markers of lung immune function in HIV-infected patients (71, 72). An enhanced susceptibility to carcinogens or the occurrence of lung injury as a result of prior infections may also be involved in the increased risk for lung cancer in HIV.

Diagnosis and treatment of lung cancer in HIV-infected patients is similar to that in non–HIV-infected individuals. Overall, prognosis for HIV-infected patients with lung cancer is poor, with average survival of 10% at 24 months (73). Lung cancer screening is not recommended in the general population; whether HIV-infected smokers represent a group that might benefit from screening and early detection is not known.

Chronic Obstructive Pulmonary Disease

Observational studies have demonstrated an increased prevalence of COPD among HIV-infected patients. This risk is independent of other risk factors for COPD, including smoking, illicit drug use, and previous pulmonary opportunistic infections. In one study conducted largely prior to ART, the prevalence of emphysema by chest computed tomography was significantly higher in HIV-infected subjects (15%) compared with the HIV-seronegative subjects (2%, $P = 0.03$) (74). In a study during the combination ART era, an independently increased prevalence of COPD by ICD-9 codes was also demonstrated in HIV-infected veterans compared with HIV-uninfected veterans (75). Reasons for increased COPD in HIV-infected patients are not completely understood. HIV-associated factors may play a role. For example, HIV infection may result in increased pulmonary inflammation, including increased numbers of CD8+ T cells and IFN-γ production in the alveolar space (76, 77). Altered antioxidant balance occurs in HIV infection, and BAL glutathione levels

decrease over time (78). HIV itself and its peptides may also induce apoptosis of endothelial cells, an important factor in the pathogenesis of COPD (79, 80).

Microbial colonization of the respiratory tract may play a key role in the pathogenesis of COPD in the HIV-uninfected population, and it is likely that infections are also important in COPD pathogenesis in HIV-infected patients. Lung infections could perpetuate lung injury and inflammation, thus contributing to COPD progression (81). The role of *Pneumocystis* in the pathogenesis of COPD is of particular interest in HIV, as HIV-infected patients are commonly colonized with *Pneumocystis* (61), and lung colonization has been associated with COPD severity in HIV-uninfected patients (62).

The role of ART in the development or progression of COPD in HIV-infected patients is under investigation. One intriguing study reported that ART use was an independent predictor of airflow obstruction (82). ART might be associated with COPD either through direct effects of antiretroviral medications, through development of a "modified immune reconstitution inflammatory syndrome" to low levels of pathogens or self-antigens, or through some modifying factor associated with ART use (82).

Pulmonary Arterial Hypertension

Studies have reported an increased frequency of PAH in HIV-infected populations with a prevalence of 0.5% to 0.8% (83, 84). In addition, preclinical disease may be more common than previously thought with one study finding that 35% of HIV-infected subjects had pulmonary arterial systolic pressures greater than 30 mm Hg on screening echocardiography (85).

PAH symptoms are similar in HIV-infected and HIV-uninfected patients and include progressive dyspnea, pedal edema, nonproductive cough, fatigue, syncope, and chest pain (86). Many HIV-infected patients with PAH have an injection drug-use history that further contributes to elevated pulmonary pressures (85). There is no apparent relationship with plasma HIV viral levels or CD4$^+$ cell counts. Pathologic findings are typical of plexogenic pulmonary arteriopathy. Most patients die of progressive right heart failure and/or sudden death, rather than from AIDS-related causes (86).

Pathogenesis of PAH in HIV infection is not fully understood. Potential HIV-related mechanisms include stimulation of endothelin by HIV glycoprotein-120, stimulation of cytokines and growth factors by chronic HIV infection, or involvement of HIV trans-activator of transcription (Tat) or HIV negative factor (nef) antigen (87, 88). Nef is an abundant early viral protein and is believed to play an important role in pathogenesis and progression of AIDS, as well as a potential role in HIV-PAH (89). The role of co-infection with human herpesvirus 8 in HIV-associated PAH is unclear (85).

Limited studies exist to guide therapy for PAH in HIV. Epoprostenol and bosentan result in improved functional and hemodynamic parameters in small studies of HIV subjects with PAH (90). Other treatments such as sildenafil and iloprost may also be useful (91, 92). Whether ART improves PAH in HIV infection is controversial. Studies from the Swiss HIV Cohort Study suggest that HIV-infected patients treated with antiretroviral medications have decreased right ventricular systolic pressures and improved survival (83, 93). On the other hand, another study found that patients receiving combination ART were almost three times more likely to develop PAH compared with HIV-infected patients on nucleoside reverse transcriptase inhibitors alone (94), and laboratory-based work has found increased endothelial dysfunction associated with ART exposure (95). Another study has demonstrated an increased incidence of PAH in patients on combination ART compared with those not

on these medications (96). These data are difficult to interpret given the overall increased survival of patients on combination ART and thus increased opportunity to develop PAH.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS; also called immune reconstitution syndrome, IRS) describes a paradoxical worsening of clinical status related to recovery of the immune system after immunosuppression, as can occur after the initiation of ART in HIV-infected patients. IRIS is thought to result from immune system reconstitution leading to host inflammatory responses to previously recognized or subclinical infections. IRIS may also result from an inflammatory or immune response to cancer or self-antigens, as cases of IRIS have been reported to present with worsening tumors or autoimmune disease (97, 98). Among infections, mycobacterial infections, particularly *M. tuberculosis* and MAC, are most frequent. Fungal infections including *Cryptococcus* and PCP or viral infections such as cytomegalovirus can also be associated with IRIS. Initiating ART in close proximity to treatment for an acute opportunistic infection increases risk of IRIS (99, 100). Patients who develop IRIS are more likely to be antiretroviral naive at ART initiation (101). Lower CD4$^+$ cell counts are also associated with IRIS (102–104).

Common presenting symptoms of IRIS consist of fever and lymphadenopathy. Specific chest radiographic patterns of disease include pulmonary infiltrates, nodules or masses, intrathoracic lymphadenopathy, and pleural effusion. Diagnosis of IRIS is essentially one of exclusion of other causes. The majority of IRIS cases occur within the first 1 to 3 months after ART initiation, although cases may present months later (105).

The pathogenesis of IRIS is incompletely understood. Possible mechanisms include a normal response to high antigen burden versus an exaggerated response by the recovering immune system, excessive production of proinflammatory cytokines, or a deficiency in immune regulatory cytokines (106–108). Early forms of infectious IRIS are thought to result from immune responses to viable organisms from either known opportunistic infections or undetected, subclinical infections.

Most cases of IRIS are mild in severity, and outcomes are generally good with supportive therapy. Nonsteroidal antiinflammatory drugs and steroids may be used to treat excessive inflammation (54). In general, patients on ART can continue their regimens. When to start ART in patients with opportunistic infections remains controversial (54), although data are beginning to emerge that early ART may be beneficial. Unfortunately, studies have not specifically addressed the timing of ART initiation in critically ill patients, where toxicity from ART and inflammatory reactions could potentially cause significant harm, but the risks associated with delaying ART may also be enhanced. Further research is needed to better understand the incidence, risk factors, optimal management, and pathogenesis of IRIS.

CONCLUSION

HIV-associated pulmonary diseases remain a major cause of morbidity and death in HIV-infected patients worldwide. The epidemiology, manifestations, and outcomes of pulmonary disease vary depending on availability of ART, and noninfectious conditions may become more common in the current era of the AIDS epidemic, particularly in those with access to ART. Because of the importance of HIV-associated pulmonary diseases and the rapidly evolving understanding of their pathogenesis and epidemiology, we convened a workshop of experts to discuss

current trends and emerging issues in HIV-associated pulmonary disease. This document summarizes that workshop.

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Members of the Writing Committee:
ALISON MORRIS, M.D., M.S. (*Chair*)
JAMES M. BECK, M.D.
KRISTINA CROTHERS, M.D.
LAURENCE HUANG, M.D., M.A.S.

Workshop Participants:
ALISON MORRIS, M.D., M.S. (*Chair*)
JAMES M. BECK, M.D.
DAVID COHN, M.D.
CHARLES L. DALEY, M.D.
PHILIP C. DIAZ, M.D.
KRISTINA CROTHERS, M.D.
CHARLES FELDMAN, M.D.
SONIA FLORES, Ph.D.
HENRY KOZIEL, M.D.
MICHAEL IEONG, M.D.
LAURENCE HUANG, M.D., M.A.S.
ANDREW LIMPER, M.D.
HENRY MASUR, M.D.
MARK METERSKY, M.D.
ROBERT MILLER, M.D.
JOHN F. MURRAY, M.D.
NAIMISH R. PATEL, M.D.
HOMER TWIGG, M.D.

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