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COPD in People with HIV: Epidemiology, Pathogenesis, Management, and Prevention Strategies

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Abstract: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by airflow limitation and persistent respiratory symptoms. People with HIV (PWH) are particularly vulnerable to COPD development; PWH have demonstrated both higher rates of COPD and an earlier and more rapid decline in lung function than their seronegative counterparts, even after accounting for differences in cigarette smoking. Factors contributing to this HIV-associated difference include chronic immune activation and inflammation, accelerated aging, a predilection for pulmonary infections, alterations in the lung microbiome, and the interplay between HIV and inhalational toxins. In this review, we discuss what is known about the epidemiology and pathobiology of COPD among PWH and outline screening, diagnostic, prevention, and treatment strategies.

Keywords: HIV, COPD, tuberculosis, air pollution, immune activation, smoking, pulmonary infections

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory condition that represents the third leading cause of death worldwide.^{1,2} According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 definition, COPD is a

Heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.²

People with HIV (PWH) are particularly vulnerable to the development and progression of COPD, with both higher rates of COPD and an earlier and more rapid decline in lung function than in the general population, even after accounting for cigarette smoking and other known risk factors, such as intravenous drug use.³⁻⁷ The exact mechanisms that underlie HIV-associated COPD are incompletely known, but environmental exposures, heightened immune activation and systemic inflammation, accelerated aging, a predilection for the development of pneumonia, and alterations in the lung microbiome likely play important roles (Figure 1).⁸⁻¹¹ The purpose of this review is to describe what is currently understood about the epidemiology and pathobiology of COPD among PWH, to indicate selected areas of active investigation, and to outline screening, diagnostic, prevention, and treatment strategies.

Epidemiology

Prevalence

As survival among PWH has improved with the use of antiretroviral therapy (ART), COPD has become an increasingly important comorbidity. PWH develop an earlier and more rapid decline in lung function, even after adjustment for traditional risk

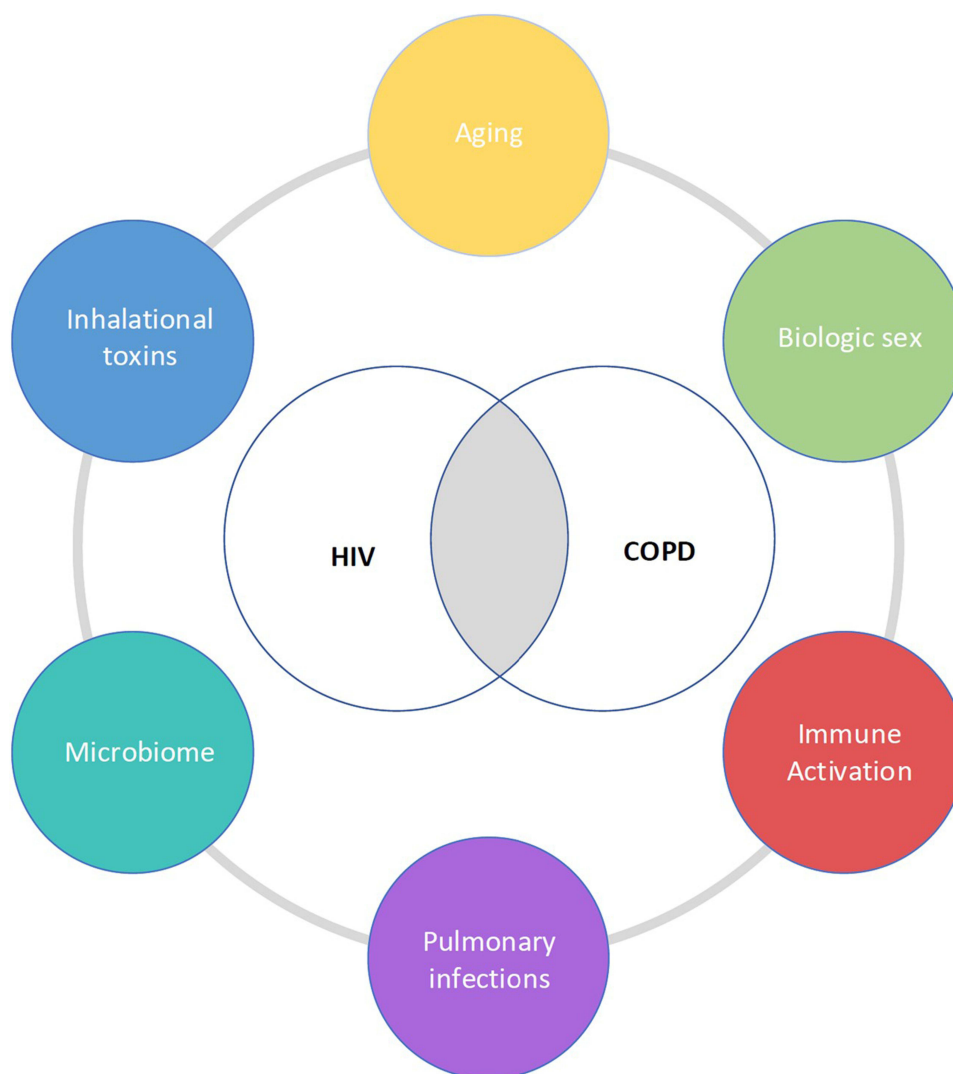


Figure 1 Drivers of COPD in PWH.

factors.^{3,5-7,12-15} A recent retrospective study evaluating comorbidities in PWH based on hospital discharge data found that COPD was the most common comorbidity across the 10-year study period and that COPD prevalence was higher among PWH than among those without HIV (23.5% versus 14.0%).¹⁶ Prevalence estimates of COPD among PWH have ranged from 3.4% to over 40% in prior studies; notably, most of these have been conducted in Europe and North America.^{17,18} Part of this heterogeneity is due to differences in COPD classification methods, such as self-report, International Classification of Diseases (ICD) diagnostic codes, use of CT scans, and spirometry.^{17,19} For example, a systematic review and meta-analysis by Bigna et al evaluating the global prevalence of COPD among PWH found that the prevalence varied from 5.6% to 10.6% depending on the diagnostic criteria used, with a higher prevalence when using spirometric criteria instead of self-report or ICD diagnostic codes.⁴

Geography

COPD in PWH occurs anywhere PWH reside. However, the risk factors for the development of COPD in PWH vary regionally due to differences in age, rates and duration of tobacco smoking, exposure to biomass fuels, and prevalence of tuberculosis, all of which have been implicated in COPD development.^{2,20-22} While the majority of studies on COPD in PWH have been conducted in the US and Europe, most PWH live in sub-Saharan Africa, where there is a high prevalence of both tuberculosis (TB) and exposure to biomass fuels, and where patients are typically younger and less

likely to smoke tobacco. While earlier studies suggested that ART itself may be a risk factor for worsening lung function,^{23,24} Kunisaki et al conducted a multinational randomized controlled trial (RCT) in the modern ART era and did not find a difference in lung function based on timing of ART initiation.²⁵

Biologic Sex

Biologic sex may also contribute to differences in COPD trajectories among PWH. In one study of longitudinal lung function changes in PWH, female sex was associated with distinct lung function trajectories, including baseline low diffusing capacity for carbon monoxide (DLco).²⁶ In a study by McNeil et al of virally suppressed adults with HIV and their seronegative counterparts in Uganda, women with HIV demonstrated an accelerated FEV1 decline as compared to women without HIV, a finding that was not seen among men with and without HIV.²⁷ Interestingly, in a large US-based cross-sectional analysis comparing women with and without HIV, women with HIV had a lower DLco than women without HIV, but there were no differences in spirometric outcomes by HIV status.^{28,29} In another study including the same cohort of women, baseline COPD prevalence was similar among men with and without HIV and women with and without HIV, but COPD incidence was higher among men with HIV when compared to men without HIV.³⁰ In contrast, Abelman et al found in a post-pneumonia Ugandan cohort that women with HIV had over three-fold higher odds of COPD on spirometry compared to men with HIV, a sex-based difference not found in women and men without HIV.³¹ Further work is currently underway to investigate whether these reported HIV-associated sex-specific differences in COPD rates are driven by immunologic, hormonal, or environmental factors.

Risk Factors for COPD in PWH

There are many risk factors for the development of COPD in PWH including HIV itself,^{5,32} cigarette smoking and other inhalational exposures, air pollution, opportunistic infections and pneumonia, microbiome alterations,^{33,34} accelerated aging,^{35–38} and socioeconomic factors.³⁹ This section focuses on the major drivers, such as smoking, as well as potential risk factors under investigation, such as chronic cytomegalovirus (CMV) coinfection.

Smoking

Smoking is the key risk factor for COPD in PWH. Smoking is more prevalent among PWH compared to their seronegative counterparts.^{40–42} However, studies of co-exposure to HIV and tobacco smoke suggest that PWH who smoke may also be more susceptible to smoking-induced lung damage than HIV-uninfected people who smoke. For example, Diaz et al found emphysema to be more prevalent among smokers with HIV as compared to smokers without HIV.⁴³ Further, in a longitudinal multi-center cohort of 13,687 veterans with and without HIV, Crothers et al found that the prevalence and incidence of both COPD and lung cancer were higher among those with HIV compared to those without HIV despite similar levels of smoking.⁵ Importantly, among PWH on ART, smoking may reduce life expectancy more than HIV itself.^{44–46} While the pathophysiologic mechanism driving this HIV-associated difference is incompletely known, recent work suggests that, among PWH, tobacco smoke suppresses alveolar macrophage production of T-cell recruiting chemokines. This impairs the migration of cytotoxic T cells from the airway mucosa into the alveolar space, leading to localized airway mucosa inflammation and tissue destruction.⁴⁷

Air Pollution

Air pollution – the leading environmental cause of death globally⁴⁸ – is now the greatest threat to human health,⁴⁹ and COPD is a leading cause of the nearly 7 million annual deaths attributed to air pollution.^{48,50} Air pollution results from a variety of human-related activities and natural events that include emissions from vehicles, factories, and power plants; traffic-related products; biomass fuel burning (ie, charcoal, firewood, animal dung, crop residues) for cooking and heating; dust storms; forest fires; and volcanic eruptions. The dominant pollution sources vary by region. Traffic- and industry-related sources drive exposure in high-income countries and urban settings, while biomass-related sources drive exposure in low- and middle-income countries and rural settings.⁵¹ Air pollution causes acute and chronic lung dysfunction, structural lung abnormalities, submaximal lung growth in childhood and adolescence, and augments lung disease risk in vulnerable populations.^{52–63} Even small acute increases in fine particulate matter (PM_{2.5}) exposure

worsen mortality,⁶⁴ and there is no “safe” level of exposure.⁶⁵ Biomass-associated COPD, compared to tobacco-associated COPD, is characterized by more small airways disease and fibrosis, less emphysema, higher DLco, and less airflow obstruction – in effect, a more fibrotic and less emphysematous phenotype.^{66–69} Exposure to biomass fuel smoke has also been associated with defective bacterial phagocytosis.⁷⁰ In addition, PM_{2.5} exposure may also potentiate TB risk,^{21,71,72} which by itself is a risk factor for COPD and an important consideration in TB-endemic regions.

Similar to the influence of tobacco smoke, PWH may be more susceptible to air pollution-associated lung damage. For example, among PWH living in San Francisco, exposure to higher levels of outdoor air pollution was associated with increased susceptibility to *Pneumocystis* infection.^{73–75} Using ambulatory carbon monoxide (CO) sensors to measure personal air pollution exposure among 260 adults with and without HIV in rural Uganda, North et al found that exposure to short-term CO levels that exceed WHO air quality guidelines was associated with self-reported respiratory symptoms among PWH but not among HIV-uninfected comparators.⁷⁶ Characterizing air pollution exposure among PWH and exploring the potentially outsized influence of air pollution exposure on lung health in this population is an area of ongoing investigation. As global smoking prevalence continues to decline and rapid industrialization and urbanization progresses, air pollution is poised to replace tobacco as the leading cause of chronic lung disease,^{77–79} and a multifaceted approach that also focuses on this often overlooked risk factor for lung disease among PWH is critical.

Opportunistic Infections and Pneumonia

PWH have historically had higher rates of pneumonia, and while incidence of bacterial pneumonia has decreased with the advent of ART,^{80,81} it remains common in this population.^{82–84} In the current era, PWH have similar rates of acute respiratory infections as people without HIV, but PWH experience more severe disease.⁸⁵ Pneumonia has been associated with higher rates of COPD and lung function abnormalities in PWH.^{86–89} For example, Drummond et al conducted a US-based multi-center study evaluating spirometry in adults with and without HIV and found that participants with airflow obstruction were more likely to have a history of bacterial pneumonia and *Pneumocystis jirovecii* (PJP) infection.⁹⁰ Specifically, PJP, an opportunistic infection that occurs in PWH with CD4 counts <200 cells/mm,³ elevated HIV RNA, and colonization by *Pneumocystis* have each been associated with higher risk of COPD among PWH.^{88,91,92} There are numerous contributors to the increased risk of pneumonia in PWH, including alterations in immunity, which lead to persistently elevated markers of immune activation and inflammation, as well as environmental and behavioral risk factors, and a higher prevalence of COPD, which is both a consequence of and a risk factor for pneumonia.^{9,93–96}

Globally, tuberculosis is the leading infectious cause of death among PWH,⁹⁷ PWH are 19 times more likely to develop TB disease than their seronegative counterparts.^{98,99} Pulmonary TB has been found to cause permanent scarring, bronchiectasis, pleural fibrosis, damage to small and large airways, as well as lung parenchymal damage, all of which may contribute to permanent lung function impairment.^{20,100} Whereas during the treatment phase of TB this impairment is typically restrictive, there is increasing evidence of a relationship between prior pulmonary TB infection and the subsequent development of obstruction and COPD.^{20,87} Rates differ significantly by the population under study, but pulmonary TB has been found to lead to airway obstruction in 18.4–86% of people in the general population.¹⁰⁰ HIV is now recognized as a risk factor for post-TB lung disease, although the extent of this relationship is currently under study.^{87,100–104} There is some evidence to suggest that HIV may be associated with reduced severity of post-TB lung disease, but this is an area that merits further evaluation.^{100,105,106}

Chronic CMV Infection

CMV is an important and omnipresent coinfection in HIV that has been associated with cardiovascular and cerebrovascular disease, other non-AIDS events, and increased mortality.^{107–112} Given the high rates of CMV antibody seropositivity among PWH, CMV IgG titers are commonly used as markers of CMV activity and have been shown to correlate with adverse outcomes.^{112,113} However, studies of CMV’s effect on lung function and COPD in PWH are limited. While chronic CMV infection in children with perinatally acquired HIV on ART has been associated with an abnormal FEV1,¹¹⁴ CMV’s association with COPD and other chronic lung diseases in adults with HIV has not been evaluated. Emerging

data from the general population, however, suggest that chronic CMV infection is associated with COPD,¹¹⁵ and that higher CMV IgG titers are associated with COPD-related mortality.¹¹³ CMV is also associated with abnormal DLco in solid organ transplant recipients, although this has not been studied in PWH.^{116–118}

There are several proposed mechanisms for CMV-mediated systemic immune effects, including persistent immune activation, endothelial dysfunction, and alterations in the gut microbiome.^{17,119–121} Similar biomarker activation patterns are noted in PWH with CMV and those with COPD. For example, sCD163, sCD14, and IL-6 are increased in both CMV IgG-positive PWH^{122–124} and PWH with lung function abnormalities, including both abnormal spirometry and abnormal DLco.^{10,121} These data suggest that there may be a shared mechanistic pathway between chronic CMV infection and chronic lung disease in PWH, but further work is needed to understand and characterize this relationship.

HIV-Specific Influences on COPD Pathogenesis

Several HIV-specific mechanisms may contribute to the increased incidence and accelerated development of COPD in PWH. Chronic HIV infection and the direct effects of HIV-related proteins on lung cells, altered lung and systemic immune responses (both immunosuppressive and pro-inflammatory), altered airway and gut microbial communities, impaired response to pathogens, and toxicity from antiretroviral therapies may all contribute to COPD pathogenesis in this population.^{23,24,125–132}

HIV Infection

As the lung acts as a reservoir for HIV even after viral suppression, chronic HIV infection may directly contribute to COPD pathogenesis in various ways.^{132–134} Newly replicated viral particles released slowly over time bind to and interact with many cell types within the lung, which can lead to direct injury, oxidative stress, low-level chronic inflammation, and impaired response to pathogens.^{128,135} Although other cell types in the lung may be infected, alveolar macrophages are the best studied reservoir of HIV in the lung.¹³² HIV infection impairs macrophage phagocytic activity, thus hindering response to pathogens.^{127,132} HIV also skews the macrophage phenotype towards a pro-inflammatory and protease-producing phenotype through the release of a host of cytokines, chemokines, oxidants, and proteases, all of which contribute to COPD pathology. Cytokine and chemokine signaling in HIV-infected macrophages trigger a pro-inflammatory response including neutrophil and lymphocyte infiltration. Kaner et al found that alveolar macrophage expression of proteases such as matrix metalloproteinases 9 and 12 (MMP-9, MMP-12) is higher in PWH who smoke with emphysema than their seronegative counterparts.¹³¹ In murine models, MMPs degrade the extracellular matrix, directly contributing to emphysematous tissue destruction.¹³⁶

Altered Adaptive Immune Responses

COPD development is not only mediated by HIV direct effects, but also by the altered cell-mediated adaptive immune responses in PWH, in particular, altered CD4+ T-cell responses. Numerous studies have shown a relationship between low CD4+ T cell counts and COPD or accelerated lung function decline, although conflicting data also exists.^{23,125,126,137} T cell exhaustion is typically seen in response to chronic antigen stimulation, such as chronic viral infection, and results in decreased functionality. In PWH, CD4+ T cells show signs of exhaustion even in the presence of ART, with an increased expression of programmed cell death protein-1 (PD-1), as well as impaired proliferative capacity.^{130,138,139} Furthermore, in PWH with COPD, airway mucosal CD4+ T cell numbers are depleted and poorly responsive to pathogens.¹³⁰ These findings suggest that dysfunctional CD4+ T cell responses may uniquely contribute to COPD pathogenesis in PWH.

Activated and dysfunctional CD8+ T cells also appear to contribute to the disordered adaptive immune response in chronic HIV infection, and thus could contribute to COPD pathogenesis.^{138,139} PWH show persistent expansion of CD8+ T cells in blood and alveolar compartments, and the decreased CD4+/CD8+ ratio is associated with lung abnormalities even in PWH on ART.^{140,141} These expanded CD8+ T cell populations also show dysfunction, which is typically indicative of an accelerated aging or “immunosenescent” response. Like CD4+ T cells, CD8+ T cells display exhaustion markers, including PD-1, and a low proliferative capacity.^{138,139} The expanded population skews towards memory T cell and terminally differentiated CD8+ T cell populations unable to respond to new insults. Despite their impaired function,

these exhausted T-cells produce a low-grade inflammatory response at mucosal surfaces, which is considered central to COPD pathology.

Changes to the Airway Epithelium

Alterations to the airway epithelium, the main barrier protecting the lungs from outside insults, such as cigarette smoke, air pollution, and inhaled toxins, can also play a major role in COPD pathogenesis. HIV has both direct and indirect effects on the airway epithelium, contributing to disordered barrier function, decreased mucociliary clearance, and generation of pro-inflammatory mediators. For example, HIV enters epithelial cells and disrupts cell–cell adhesion.¹²⁹ HIV-associated proteins released from other infected cells disrupt epithelial tight junctions and induce oxidative stress.¹⁴² HIV and cigarette smoke synergistically disrupt mucociliary clearance, additively suppressing CFTR expression to decrease mucus hydration in cell culture models and inducing goblet cell metaplasia/hyperplasia to increase mucus production in simian models.^{143,144} Finally, when HIV binds specifically to basal cells, epithelial progenitor cells release proteases such as MMP-9 and pro-inflammatory mediators that induce migration and proliferation of macrophages and neutrophils.¹⁴⁵

Changes in the Lung and Gut Microbiome

Lastly, shifts in both the lung and the gut microbiome can also contribute to chronic inflammatory responses in the lung and, hence, COPD pathogenesis. Data are conflicting on whether lung microbial communities differ in PWH based on 16S sequencing.^{146–148} However, subtle differences in the microbiome at the species or strain level or at a functional level cannot be discerned via these sequencing methods. It is plausible that at least a subset of PWH experience pathologic microbial alterations in the airways because of a more hospitable environment for pathogen growth. If present in PWH, microbiome perturbations could contribute to chronic airway inflammation. Furthermore, microbial translocation from a compromised gut mucosa, stimulating a chronic systemic inflammatory response, may contribute to lung disease in PWH as has been seen in asthma and pulmonary infections.¹⁴⁹

Diagnosis and Clinical Findings of COPD in PWH

Screening and Diagnosis

COPD remains both underdiagnosed and misdiagnosed in people with HIV.^{150,151} While currently the US Preventative Services Task Force does not recommend screening for COPD in the general population,¹⁵² higher COPD prevalence among PWH raises the question whether screening should be done in this subpopulation. Currently, there are no screening and diagnostic criteria specific to PWH. While several studies have evaluated different screening approaches, no conclusive recommendations can be made regarding COPD screening and diagnosis in PWH at this time.^{150,153–156} For example, a group in Canada offered screening spirometry to all patients in an HIV clinic,¹⁵⁶ notably, less than a third of the invited participants agreed to participate, and only 11% had airflow obstruction.

Recruitment and retention throughout the screening-to-diagnosis cascade have been major challenges in all studies. For example, a group in Italy implemented a three-step case-finding program, involving a 5-question screening questionnaire (which included questions about age, smoking history, cough and sputum production, shortness of breath, and exercise limitation), portable spirometry, and diagnostic spirometry.¹⁵⁰ They found that 282 participants (19.6%) had a positive screening questionnaire, defined as having a positive answer to at least three questions, but only 33 participants ultimately completed diagnostic spirometry, of whom 22 met criteria for COPD. High participant dropout at each step of the screening process has been similarly reported elsewhere,^{153–155} even when the authors bypassed the screening spirometry and had a shorter questionnaire.¹⁵⁵ Even within these limitations, COPD prevalence based on the screening outcomes has been consistently higher than the known COPD prevalence in each respective clinic,¹⁵⁴ further underscoring the underappreciated burden of chronic lung disease in this population. Additional challenges with screening this high-risk population include lack of a high-performing, validated screening questionnaire in PWH and poor correlation between respiratory symptoms and obstruction on pulmonary function tests (PFTs).¹⁵⁵ To our knowledge, qualitative studies focused on identifying patient, provider, or systems-level issues contributing to high dropout rates in screening

studies among PWH have not been conducted. Having diagnostic spirometry available at the time of a positive screening questionnaire may help reduce high dropout rates.

Any PWH suspected of having COPD should undergo diagnostic testing with, at a minimum, portable spirometry and, in our opinion, full PFTs with pre- and post-bronchodilator spirometry, total lung capacity and lung volumes if spirometry is abnormal, and DLco measurement. Chest radiography demonstrates classic findings (Figure 2) mostly in individuals with advanced disease but is useful in ruling out alternative etiologies that also present with respiratory symptoms similar to those of COPD. Occasionally, additional testing such as chest computed tomography (CT) scans may be warranted to characterize the observed PFT abnormalities, and certain CT findings such as the presence of large bulla (Figure 3) may lead to consideration of additional therapies (eg, bullectomy).

Longitudinal Lung Function Trajectories of COPD in PWH

While there is a paucity of data on the natural history of COPD in PWH, lung function declines faster in PWH compared to HIV-negative controls, even when HIV is well-controlled and smoking rates are comparable.^{6,7,157} Notably, findings from the Pittsburgh HIV Lung Cohort suggested that there may be distinct lung function trajectories among PWH, in which differences in the rate of decline are associated with specific symptoms and distinct profiles of elevated immune activation biomarkers.²⁶ Importantly, this study did not exclusively enroll individuals with COPD. In the general population, COPD studies have shown that lung function decline accelerates as COPD severity increases,¹⁵⁸ but whether similar trajectories are seen in PWH is an area currently under study. In a study evaluating factors associated with lung function decline among PWH by Li et al, the authors found that lung function decline occurred more rapidly in older individuals and those with GOLD stage 1 than those with GOLD stage 0 COPD.¹²⁶ Taken together, these studies suggest that PWH with COPD may demonstrate distinct lung function trajectories when compared to their seronegative counterparts, although additional study is needed in this area.

Lung Function Trajectories in People with Perinatally Acquired HIV

While this review is focused on COPD in adults with HIV, the growing number of individuals with perinatally acquired HIV and their lung function trajectory should also be considered. Children and adolescents with HIV have a higher risk of pulmonary infections, including TB, and even with early ART initiation they remain more vulnerable to small airways dysfunction and risk of obstructive lung disease and other pulmonary abnormalities on spirometry and imaging.^{159–166} Even children who were exposed to but not infected with HIV remain at risk for abnormal lung function.¹⁶⁷ Further, lung

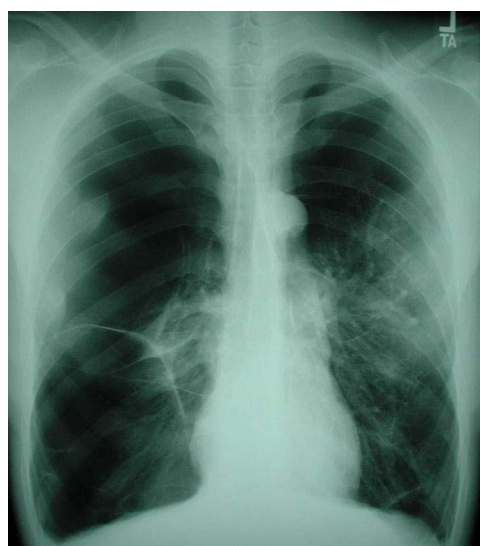


Figure 2 Chest radiograph from person with HIV and COPD demonstrating hyperinflation, flattened diaphragms, and bilateral bullous lung disease (Courtesy of Laurence Huang, MD).



Figure 3 Chest computed tomography from the same person with HIV and COPD demonstrating large, bilateral bullae. This individual eventually underwent bullectomy with dramatic improvement in his respiratory status (Courtesy of Laurence Huang, MD).

function in children seems to be affected by the timing of maternal ART initiation (pre-pregnancy versus during pregnancy).¹⁶⁷ In addition, lung development and the ability to reach maximal lung function is impaired by HIV, repeat infections, smoking, pollution, and poverty, which in turn increases the risk for the development of chronic lung disease in adulthood.^{168,169} As this vulnerable population ages, we are likely to see an increased burden of chronic obstructive disease earlier in life. As most of our understanding of lung function trajectories in PWH with COPD comes from adult PWH from higher income settings, focused efforts for early screening, diagnosis, and management of this condition are needed in areas with high prevalence of adolescents and adults with perinatally acquired HIV.

Diffusing Capacity for Carbon Monoxide

Abnormal diffusing capacity for carbon monoxide is the most prevalent finding on PFTs in PWH, even when spirometry is normal.^{29,170} DLco impairment is non-specific and can be attributed to emphysema, fibrosis, pulmonary hypertension, or anemia. In PWH, it is also often associated with prior respiratory infections such as PJP, TB, or bacterial pneumonia, and the DLco abnormality may persist long after clinical and radiographic resolution of infection.^{89,126} Other risk factors for abnormal DLco include HIV infection, CD4 < 200 cells/mm,³ intravenous drug use, and hepatitis C infection.^{29,101,170-172}

DLco abnormalities can predict the development, symptoms, and outcomes of COPD. Among people who smoke, DLco can become abnormal before spirometric criteria for COPD are met; DLco may also be a marker of early emphysema prior to the development of spirometric obstruction, small airways disease, or early vascular abnormalities.¹⁷³⁻¹⁷⁵ While there are additional and unique risk factors for abnormal DLco in PWH compared to the general population, perhaps suggestive of an HIV-specific lung function abnormality,^{10,176} it is also plausible that isolated DLco abnormalities may serve as a marker for early COPD in some patients. Among PWH, abnormal DLco, like abnormal FEV1, is an independent predictor of worse respiratory symptoms (such as dyspnea, cough, and mucus production),¹⁷⁰ as well as a worse 6-minute walk test.^{177,178} Finally, abnormal DLco is an independent predictor of mortality in PWH with COPD.^{179,180}

Imaging Findings in PWH with COPD

New techniques for quantitative imaging assessment have allowed in-depth characterization of imaging abnormalities in people with COPD. As current GOLD criteria define COPD based on chronic respiratory symptoms,² chest imaging findings such as emphysema describe the structural abnormalities that drive this clinical entity. In the general population of people who smoke, studies have found that evidence of small airways disease and air trapping on imaging could predict COPD development and faster spirometry decline.^{181,182} Importantly, multiple imaging findings such as early interstitial lung abnormalities,¹⁸³ pulmonary artery to aorta ratio >1,¹⁸⁴ pulmonary arterial vascular pruning,¹⁸⁵

progression¹⁸⁶ and homogeneity of emphysema,¹⁸⁷ airway wall thickness,^{188,189} and air trapping have all been associated with disease severity and adverse outcomes in COPD.¹⁸¹

Studies in PWH have shown a high prevalence of emphysema even in individuals without overt respiratory disease.¹⁹⁰ In addition, Leung et al found that people with low DLco and a combination of centrilobular and paraseptal emphysema were more likely to have progression of emphysema,¹⁹¹ and significant emphysema burden was associated with increased mortality.¹⁹² Elevated TNF α and IL-1 β , soluble CD14, nadir CD4, and low CD4/CD8 ratio are also independently associated with emphysema in PWH,^{140,193,194} although reports of a direct association of HIV with emphysema are contradictory.^{194,195} While the exact mechanisms are an area of active investigation, HIV-mediated chronic inflammation and immune dysregulation likely play an important role in emphysema formation.

Symptoms, Exacerbations, and Mortality

Compared to HIV-negative individuals, PWH with COPD have a higher respiratory symptom burden, worse quality of life, and an increased risk for COPD exacerbations.^{24,196–202} For example, PWH with emphysema have a worse chronic cough, increased mucus production, and decreased 6-minute walk distance compared to HIV-negative controls.¹⁹⁸ In PWH who inject drugs, obstructive lung disease has been associated with more severe dyspnea than in their seronegative counterparts.²⁰³ In addition, PWH perform worse on six-minute walk testing.¹⁷⁸ While COPD is associated with increased frailty in individuals with and without HIV, physical limitation scores are worse among PWH.^{204,205} Finally, COPD in PWH is not only often comorbid with cardiovascular disease, but also a risk factor for myocardial infarction²⁰⁶ and has been associated with increased mortality.^{180,192}

Management of COPD in PWH

PWH have historically been excluded from large randomized controlled trials of COPD treatments. Therefore, there are very few HIV-specific data on COPD management, and instead general COPD guidelines for both chronic disease management and COPD exacerbations are applied to PWH.²⁰⁷ These management strategies include guideline-driven inhaler therapy, pulmonary rehabilitation, routine vaccinations, surgical or bronchoscopic lung volume reduction in qualifying patients, and management of other medical comorbidities.² Here, we will focus on a few HIV-specific considerations.

Smoking Cessation

Given the high smoking prevalence among PWH and the excess morbidity and mortality associated with smoking in this population, smoking cessation remains a fundamental aspect of COPD care in PWH. Unfortunately, prescribing rates for smoking cessation therapies have been low for PWH with tobacco use disorder for many reasons, including competing clinical priorities, lack of time, low rates of provider training in smoking cessation interventions, and limited knowledge of nicotine replacement therapies and varenicline.^{208,209} In addition, PWH face additional challenges on the path to sustained smoking cessation that are due to HIV-related stigma, high rates of comorbid substance use, anxiety and depression, financial instability, lack of insurance, low level of education, and racial biases.^{210–213} Tailoring smoking cessation therapies to this population is an active area of research.^{209,214–226} Increased awareness among HIV care providers of the importance of smoking cessation, financial support for smoking cessation initiatives, and intervention studies inclusive of PWH are needed to identify the best ways to support smokers with HIV on their path to quitting.

Choice of Inhalers

Special attention should be paid in the treatment of COPD to PWH who are taking ritonavir or other boosted ART regimens. Ritonavir and cobicistat block the CYP3A4 isozyme and can increase the concentration of most corticosteroids. As a result, use of inhaled corticosteroids (ICS) in patients on these medications has been reported to cause Cushing's syndrome.^{227–230} Beclomethasone is the ICS drug with the best side effect profile and can be used in PWH treated with ritonavir or cobicistat.²³⁰ In PWH who are receiving ritonavir or cobicistat, an added consequence is the inability to use any combination medication for COPD that includes an ICS as fluticasone- and budesonide-containing combination inhaler therapies are contraindicated and beclomethasone is only available as a single, standalone inhaler.

Given the already elevated risk of pulmonary tuberculosis and other pneumonias in this population, additional caution should be applied when using ICS, as they can increase the risk of lung infections in this already vulnerable population.^{231,232}

Modulation of Chronic Inflammation

While no HIV-specific COPD therapies exist, there is an interest in the role of modulating chronic inflammation to improve lung function and clinical outcomes. For example, in a small double-blind pilot clinical RCT of rosuvastatin taken daily for the management of COPD in PWH, Morris et al showed that after 24 weeks of daily rosuvastatin therapy, FEV1 stabilized and DLco improved significantly.²³³ Another trial studied the role of weekly azithromycin in HIV-related chronic lung disease, defined as an irreversible obstructive defect with minimal radiographic abnormalities, in children and adolescents.²³⁴ While the authors found no improvement in lung function parameters after 72 weeks of treatment, they noted an increased time to and fewer total exacerbations. Furthermore, data in the general population have shown benefit of using angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) in slowing down the progression of emphysema on chest CT in COPD, albeit with no effect on longitudinal lung function on spirometry.²³⁵ A randomized controlled trial by MacDonald et al measured pneumoprotein levels as a proxy for lung function decline in PWH with COPD randomized to placebo or losartan treatment, but did not see any significant changes in the pneumoprotein plasma concentrations after 12 months of follow-up.²³⁶ Finally, an NHLBI-funded multi-site randomized controlled trial evaluating the influence of twice daily doxycycline on change in DLco among PWH who smoke is currently underway.²³⁷ In sum, findings from prior studies suggest that targeting chronic inflammation has the potential to improve lung function of PWH with COPD, but currently there are no definitive data to support any single drug's use.

Prevention of COPD in PWH

Smoking Cessation

Smoking is perhaps the single most important modifiable risk factor for COPD among PWH. Evidence suggests that PWH may metabolize nicotine more rapidly than HIV-uninfected smokers,²³⁸ which could have important implications for the effectiveness of smoking cessation interventions among this population. A growing body of literature is focused on identifying effective smoking cessation interventions among PWH; [Table 1](#) summarizes the randomized controlled trials that have been conducted or have recently completed enrollment on smoking cessation in PWH.^{218,220,225,226,239–262} For example, O'Cleirigh et al found that among 41 PWH who smoke and reported motivation to quit, those who were randomized to receive cognitive behavioral therapy for smoking cessation and anxiety/depression treatment in addition to nicotine replacement therapy were more likely to quit smoking compared to those who received nicotine replacement therapy alone,²²⁵ highlighting the importance of focusing concomitantly on smoking cessation and mental health in this population. A Cochrane review summarizing 14 randomized controlled trials of smoking cessation interventions among PWH in the United States found that pairing behavioral interventions with medications may facilitate short-term abstinence in comparison to medications alone but did not appear to facilitate long-term abstinence.²⁶³ Further, a systematic review of smoking cessation interventions among PWH found that successful smoking cessation was most likely when the intervention included cellphone-based technology.²⁶⁴ Although long-term smoking cessation is the goal, any reduction in exposure to tobacco products is likely to have significant health impacts. Using a Monte Carlo microsimulation model, Reddy et al demonstrated that sustained smoking cessation among PWH could result in over 260,000 expected years of life gained.⁴⁴ This per-person survival gain is more than the life expectancy gained with early ART initiation or improved ART adherence, and among the general population is more than the life expectancy gained by initiating statins for primary cardiovascular disease prevention or clopidogrel for secondary cardiovascular disease prevention. Therefore, encouraging and supporting smoking cessation must remain a priority in the care for PWH.

Table I Summary of Randomized Controlled Trials of Smoking Cessation in People with HIV

Author	Year	Intervention/Control	Key Findings
Vidrine, et al ^{242,243}	2006a, b	Intervention: cell phone counseling intervention in 8 sessions + advice to quit +NRT* + self-help material Control: advice to quit + NRT + self-help materials	Significant difference in abstinence prevalence (36.8% vs 10.3%), OR for abstinence = 5.1 (95% CI 1.5–17.4, p =0.009)
Ingersoll, et al ²⁴⁵	2009	Intervention: motivational interviewing +NRT Control: self-guided reading + NRT	No between-group difference; significant decline in mean CO level and number of cigarettes/ day (17.3-> 6.2)
Lloyd-Richardson, et al ²⁴⁶	2009	Intervention: motivational interviewing (4 sessions), quit-day counseling call, NRT Control: two brief sessions with a health educator, self-help materials and NRT	No significant difference in abstinence between groups (12%, 9%, 9% vs 13%, 10%, 10% in treatment vs control groups)
Moadel, et al ²⁴⁷	2012	Intervention: 8 weekly, 90 minute in-person sessions designed to 'address the needs and concerns of HIV-infected smokers' + NRT Control: quit smoking brochure, brief cessation counseling (<5 min) +NRT	<ul style="list-style-type: none"> 19.2 vs 9.7% quit rate in intention-to-treat analysis, p=0.11; as-treated analysis OR for quitting 3.55 (95% CI 1.04–12.0) Treatment arm with significant decrease in number of cigarettes smoked daily (6.6 less vs 2.6, p=0.02) and improved self-efficacy and motivation to quit
Cropsey, et al ²⁴⁸	2013	Intervention: 8 weeks of NRT + counseling using SBIRT framework Control: no smoking cessation-specific intervention	Treatment group with significantly lower nicotine dependence (p=0.01), lower urge to smoke (p=0.01). Non-significant decrease in number of cigarettes smoked per day (p=0.13)
Gritz, et al ²⁴¹	2013	Intervention: usual care + 11 cell phone-based counseling sessions over 3 months Control: advice to quit, self-help materials and NRT	Intervention group had 2.41 times the odds of staying abstinent (p=0.049) at 3 months with diminishing effect after 3 months
Humfleet, et al ²⁵⁰	2013	Arm 1 = individual counseling + NRT Arm 2 = computer-based Internet smoking cessation program + NRT Arm 3 = self-help + NRT	No statistically significant differences in abstinence between groups over time (24–29% at week 12, 19.7–25.6% at week 52) but overall decline in cigarette use over time
Manuel, et al ²⁵¹	2013	Intervention: one motivational interviewing session Control: prescribed advice All female participants	No significant differences in abstinence between groups (3 vs 0 participants, p=0.067) Intervention group had a significant decrease in cigarettes smoked per day compared to control (15.5 to 7, compared to 16.7 to 15.8 in control, p<0.05)
Shuter, et al ²²⁶	2014	Intervention: 8 session, 7-week targeted tobacco treatment online program + NRT Control: brief advice to quit + self-help brochure +NRT	10% of intervention vs 4.3% control group participants achieved end point (p=0.33); among those who completed full course, more women achieved abstinence (30.8% vs 17.9%)
Cropsey, et al ²⁴⁹	2015	Intervention: 12-week pharmacotherapy-based algorithm (stepwise) Control: 'treatment as usual'-baseline smoking cessation counseling (20 min)	At 1 month, 10 vs 6 cig/day reduction and 50 vs 38% quit attempts across follow-up
Pengpid, et al ²⁵²	2015	Arm 1: brief counseling (tobacco + alcohol) for dual substance users Arm 2: brief counseling (tobacco only) for dual substance users Arm 3: brief counseling (alcohol only) for dual substance users	Tobacco only control arm outperformed joint intervention on smoking outcomes (eg, tobacco abstinence at 6 months 49% vs 17.7%); overall tobacco and alcohol use declined significantly on follow-up in all three arms
Stanton, et al ²³⁹	2015	Intervention: 4 in-person sessions of tailored intervention +NRT Control: 2 in-person sessions of brief advice ('enhanced standard of care') + NRT Latino/a participants only	Abstinence was not significantly different at 6 and 12 months (8 vs 11%, and 6 vs 7%)

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Table 1 (Continued).

Author	Year	Intervention/Control	Key Findings
Tseng, et al ²⁴⁰	2017	Arm 1: 12 weeks of varenicline + text message support cell phone-delivered adherence-focused motivational and behavioral therapy Arm 2: 12 weeks of varenicline + text message support Control (Arm 3): 12 weeks of varenicline	Arm 1 with significantly higher abstinence rate at week 8 (17.7 vs 5.7 vs 3.7%, p=0.03) and borderline significantly higher (15.7 vs 5.7 vs 3.7%, p=0.07) at week 12 compared to the other groups ; varenicline adherence decreased significantly over the course of the study in all arms (OR 0.09, p<0.001)
Kim, et al ²¹⁸	2018	Intervention: eight 30-minute weekly counseling sessions via video call+ NRT Control: eight 30-minute weekly counseling sessions via telephone call + NRT Female participants only	Video arm significantly more likely to maintain abstinence at 6 months (p<0.05)
Mercie, et al ²⁵³	2018	Intervention: Varenicline + face-to-face counseling x12 weeks Control: placebo + face-to-face counseling x 12 weeks	Significantly higher rates of abstinence in intervention arm (15% vs 8%; aOR 2.5, 95% CI 1.0–6.1; p=0.041), higher continuous abstinence (18% vs 7%, aOR 2.7; 95% CI 1.1–6.5; p=0.029)
Mussulman, et al ²⁵⁴	2018	Intervention: 'warm handoff' for hospitalized PWH who smoke – staff called quit line for enrollment/ counseling at bedside Control: fax-referred to quit line on day of discharge from hospital	45.5% vs 14.3% verified abstinence rates (p=0.18)
O'Cleirigh, et al ²²⁵	2018	Intervention: 1 psychoeducation session + 9 weekly 1-hour cognitive behavior therapy for smoking cessation and anxiety/depression + NRT Control: 1 psychoeducation session + 4 brief weekly check-in sessions + NRT	Significantly higher rates of abstinence at end of treatment (59% vs 9%, p<0.001) and at 6 months post-intervention (46 vs 5%, p<0.001)
Ashare, et al ²⁵⁵	2019	Intervention: varenicline x 12 weeks + 6 smoking cessation counseling sessions Control: placebo x 12 weeks + 6 smoking cessation counseling sessions	At 12 weeks, abstinence significantly higher with varenicline (28.1 vs 12.1%, OR 4.54, 95% CI 1.83–11.25; p=0.001) but not at 24 weeks (14.6 vs 10%). Continuous abstinence significantly better in treatment group weeks 9–12 (23.6 vs 10%, OR 4.65, 95% CI 1.71–12.67; p=0.003), but effect lost by week 24 (10.1 vs 6.7%)
Gryaznov, et al ²⁵⁷	2020	Intervention: CO self-monitoring, mobile phone-based feedback, and app-based smoking cessation support, NRT Control: counseling by program physicians, NRT	14% vs 13% quit rate at 6 months (not statistically significant; could not recruit desired number of participants)
Kim, et al ²²⁰	2020	Intervention: screening of movie in which women with HIV discuss quitting smoking, 8 live video counseling sessions + NRT Control: screening of movie of women with HIV talking about HIV infection, 8 live video counseling sessions + NRT Female participants only.	No significant difference in 7-day point prevalence abstinence at 3 months by both self-report and cotinine test (40.7 vs 15.4%) Significantly higher odds sustained abstinence in intervention group 3 months after quitting (OR 4.23, 95% CI 1.10–16.27)
Shuter, et al ²⁵⁹	2020	Intervention: web-based + text message-based support/ quit program (42 days)+NRT Control: brief quit advice + NRT	No difference in quit rate between arms: 10.4% vs 9.6% (OR 1.09, 95% CI 0.3–4.04; p=1.0), number of quit attempts (7.3 vs 5.9; p=0.28), and change in daily cigarette consumption (–7.5 vs –4.7, p=0.06)
Stanton, et al ²⁶⁰	2020	Intervention: 8 session intensive group therapy + NRT Control: brief quit advice + NRT	Significantly higher quit rate in treatment group at 3 months (13 vs 6.6%, OR= 2.1, 95% CI 1.1–4.1; p=0.04) but not at 6 months (13% vs 13.3%) Barriers to cessation: lower education level, current cocaine use, high distress tolerance, prior NRT use
Schnall, et al ²⁶¹	2022	Intervention: Lumme Quit smoking app and smartwatch + control interventions Control: 8-week supply of NRT, 30 min smoking cessation counseling and weekly check-in calls	<ul style="list-style-type: none"> • 2 (12%) vs 3 (15%) with eCO-verified abstinence (p=0.77) • 4 (24%) vs 6 (30%) with self-reported 7-day abstinence (p=0.66) • Trend towards a decrease in eCO in both groups by the end of the study

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Table I (Continued).

Author	Year	Intervention/Control	Key Findings
Shuter, et al ²⁵⁸	2022	Intervention: 8 online education sessions over 6 weeks + online platform and community access + NRT Control: access to AHA website online health-promotion intervention (only 1/7 on smoking) + NRT	Significantly higher quit rate in treatment group (14.9 vs 8.8%, OR 1.82, 95% CI 1.04–3.18; p=0.03)
Tindle, et al ²⁶²	2022	Arm 1: active varenicline + placebo NRT + alcohol/tobacco counseling Arm 2: placebo varenicline + active NRT + alcohol/tobacco counseling Arm 3: active cytisine + placebo NRT + alcohol/tobacco counseling Arm 4: placebo cytisine + placebo NRT + alcohol/tobacco counseling	No significant difference between groups in heavy drinking days or abstinence from alcohol or tobacco; smoking cessation rate 15–19% in all groups

Abbreviation: *NRT, nicotine replacement therapy.

Air Pollution Mitigation

Interventions aimed at reducing personal air pollution exposure can be categorized into policy-level approaches (regional, national, international) and personal-level approaches. Overall, there is no level of air pollution exposure below which there are no negative health impacts. In fact, evidence suggests that the greatest gains in health per unit reduction in air pollution exposure may occur at the lowest end of the exposure spectrum.²⁶⁵ While attention is being paid to regional and national air quality guidelines, individuals with HIV can adopt behavioral changes that may reduce their personal exposure. Evidence to guide these decisions is still an area of active research. In 2019, Carlsten et al published a summary of 10 key approaches to reduce personal exposure to outdoor and indoor pollution sources, including: using close-fitting face masks when exposure is unavoidable; preferential use of active transport (walking or cycling) rather than motorized transport; choosing travel routes that minimize near-road air pollution exposure; optimizing driving style and vehicle settings when in polluted conditions; moderating outdoor physical activity when and where air pollution levels are high; monitoring air pollution levels to inform when individuals should act to minimize exposure; minimizing exposure to household air pollution by using clean fuels, optimizing household ventilation, and adopting efficient cookstoves where possible; and using portable indoor air cleaners.²⁶⁶ Unfortunately, the data supporting these strategies are not of high quality, which highlights the importance of future work focused on carefully designed studies leveraging implementation science methodology to characterize the feasibility, acceptability, and effectiveness of behavioral interventions focused on improving air pollution-associated lung disease.

Infection Prevention

As pulmonary infections, many of which are preventable, have been implicated in the development of COPD among PWH, infection prevention is important for mitigating COPD risk. First, early ART initiation is imperative, as many pulmonary infections such as PJP are opportunistic infections and develop in the setting of high HIV viral loads and low CD4 counts. Primary prophylaxis for PJP prevention is recommended in PWH with CD4 counts <200 cells/mm³ and considered in those with CD4% <14%.²⁶⁷ Given the high morbidity and mortality associated with pneumococcal infection in PWH, pneumococcal immunization has been recommended in all adults with HIV.²⁶⁸ Consistent with general population recommendations, PWH should also receive annual flu vaccination, as well as the full COVID-19 vaccination series. Given the increased risk of TB disease and its associated mortality among PWH, screening for TB is recommended for all PWH at the time of HIV diagnosis and once a CD4 count \geq 200 cells/mm³.²⁶⁹ PWH should be tested annually only if they have a history of a negative test for latent TB infection and are at high-risk for repeated or ongoing exposure to people with active TB disease.²⁶⁹ Among PWH diagnosed with latent TB, TB preventive treatment reduces both mortality and progression to active TB and thus should be offered to all PWH with a positive TB screening test without evidence of active TB disease.^{269,270}

Future Directions

Although progress has been made in understanding the underlying mechanisms of COPD among PWH, significant knowledge gaps remain. For example, there are many cross-sectional studies evaluating the prevalence of COPD among PWH but only limited data on the natural disease course of COPD in PWH and whether it differs from the general population. Additionally, while studies suggest that PWH demonstrate a higher risk of COPD and a higher symptom burden, there are no HIV-specific screening guidelines for COPD in PWH. Further research is also needed on the interplay between risk factors such as mode of HIV transmission, biologic sex, aging, CMV infection, air pollution, and TB, as well as a deeper understanding of the epidemiology, development, and progression of chronic lung disease in PWH. Management strategies designed specifically for PWH with COPD are also warranted. Lastly, while much progress has been made in understanding the mechanistic pathways that render PWH particularly vulnerable to developing COPD, we remain limited in our ability to counteract these pathways and prevent COPD development. These are only a few examples highlighting the multiple avenues for future research, all of which have the potential to substantially improve both our scientific understanding of COPD among PWH and our ability to effectively prevent and treat this deadly, irreversible condition.

Conclusions

COPD is highly prevalent among PWH. With an aging global population of PWH, high rates of cigarette smoking, and air pollution, COPD is a growing health challenge, and improved diagnosis and treatment of COPD in PWH will become increasingly important. Further research is needed to understand the underlying mechanisms driving COPD in PWH, as well as HIV-specific screening and treatment modalities.

Disclosure

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