Chapter 12
Lung Disease in Older Patients with HIV*

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Keywords Lung disease • Older patients • HIV • Antiretroviral therapy • Non-HIV-associated comorbid diseases • Respiratory symptoms • Pulmonary function • Chronic obstructive pulmonary disease • Pulmonary hypertension • Lung cancer

Background

Successful treatment of HIV with combination antiretroviral therapy (ART) has resulted in an aging HIV-infected population. As HIV-infected patients are living longer, noninfectious pulmonary diseases are becoming increasingly prevalent with a proportional decline in the incidence of opportunistic infections (OIs). Pulmonary OIs such as *Pneumocystis jirovecii* pneumonia (PCP) and tuberculosis are still responsible for a significant proportion of pulmonary diseases in HIV-infected patients. However, bacterial pneumonia (BP) and noninfectious pulmonary diseases such as chronic obstructive pulmonary disease (COPD), lung cancer, pulmonary arterial hypertension (PAH), and interstitial lung disease (ILD) account for a growing number of pulmonary diseases in aging HIV-infected patients. The purpose of

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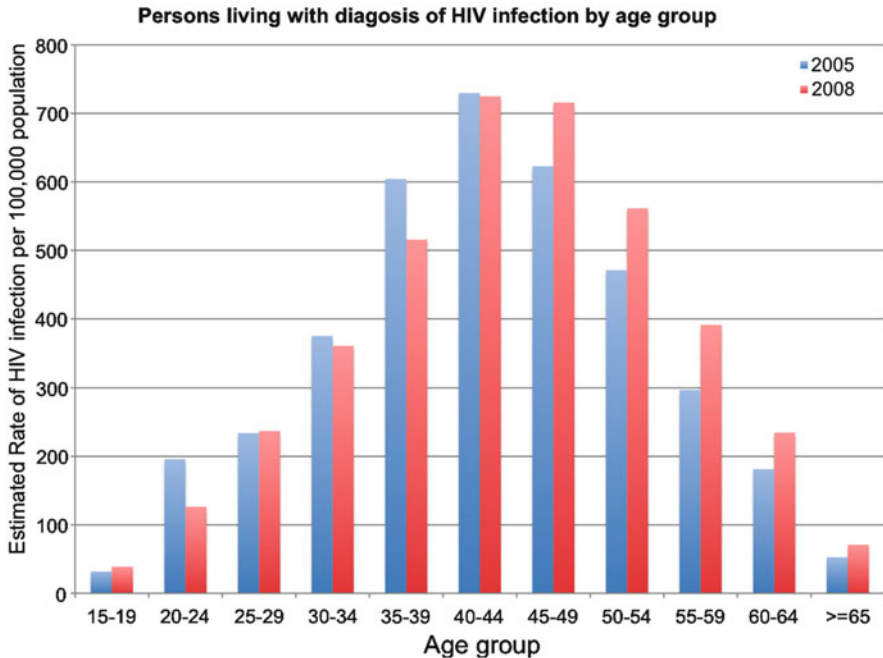e-mail: Kathleen.akgun@yale.edu

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this chapter is to discuss the spectrum and management of pulmonary diseases in aging HIV-infected patients, although limited data exists to guide management of many noninfectious pulmonary diseases in HIV-infected patients. In the absence of such data, treatment of lung diseases in HIV-infected patients should generally follow guidelines for management established in HIV-uninfected patients.

Aging and HIV: A Paradigm Shift

Life expectancy for HIV-infected patients receiving ART has improved significantly since the earliest HIV era. Older HIV-infected adults, defined as patients aged 50 years and older, comprised 25% of the HIV-infected population in 2007 (Fig. 12.1) [1, 2]. By 2015, half of the HIV-infected population is projected to be over 50 years of age [3]. Patients on successful ART with high baseline CD4+ T-cell counts may even reach their eighth decade [2, 4]. Despite these improvements, survival for HIV-infected patients still lags behind HIV-uninfected patients [5–13]. Increased comorbid disease, OIs, and HIV infection, itself, contribute to continued discrepancies in life expectancy between HIV-infected and uninfected patients despite the use of ART [5–13].

Fig. 12.1 Persons living with diagnosis of HIV infection by age group
http://www.cdc.gov/hiv/surveillance/resources/reports/2008report/table15b.htm and
http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/pdf/table15a.pdf

Antiretroviral Therapy

Antiretroviral therapy (ART) has transformed HIV from a universally fatal disease afflicting young people to a manageable chronic disease affecting and infecting older patients. Compared with the first therapies for HIV developed in the early 1990s, more recent combination ART is less toxic, easier to administer, and more effective. However, the ideal timing of ART initiation remains controversial. It has been well established that patients with CD4+ T-cell counts < 200 cells/mm^3 benefit from ART. More recent recommendations suggest that HIV-infected patients benefit from ART initiation when CD4+ T-cell counts are less than 350 cells/mm^3. Furthermore, untreated viremia in asymptomatic patients with CD4+ T-cell > 350 cells/mm^3 has been associated with progression of non-AIDS-related comorbid medical conditions such as cardiovascular, hepatic, and renal diseases [14–16]. In response these findings, some experts advocate for ART initiation even when CD4+ T-cell counts are greater than 350 cells/mm [3, 17]. However, the timing of ART initiation requires goals specifically tailored to the individual patient.

Age at ART initiation appears to influence response to therapy. Older HIV-infected patients started on ART have faster viral suppression, potentially related to improved adherence compared with younger HIV-infected patients [18, 19]. Yet, despite better adherence and at least comparable if not superior viral suppression, older HIV-infected patients who initiate ART still have lower on-treatment CD4+ T-cell counts, delayed improvement in CD4+ T-cell counts, shorter time to development of AIDS, and higher mortality [18–27]. One study showed that despite fewer AIDS-defining OIs in older patients (22% vs. 31% in younger patients, $p < 0.01$) and more rapid viral suppression, mortality was still significantly higher in older HIV-infected patients (37% vs. 27% in younger patients, $p = 0.04$) [18].

Aging, Changes in Immunity, and HIV Infection

While a comprehensive discussion of declining immunity associated with aging is beyond the scope of this chapter and is covered in greater detail in an earlier chapter, it is important to highlight immunologic changes common to both HIV infection and normal physiologic aging (Table 12.1). The HIV-infected immune system appears to be a model of multimorbidity and progressive immune dysfunction [3, 27]. The immune system of HIV-infected patients has been compared to that of HIV-uninfected patients 20–30 years older [3, 27–31]. HIV progression is strongly influenced by age at seroconversion and the time since seroconversion [1, 20, 32–38]. Patients diagnosed with HIV at age 50 years and older have lower baseline CD4+ T-cell counts compared with younger patients [14].

Many changes in the immune system that occur with HIV infection are similar to those that occur with normal physiologic aging (Table 12.1). HIV-infected persons experience a gradual but persistent loss of host immunity following infection that

Table 12.1 Changes in immunity in HIV infection and aging

Immunologic change	HIV-infected patients	Physiologic aging
T-cell subpopulations		
CD4+ cells		
Naïve cell number	Decreased	Decreased
Memory cell number	Decreased	Normal-high
Resting activation	Highly increased	Increased
Cytokine production	Low	Low-normal
CD8+ cells		
CD8+ CD57+	Increased	Increased
Naïve cell number	Decreased	Decreased
Memory cell number	Decreased	Normal-high
Resting activation	Highly Increased	Increased
Cytokine production	Low	Low-high
Senescent phenotype	Very high	High
B-cell subpopulation		
Naïve cell number	Normal-low	Normal-low
Memory cell number	Increased	Increased
Resting activation	Increased	Normal
Cytokine production	Increased	Normal
Total IgA and IgG level	Polyclonal increase	Normal
Memory response	Low-normal	Normal
Thymic involution	Increased	Increased

Adapted from Effros (2008)

results in a syndrome of immune deregulation, dysfunction, and deficiency. One of the earliest immunologic impairments seen in HIV infection, similar to aging, is depletion of gut-associated lymphoid tissue, predominantly due to loss of CD4+ T-cell lymphocytes of the effector memory type [39]. During the chronic phase of HIV infection, generalized immune activation occurs and ultimately, progressive decline in the naïve and memory T-cell pool results in systemic CD4+ T-cell lymphocyte depletion [39, 40]. Aging, likewise, results in a decline in CD4+ T-cell counts [3, 41, 42]. Decreased naïve T-cell reserve and thymic involution that occur in HIV-infected patients mirror changes associated with physiologic aging in an HIV-uninfected population [22, 25, 27, 43].

Similar to normal aging, B-cell and T-cell lines display qualitative as well as quantitative abnormalities in HIV infection. B-cell dysfunction can result in polyclonal activation, hypergammaglobulinemia, and lack of specific antibody responses. T-cell dysfunction can result in abnormal host responses to T-cell-dependent antigens. T-cells may also be abnormally activated in a resting state, and cytotoxic T-cell expansion and increased production of proinflammatory cytokines such as tumor necrosis factor-alpha and interferon gamma can occur [3, 44, 45]. In both HIV and physiologic aging, there is evidence of T-cell senescence, the hallmarks of which include decreased expression of costimulatory receptors, shortened telomeres, impaired replication, and excessive cytokine production [3]. Accelerated T-cell

immune senescence in aging HIV-infected patients may be partially explained by persistent antigen stimulation [3].

Dysfunctional and declining immunity may lead to increased susceptibility to OIs normally associated with advanced HIV infection in aging patients who are not HIV infected [42]. These changes in immunity that occur in both HIV infection and physiologic aging contribute to impaired host defenses and resultant increased susceptibility to a wide range of bacterial and fungal infections [3].

Non-HIV-Associated Comorbid Diseases in HIV

Aging HIV-infected patients are experiencing a growing burden of noninfectious comorbid diseases that likely contribute to excessive morbidity and mortality despite virologic control and immunologic response to ART [1, 5, 11, 34–38, 46–51]. Longer duration of HIV-infection leads to accelerated non-AIDS-related organ dysfunction, advanced physiologic aging, and frailty [14–16, 52, 53]. However, mechanisms for increased comorbid diseases in HIV-infected patients are not fully understood.

Increasingly prevalent comorbid diseases such as cardiovascular disease, renal disease, liver disease and pulmonary disease in HIV-infected patients may arise, in part, from physiologic changes classically associated with aging (Fig. 12.2) [5, 6, 11, 13, 31, 52–55]. HIV-infected patients are at increased risk of noninfectious pulmonary diseases such as COPD and lung cancer compared with HIV-uninfected individuals [1, 11, 34–38, 46–51]. While HIV-associated dementia has become less common since the introduction of ART, cognitive impairment is still common in patients with stable HIV disease, particularly those with multiple comorbidities [56, 57]. Furthermore, in a small series comparing functional magnetic resonance imaging (fMRI) of the brain in HIV-infected and HIV-uninfected patients, fMRI activity was decreased among HIV-infected patients to a level equivalent to HIV-uninfected patients 15–20 years older [58].

Frailty and HIV-Infected Patients

Multiple studies support the hypothesis that HIV infection results in advanced physiologic aging and progressive frailty even with successful ART use [3, 21, 29, 31, 52, 59–61]. Frailty is a clinical syndrome defined by the presence of at least three of the following factors: weight loss, low physical activity, exhaustion, weak grip strength, and slow walking time. HIV infection is associated with changes in the immune system that may contribute to development of frailty and accelerated progression to AIDS [29, 59, 61]. Frailty in HIV-infected patients has been increasingly recognized and may affect nearly 10% of patients evaluated in an outpatient setting [31, 52, 62]. Accelerated, progressive immune deficiency may contribute to the frailty phenotype, independent of ART use [31, 52]. As in HIV-uninfected patients

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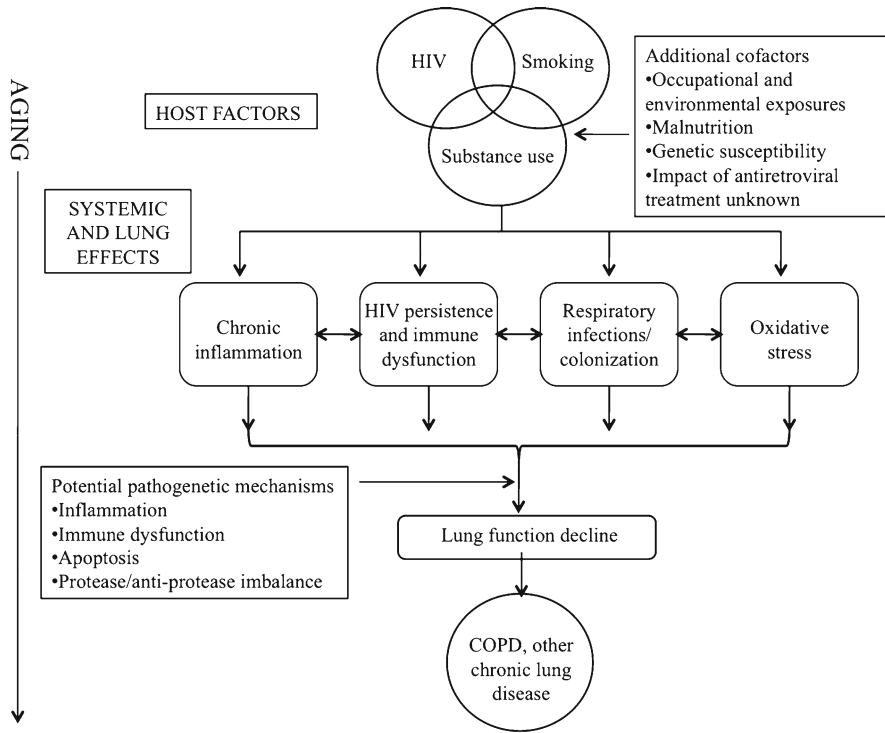
Fig. 12.2 Model for accelerated progression of chronic lung diseases among HIV-infected patients. Reprinted with permission of the American Thoracic Society. Copyright(c) American Thoracic Society. CITE: CROTHERS, K et al./2011/HIV Infection and Risk for Incident Pulmonary Diseases in the Combination Antiretroviral Therapy Era/AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE/VOLUME 183/PAGES 388–395. OFFICIAL JOURNAL OF THE AMERICAN THORACIC SOCIETY; DIANE GERN, Publisher

Table 12.2 Odds ratio of frailty phenotype and duration of HIV infection [52]

Duration of HIV (in years)	Including all person-visits			Excluding AIDS-related person-visits		
	Adjusted odds ratio	95% Confidence interval	p for trend	Adjusted odds ratio	95% Confidence interval	p for trend
0	1		<0.01	1		<0.01
4 or less	3.38	1.25–9.11		2.42	0.78–7.53	
4.01–8	12.95	6.60–25.40		4.17	1.52–11.45	
8.01–12	14.68	7.60–28.35		6.25	2.30–16.95	

[63–65], lower CD4+ T-cell counts are independently associated with frailty in HIV-infected patients, regardless of virologic response [31, 66]. In the Multicenter AIDS Cohort Study, frailty was equally prevalent in HIV-infected patients as in HIV-uninfected patients who were 10 years older, even in those with the shortest duration of HIV infection [52] (Table 12.2). In addition to low CD4+ T-cell count, HIV-specific risk factors for frailty also include longer time since diagnosis of HIV

and history of OIs [62, 66], and frailty in HIV-infected patients increases with duration of HIV infection [52]. Prevalence of the frailty phenotype in HIV declines with ART [31].

As seen in HIV-uninfected patients, additional factors associated with greater likelihood of frailty among HIV-infected patients are a greater burden of comorbid disease and lower serum albumin [62]. Psychosocial risk factors for frailty in HIV-infected patients are higher depression severity scores, treatment with antidepressant medication and unemployed work status [62]. Frailty, in addition to more advanced HIV disease and greater comorbid disease, are risk factors for higher hospitalization rates [62]. Hospitalizations likely further contribute to progressive frailty. Future research is needed to identify modifiable risk factors for frailty and to minimize frailty in aging HIV-infected patients.

Respiratory Symptoms and Aging

Respiratory symptoms such as dyspnea are common in older HIV-infected patients [67–72]. There are diverse etiologies for dyspnea, regardless of HIV infection. These include primary pulmonary pathology (e.g., obstructive lung disease, pulmonary fibrosis), pulmonary vascular disease (e.g., pulmonary hypertension), and comorbidities including cardiovascular disease (e.g., congestive heart failure, cardiac ischemia) and musculoskeletal disease (e.g., kyphoscoliosis, myopathy) (Table 12.3). A variety of pulmonary infections may also be responsible for more pulmonary symptoms in HIV-infected patients [13]. For example, prior infection with bacterial pneumonia or PCP is associated with long-term dyspnea and expiratory flow impairments on pulmonary function testing [73].

Functional decline and exercise intolerance appear to be accelerated in HIV-infected patients and can contribute to dyspnea. In an early case–control study of HIV-infected patients without OIs, pulmonary function on exertion and workload were significantly poorer in HIV-infected patients compared to HIV-uninfected controls [74]. HIV-infected patients were tachypneic compared with HIV-uninfected patients and had greater oxygen delivery impairment compared with similar HIV-uninfected patients [74].

Skeletal muscle weakness from muscle wasting or HIV myopathy may contribute to functional decline, exercise intolerance, and resultant dyspnea in HIV-infected patients [75]. In a small study comparing HIV-infected men without prior AIDS-related pulmonary complications (mean CD4+ T-cell count 331 cells/mm^3) to age- and weight-matched HIV-uninfected men, lower maximal inspiratory pressure and respiratory muscle endurance were found in HIV-infected patients [75]. Impaired respiratory muscle strength was associated with increased dyspnea compared with HIV-uninfected patients [75].

Risk factors for respiratory symptoms among HIV-infected patients include cigarette smoking, low CD4+ T-cell count, high HIV viral load, and lower pulmonary function [69, 76, 77]. In several studies, cigarette smoking is the strongest risk factor for dyspnea (in one such study, the odds ratio [OR] for respiratory symptoms in ever

Table 12.3 Causes of dyspnea in HIV-infected patients

Lung diseases
  Obstructive lung disease
    Emphysema/chronic obstructive pulmonary disease
  Asthma
    Bronchiectasis
  Interstitial lung disease
    Nonspecific interstitial pneumonitis (NSIP)
    Lymphocytic interstitial pneumonitis (LIP)
    Sarcoidosis
  Pulmonary vascular diseases
    Pulmonary arterial hypertension (PAH)
    Chronic thromboembolic disease (CTED)
    Other secondary causes of pulmonary hypertension
  Other
    Tuberculosis
    Prior PCP infection
    Recurrent pneumonia
    Sequelae of acute respiratory distress syndrome (ARDS)
    Kaposi sarcoma
    Diseases of the pleura
Cardiovascular diseases
  Congestive heart failure
  Cardiomyopathy
Neuromuscular causes
  Skeletal muscle weakness
Metabolic
  Anemia
  Thyroid disease
Other
  Hepatopulmonary disease
  Deconditioning
  Frailty

vs. never smoker was 2.7, 95% confidence interval [CI] = 1.41–5.22, $p = 0.003$) [69, 71, 72, 76]. Considering that nearly 50% of HIV-infected patients smoke, respiratory symptoms are likely to become increasingly more prevalent in aging HIV-infected patients [78], unless improved rates of sustained smoking cessation can be achieved in this population.

Lower CD4+ T-cell count (less that 200 cells/mm^3) is also a risk factor for dyspnea in HIV-infected patients [69, 77]. Other pulmonary symptoms such as cough, phlegm, and wheeze, are more common in HIV-infected patients regardless of CD4+ T-cell count [69]. Increased respiratory symptoms were reported even in the absence of AIDS-related pulmonary complications such as PCP or recurrent bacterial pneumonia [69]. Higher log plasma HIV viral levels and lower forced expiratory volume in one second/forced vital capacity (FEV$_1$/FVC) are also risk factors for respiratory symptoms in HIV-infected patients [76].

Pulmonary Function and HIV

Several studies have evaluated the prevalence of pulmonary function test abnormalities in the setting of HIV infection. The most commonly encountered abnormality in this population is a decrease in the diffusing capacity of the lung (D_LCO). Impairments in D_LCO have been reported since the earliest HIV era [68, 77, 79–81]. In a cohort of 1,294 HIV-infected patients without AIDS-related diagnoses during the pre-combination ART, isolated impairment of D_LCO was common, particularly among injection drug users [77]. Recent studies continue to report impaired D_LCO in HIV-infected patients as an early and prominent feature of HIV-associated pulmonary disease [81]. Early emphysematous changes that correlate with D_LCO impairment have also been identified on chest CT scan [68].

Black race, injection drug use and cigarette smoking are risk factors for impaired D_LCO [77]. In the pre-combination ART, recurrent pulmonary infections were suspected as the main contributor for D_LCO impairment in HIV-infected patients [77], and declining D_LCO may herald the onset of PCP [80]. Recurrent pulmonary infections are likely to worsen lung function, which may, in turn, contribute to greater susceptibility to repeat infections. Changes in pulmonary function encountered with aging in HIV-infected patients include a decrease in FEV_1/FVC with advancing age, similar to that seen in HIV-uninfected patients [76].

Airway hyper-responsiveness (AHR) in HIV-infected patients was first suspected in persons with AIDS during the pre-ART era [82]. However, when formally evaluated with methacholine challenge, results linking HIV with increased risk of AHR have not been consistent [83, 84]. In a study comparing methacholine challenge between 66 HIV-infected patients with eight matched control subjects, Wallace et al. found no increased prevalence of AHR in HIV-infected patients [84]. While AHR was present, there was no independent association with HIV. Similar to HIV-uninfected patients, HIV-infected patients with AHR were more likely to have a history of asthma, recent history of pneumonia or report dyspnea or wheezing during their clinic visit [84]. However, another cross-sectional study comparing 248 HIV-infected men to 236 HIV-uninfected men found that AHR was more common in HIV-infected patients (26.2% HIV-infected patients vs. 14.4% HIV-uninfected patients), especially among HIV-infected smokers [83]. T-cell dysfunction, in the setting of HIV and cigarette smoking, may contribute to occult airway disease and AHR in HIV-infected patients. However, there is no data linking age and increased risk of AHR in HIV-infected patients.

Pulmonary Diseases in Aging HIV-Infected Patients

With improved survival on combination ART, HIV-infected patients have a greater likelihood of developing pulmonary diseases normally associated with aging. In addition, HIV-infected patients appear to be at risk of developing comorbid diseases earlier than HIV-uninfected patients resulting in earlier symptomatology and greater morbidity as they age. Many pulmonary diseases are more common in HIV-infected

patients compared with HIV-uninfected patients, and HIV is independently associated with a risk for a number of infectious and noninfectious pulmonary diseases after adjusting for the presence of smoking and other risk factors [13]. The incidence of most of these pulmonary diseases increases with age, regardless of HIV status [13]. A recent study found that physical function may be worse in older HIV-infected patients with chronic pulmonary disease compared with similar HIV-uninfected patients with chronic pulmonary disease, although severity of underlying chronic pulmonary disease was not assessed with pulmonary function tests in this study [85].

Infectious and noninfectious pulmonary diseases continue to account for a significant burden of disease in HIV-infected patients. Respiratory failure is responsible for the majority of intensive care unit (ICU) admissions [86–88]. With increasingly prevalent noninfectious pulmonary diseases, exacerbations of these chronic diseases in aging HIV-infected patients are likely to contribute to hospitalizations and ICU admissions.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) in HIV-infected patients has been well described in the current ART era [5, 81, 83, 89, 90]. During the early pre-ART era, premature and more pronounced bullous emphysema was reported radiographically [91]. Accelerated emphysema in HIV-infected patients was described by Diaz et al. in 2000 [90]. After matching for age and smoking history, the incidence of emphysema as determined by chest CT scans was 15% in HIV-infected patients compared with 2% in the HIV-uninfected patients ($p = 0.025$) [90]. In a recent study examining the prevalence of COPD in a cohort of Veterans, HIV was an independent risk factor for COPD [5]. International Classification of Diseases, 9th Edition (ICD-9) codes for COPD and patient self-report of COPD were more common in HIV-infected Veterans (ICD-9 codes, OR = 1.47; 95% confidence interval [CI], 1.01–2.13; $p = 0.04$; patient self-report: OR, 1.58; 95% CI, 1.14–2.18; $p = 0.005$) [5].

Risk factors for COPD in HIV-infected patients include current or prior smoking, injection drug use, and a history of bacterial pneumonia (BP) [69, 76, 77, 79, 81, 90]. Earlier studies identified lower CD4+ T-cell counts as a risk factor for COPD but this finding has not been consistently replicated [69, 77]. While smoking is one of the strongest risk factors for COPD, it does not seem to fully account for the increased risk of COPD in HIV infection. Gingo et al. found that while patients with any smoking history had more $D_L CO$ impairments than those who never smoked, nearly 50% of never-smokers still had significantly abnormal $D_L CO$ on PFTs which may correspond to emphysematous changes on chest CT [81].

The explanations for increased incidence and faster progression of emphysema in HIV-infected patients are not known. The role of past infections or colonization by pulmonary pathogens in the development and progression of COPD has been the focus of investigations in HIV-infected as well as in uninfected patients. Colonization with *Pneumocystis* has been proposed to play a role in the progressive decline of

pulmonary function in HIV-infected patients [92–94]. In nonhuman primate models, low levels of *Pneumocystis* result in inflammatory changes in the lung with resultant emphysematous changes [92, 93]. In human subjects found to be colonized with *Pneumocystis*, systemic inflammatory mediators are elevated which may contribute to development of COPD and airway diseases [94]. In HIV-uninfected patients, latent viral infections have also been implicated in exacerbations of COPD [95]. HIV virus has been identified in the lung epithelial cells of HIV-infected patients and may act similarly to other viruses in contributing to COPD development and exacerbation [96].

Additional mechanisms are likely to contribute to progressive COPD in HIV-infected patients. Cytotoxic CD8+ T-cells are found in the bronchoalveolar lavage (BAL) fluid of HIV-infected patients at all stages of HIV disease, even in the absence of respiratory symptoms or clinical infection [96, 97], and may play a role in the development of COPD in HIV-infected patients. In fact, HIV-infected smokers with emphysema have higher proportions of cytotoxic lymphocytes in BAL fluid [90]. Increased enzyme production by alveolar macrophages in HIV-infected patients may play a role in the development of COPD as well. Matrix metalloproteinases (MMPs) contribute to destruction of the lung parenchymal architecture resulting in emphysema. MMP production by activated alveolar macrophages may be up-regulated in HIV-infected patients leading to advanced emphysema [98]. Finally, alveolar epithelial cell senescence that increases with age may also contribute to the development of COPD in HIV-infected patients [99].

In the absence of studies examining treatment of COPD in HIV-infected populations, management of COPD should generally follow the same guidelines established for HIV-uninfected persons according to the Global Initiative for Chronic Obstructive Lung Disease [100]. Treatment with bronchodilators and inhaled corticosteroids based on symptoms and severity of airflow obstruction are the hallmark for treatment of COPD in HIV-uninfected patients [100]. As with HIV-uninfected patients, smoking cessation should be prioritized. Providers should review vaccination records with their HIV-infected patients to ensure that all patients have received the recommended pneumococcal and yearly influenza vaccines.

However, several aspects of COPD medications in HIV-infected patients on ART warrant consideration. The use of high-dose inhaled corticosteroids requires careful monitoring, as inhaled corticosteroids are associated with increased risk of oral candidiasis, bacterial pneumonia [101], and tuberculosis [102]. Regular use of systemic steroids should be avoided. In addition, drug interactions can result in significant medication toxicities. For example, ritonovir, a commonly prescribed protease inhibitor, suppresses the hepatic cytochrome p450 3A4 system (CYP3A4). CYP3A4 is responsible for degrading inhaled corticosteroids, particularly fluticasone [103]. Concurrent use of ritonovir and nasal or inhaled corticosteroids could result in increased levels of circulating exogenous corticosteroid. Elevated serum corticosteroid levels may result in inhibition of the hypothalamus–pituitary axis. Cushing syndrome and adrenal insufficiency have been reported in HIV-infected patients taking ritonovir and fluticasone [104–106]. Future studies are needed to determine the optimal pulmonary regimen for HIV-infected patients with COPD.

COPD is associated with several comorbidities and poor functional status that may complicate care, particularly of older HIV-infected and uninfected patients. Comorbidities associated with COPD include cardiovascular disease, muscle wasting, osteoporosis, malnutrition, anxiety and depression [107]. Notably, many of these diseases are already encountered with increased frequency among HIV-infected patients even in the absence of COPD. HIV-infected patients with COPD should be considered for participation in pulmonary rehabilitation programs, as chronic obstructive lung disease is associated with self-reported increased physical disability [108]. In studies of HIV-uninfected patients with COPD, physical functioning is significantly improved with participation in pulmonary rehabilitation programs [109]. Studies support the safety and potential benefit of exercise training in HIV-infected patients [110], although further studies are needed to determine the role and optimal type of exercise training in HIV-infected patients, particularly older patients with concomitant comorbid diseases such as COPD.

Pulmonary Infections

Bacterial Pneumonia

Early in the HIV epidemic, an increased risk of BP was reported in HIV-infected patients [111]. In a cohort of HIV-infected and uninfected women who used injection drugs or practiced high-risk sexual behavior, HIV-infected women had a higher incidence rate of BP (8.5 cases/100-person years (py) vs. 0.7 cases/100-py in HIV-uninfected women ($p < 0.001$)) [112]. Rates of BP increase with greater immunosuppression. For example, in another study, 2.3 episodes of BP per 100-py were found in patients with CD4+ T-cell counts greater than 500 cells/mm^3 compared with 10.8 episodes per 100-py in patients with CD4+ T-cell counts less than 200 cells/mm^3 [111].

However, the incidence rates of BP have been declining since the routine use of ART [13, 113, 114] and BP is less likely in patients on ART [13, 113, 114]. PCP prophylaxis may also decrease the risk of BP [111, 112, 115, 116]. Prior to the advent of ART, the risk of BP was decreased in HIV-infected treated with trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis [112, 117]. Studies conducted since the introduction of combination ART have not found similar results with TMP-SMX but did find a protective effect of ART, specifically protease inhibitors, with respect to a decreased risk of BP [113]. Despite these decreases in rates of BP, even with successful ART, the risk of BP remains elevated for HIV-infected patients compared with HIV-uninfected patients [13, 116]. In addition, as the risk of BP increases with age, BP will likely continue to contribute to morbidity and mortality in aging HIV-infected patients.

Bacterial pathogens responsible for BP in HIV-infected patients are similar to those seen in HIV-uninfected patients. *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* are the most common BP pathogens [118, 119]. *Pseudomonas aeruginosa* is another frequent cause of BP in HIV-infected patients

[118, 119]. *Pseudomonas* pneumonia is more common in patients with lower CD4+ T-cell counts and is associated with longer hospital stays [118, 120, 121]. There may be a relative absence of BP due to atypical organisms, although this may be impacted by limitations in the ability to detect these organisms [119]. TMP-SMX use as prophylaxis against PCP may increase risk of BP with resistant organisms. Bacteremia is common in HIV-infected patients who develop BP with up to 30% of patients affected in one series [118, 119].

Risk factors for BP include cigarette smoking, injection drug use, alcoholism, declining CD4+ T-cell count, prior PCP, and anemia [111–113, 115, 122]. Risk factors for invasive pneumococcal disease include shedding of pneumococcal antigen in the urine and absence of ART use [112, 113, 123]. Mortality is significantly increased in HIV-infected patients with BP [111, 112, 118, 122], especially patients who are bacteremic with pneumococcus [123]. However, a recent study of the effect of HIV on mortality from BP showed no difference between HIV-infected or HIV-uninfected patients hospitalized for BP with respect to length of hospital stay, recovery, or mortality [124].

Treatment of community acquired pneumonia (CAP) in HIV-infected patients should generally follow Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines established for treatment of HIV-uninfected patients, although these guidelines were not developed to specifically address BP or CAP in HIV-infected patients [125]. According to the IDSA/ATS guidelines, HIV-uninfected patients with any of the following features are at greatest risk of death from CAP and should at least be admitted to the hospital: age greater than 50 years; comorbid heart failure, cancer, renal, liver, or cerebrovascular disease; altered mental status, heart rate >125 beats/min, respiratory rate >30 breaths/min, systolic blood pressures <90 mmHg, or temperature >40°C or <35°C [125, 126]. Studies have not systematically addressed risk stratification of HIV-infected patients with pneumonia and the need for hospitalization.

In patients with immunosuppressing conditions such as HIV, respiratory fluoroquinolones or a beta-lactam agent with a macrolide is recommended for initial outpatient or non-ICU inpatient therapy [125]. Patients admitted to the ICU for CAP should be treated with combination therapy, consisting of an antipneumococcal beta-lactam and either azithromycin or a respiratory fluoroquinolone [125]. If *Pseudomonas* is suspected, treatment should include an appropriate antipseudomonal beta-lactam, and either ciprofloxacin, levofloxacin or an aminoglycoside, with either azithromycin or a respiratory fluoroquinolone for atypical coverage. For patients with severe CAP and a penicillin allergy, aztreonam should be substituted for the beta-lactam. Given the relatively high proportion of *Pseudomonas* infections among HIV-infected patients with CAP, providers should consider initial empiric antipseudomonal coverage, particularly in those with more severe immunosuppression and in those who are critically ill [127].

In terms of prevention of BP, pneumococcal vaccination is recommended for HIV-infected patients [128]. Similar to recommendations made for patients aged 65 years and older, single revaccination is also recommended for HIV-infected patients if 5 or more years have passed since the initial vaccine. Current recommendations are for use of the 23-valent polysaccharide pneumococcal vaccine.

There is conflicting data regarding the response of HIV-infected patients to the pneumococcal vaccine. Appropriate immunologic response has been reported in HIV-infected patients on ART who receive the 23-valent polysaccharide pneumococcal vaccine [129], but reduced efficacy of the pneumococcal vaccine in HIV-infected patients due to inadequate immune response, particularly in those with more severe immunosuppression at the time of vaccination, has also been demonstrated [115]. In patients with CD4+ T-cell counts greater than 200 cells/mm^3, pneumococcal vaccine has been shown to be effective in preventing pneumococcal pneumonia [114, 122]. In one series of HIV-infected Veterans with no difference in baseline CD4+ T-cell counts between vaccinated and unvaccinated HIV-infected patients, 23-valent pneumococcal vaccine was associated with a trend towards decreased incidence of BP (HR = 0.75; 95% CI, 0.50–1.13) [122]. However, patients with higher HIV viral load may have a less effective response to the pneumococcal vaccine [130]. Ongoing studies are evaluating the use of the newer pneumococcal conjugate vaccines in different populations.

Pneumocystis jirovecii Pneumonia

While the incidence of *Pneumocystis jirovecii* pneumonia (PCP) has decreased since the advent of ART, it is still a common cause of pulmonary morbidity and mortality in HIV-infected patients, especially patients without access to ART, with inadequate response to ART, or who are noncompliant with ART [13, 119, 131, 132]. ART use and lower HIV viral load is associated with lower incidence of PCP and improved survival after diagnosis of PCP [13, 133]. Older patients may be particularly susceptible to poor outcomes after PCP infection. In a study by Dworkin et al. older patients (age greater than or equal to 60 years) with a history of PCP had an increased risk of death (OR = 3.7) when compared to younger patients with PCP [133].

Non-ICU patients with PCP should be treated with two double-strength TMP-SMX tabs every 8 h for 21 days total [134, 135]. For critically ill patients, or for patients in whom there is concern for poor absorption of enteral medications, intravenous therapy may be necessary at a dose of 15 mg/kg of TMP divided over 3–4 doses per 24 h period. Patients with PCP and hypoxemia (defined as the partial pressure of arterial oxygen while the patient is breathing room air of less than 70 mmHg or an alveolar–arterial difference greater than 35) also require 21 days of adjuvant corticosteroid therapy. While TMP-SMX is the preferred therapy, alternative regimens may be necessary due to sulfa allergy or failure to respond to intravenous TMP-SMX after 1 week. Alternative regimens include pentamidine, atovaquone, TMP and dapsone, or primaquine plus clindamycin. There are several side effects associated with these alternative regimens, and dapsone and atovaquone require evaluation for glucose-6-phosphate dehydrogenase deficiency (G6PD) prior to initiation of therapy. Patients with CD4+ T-cell counts <200 cells/mm^3 should receive PCP prophylaxis, usually with TMP-SMX.

Patients recovering from PCP who are started on ART may be at risk of immune reconstitution inflammatory syndrome (IRIS). IRIS is a paradoxical clinical worsening of AIDS-related conditions or infections in the setting ART initiation with rapidly improved CD4+ T-cell count and rapidly dropping HIV viral load. IRIS has commonly been associated with PCP. Older HIV-infected patients may have a blunted IRIS response; however, the effect of age on IRIS incidence or severity is not well described [26].

PCP prophylaxis can safely be discontinued in patients successfully treated with ART and with sustained CD4+ T-cell increases to ≥200 cells/mm^3 for at least 3 months [136]. However, these data are derived generally from studies of younger patients, with a median age of approximately 35 years [136]. Whether these same guidelines for discontinuation of PCP prophylaxis are suitable for older HIV-infected patients has not been studied [136].

Lung Cancer

ART has reduced the incidence of AIDS-related tumors such as Kaposi sarcoma or non-Hodgkin lymphoma. However, HIV-infected patients are at increased risk for non-AIDS related tumors such as lung cancer [13, 137–140]. Survival in HIV-infected patients with lung cancer has been reported to be lower than that of the general population [139, 141]. Greater immunosuppression may be responsible for an increased risk of lung cancer and poorer outcomes among HIV-infected patients [138, 142], although more recent studies do not show an association between CD4+ T-cell count and the incidence of lung cancer [140, 143, 144]. Adenocarcinoma is the most common lung cancer histology in HIV-infected patients [145].

Studies of lung cancer in HIV-infected patients are problematic due to the presence of confounding factors, particularly smoking [145]. However, in studies that were able to adjust for smoking, the risk of lung cancer remained elevated in HIV-infected patients [143, 144, 146]. There does not appear to be a synergistic effect of smoking and HIV infection for the risk of lung cancer, although the majority of lung cancer cases in HIV-infected patients are in smokers [146]. Recurrent pneumonia may be a risk factor for lung cancer in younger patients with AIDS [147]. Whether this is due in part to detection bias is unclear.

Given the high prevalence of smoking in HIV-infected patients and an increased life expectancy with successful ART, lung cancer incidence is likely to continue to increase in older HIV-infected patients. As no present studies have addressed the role of screening or treatment of lung cancer in HIV-infected populations, current management of the HIV-infected patient with lung cancer should follow similar guidelines as for HIV-uninfected patients. Future studies need to specifically focus on early detection and optimal treatment of lung cancer in HIV-infected patients.

Pulmonary Hypertension

HIV infection is a risk factor for pulmonary arterial hypertension (PAH) regardless of ART use, CD4+ T-cell count or HIV viral suppression [148–150]. Older age does not appear to be a risk factor for PAH, although chronic cardiovascular, pulmonary, and liver diseases may contribute to secondary pulmonary hypertension. Increased rates of secondary pulmonary hypertension may be expected as HIV-infected patients are aging with these comorbidities. HIV-infected patients with PAH may present at later stages of PAH and die more quickly from untreated PAH compared to HIV-uninfected patients [148]. Typical plexogenic arteriopathy seen in non-HIV-associated PAH is also seen in HIV-associated PAH [148]. Direct activity of HIV in the pulmonary vascular bed has been suspected to contribute to risk of PAH. However, HIV has not been identified on pathologic examination of the pulmonary endothelial cells [151].

Medications routinely used to treat PAH in HIV-uninfected patients such as the endothelin antagonist, bosentan, and synthetic prostacyclins such as epoprostenol may be used to treat PAH in HIV-infected patients [152–155]. Small case series and case reports show improved outcomes for HIV-infected patients with PAH treated with these agents. Some studies suggest improvement in PAH symptoms, physiologic derangements, and survival with both PAH-specific treatment and with ART [153, 156–158].

The role of ART in the development of PAH, however, is controversial. Some studies have suggested a role for ART in the development of PAH in HIV-infected patients [159–161]. Endothelial dysfunction related to ART may partially account for an increased risk of PAH in HIV-infected patients treated with ART [162]. Nonetheless, until more definitive data become available, PAH-specific therapies and ART should be offered to eligible HIV-infected patients with PAH given the otherwise documented benefits of ART and of PAH-specific therapies. Providers should be aware of the potential for medication side effects and toxicities, particularly in patients with viral hepatitis coinfection. Further studies need to determine which HIV-infected patients are candidates for PAH treatment and which PAH treatments are most effective and best tolerated in HIV-infected patients.

Interstitial Lung Disease

Interstitial lung diseases (ILD) increase with age in HIV-uninfected patients [163]. HIV infection is associated with nonspecific interstitial pneumonitis (NSIP), lymphocytic interstitial pneumonitis (LIP), and sarcoid-like IRIS [96, 164, 165]. However, compared with other pulmonary disease, pulmonary fibrosis has been relatively rare in HIV-infected patients. Studies from the pre-ART era showing lymphocyte-rich alveolitis in the BAL fluid from HIV-infected patients also reported a notable absence of radiographic evidence of pulmonary fibrosis [97, 166]. A recent study comparing lung disease in HIV-infected and HIV-uninfected Veterans found a greater incidence of pulmonary fibrosis in the HIV-infected group [13]. However,

diagnoses were based on ICD9 codes, and no data on specific etiology of pulmonary fibrosis was available.

Role of ART in Pulmonary Diseases

ART is clearly associated with decreased OI's and improved survival [167]. Systemically, treatment with ART decreases HIV replication, immune activation, chronic inflammation and increases CD4+ T-cell lymphocyte counts. Within the alveolar space, ART similarly decreases pulmonary HIV viral load and decreases nonspecific pulmonary inflammatory response [168, 169]. Infectious complications such as BP and PCP are less frequent among those on ART [13, 73, 112, 113, 115, 118, 123]. In an earlier study, the initiation of lamivudine was associated with improved dyspnea [69]. With less frequent and less severe infectious complications, risk of ILD – and other chronic lung diseases – may also be reduced with ART use. Indeed, a cohort study of 33,420 HIV-infected Veterans found that incident pulmonary disease was lower in patient already on ART at study enrollment [13].

However, ART use has also been associated with airflow obstruction, the physiologic hallmark of COPD, in two recent studies [76, 81]. In a cohort of 167 HIV-infected patients, ART use was independently associated with irreversible airflow obstruction (OR=6.22; 95% CI 1.19–32.43; p=0.03) [81]. These data suggest that further research studies on the long-term impact of ART on lung health are warranted.

Future Directions

As HIV-infected patients are treated successfully with ART, the prevalence of chronic pulmonary diseases is likely to increase. Progression of diseases such as COPD may significantly affect quality of life for HIV-infected patients. Cigarette smoking is a major contributor to pulmonary morbidity and mortality in the current ART era. In addition, recurrent respiratory tract infections are likely to contribute to pulmonary impairment in this population. It is important to identify mechanisms to preserve lung function and quality of life among HIV-infected patients. Between the shift of HIV to a chronic disease, the high prevalence of smoking and strong association between aging, smoking, and lung disease, future efforts need to focus on effective smoking cessation strategies specifically geared towards HIV-infected patients [170]. In addition to smoking cessation, safe and effective treatment of pulmonary diseases such as COPD, lung cancer, and PAH in aging HIV-infected patients on ART needs to be established. The role of ART in the development of pulmonary diseases must also be further investigated. Finally, as HIV-infected patients progress in age, the role of screening for chronic lung diseases such as COPD and lung cancer needs to be addressed.

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