

# Chronic Obstructive Pulmonary Disease in Patients Who Have HIV Infection

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Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death worldwide and is projected to increase further as a cause of morbidity and mortality in the coming decades [1,2]. Yet COPD continues to be underdiagnosed [1,3] and risk factors that contribute to the development of COPD are incompletely understood. Cigarette smoking is the major risk factor for the development of COPD. Because not all smokers develop COPD, however, other factors appear to be involved [4]. For example,  $\alpha_1$ -antitrypsin deficiency accounts for a small number of cases of COPD. Other genetic factors are under investigation [5]. In addition, studies suggest that COPD susceptibility may vary by gender and race [6–8]. HIV-positive patients may represent another population that has an increased susceptibility to COPD.

This article considers the evidence suggesting an increased risk for COPD, namely emphysema and chronic bronchitis, and the potential increased risk for small airways abnormalities and nonspecific airway hyper-responsiveness among patients who have HIV. Additionally, risk factors for COPD and possible reasons for increased COPD among patients who have HIV infection are discussed. Finally, the management of COPD in HIV-positive patients is reviewed.

## **Evidence for increased prevalence of chronic obstructive pulmonary disease among HIV-positive patients**

COPD is defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases” [1]. COPD may result from emphysema, small airways inflammation, bronchoconstriction, excess mucus in the airways, or a combination of these factors. HIV infection is associated with several different manifestations of COPD and airways abnormalities, including features of emphysema [9–11], chronic bronchitis [12], nonspecific airway abnormalities, and bronchial hyper-responsiveness [13,14]. Although separate from COPD and not considered further in this review, bronchiectasis likewise causes an obstructive ventilatory defect and is described in patients who have HIV [15,16].

Somewhat challenging to discern from prior studies is whether HIV infection is an independent risk factor for the development or progression of COPD or whether the increased rates of COPD among patients who have HIV infection may be attributable to the greater rates of smoking, drug abuse, pulmonary infections, and other risk factors for COPD that frequently are encountered in HIV-positive patients. Interpretation of studies reporting increased rates of COPD and airway abnormalities in HIV-positive populations requires careful consideration of the patient populations included and the methods used to control for potential confounders. A summary of the

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major studies conducted to date of COPD and airway abnormalities in HIV-positive persons is provided in Tables 1 and 2.

One of the major manifestations of COPD, emphysema is described HIV-positive patients in several studies conducted before the advent of highly active antiretroviral therapy (HAART). In studies that included a majority of patients who had a history of prior AIDS-related pulmonary infections, radiographic findings of emphysematous, bullous, or cystic lung disease were encountered in approximately 40% [10,11]. It is unclear if findings such as these share the same pathogenesis as smoking-related emphysema or if they are primarily the result of pneumatoceles and other sequelae of previous infections.

Emphysema is also described, however, in HIV-positive patients who have not had prior AIDS-related pulmonary complications. In one study by Diaz and colleagues, emphysema was found to be the predominant cause of a low diffusing capacity of the lung (DLCO) in HIV-positive patients [17]. In HIV-positive patients who had DLCO values in the bottom 25th percentile (corresponding to values <72% predicted), 50% had detectable emphysema on CT scan. Abnormalities in DLCO in turn were primarily due to decreases in the blood volume component and were accentuated by cigarette smoking, as HIV-positive patients who had the greatest decreases in diffusing capacity had higher mean pack years of cigarette smoking. Decreases in DLCO were not associated with significant obstructive or restrictive ventilatory defects.

An additional study by Diaz and colleagues suggests that HIV infection alone is an independent risk factor for emphysema. In a study of 114 consecutive HIV-positive patients compared with 44 age-, sex-, and smoking-matched HIV-negative controls, 15% of the HIV-positive patients had emphysema on CT scan compared with only 2% of HIV-negative patients ( $P = .025$ ) [9]. DLCO was significantly lower in the HIV-positive patients, although there was no difference in the forced expiratory volume in 1 second ( $FEV_1$ ), forced vital capacity (FVC), or total lung capacity (TLC) between groups. In patients who had emphysema, the degree of airflow obstruction was mild, with a mean  $FEV_1/FVC$  of 69.2%. HIV-positive smokers who had emphysema and underwent bronchoscopy were found to have a significantly higher percentage of cytotoxic lymphocytes compared to HIV-positive smokers who did not have emphysema and to HIV-negative smokers.

In addition to emphysema, HIV infection is associated with an increased frequency of symptoms suggestive of chronic bronchitis, another of the major manifestations of COPD. In one study conducted before HAART, significantly more HIV-positive patients had symptoms of cough and phlegm production "on most days for  $\geq 3$  months during the year" than HIV-negative persons (approximately 25% HIV-positive versus 12% HIV-negative,  $P < .05$ ) [12]. Although the overall duration is not clear, these symptoms appear consistent with the clinical criteria for chronic bronchitis. The most important predictor of these symptoms was current or former cigarette smoking. In this study, CD4 count was not associated with the presence of airway symptoms, such as cough, phlegm, or wheeze. A low CD4 count, however, was an independent predictor of dyspnea and use of the antiretroviral agent lamivudine was associated with a reduction in dyspnea. Reasons for these findings are unclear, and it is unknown whether a patient's degree of immunosuppression and use of antiretroviral therapy may have any impact on the development or progression of COPD.

Thus far, only one study has examined the association between HIV infection and COPD among patients in the HAART era. This study also suggests that HIV infection may be an independent risk factor for COPD [18]. In an analysis of 1014 HIV-positive and 713 HIV-negative men enrolled in the Veterans Aging Cohort 5 Site Study, conducted at five United States Veterans Affairs medical centers, diagnoses of COPD were determined by *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic codes and patient self-report on questionnaire. The unadjusted prevalence of COPD by ICD-9 codes was 10% in HIV-positive patients and 9% in HIV-negative patients ( $P = .4$ ) and by patient self-report was 15% and 12%, respectively ( $P = .04$ ). In both HIV-positive and HIV-negative patients, the prevalence of COPD increased according to pack years of smoking and age. The HIV-positive patients were younger and had fewer pack years of smoking than the HIV-negative controls. After adjusting for differences in age, smoking, race/ethnicity, and other potential confounders such as injection drug use and alcohol abuse, HIV-positive patients were approximately 50% to 60% more likely to have COPD than HIV-negative patients by ICD-9 codes or patient self-report. Thus, combined data from the above studies suggest that the risk for COPD is increased as a result

of HIV infection, as the prevalence of COPD remains significantly greater among HIV-positive patients after controlling for smoking, age, and other common risk factors for COPD.

#### **Evidence for increased prevalence of airway abnormalities in HIV-positive patients**

HIV infection may also be associated with an increased prevalence of small airways abnormalities, expiratory flow abnormalities, and bronchial hyper-responsiveness, particularly in smokers (see Table 2). Nonspecific focal air trapping with decreased expiratory flow rates were significantly more common among HIV-positive patients compared with HIV-negative patients who did not have prior AIDS-related pulmonary complications [19]. In this study, the presence of focal air trapping was more likely in patients who had a longer duration of HIV infection. Bronchial dilatation in the absence of significant airflow obstruction has also been described in HIV-positive patients [20]. Bronchial dilatation was found to correlate with increased neutrophilia in bronchoalveolar lavage specimens, suggesting the presence of increased airways inflammation. In another study, a decreased expiratory flow rate or a significant response to inhaled bronchodilator was encountered in 44% of 99 HIV-positive patients, many of whom had a history of *Pneumocystis pneumonia* (PCP) or systemic Kaposi's sarcoma [14].

Data regarding the association of HIV infection with bronchial hyper-responsiveness is conflicting. Although more HIV-positive subjects tended to have bronchial hyper-responsiveness to methacholine challenge than HIV-negative subjects in a study from the Pulmonary Complications of HIV Infection Study Cohort (19.3% HIV positive versus 12.9% HIV negative), this difference was not statistically significant [21]. Of the HIV-positive patients who had airway hyper-responsiveness, however, 70% had no prior history of asthma. In contrast, another investigation of 236 HIV-positive and 236 HIV-negative men found significantly increased bronchial hyper-responsiveness to methacholine challenge in HIV-positive compared to HIV-negative subjects [13]. Smoking status influenced bronchial hyper-responsiveness, as bronchial hyper-responsiveness was significantly greater only among HIV-positive current smokers compared with HIV-negative current smokers (30% versus 13%,  $P < .05$ ) but

was not significantly different for the comparison of HIV-positive nonsmokers to HIV-negative nonsmokers (20% versus 15%). As bronchial hyper-responsiveness is a risk factor for progressive COPD [22], these data suggest that an interaction between smoking and HIV infection could enhance susceptibility to the progression of COPD.

Taken together, these data support that COPD is increased in prevalence among HIV-positive patients and suggest that HIV infection may increase the risk for COPD independently, apart from smoking. Data is limited, however, in understanding whether or not the pathogenesis of COPD and the progression of COPD are similar in HIV-positive and in HIV-negative patients. How HIV infection might alter the course of established COPD is also unknown. Further, whether COPD described in HIV-positive patients is primarily in the form of emphysema, chronic bronchitis, small airways disease, or even asthma or a combination of these abnormalities is unclear. Nonetheless, these retrospective and cross-sectional data do not definitively rule out the possibility that the greater prevalence of COPD among HIV-positive patients may be the result of residual confounding, related to the generally greater prevalence of other known risk factors for COPD in HIV-positive populations, such as smoking or infection, which are discussed later in further detail.

#### **Risk factors for chronic obstructive pulmonary disease among HIV-positive patients**

Exposures to a variety of substances are associated with risk for COPD. Cigarette smoking, the most potent risk factor for COPD, is highly prevalent in HIV-positive populations [23]. Previous studies reported that nearly 75% of HIV-positive patients have ever smoked [23,24] and approximately 40% to 50% are current smokers [24–26]. In contrast, the prevalence of current smoking in the general HIV-uninfected population in the United States is approximately 21% [27].

Additional potential risk factors for COPD that tend to be more common in HIV-positive compared with HIV-negative populations include inhaled and intravenous substance abuse [12,28]. The use of inhaled drugs, such as marijuana, cocaine, and heroin, are variably reported to be associated with airflow obstruction [29]. Although use of these drugs is clearly associated with increased frequency of respiratory symptoms, it

Table 1  
Evidence for increased emphysema and chronic bronchitis in HIV-positive patients

Author, year	Design and population	Findings	Relationship to smoking and other factors
Kuhlman et al [11], 1989	Retrospective chart review of 55 HIV+ patients who had AIDS and 50 neutropenic patients who had acute leukemia.	42% of HIV+ patients compared with 16% of leukemia patients had bullous changes on CT scan ( $P < .01$ ).	70% of patients who have premature bullous damage had prior or recurrent pulmonary infections, with 61% having prior PCP; no difference in smoking or injection drug use in AIDS patients $\pm$ bullous damage; overall prevalence of smoking not stated.
Guillemi et al [10], 1996	Cross-sectional evaluation of 32 consecutive HIV+ men who had AIDS referred for initiation of PCP prophylaxis; 78% had ever smoked.	60% with unexpected lung lesions on CT scan; nearly half consisted of emphysematous or cystic changes.	No patients had history of intravenous drug use; patients who had prior lung infections were not excluded; no difference in smoking between patients $\pm$ lung abnormalities.
Diaz et al [17], 1999	Baseline, cross-sectional analysis of prospective cohort of 243 HIV+ patients and 30 HIV- controls; 67% HIV+ and 63% HIV- group were smokers.	Of the 95 HIV+ patients who underwent HRCT, emphysema was found to correlate with decreased DLCO, which primarily was due to decreases in the capillary blood volume component; HIV+ patients who had decreased DLCO had significantly decreased VC and FEV <sub>1</sub> , although still within normal ranges, with preserved TLC and no significant difference in FEV <sub>1</sub> /FVC ratio. Of patients who had DLCO < 25th percentile, 50% had CT evidence of emphysema.	Patients who had prior AIDS-related pulmonary complications were excluded; HIV+ subjects who had DLCO below the 25th percentile (<72% predicted) had greater pack years of smoking than HIV+ subjects who had DLCO > 25th percentile. No significant difference between groups in occupational exposures, family history of COPD, or diagnoses of pneumonia.
Diaz et al [9], 2000	Cross-sectional sample of larger prospective cohort study included 114 consecutive HIV+ patients and 44 age-, sex-, and smoking-matched HIV- controls. 60% of HIV+ and 56% of HIV- patients were smokers.	Radiographic emphysema observed in 15% of HIV+ compared with 2% of HIV- patients; no difference in FEV <sub>1</sub> , FVC overall between HIV+ and HIV-, although DLCO was significantly lower among HIV+ patients ( $P = .03$ ). Only mild airflow obstruction in HIV+ patients who had emphysema (FEV <sub>1</sub> /FVC 69.2%). HIV+ emphysema had higher % cytotoxic lymphocytes on BAL compared with HIV+ without emphysema and HIV- smokers without emphysema.	Patients who had prior AIDS-related pulmonary complications were excluded; approximately 10% of HIV+ and HIV- patients had a history of injection drug use; <10% of patients were on protease inhibitors. Age and smoking controlled for by matching.

Diaz et al [12], 2003	Baseline, cross-sectional analysis of respiratory symptoms in a prospective cohort study of 327 HIV+ patients and 52 HIV- patients. 54% of HIV+ and 50% of HIV- were current smokers.	Significantly increased cough, phlegm, wheeze, and dyspnea in HIV+ compared with HIV- patients; specifically, both increased cough and phlegm production “on most days for ≥3 months during the year” (approximately 25% HIV + versus 12% HIV-, <i>P</i> <.05). Use of lamivudine associated with less dyspnea.	Patients who had prior AIDS-related pulmonary complications were excluded; greater prevalence of intravenous drug use among HIV+; smoking was significantly associated with all respiratory symptoms; unclear if symptom duration of cough/phlegm was ≥2 years, required for chronic bronchitis diagnosis.
Crothers et al [18], 2006	Baseline cross-sectional analysis of a prospective cohort study included 1014 HIV+ and 713 HIV- men; 75% of both HIV+ and HIV- patients had ever smoked.	HIV+ patients 50%–60% more likely to have COPD, adjusting for age, race/ethnicity, pack years of smoking, injection drug use, and alcohol abuse (OR 1.5 for diagnosis of COPD by ICD-9 codes and 1.6 for patient self-report, <i>P</i> <.05).	Patients who had prior lung disease were not excluded; COPD was based on ICD-9 codes and patient self-report; approximately 80% of HIV+ patients were on HAART. Smoking and injection drug use controlled for in multivariate analyses. Women were excluded in these analyses due to low percentage in overall study.

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*Abbreviations:* BAL, bronchoalveolar lavage; HIV-, HIV negative; HIV+, HIV positive; HRCT, high-resolution chest CT; OR, odds ratio; VC, vital capacity; ±, with and without.

Table 2  
Evidence for increased airway abnormalities in HIV-positive patients

Author, year	Design and population	Findings	Relationship to smoking and other factors
O'Donnell et al [14], 1988	Retrospective chart review of 99 HIV+ patients who had AIDS referred for pulmonary physiologic assessment in PFT laboratory; 35% were smokers.	44% with abnormal airway function: decreased airflow in 33% (defined as an FEV <sub>1</sub> , FVC, or FEF 25-75 of 1.65 standard deviations below predicted values) and significant response to bronchodilator in 31% (defined as increase in the FEV <sub>1</sub> of ≥12% or if the FEF 25-75 increased ≥25% with a change in VC of <10%).	54% of patients had PCP and 29% had systemic KS within 3 months before testing; abnormal airway function was found in 8 of 18 (44%) patients who had KS, 9 of 42 (21%) of those who had PCP, 7 of 11 (64%) of those who had PCP and KS, and 20 of 28 (71%) of those who did not have PCP or KS. No difference in airflow abnormalities according to smoking status.
King et al [20], 1997	Cross-sectional subset of prospective cohort study, included 50 HIV+ and 11 HIV- patients; 69% had ever smoked.	36% of HIV+ and none of HIV- patients had bronchial dilatation on CT; significantly decreased DLCO but no difference in airflow obstruction in subjects ± bronchial dilatation. BAL neutrophilia (>4%) in 22% of HIV+ compared with 9% of HIV- patients; BAL neutrophil counts significantly higher in those who had bronchial dilatation ( <i>P</i> = .014).	Patients who had prior AIDS-related pulmonary complications were excluded; no significant difference in smoking history between HIV+ and HIV- patients, in those ± bronchial dilatation, and in those ± BAL neutrophilia. No pulmonary infections diagnosed on BAL. Significantly longer duration of HIV infection in those who had bronchial dilatation.
Wallace et al [21], 1997	Cross-sectional substudy of prospective cohort study, consisting of 62 HIV+ and 11 HIV- patients matched by age, gender, race, smoking, prior asthma, and baseline FEV <sub>1</sub> ; 52% of each group had ever smoked.	Hyper-responsiveness to methacholine challenge detected in 19.3% of HIV+ and 12.9% of HIV- ( <i>P</i> > .1).	HIV- controls were selected from another cohort study; study underpowered to detect a difference of this magnitude. Smoking controlled for by matching.
Gelman et al [19], 1999	Cross-sectional subset of prospective cohort study included 48 consecutive HIV+ and 11 consecutive HIV- patients; 54% of HIV+ and 55% of HIV- patients were current smokers.	63% of HIV+ and 27% of HIV- patients had focal air trapping on expiratory HRCT scan ( <i>P</i> = .03); subjects who had air trapping had lower mean FEV <sub>1</sub> , FEF 25-75, and DLCO than those who had normal HRCT ( <i>P</i> < .05). Air trapping was associated significantly with bronchial dilatation.	Patients who had prior AIDS-related pulmonary complications and coexistent lung disease, including bronchiectasis and emphysema, were excluded; no difference in current smoking and pack years of smoking according to presence of focal air trapping or HIV. Significantly longer duration of HIV infection in those who had focal air trapping.

Poirier et al [13], 2001	Cross-sectional study of 248 HIV+ and 236 healthy HIV- men, ages 20-44 years. 62% of HIV+ compared with 35% of HIV- men were current smokers ( $P < .05$ ).	Hyper-responsiveness to methacholine challenge found in 26.2% of HIV+ and 14.4% of HIV- patients ( $P < .05$ ); when stratified by current smoking, bronchial hyper-responsiveness significantly different in HIV+ current smokers compared with HIV- current smokers only (30.3% versus 13.3%, $P < .05$ ).	Subjects required to have a normal chest x-ray, no respiratory infections in the 6 weeks, and no PCP in the 3 months before study participation. Although not statistically significant, 17.3% of HIV+ patients reported a history of asthma compared with 12.3% of HIV- patients. Subjects stratified by smoking status in analyses; no data on other drug use or occupational exposures.
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*Abbreviations:* BAL, bronchoalveolar lavage; FEF 25-75, forced mid-expiratory flow; HIV-, HIV negative; HIV+, HIV positive; HRCT, high-resolution chest CT; KS, Kaposi's sarcoma; PFT, pulmonary function test; VC, vital capacity; ±, with and without.

is not entirely clear whether or not they are associated independently with the development of airflow obstruction or emphysema after controlling for concomitant cigarette smoking [30–32]. For example, a recent systematic review on the pulmonary complications of marijuana found that although marijuana smoking was associated with increased respiratory symptoms, no clear association with long-term abnormalities in pulmonary function testing was demonstrated [33]. The effects of intravenous drug use on the lung are also varied. Although associated more commonly with talc granulomatosis, restrictive ventilatory defects, and pulmonary hypertension, the intravenous use of illicit drugs—particularly of methylphenidate—also can be associated with the development of precocious emphysema [29]. Although data on the association of alcohol abuse with obstructive lung disease is conflicting [34,35], alcohol abuse is also prevalent in HIV-positive patients [28]. Whether or not alcohol plays a greater role in the susceptibility to COPD in patients who have HIV infection has not been investigated.

Other possible risk factors to consider in HIV-infected populations that may have an impact on the development or progression of COPD but that have been addressed incompletely in prior studies include occupational or environmental exposures [36] and low socioeconomic status [37,38]. In addition, recurrent pulmonary infections or colonization with microorganisms in the respiratory tract may influence the course of COPD. Although the pathogenic role of microorganisms in the course of COPD is controversial [39–41], increased airflow obstruction subsequent to episodes of bacterial pneumonia and PCP has been documented in HIV-positive patients [42]. It is as yet unknown whether or not CD4 count, HIV viral load, or HAART influences the development or clinical course of COPD.

### **Potential mechanisms of increased risk for chronic obstructive pulmonary disease in HIV**

Pathophysiologic studies offer several potential observations as to why HIV may increase susceptibility to COPD. CD8+ T cells are believed to play a critical role in the development of COPD [43,44], and HIV infection can result in intense infiltration of CD8+ T cells in the lung, particularly in early to mid stages of disease [45,46]. These T cells are shown to secrete interferon- $\gamma$  (IFN- $\gamma$ ) [45]. Although it is unclear whether or not the lymphocytic alveolitis and expression of IFN- $\gamma$  play any role in

the development of COPD in HIV-positive persons, overexpression of IFN- $\gamma$  is shown to cause emphysema in animal models [43].

Chronic viral infections are also believed to be involved in the pathogenesis of COPD [47]. Latent adenoviral infections in the lung are postulated to play a role in amplifying the development of cigarette smoke-induced emphysema. The local consequences of HIV infection in the pathogenesis of COPD are unknown, however, and the impact of immune reconstitution and HAART on the development and progression of COPD has not been investigated.

Additionally, episodes of clinical pneumonia or colonization with respiratory organisms may contribute to airway obstruction [42–49], which may be of particular relevance to the pathogenesis of COPD in immunosuppressed persons who have HIV disease. For example, a history of bacterial pneumonia or PCP is associated with significant expiratory airflow limitation in subjects who have HIV infection [42]. In addition, colonization with *Pneumocystis jirovecii*, the organism responsible for human PCP, is associated with the presence and severity of COPD in HIV-negative patients [41]. *P. jirovecii* has also been identified in the sputum of asymptomatic HIV-negative patients who have chronic bronchitis [50] and has been detected with higher frequency in HIV-positive smokers compared with nonsmokers in the absence of active PCP [51].

Oxidative stress may play a key role in the development and progression of COPD, particularly in patients who have HIV. Increased oxidative stress is demonstrated systemically and in the lungs of patients who have COPD and asthma above that seen in healthy smokers [52]. A decreased ability to maintain an antioxidant defense may enhance susceptibility to COPD [53]. HIV-positive patients have evidence of abnormal systemic and lung oxidant/antioxidant balance, as demonstrated by decreased antioxidant defenses, most notably superoxide dismutase and glutathione [54,55], and elevated serum levels of lipid peroxidation products, such as malondialdehyde and hydroperoxide [56]. Smoking may enhance this oxidative stress, further depleting antioxidant defenses systemically and in the lung that already are abnormal in HIV-positive patients [57]. Further work is needed to elucidate which, if any, of these processes plays a causal role either alone or in conjunction with cigarette smoking or other risk factors in the pathogenesis of COPD in HIV-positive persons.



### **Clinical impact of chronic obstructive pulmonary disease in HIV**

Given the high frequency of smoking [23], increasing age, and greater prevalence of COPD in patients who have HIV infection [9,18], COPD is emerging as an important clinical problem in HIV-positive patients in the era of HAART. This is likely to be true particularly in areas of the world with access to HAART, such as in the United States, where an estimated 1 million people are living with HIV. Overall, noninfectious complications and comorbid illnesses in HIV-positive patients have generally increased in frequency as survival has improved among those on HAART [58–60]. Consistent with this, COPD is the second most frequently encountered new pulmonary condition after bacterial pneumonia in a cohort of HIV-positive veterans studied in the HAART era [61]. This is in contrast to the pre-HAART era, when infectious complications, such as bacterial pneumonia and PCP, were the two most common lung complications among HIV-positive patients [62].

Furthermore, the chronic complications from smoking now contribute significantly to morbidity and mortality of HIV-positive patients, whereas studies before HAART had conflicting conclusions regarding the association of smoking with mortality [63]. Compared to those who have never smoked, current smokers who have HIV have a significantly increased prevalence of COPD and a greater mortality [63]. These findings, in turn, raise the possibility that the increased mortality may be attributable in part to COPD and underscore the increasing importance of COPD and other noninfectious comorbid conditions among HIV-positive patients on effective HAART.

### **Management of chronic obstructive pulmonary disease in HIV-positive patients**

To date, no studies have addressed the management of COPD specifically in HIV-positive patients. Given the absence of such data, current therapy should follow the COPD management guidelines proposed for HIV-uninfected patients [64]. Special consideration should be given, however, to a few key aspects of COPD management for HIV-positive patients. First, the use of inhaled steroids for COPD in HIV-positive patients requires careful follow-up. Given the risks for oral candidiasis and the recently identified concern for an increased risk for bacterial pneumonia

associated with high-dose inhaled steroids [65], providers should monitor for infectious complications, particularly in patients who have low CD4 T-cell counts. Likewise, the regular use of systemic steroids preferably should be avoided in HIV-positive patients. In addition, providers should review vaccination records with their HIV-positive patients to ensure that all patients have received the recommended pneumococcal and yearly influenza vaccine.

Second, smoking cessation is of paramount importance, as current smoking is associated with increased respiratory symptoms, COPD, bacterial pneumonia, mortality, and decreased quality of life in HIV-positive patients [63]. Rates of current smoking are nearly twofold higher in most HIV-positive compared with HIV-negative populations [27]. Health care providers, however, of HIV-positive patients may be less aware of current smoking and less confident in their ability to counsel their patients regarding smoking cessation [66]. These findings highlight the need to increase efforts at smoking cessation among patients who have HIV. Although the number of studies is limited, data suggest that smoking cessation interventions can be effectively applied in HIV-positive populations [67–69]. One study combining the nicotine patch and counseling found a smoking cessation rate of 50% after 8 months among HIV-positive smokers [69]. Another study using cellular telephones for counseling in HIV-positive smokers increased cessation rates to 37% compared with 10% in the usual care group [68]. These results are similar to those from a study of HIV-negative patients using telephone intervention [70].

Third, as with HIV-negative patients, HIV-positive patients who have COPD should be considered for participation in pulmonary rehabilitation programs. In HIV-positive veterans, COPD or asthma was among the top comorbid conditions independently associated with self-reported increased physical disability [71]. In studies of HIV-negative patients who have COPD, physical functioning can be improved significantly with participation in pulmonary rehabilitation programs [72].

Referral for pulmonary rehabilitation thus should be considered early in HIV-positive patients who have COPD, as the systemic and skeletal manifestations encountered in HIV-negative patients who have COPD may potentially be exaggerated and associated with even greater decrements in physical capacity in patients who have HIV.

Possible reasons for this include the concomitant skeletal muscle dysfunction and mitochondrial abnormalities related to HIV infection and its treatment superimposed on those associated with COPD alone [73]. Furthermore, peak aerobic capacity is decreased in HIV-positive patients: a 41% decrease in the maximal oxygen consumption was noted in HIV-positive patients compared with expected values from age- and gender-matched healthy sedentary HIV-negative controls [74]. Respiratory muscle function also may be affected in HIV, as another study found decreased respiratory muscle strength in otherwise healthy HIV-positive patients compared with HIV-negative patients [75]. No studies to date have investigated the systemic manifestations of COPD in HIV-positive patients or have compared the anatomic or functional features of skeletal muscle dysfunction in HIV to those found in HIV-negative patients who have COPD. Although studies support the safety and potential benefit of exercise training in HIV-positive patients [76,77], further studies are needed to determine the role and optimal type of exercise training in HIV-positive patients, in particular those who have concomitant comorbid diseases such as COPD.

### Summary

HIV-positive patients appear to have an increased risk for COPD, although whether this represents increased emphysema, chronic bronchitis, other obstructive lung diseases including asthma, or a combination of these disorders has not been evaluated fully. Although some of the increased COPD may be attributable to the greater rates of smoking and drug abuse in HIV-positive populations, the apparent risk for COPD remains elevated in HIV-positive patients even after controlling for these and other potential confounders [9,18]. It also remains unclear whether HIV infection accelerates the course of COPD. Further work is needed to elucidate the pathogenesis of COPD in HIV-positive persons, and can provide insights relevant to understanding COPD in HIV-negative patients as well.

Given the increasing age of HIV-positive patients as survival has improved for those on HAART combined with the high prevalence of smoking, health care providers are likely to encounter a substantial number of HIV-positive patients who have COPD. Increased awareness of COPD among health care providers of

HIV-positive patients is warranted. Identification of COPD is important, as undiagnosed airway obstruction is associated with impaired health and functional status [78]. Appropriate management of COPD is associated with health benefits, such as decreased symptoms and COPD exacerbations, and improved smoking cessation, exercise capacity, and quality of life [79,80]. Additional studies are needed to determine whether or not the pharmacologic and nonpharmacologic management strategies for COPD should differ in HIV-positive patients versus HIV-negative to best maintain patient health over time.

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