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Obstructive Lung Diseases in HIV: A Clinical Review and Identification of Key Future Research Needs

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Abstract

HIV infection has shifted from what was once a disease directly impacting short-term mortality to what is now a chronic illness controllable in the era of effective combination antiretroviral therapy (ART). In this setting, life expectancy for HIV-infected individual is nearly comparable to that of individuals without HIV. Subsequent to this increase in life expectancy, there has been recognition of increased multimorbidity among HIV-infected persons, with prevalence of comorbid chronic illnesses now approaching 65%. Obstructive lung diseases, including chronic obstructive pulmonary disease (COPD) and asthma, are prevalent conditions associated with substantial morbidity and mortality in the United States. There is overlap in risk factors for HIV acquisition and chronic lung diseases, including lower socioeconomic status and the use of tobacco and illicit drugs. Objectives of this review are to (1) summarize the current state of knowledge regarding COPD and asthma among HIV-infected persons, (2) highlight implications for clinicians caring for patients with these combined comorbidities, and (3) identify key research initiatives to reduce the burden of obstructive lung diseases among HIV-infected persons.

Keywords

HIV infection; obstructive lung disease; COPD; asthma; comorbidities

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Conflict of Interest

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nearly comparable to that of individuals without HIV infection.[1] Subsequent to this increase in life expectancy, there has been recognition of increased multimorbidity among HIV-infected persons, with prevalence of comorbid chronic illnesses now approaching 65%.[2] As morbidity and mortality from opportunistic infections has decreased, it has become evident that HIV-infected persons are susceptible to chronic diseases at greater rates than those observed in HIV-uninfected persons.[3–6] Obstructive lung diseases, including chronic obstructive pulmonary disease (COPD) and asthma, are prevalent conditions associated with substantial morbidity and mortality in the United States.[7–9] There is overlap in risk factors for HIV acquisition and chronic lung diseases, including lower socioeconomic status, and the use of tobacco and illicit drugs.[10–14] The objectives of this review are to (1) summarize the current state of knowledge regarding COPD and asthma among HIV-infected persons, (2) highlight implications for clinicians caring for patients with these combined comorbidities, and (3) identify key research initiatives to reduce the burden of obstructive lung diseases among HIV-infected persons.

HIV and COPD Are Related Global Health Problems

The importance of HIV and COPD as global health problems is increasing. COPD was the world's third leading cause of death in 2010,[15] having risen from the fourth leading cause of death in 1990. Between 1990 and 2010, HIV infection as a global cause of death rose more dramatically, rising from 35th to 6th. While COPD and HIV have traditionally been thought of as two unrelated diseases, respectively caused by smoke inhalation (COPD) and human-to-human viral transmission (HIV), emerging data suggest that HIV infection may be an independent risk factor for COPD. As HIV-infected persons are increasingly older in age, have high rates of cigarette smoking, and have a chronic infection associated with higher COPD risk, providers should anticipate needing to care for more HIV-infected persons with COPD in the coming years.

HIV Infection Is Associated with Heightened Risk for COPD

During the first decade of the AIDS epidemic, opportunistic pneumonias dominated the landscape of HIV-associated pulmonary diseases. Since then, noninfectious complications including COPD have gained in prominence. The first published report of HIV-associated emphysema came in 1989.[16] Diaz and colleagues performed thoracic computed tomography (CT) of consecutive patients presenting with HIV infection and reported CT evidence of emphysema in 15% of 114 HIV-infected persons, compared with 2% of 44 HIV-uninfected persons matched on smoking history, age, and gender ($p = 0.025$).[17] Another major pre-ART study, the Pulmonary Complications of HIV Infection Study, enrolled 1,183 HIV-infected persons and 170 HIV-uninfected controls at six sites between 1988 and 1990. Participants were prospectively followed up until death or March 1994. Pulmonary function test was performed at specified intervals (every 3 or every 12 months). As time in the study increased (considered a surrogate for time with HIV infection), the rate of decline in the forced expiratory volume in 1 second (FEV_1) increased over that accounted for by normal aging.[18] The magnitude of this excess rate of FEV_1 decline was estimated to be an additional 27 mL/year. While these pre-ART data might be considered less relevant to

contemporary HIV-infected persons with access to ART, current ART-era data continue to suggest that HIV infection is an independent COPD risk factor.

Crothers and colleagues analyzed ART-era data (2001–2002) in a veterans affairs (VA) cohort of 1,014 HIV-infected persons and 713 HIV-uninfected controls.[19] After adjusting for age and smoking, HIV remained an independent risk factor for COPD diagnosis by ICD-9 codes (odds ratio [OR] =1.47; 95% confidence interval [CI] =1.01–2.13) and self-report (OR: 1.58; 95% CI: 1.14–2.19). Crothers and colleagues also used ART-era VA administrative data (n = 33,420 HIV infected, n = 66,840 HIV uninfected) to evaluate prospective incidence of COPD and found that HIV-infected persons had higher incident COPD than HIV-uninfected controls.[20] Although data were limited by a lack of spirometry measures to confirm COPD, the study size and geographic distribution (VA wide) are notable strengths and validate smaller, single-, or multicenter studies where spirometry was measured. In a smaller study (n = 49 HIV-infected persons, n = 208 HIV-uninfected persons) from Japan, HIV infection was associated with a markedly increased odds of spirometry-confirmed COPD, even after adjusting for age and smoking (OR: 10.93; 95% CI: 1.99–60.1).[21] Although the confidence interval was very wide, likely due to small sample size, these data support the notion that HIV infection is an independent risk factor for COPD.

COPD Is Common in HIV

ART-era spirometry studies in HIV-infected persons, summarized in Table 1, have demonstrated COPD prevalence between 3 and 23%.[21–36] The wide variation in these studies may be largely due to variability in the prevalence of smoking, age at study entry, and other factors in these different cohorts. We also note the study from Denmark, where a baseline COPD prevalence of 9.5% had doubled to 19% at a median follow-up time of 4.4 years. These data, in combination with other longitudinal studies,[18,20] suggest that HIV-infected persons lose FEV_1 and develop worsening airflow obstruction at a rate exceeding that of noninfected persons. If true, this would suggest that COPD is poised to soon emerge as a major HIV comorbidity, as HIV-infected persons continue to live longer. As more than half of the population in the United States living with HIV/AIDS is now older than 50 years, the impact of HIV-associated COPD is also expected to increase substantially.

Decreased Carbon Monoxide Diffusing Capacity Is Common in HIV

ART-era studies of carbon monoxide diffusing capacity (DL_{CO}) also show a very high prevalence of diffusion impairment in HIV-infected persons and an association with respiratory symptoms.[37,38] In one study of women with and without HIV infection, the HIV-infected women had a significantly lower mean DL_{CO} compared with the HIV-uninfected women (66.5% predicted vs. 72.7% predicted, p = 0.01) and, importantly, over half of the women with moderate-to-severe reduction in their DL_{CO} (<60% predicted) had no evidence of concurrent airflow obstruction.[38] In multivariable analysis, a DL_{CO} <60% predicted was an independent predictor associated with the presence of dyspnea. In a similar study of HIV-infected and HIV-uninfected men, the men with HIV infection had a significantly lower mean DL_{CO} compared with the men without HIV (69% predicted vs. 76% predicted, p <

0.001) and the HIV-infected men also had a higher prevalence of a DL_{CO} ≤60% predicted (30 vs. 18%, $p < 0.001$).[37] As in the prior study in women, the majority of men with moderate-to-severe reduction in their DL_{CO} (≤60% predicted) had no evidence of concurrent airflow obstruction. Furthermore, the HIV-infected men with a DL_{CO} ≤60% predicted were significantly more likely to report cough and phlegm and have a higher dyspnea scale than those with a DL_{CO} >60% predicted. Thus, an isolated reduction in DL_{CO} is a frequent finding on lung function testing in persons with HIV and is associated with respiratory symptoms.

DL_{CO} is not specific for COPD and this measure can be decreased in a wide range of medical conditions such as restrictive lung disease, pulmonary vascular disease, or abnormal lung inflammation. One single-center study of 158 HIV-positive individuals suggested that the causes of diffusion impairment also vary in smokers (airflow obstruction and emphysema) versus nonsmokers (vital capacity and airway inflammation).[29] The causes and clinical implications of these commonly observed gas exchange abnormalities in HIV remain unclear, and this remains an active area of investigation.

Emphysema Is Common in HIV

Spirometry remains the gold standard for COPD diagnosis and a decreased DL_{CO} may represent an important pulmonary function finding in HIV-infected persons, but CT-based assessment of emphysema is an emerging area of research and may represent a more sensitive method for detecting early disease. The prevalence of emphysema among HIV-infected persons in recent cross-sectional studies has varied widely, from 10 to 65%.[31,39–43] Reasons for this high variability might include variable cohort demographics, and also methodologic variability, such as the lack of consensus for CT-based definitions of emphysema, visual assessment versus densitometry to categorize emphysema, and analysis of lung tissue visualized on cardiac versus whole-lung CT imaging.

Despite the limitations in determining the true prevalence of emphysema in HIV-infected persons, cross-sectional data from HIV-infected persons and HIV-uninfected controls have shown that CT evidence of emphysema is common in HIV-infected persons. In one study of 114 HIV-infected persons and 89 HIV-uninfected controls, HIV infection was associated with significantly higher risk of emphysema, even after adjusting for pack-years of smoking (OR: 2.24; 95% CI: 1.12–4.48).[44] A cross-sectional analysis of 510 HIV-infected persons from multiple sites across the United States has recently been published.[43] This study reported that 25% of the cohort had at least trace levels of emphysema, defined using a CT threshold of more than 2.5% of lung voxels with density less than −950 Hounsfield units. Demographic characteristics associated with trace emphysema included age, smoking, and pulmonary function. Markers of HIV disease control (CD4 cell count, HIV viral load) did not correlate with emphysema. These data suggest that factors other than smoking may contribute to emphysema in HIV infection. New insights should emerge from several mechanistic studies and longitudinal studies collecting CT measurements in HIV-infected patients are currently ongoing.

Respiratory Symptoms Are Common in HIV

HIV-infected persons have long been reported to have a high prevalence of respiratory symptoms in the era prior to effective combination ART,[45–47] but modern ART-era data continue to show that HIV-infected persons commonly report respiratory symptoms such as cough, wheeze, and sputum production. These studies are less clear on whether HIV infection is the cause of these various respiratory symptoms. Some studies have suggested that HIV-infected persons have more respiratory symptoms than those without HIV,[23,25,48,49] while other studies have shown mixed results with a higher reported frequency of certain symptoms such as dyspnea,[50] and yet others have shown no difference.[38] One study suggested that among HIV-infected persons, respiratory symptoms are more commonly reported in men,[51] although another study did not find a significant gender difference.[49]

Perhaps not surprisingly, respiratory symptoms are also more common in those with pulmonary hypertension,[52] in those with COPD,[49] and in smokers.[28,33] Despite these expected associations, in a cohort study of 461 HIV-infected persons in Cameroon, of whom 87% were lifelong non-smokers, those with HIV had a much higher prevalence of cough and dyspnea (26 and 36%, respectively) compared with 461 HIV-uninfected controls (2 and 6%; $p < 0.001$ for both symptoms),[23] suggesting that smoking is not necessary for the development and presence of respiratory symptoms in HIV. Similarly, those reporting no respiratory symptoms can still have unrecognized COPD.[53] The clinical impact of respiratory symptoms in HIV-infected persons is incompletely known, but those with respiratory symptoms have shorter 6-minute walk distance[48] and more lower airway bacterial colonization.[32]

HIV-Infected Persons May Have Higher Risk of Acute Exacerbations of COPD

Acute exacerbations of COPD account for the majority of cost, morbidity, and mortality in COPD, and HIV-infected persons may have a higher risk of acute exacerbations of COPD compared with HIV-uninfected persons. One study assessed a cohort of HIV-infected persons ($n = 53$) and HIV-uninfected controls ($n = 114$) over 1.5 median years of follow-up and found that the HIV-infected persons had increased odds of self-reported exacerbations (OR: 2.47; 95% CI: 1.22–5.00; $p = 0.01$).[54] Their data also suggested that those with better markers of HIV control (e.g., higher plasma CD4 counts and lower viral RNA levels) actually had a higher exacerbation rate than those with worse HIV control. The precise explanation for this finding is unclear, but this could represent reporting bias or other confounders associated with poor HIV control. A longitudinal analysis of 43,618 HIV-infected and 86,492 HIV-uninfected veterans from the Veterans Aging Cohort study assessed the incidence rate ratios for first acute exacerbation of COPD over 2 years.[55] COPD exacerbation was defined as an inpatient or outpatient COPD ICD-9 diagnosis accompanied by steroid and/or antibiotic prescription within 5 days. HIV-infected veterans had a greater rate of COPD exacerbation than HIV-uninfected veterans (18.8 vs. 13.3 per 1,000 person-years; $p < 0.001$). In adjusted analyses, COPD exacerbation risk was greater in HIV-infected individuals, with higher risk seen with more severe immunosuppression. The

exacerbation risk with worse immunosuppression reported here differs in directionality from the findings of the prior study. These differences may be a result of methods used to ascertain COPD exacerbations or the unique characteristics of the study populations.

Potential Mechanisms Explaining Heightened COPD Risk in HIV

Multiple mechanistic explanations for the relationship between HIV infection and COPD have been proposed, based primarily on findings common to both HIV infection and non-HIV COPD such as the following: (1) accumulation of CD8+ cytotoxic T cells in the lungs of patients with HIV[56] and COPD,[57] (2) effect of acute lower respiratory infections on reduced lung function in HIV[18] and COPD,[58] (3) colonization of airways by *Pneumocystis jirovecii* in HIV[59] and COPD,[60] and (4) increased oxidant stress seen in both HIV[61,62] and COPD.[63] More recent studies have also identified other potential mechanisms such as airway colonization by *Tropheryma whipplei*,[64] monocyte activation,[44] and T-cell dysregulation[65] and shortened telomere length.[66] In low-to-middle income countries, biomass smoke exposure and pulmonary tuberculosis may also contribute to HIV-associated COPD.[23] Multiple ongoing investigations continue to explore these and other possible mechanisms. Mechanistic studies to understand how HIV might increase COPD risk have relevance to HIV-infected persons, but these data also have potential relevance to non-HIV, smoking-related COPD, as HIV infection may represent a novel human model of disease development that may open new investigations to improve our currently limited understanding of COPD pathogenesis.

ART Treatment Regimens and COPD Risk

Since its introduction in 1996, effective combination ART has transformed HIV from a fatal infection to a chronic, lifelong disease. While combination ART clearly reduces the risk for opportunistic infections of the lung (see relevant reviews in this issue), the potential effect of ART on COPD risk has been questioned. Administrative data for approximately 33,000 HIV-infected U.S. veterans found ART use was associated with a lower risk of incident COPD (incident rate ratio: 0.90; 95% CI: 0.82–0.99).[20] However, the main limitation of this analysis was its lack of spirometry to confirm COPD, an important methodological point, given that administrative data may not be very reliable when compared with spirometry.[67,68] Two single-center cross-sectional studies performed spirometry in HIV-infected persons and somewhat surprisingly concluded that ART was actually associated with *worse* lung function. These two studies sampled 215 HIV-infected persons from Los Angeles[28] and 167 HIV-infected persons from Pittsburgh,[29] and while they suggest possible pulmonary harm from ART, they relied on retrospective, observational ART data. The first study to report longitudinal measurements of spirometry in HIV-infected persons was the AIDS Linked to the Intravenous Experience (ALIVE) cohort. ALIVE measured spirometry in 316 injection drug user HIV-infected persons and 748 injection drug users without HIV in Baltimore over a median of 2.75 years.[27] There was interestingly no association between HIV infection nor ART use and rate of FEV_1 decline. However, among those with viral load >75,000 copies/mL (n = 33), there was a substantially faster rate of FEV_1 decline compared with those with viral load ≤75,000 copies/mL (n = 279) and compared with those with no HIV (n = 748). The magnitude of this difference was substantial, with adjusted rate of FEV_1 decline

in those with viral load >75,000 copies/mL being −99.1 mL/year, which is markedly worse than the typical age-related decline of −25 to −30 mL/year in healthy individuals and the typical −60 mL/year seen in smokers susceptible to COPD.

A recently completed multisite, international, randomized, controlled trial (n = 1,026) randomized HIV-infected persons, naive to ART with baseline CD4 counts >500 cells/mm^3 to either immediate ART or deferral of ART until CD4 counts were <350 cells/mm^3.[69] Those randomized to immediate ART had lung function decline that was no different from those randomized to deferred ART, demonstrating the lack of either pulmonary harm or pulmonary benefit with early ART initiation in HIV with CD4 counts >500 cells/mm^3. This is the only large-scale randomized trial that we are aware of investigating a pulmonary outcome in HIV. This trial addressed a clinically relevant question in HIV-associated COPD, and also demonstrated the feasibility of future intervention trials aiming to reduce the burden of COPD in those with HIV. It remains unclear how ART might impact lung function decline in HIV-infected individuals who present with lower CD4 cell counts.

Asthma in HIV

Asthma is a clinical syndrome with heterogeneous clinical, physiologic, and atopic characteristics that impact the disease course and therapeutic responses. While the increased risk of COPD in HIV-infected persons is well established, current epidemiological data yield conflicting results regarding asthma risk in HIV-infected persons. The few studies from the pre-ART era were inconclusive regarding asthma risk in HIV infection.[70,71] In a study of 62 HIV-infected persons compared with 62 HIV-uninfected controls, the prevalence of airways hyperresponsiveness, as measured by methacholine inhalation challenge, did not differ significantly (19 vs. 13%, $p > 0.1$).[70] When comparing a larger study of 248 HIV-infected men to 236 healthy male controls, individuals with HIV infection more frequently reported asthma diagnosis (17.3 vs. 12.3%) and wheezing (54.4 vs. 21.2%), as well as demonstrated more bronchial hyperresponsiveness to methacholine (26.2 vs. 14.4%) (all values noted to be statistically significant although no p-values provided).[71] The differences in bronchial hyperresponsiveness observed between HIV-infected and HIV-uninfected men were only significant among smokers (30.1 vs. 13.3%; $p < 0.05$). For nonsmokers, the prevalence of bronchial hyperresponsiveness was 20% among HIV-infected men and 14.9% among HIV-uninfected men ($p > 0.05$).

Asthma Prevalence Increased in HIV-Infected Children

The earliest literature regarding asthma risk in HIV infection in the post-ART era focused on HIV-infected pediatric populations with vertically acquired infection.[72–75] Asthma was more common in 451 HIV-infected children compared with 227 HIV-exposed but HIV-uninfected children regardless of definition used (diagnosis: 25 vs. 20% [$p = 0.10$], asthma medication use: 31 vs. 22% [$p = 0.01$], clinical diagnosis and/or medication use: 34 vs. 25% [$p = 0.01$]).[72] In this study, the risk of asthma diagnosis was higher in HIV-infected children (hazard ratio: 1.37; 95% CI: 1.01–1.86). Interestingly, in a larger study of vertically infected children, asthma incidence was highest among children treated with ART.[74] In this study, asthma prevalence, defined by asthma medication use, was 10.4% among HIV-infected

children on ART compared with 3.8% among HIV-infected children who were ART naive ($p = 0.02$). The cumulative incidence of asthma in HIV-infected children on ART was 33.5% compared with 11.5% among ART-naive children ($p = 0.01$). There was no difference in asthma prevalence between HIV-uninfected children and HIV-infected children on ART (33.5 vs. 31.2%, $p = 0.78$). These data suggest that the incidence of asthma may be driven by restoration of the immune system in the setting of ART, consistent with a prior report of HIV-infected adults with asthma in the pre-ART era, where CD4 cell count ≥200 cells/dL was significantly associated with current asthma.[76]

The Risk of Asthma with HIV Infection in the Post-ART Era Remains Unclear

Limited prevalence data exist regarding the risk of asthma among HIV-infected adults in the post-ART era. The largest database analysis of risk for incident pulmonary disease in the post-ART era examined more than 33,000 HIV-infected U.S. veterans and 66,840 HIV-uninfected matched veteran controls. In unadjusted analyses using ICD-9 diagnoses to define asthma, the asthma incidence was similar comparing HIV-infected persons and HIV-uninfected controls (5.6 per 1,000 person-years).[20] After age stratification with and without adjustments for smoking, the incidence rate for asthma did not differ between HIV-infected and HIV-uninfected persons. The authors highlighted that asthma, a diagnosis typically occurring earlier in life, may have preceded HIV infection in this older population. In a separate cross-sectional analysis of 223 HIV-infected adults from a single center, physician-diagnosed asthma was present in 46 (21%).[77] This prevalence is more than double the 8% prevalence of the general U.S. population.[78]

More recent epidemiological data, however, have failed to conclusively determine the impact of HIV infection on asthma prevalence and incidence.[49] Self-report of respiratory diagnoses were obtained via annual questionnaire for 3 years in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). MACS is a prospective cohort study of 6,972 men with or at-risk for HIV, followed up since 1984. WIHS has followed up 3,766 women with or at-risk for HIV infection since 1983. Asthma was the most common respiratory diagnosis in MACS and WIHS, with baseline prevalence in MACS of 13.5% and WIHS of 22.9%. HIV infection was not associated with an increased prevalence of asthma diagnosis either in MACS or WIHS (prevalence ratio for HIV infected = 1.04 [95% CI: 0.80–1.34] and 1.05 [95% CI: 0.88–1.25] for HIV uninfected, respectively). Incidence of asthma diagnosis during 2 years of follow-up was also determined. Incidence rate for asthma was higher in women compared with men (2.59/100 person-years and 0.69/100 person-years, respectively; *p*-value not provided). No difference was observed in incident asthma diagnosis in either MACS or WIHS and comparing HIV-infected with HIV-uninfected persons.

Contrasting these findings, a Canadian cross-sectional, population-based study of HIV-infected persons and randomly selected population controls demonstrated an increased prevalence of asthma diagnosis among HIV-infected persons.[79] After identifying 14,005 HIV-infected persons and 71,410 HIV-uninfected comparators, the authors determined asthma diagnosis using a validated asthma case definition. Asthma prevalence among HIV-

infected persons was 12.7%, yielding a prevalence ratio of 1.31 (95% CI: 1.20–1.43) compared with HIV-uninfected persons. These large cohort studies demonstrate that the understanding of prevalent and incident asthma risk associated with HIV infection is not resolved. Differential findings may result from particular characteristics of the cohort (age, race) and ascertainment of asthma diagnosis (self-report, ICD-9 data, or asthma medication use).

HIV Infection and Asthma Manifestations

Bronchodilator Reversibility and Airways Hyperresponsiveness

To date, only one study has examined bronchodilator reversibility in HIV-infected persons. In the analysis of 224 HIV-infected persons by Gingo et al discussed previously,[77] bronchodilator reversibility (defined as improvement in FEV_1 or forced vital capacity [FVC] of at least 200 mL and 12%) was present in 9% of the cohort. The presence of a bronchodilator response was not associated with CD4 count, HIV RNA level, or ART use.

Airways hyperresponsiveness to methacholine, a measure of bronchial hyperreactivity frequently seen in asthma, has been examined in pre-ART and post-ART HIV-infected persons. Two pre-ART studies failed to find an association between HIV infection and airway hyperresponsiveness to methacholine.[70,80] In one study, airways hyperresponsiveness, defined as 20% or more decline in FEV_1 after methacholine challenge, was similar between HIV-infected and otherwise similar HIV-uninfected control participants (19.3 vs. 12.9%; $p > 0.1$).[70] The second study, examining hyperresponsiveness to methacholine in 25 HIV-infected persons with AIDS and 25 HIV-uninfected persons found no significant difference in hyperresponsiveness between groups (8% HIV infected vs. 16% HIV uninfected, *p*-value reported “nonsignificant”).[80] To date, only one study has examined airways hyperresponsiveness in HIV-infected persons in the current ART era.[71] This study examined 248 HIV-infected men recruited from an HIV clinic. The control group for this study was drawn from a general population. HIV-infected men had greater bronchial hyperresponsiveness to methacholine (26.2; 95% CI: 18.9–31.0%) compared with HIV-uninfected men (14.4%; 95% CI: 10.1–18.7%; no *p*-value provided). Differences in methacholine response were significant only among smokers. Among HIV-infected men, reduced FEV_1/FVC and IgE >100 IU/mL were both associated with airways hyperresponsiveness. However, among HIV-infected men, smoking status and CD4 cell count were not associated with methacholine response. Importantly, the rate of current cigarette use was higher in HIV-infected versus HIV-uninfected persons (62 vs. 35%), potentially confounding some observations.

HIV Infection and Markers of Atopy

Elevated serum IgE levels in HIV infection were recognized early in the AIDS epidemic,[81–83] but the relationship between these levels and asthma in HIV infection has not been extensively studied. In the study by Poirier and colleagues, more HIV-infected men had elevated total serum IgE levels compared with a control population (38% [95% CI: 32–44] vs. 26% [95% CI: 21–31]; no *p*-value provided).[71] When determining the prevalence of atopy in 74 hospitalized HIV-infected persons (62% with AIDS), 31% presented with IgE

>150 kU/L[84] Elevated IgE levels did not differ by severity of immunodeficiency (39% of patients without AIDS vs. 26% of patient with AIDS; $p = 0.23$). HIV-infected persons without AIDS had nonstatistically significant higher IgE levels compared with HIV-infected persons with AIDS (346 vs. 175 kU/L; $p = 0.16$). The presence of atopy, defined by positive skin prick test to at least 1 of 20 common environmental allergens, was borderline higher in HIV-infected persons without AIDS than those with AIDS (28 vs. 11%; $p = 0.06$).

Mechanisms for Asthma Risk in HIV Infection

The potential mechanisms underlying asthma in HIV infection remain unclear.[85] Asthma is mediated in part by a CD4 Th2-dominant cellular phenotype.[86,87] The Th1–Th2 balance varies over HIV disease progression. Early-stage HIV infection has a Th1-predominant profile characterized by production of IL-2 and interferon gamma,[88] while late HIV infection has a Th2-predominant profile characterized by increased IL-4 and IL-10 production.[89,90] Immune restoration with ART partially reverses this cytokine profile.[91,92] Within this construct, it is possible that asthma prevalence and manifestations increase as HIV disease worsens, and are reduced in populations with well-controlled HIV. Alternatively, HIV infection and the associated overall CD4 cellular depletion might reduce atopy and asthma risk, while restoration of the immune system with ART can lead to a global increase in inflammation and worsening asthma manifestations.[28,76,93] Several other potential mechanisms for increased asthma risk in HIV-infected persons have been proposed (see review by Puri and colleagues[85]), but ultimately this area of study remains inconclusive.

Need for More Data Regarding HIV and Asthma

The limited available data regarding asthma prevalence and manifestations prevent any definitive conclusions in these areas. Several studies suggest that HIV may increase asthma risk and alter manifestations, but they have been relatively small, single-center studies with potential confounding. Future studies incorporating refined definitions of asthma phenotypes, adequate sample sizes, and epidemiologically appropriate control groups are needed to definitely understand the association between HIV and asthma.

Implications for Clinicians

Diagnosis

The high frequency of obstructive lung disease and respiratory symptoms in HIV-infected populations, the high prevalence of cigarette smoking, and the aging of the HIV population indicate that clinicians caring for HIV-infected patients should consider the diagnosis of COPD or asthma in HIV-infected patient presenting with respiratory symptoms (e.g., shortness of breath, cough with or without sputum production, and progressive limitation of activity) of a subacute nature. This is especially the case for individuals with risk factors for COPD such as a history of cigarette smoking or prior pneumonia. In low-to-middle income countries, exposure to biomass and other forms of smoke should also heighten suspicion for COPD.

In general, the evaluation and diagnosis of suspected COPD or asthma in HIV-infected patients is similar to that in the general population and should include pre- and post-bronchodilator spirometry. The high frequency of isolated decreases in the DL_{CO} in HIV argues for consideration of DL_{CO} testing in HIV populations. While reductions in lung function and DL_{CO} are consistent with a diagnosis of emphysema, the presence of reduced DL_{CO} in the setting of normal spirometry testing should also raise the question of pulmonary vascular disease or early interstitial lung disease. Typically, chest radiography is performed as part of the standard evaluation for respiratory symptoms and can be more useful in excluding alternative diagnoses (e.g., acute pneumonia) than confirming the presence of COPD. Similarly, chest CT scanning may be performed as part of the evaluation of respiratory symptoms, but its use specifically to evaluate for the presence of CT emphysema, in the absence of spirometric (or diffusing capacity) abnormalities, is currently unclear.

Treatment

No studies have specifically addressed whether COPD or asthma treatment in HIV-infected persons should be different from treatment in HIV-uninfected persons. As a result, the available treatment algorithms outlined in clinical guidelines used in HIV-uninfected persons (e.g., www.goldcopd.org, www.ginasthma.org) should probably also be used for HIV-infected persons. Therapeutic options include short-acting β-agonists, short-acting muscarinic antagonists, long-acting β-agonists, long-acting muscarinic antagonist, and inhaled corticosteroids. COPD patients with low symptom burden and low risk of future exacerbations can be treated with short-acting agents alone. For those with high symptom burden but low exacerbation risk (defined as $FEV_1 > 50\%$ predicted and less than two exacerbations in the prior year), long-acting antimuscarinic therapy is the recommended second agent. For patients at high risk for COPD exacerbations (defined as $FEV_1 < 50\%$ predicted or two or more exacerbations in the prior year), addition of an inhaled corticosteroid regimen or long-acting antimuscarinic is indicated. In asthma, short-acting β-agonists, followed by inhaled corticosteroid regimens, is the desired approach.

The decision to prescribe inhaled corticosteroids in an HIV-infected patient requires additional thought. First, in non-HIV populations with COPD, inhaled corticosteroids have been associated with an increased risk of pneumonia.[94] Next, there are important drug–drug interactions between many of the inhaled corticosteroids and several antiretroviral medications. In HIV therapy, a frequent method to augment blood levels of protease inhibitors is through “boosting” with a second agent (i.e., ritonavir, cobicistat), which inhibit the cytochrome P450 pathway and allows for a simplified protease inhibitor dosing regimens. Coadministration of inhaled (or intranasal) budesonide, fluticasone, or mometasone with a ritonavir or cobicistat-containing regimens has the potential to increase the levels of glucocorticoids. This can result in excess glucocorticoid levels in the blood resulting in adrenal insufficiency and Cushing syndrome (http://aidsinfo.nih.gov/guidelines). A similar interaction exists between boosted regimens and glucocorticoids such as prednisone and methylprednisolone, which might be used as part of the management of acute exacerbations of COPD or asthma. This interaction is not present with inhaled beclomethasone[95] and therefore beclomethasone should probably be the preferred inhaled

corticosteroid for patients on ritonavir or cobicistat. Alternatively, those requiring inhaled corticosteroids for control of their respiratory condition can be considered for alternate ART regimens that do not contain ritonavir or cobicistat.

Smoking Cessation and Vaccination

Persons with HIV who smoke cigarettes should be strongly urged to quit. There have been few published smoking cessation trials specific to HIV-infected persons, but, in general, these studies suggest that interventions for smoking cessation that are effective in the general population (e.g., nicotine replacement, oral medications, online support programs) are also effective in HIV-infected persons.[96–101]

HIV-infected patients with COPD should receive the recommended vaccinations as for all COPD patients. The current U.S. “Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents” (available at www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf) recommends that all HIV-infected persons receive the inactivated influenza vaccine annually during influenza season. HIV-infected persons should also receive the 13-valent pneumococcal conjugate vaccine (PCV13), followed by the 23-valent pneumococcal polysaccharide vaccine (PPV23) 8 weeks later in individuals with a CD4 cell count ≥200 cells/dL and either 8 weeks later or once the CD4 cell count is increased to ≥200 cells/dL in those with a baseline CD4 count <200 cells/dL who subsequently start ART. The *Haemophilus influenzae* type b vaccine is not usually recommended for adult use, unless a patient also has anatomic or functional asplenia, as the incidence of *H. influenzae* type b infection in HIV-infected adults is low. Tables 2 and 3 summarize the key points for pulmonary specialists caring for HIV-infected persons and HIV providers caring for patients with asthma or COPD.

Identification of Key Future Research Needs

As highlighted in this review, tremendous progress has been made in the understanding of the relationship between HIV infection and the obstructive lung diseases. Epidemiological data from well-designed cohort studies have provided estimates of lung disease prevalence in a variety of HIV-infected populations. More recent data have offered insight into the impact of HIV infection on manifestations of lung disease, including CT changes in COPD and atopy markers in asthma. Despite this progress, key knowledge gaps remain and should be addressed regarding mechanisms, epidemiology, and interventions for the prevention and treatment of obstructive lung diseases in HIV (Table 4).

It is unclear if the same mechanisms underlying development of asthma and COPD in HIV-uninfected persons play a role in HIV-associated obstructive lung disease. These mechanisms, including chronic inflammation, oxidative stress, innate immune activation, cellular senescence, and apoptosis, may simply be accelerated in HIV-infected persons. If this were the case, then studying such mechanisms in HIV-infected persons may provide an efficient approach to explore processes important in lung disease in those without HIV. Alternatively, novel mechanisms may be unique to HIV-infected persons.

Ultimately, these mechanistic questions will require the development of appropriate cellular and tissue models of HIV infection, as well as translational studies in well-characterized patient cohorts. At the epidemiological level, the association between HIV infection and risk of asthma remains unresolved. It also remains unclear how pulmonary vascular disease impacts HIV-associated COPD development and disease manifestations. Specific cohorts of HIV-infected individuals remain underrepresented in the analyses of lung disease. Data remain sparse from low- and middle-income countries as well as never smokers. New methods to phenotype asthma and COPD, including novel atopy markers, chest imaging modalities, "-omics" techniques, and outcome measures, continue to be developed in non-HIV populations and should be applied to HIV-infected populations as well.

Given the litany of diseases that HIV providers are expected to screen for during a routine clinical encounter, studies of methods to effectively screen for obstructive lung diseases in this population are needed. At the intervention level, there are no data on the optimal approaches to treat COPD and asthma in HIV-infected individuals, and whether such treatment approaches should differ from general populations. The research needs presented here are not exhaustive, but serve to highlight major areas of focus in future research endeavors.

Conclusion

As survival with HIV infection continues to improve, the population of HIV-infected individuals at risk for COPD and asthma will continue to increase. The current data clearly demonstrate an association between HIV infection and COPD, while the associations with asthma remain understudied. Data from large epidemiological studies highlight the impact of HIV disease control on lung-specific outcomes. Specific phenotyping modalities (i.e., CT scanning to detect emphysema) developed in general COPD populations are now being applied to the HIV-infected population, offering further insight into how HIV infection impacts lung outcomes. For the clinician caring for patients with comorbid HIV and obstructive lung diseases, it is necessary to consider the interaction of certain HIV treatment regimens with commonly used inhaled corticosteroids. Ultimately, key gaps in our understanding of mechanisms, detection, and appropriate therapeutics in HIV-associated obstructive lung disease will need to be addressed with future research initiatives.

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Table 1

Summary of regional COPD prevalence estimates among persons living with HIV in the highly active ART era

Study	Country	Sample size (*n*)	Sites (*n*)	Age, y	Female, %	ART use, %	Years of known HIV	Current smoker, %	Former smoker, %	COPD prevalence, %
Drummond et al (2015)[22]	USA	908	9	50 (44, 55)	22%	73	NR	68	19	27% (fixed ratio)
Pefura-Yone et al (2015)[23]	Cameroon	461	1	42.6 ± 10.1	67.7%	85.2	NR	5	7.8	2.2% (fixed ratio) 5.2% (LLN)
Akanbi et al (2015)[24]	Nigeria	356	1	44.5 ± 7.1	59%	97.5	7.0 ± 2.6	3.7	13.4	15.4% (fixed ratio) 22.2% (LLN)
Onyedum et al (2010)[25]	Nigeria	100	1	38 ± 9.5	51%	None	NR	0	0	3% (fixed ratio)[ab]
Makinson et al (2015)[26]	France	338	14	50 (46,53)	17%	NR[c]	17 (10,22)	NR[d]	NR[d]	26% (fixed ratio) 22% (LLN)
Drummond et al (2013)[27]	USA	316	1	48.0 ± 6.5	34.2%	55.0	NR	84.2	9.5	16.5% (fixed ratio)
George et al (2009)[28]	USA	234	1	44.1 ± 9.4	17.5%	83.3	8–10 (IQR NR)	37.1	22.6	6.8% (fixed ratio) 8.6% (LLN)
Gingo et al (2010)[29]	USA	167	1	46 (IQR NR)	26.4%	80.7	13.0 (IQR NR)	52.7	23.4	21.0% (fixed ratio) 19% (LLN)
Hirani et al (2011)[30]	USA	98	1	44.8 ± 11.2	16.3%	87.7	8.3 ± 6.5	21.0	34.0	16.3% (fixed ratio)[a]
Sampériz et al (2014)[31]	Spain	275	1	48.6 ± 6.6	21.8%	95.6	11.9 ± 5.4	61.5	25.1	17.2% (fixed ratio)
Nimmo et al (2015)[32]	UK	218	1	46.7 ± 9.8	26.6%	84.4	NR	22.9	24.2	6.8% (fixed ratio)
Cui et al (2010)[33]	Canada	119	1	43.4 ± 8.4	21.0%	84.0	9.0 ± 6.6	43.7	19.3	3.4% (fixed ratio)
Madeddu et al (2013)[34]	Italy	111	1	42.3 ± 8.1	30.6%	78.4	NR	56.8	NR	23.4% (fixed ratio)
Kristoffersen et al (2012)[35]	Denmark	63	1	43.3 ± 9.0	11.1%	88.9	9.3 ± 5.1	47.6	NR	9.5% (fixed ratio) at baseline; 19.0% at 4.4 y follow-up
Nakamura et al (2014)[21]	Japan	49	1	40 (IQR NR)	0.0%	97.9	NR	44.9	16.3	10.2% (fixed ratio)
Kunisaki et al (2015)[36]	Multiple	989	80	36 (30, 44)	29.4%	None	1.2 (0.4, 3.5)	27.5	11.0	5.5% (fixed ratio) 6.8% (LLN)
	Africa	322	7	37 (32, 44)	64.0%	None	1.5 (0.5, 4.8)	14.0	5.9	5.0% (fixed ratio) 7.8% (LLN)
	Asia	102	8	36 (30, 41)	26.5%	None	0.8 (0.2, 3.4)	19.6	9.8	0.0% (fixed ratio) 2.0% (LLN)
	Europe/Israel/Australia	298	35	38 (31, 45)	8.7%	None	1.2 (0.5, 3.5)	44.0	14.1	9.1% (fixed ratio) 9.1% (LLN)
	Mexico/S. America	182	10	34 (29, 40)	12.6%	None	0.6 (0.3, 2.0)	26.9	14.8	2.7% (fixed ratio) 3.3% (LLN)

Study	Country	Sample size (*n*)	Sites (*n*)	Age, y	Female, %	ART use, %	Years of known HIV	Current smoker, %	Former smoker, %	COPD prevalence, %
	USA	85	20	36 (29, 45)	10.6%	None	1.5 (0.4, 4.6)	32.9	12.9	7.1% (fixed ratio) 8.2% (LLN)

Studies are ordered in decreasing sample sizes of country-level data. COPD prevalence reported as both FEV_1/FVC <0.70 (fixed ratio) and FEV_1/FVC < LLN. Continuous variables reported as mean +/− standard deviation or median (IQR).

Abbreviations: ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume in 1 second/forced vital capacity; IQR, interquartile range; LLN, lower limit of normal; NR, not reported.

[a] FEV_1/FVC <0.7 and FEV_1 <80% of predicted.

[b] Study excluded smokers, those exposed to biomass smoke, those who worked in dusty environments, and those previously treated with ART.

[c] 88% had viral load <50 copies/mL.

[d] Median 30 pack-years of smoking.

Table 2

Key points for pulmonary specialists caring for HIV-positive persons

• HIV appears to increase risk of COPD and may accelerate FEV_1 decline
• Diffusion abnormalities are common in HIV, but nonspecific
• Asthma risk in HIV is unclear
• Smoking cessation therapies are effective in HIV-infected individuals
• Consider use of beclomethasone as first-line inhaled corticosteroids in those treated with ritonavir or cobicistat-containing antiretroviral regimens (due to risk of Cushing syndrome)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.

Table 3

Key points for HIV specialists caring for those with COPD

• Smokers or those exposed to biomass smoke should be asked about cough, sputum, and exercise limitations
• Those at risk and with symptoms should undergo spirometry and (consider DL_{CO} testing)
• Those with COPD should be treated with short-acting bronchodilators (albuterol, ipratropium bromide); other agents to consider are long-acting β-agonists, long-acting anticholinergics, and inhaled corticosteroids
• Beclomethasone is the safest inhaled corticosteroid in ART regimens containing ritonavir or cobicistat

Abbreviations: ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; DL_{CO}, carbon monoxide diffusing capacity.

Table 4

Key research initiatives in HIV-associated obstructive lung diseases

Mechanistic
• Quantify the role of chronic inflammation and oxidative stress
• Determine the impact of innate immune activation
• Examine the role of cellular senescence and apoptosis
• Utilize “-omics” technologies to develop novel insights
• Develop appropriate cellular and tissue models
Epidemiological
• Determine the impact of HIV infection on asthma risk and disease course
• Refine optimal approaches to screen for COPD among HIV-infected individuals
• Expand data regarding prevalence and risk factors for HIV-OLD in low- to middle-income countries
• Establish the impact of HIV infection on established COPD phenotypes
• Assess the impact of HIV-OLD on long-term functional outcomes and mortality
Interventions
• Test strategies for smoking cessation in HIV patients
• Expand research aimed at interventions to prevent development of HIV-OLD
• Implement studies to determine the efficacy, comparative effectiveness, and side effects of standard COPD and asthma therapies in HIV
• Include respiratory outcomes in ongoing trials of anti-inflammatory, antioxidant, and immune modulating therapies in HIV-infected populations

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV-OLD, HIV-associated obstructive lung disease.