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Chronic obstructive pulmonary disease in HIV

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is more prevalent in people with HIV (PWH) than in the general population and leads to an increased burden of morbidity and mortality in this population. The mechanisms behind COPD development and progression in PWH are not fully elucidated, and there are no PWH-specific guidelines for COPD management.

Areas covered: The goal of this broad narrative review is to review the epidemiology of COPD in PWH globally, highlight proposed pathways contributing to increased COPD prevalence and progression in PWH, discuss structural and functional changes in the lungs in this population, assesses the excess mortality and comorbidities in PWH with COPD, and address management practices for this unique population.

Expert opinion: Understanding how a chronic viral infection leads to COPD, independent of cigarette smoking, is of critical scientific importance. Further research should focus on the pathophysiology of the interaction between HIV and COPD, and determine the role of disease-modifying risk factors such as opportunistic pneumonias and air pollution, as well as generate data from randomized clinical trials on the safety and efficacy of specific therapies for this vulnerable patient population.

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Declaration of interest

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Keywords

air pollution; COPD; HIV; inflammation; lung function; lung structure; management; smoking

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality worldwide[1,2]. COPD is now the third leading cause of death globally[2,3]. COPD also poses a substantial concern within the HIV-positive population. People with HIV (PWH) develop comorbid chronic diseases at a younger age and at a higher rate compared to those without underlying HIV infection[1,4–8]. Among PWH, early and rapid decline in lung function is common and not explained by smoking and other traditional risk factors alone[5,9–12]. The aim of this paper is to review the data on the interplay between HIV and COPD, with a focus on the impact of HIV on COPD prevalence and clinical course. The broad nature of this review precluded use of systematic review methods, and findings are presented as a narrative review of 30 years of progress in the understanding COPD in PWH.

2. Epidemiology

COPD is common in PWH. Studies spanning 20 years predominantly from North America and Europe report a COPD prevalence ranging from 3.4% to over 40% (Table 1).[4,5,7,10,11,13–46] These studies used a variety of assessment methods to determine COPD prevalence including patient self-report, International Classification of Diseases 9th edition (ICD-9) coding, administrative health data, as well as emphysema detected on chest CT scans and the gold standard spirometry with an FEV1/FVC below 0.7 (fixed ratio) and/or below the 5th percentile of predicted values, referred to as the lower limit of normal (LLN). In general, studies using chest CT scans found a higher prevalence of emphysema (typically 25% to 35%) than studies using spirometry (typically 9–10% to ~25% with COPD). In contrast, spirometry-based studies from low- and middle-income countries in Africa, where the vast majority of persons living with HIV reside, often report lower prevalence (typically <10% with COPD) (Table 2)[30,47–54]. Several features of the study participants may explain the wide range of spirometric COPD prevalence observed, including age, tobacco smoking and exposure to biomass fuel, as well as prior history of opportunistic pneumonia(s), which are independent risk factors associated with COPD[55].

3. What is known about the effects of HIV on the lung?

HIV is associated with dysregulated immune responses and chronic inflammation at mucosal surfaces[56,57]. In the lung, this leads to airway inflammation and tissue remodeling that are key components to the pathogenesis of COPD. Damage occurring at the alveolar-capillary junction, [e.g. from microbial translocation, infection with cytomegalovirus (CMV), and acute pneumonia or colonization with *Pneumocystis jirovecii*], may explain the disproportionate deficits in gas exchange observed among some PWH, as measured by the DLco (diffusing capacity for carbon monoxide) [19,43]. Cytokines derived from myeloid cells have surfaced as major contributors to HIV-related comorbidities including COPD, thereby implicating these cells as a reservoir of HIV persistence[58,59].

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On the other hand, HIV-associated activation of the inflammatory pathways known to contribute to the pathogenesis of COPD may derive from multiple cell types, including T-cells and airway epithelium, driven by both virus-dependent and independent mechanisms[59,60].

3.1 HIV persistence in the lung

Reservoirs of HIV have been observed in almost every tissue and are thought to drive HIV-associated comorbidities, including COPD[61,62]. Although CD4+ T-cells are the major cellular reservoir of the virus, when T-cell counts are low, macrophages (MΦ are also infected with HIV [63]. Since tissue-resident MΦ are long-lived, these cells offer a compelling additional site of HIV persistence[64,65]. Lung macrophages are important regulators of lung homeostasis and play a key role in the pathogenesis of COPD[66]. Therefore, it is important to establish whether these cells harbor reservoirs of HIV that may impact their function. However, observations of HIV-infected MΦ during suppressive ART are rare and come with important caveats[67]. Therefore, the role of these cells in HIV persistence and chronic disease remains controversial.

Characterization of HIV persistence in the human lung has been limited to small studies mostly focused on cells obtained from bronchoalveolar lavage (BAL) that have found HIV within T-cells, and less consistently within MΦ[68–71]. Interestingly, observations of infected macrophages are associated with perturbations in key cellular functions that are also thought to be important to the pathogenesis of COPD, such as phagocytosis and phagolysosomal function[68,69]. Although two small studies observed HIV nucleic acids within populations of MΦ isolated from BAL, similar findings are dominated by samples from donors that are untreated with ART or incompletely virologically suppressed, and include individuals with acute lung pathologies like tuberculosis[68,69,71]. Such disease states promote recruitment of short-lived cells from the blood or lung interstitium, with differential functional capacities, that are not normally found within the airway and do not reflect the burden of HIV in longer-lived tissue resident myeloid subsets[72,73]. Therefore, these observations alone do not explain the progression of COPD during chronic HIV infection among virologically suppressed individuals on ART.

Additional limitations to quantifying MΦ reservoirs of HIV include detection of dysfunctional/non-infectious viral sequences and measurement of virus from contaminating T-cells or phagocytic remnants[67,70]. Experiments conducted in non-human primates (NHP) infected with simian immunodeficiency virus (SIV) have overcome many of these limitations and largely support the idea of MΦ as a site of viral persistence in the lung. To evaluate the specific myeloid subsets infected with SIV, Kurodra *et al* performed cellular labeling experiments in NHP and observed infection of short-lived MΦ subsets in the lung interstitium as well as longer-lived alveolar macrophages[72]. In other studies, confirmation that macrophage-associated SIV is functionally intact was achieved using modified quantitative viral outgrowth assays (QVOA) on MΦ collected from the BAL of infected animals[74,75]. Unfortunately, the progression of SIV in NHP does not accurately reflect the course of HIV in humans[76]. Therefore, prior studies, performed in humans or NHP, do not adequately address the role of local reservoirs in the progression of COPD during chronic-

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treated HIV and highlight the need for more comprehensive human-based studies to characterize tissue-reservoirs in the lung and determine the impact of HIV persistence on the progression of HIV-associated lung disease.

3.2 HIV-dependent mechanisms of lung inflammation

Chronic inflammation associated with HIV infection and COPD shares common pathways including increased inflammasome activation, production of matrix metalloproteinases (MMP), tissue fibrosis, susceptibility to oxidative stress, and persistent activation or dysfunction of lung immune cells[56,59]. Among HIV-negative individuals with COPD, this pathology is usually associated with chronic exposure to cigarette or biomass smoke[77]. In the setting of infection with HIV, smoke exposure is likely one of many factors driving inflammation, along with the direct cytopathic effects of infection or the indirect impact of persistent immune activation.

Unsurprisingly, HIV viral load (VL) in the plasma often correlates with levels of inflammatory cytokines. Activation of pathways associated with the pathogenesis of COPD is observed in cells that are either infected with HIV or exposed to inactivated viral proteins *in vitro*[58,59,78]. Tissue-macrophages and monocyte-derived macrophages (MDM) infected with HIV *in vitro* display activation of the NLRP3 inflammasome and increased production of MMPs that contribute to tissue remodeling[79–82]. Interestingly, Chung *et al* found that bronchial epithelial cells isolated from PWH who were exposed to infectious, but not inactivated, HIV increased production of MMP-9[60]. Perhaps the most striking example of the direct impact of HIV infection on lung immune cells *in vivo* are findings of impaired phagocytic function of lung MΦ isolated from BAL harboring HIV-nucleic acids [68]. The cellular response to infection with HIV or exposure to inactivated virus provides multiple mechanisms that may explain the development and progression of COPD among PWH. However, in the setting of viral suppression with ART, productively infected cells are exceedingly rare. The contribution of remaining reservoirs to the pathogenesis of COPD is likely indirect and may not necessarily correlate with local reservoirs of HIV in the lung[67].

3.3 Indirect mechanisms of HIV-related lung inflammation

While the HIV VL in plasma often correlates with levels of inflammatory cytokines, neither HIV VL, nor suppressive ART consistently correlate with the incidence or progression of COPD[83,84]. The progression of HIV-related COPD does, however, correlate with elevated systemic markers of inflammation[59]. Many of these markers (e.g., sCD14 and sCD163) are likely derived from myeloid cells, raising the possibility that these cells either serve as a site of HIV persistence or are activated by local tissue reservoirs that may not be adequately measured in the blood or BAL[72]. Regardless, the impact of chronic HIV on the immune response at mucosal surfaces offers additional virus-independent mechanisms to explain the progression of HIV-related COPD[56].

The impact of HIV on pulmonary immune responses is not limited to populations of infected cells. Both MΦ and T-cells isolated from the BAL of PWH display dysfunctional and dysregulated phenotypes, even among those who are virologically suppressed on ART[56,69,85–87]. Abnormal immune responses in the airway impact the capacity of the

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lung to control invading pathogens and to regulate the response to environmental exposures, including cigarette and biomass smoke[66]. Thus, mild exposures that are not clinically relevant to HIV-negative individuals may promote the development and progression of COPD among PWH.

Chronic inflammation occurring at mucosal surfaces, such as the lung and the gut, presumably weakens the mucosal barrier, allowing microbial translocation that promotes both local and systemic inflammation[88,89]. This leads to changes in the local microbiome and provides opportunities for colonization by opportunistic organisms. For example, the oral microbiome varies in composition between PWH and HIV-negative individuals, and in PWH it correlates with increased markers of systemic inflammation, as well as with increased airflow obstruction and lower DLco on PFTs[90]. Additionally, acute *Pneumocystis jirovecii* pneumonia (PCP) has been associated with subsequent permanent lung function decline, and colonization with *Pneumocystis* similarly carries an increased risk for COPD development in PWH[91,92].

Polymerase chain reaction (PCR) detection of *Pneumocystis* DNA in the absence of clinical or radiographic pneumonia, referred to as *Pneumocystis* colonization, has been associated with the presence of airflow obstruction and COPD in both PWH[91] and HIV-uninfected populations[93]. *Pneumocystis* colonization has been associated with increased expression of IFN-gamma and chemokine ligands CXCL9, CXCL10, and CXCL11, which are chemo-attractants for the common cognate receptor CXCR3, predominantly expressed on activated Th1 T-lymphocytes. These ligand-receptor pairs have been implicated in COPD pathogenesis, and the findings implicate *Pneumocystis* as a potential trigger[94]. In simian immunodeficiency virus (SIV)-infected macaques who become colonized with *Pneumocystis*, studies have demonstrated prolonged *Pneumocystis* colonization, a persistent influx of CD8+ T cells and neutrophils, and local increases in IL-8, IFN-gamma, and TNF-alpha[95]. The SIV-infected and *Pneumocystis*-colonized macaques develop progressive decline in lung function compared to SIV-infected, non-*Pneumocystis*-colonized control macaques.

Microbial translocation in PWH can also be associated with subclinical infection with cytomegalovirus (CMV) [96,97]. Recently, CMV has been associated with increased morbidity and mortality among HIV-negative populations, especially in the setting of cardiovascular disease[98]. Interestingly, CMV, like PCP, is one of the few pathological entities associated with isolated deficits in DLco – a unique feature of HIV-associated lung disease[19,99,100], associated with increased mortality in both people with and without HIV [19,40,43,98]. Importantly, among PWH, CMV is associated with increases in markers of immune activation including sCD14 and sCD163, which have also been linked to lower DLco and microbial translocation in this population[101–104]. Treatment of CMV in PWH is observed to decrease markers immune activation and may play a role in slowing the progression of HIV-related lung disease[105], although there are no published studies linking CMV treatment to lung function outcomes.

Specific subsets of dysregulated cell populations in the lungs of PWH with COPD promote inflammation and the progression of lung disease[69,85–87,106,107]. Both diseases are

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associated with changes to the immunophenotypic landscape of lung immune cells. By example, COPD is associated with lower expression of the regulatory protein PD-L1 on populations of lung myeloid cells, indicating inflammatory bias[108–110]. Decreases in expression PD-L1 have been observed on lung macrophages from NHP with chronic SIV infection, although human MDM infected with HIV *in vitro* increased expression of PD-L1. However, expression of the receptor for PD-L1, PD-1, which is associated with exhaustion and reduced proliferation, was decreased on HIV-specific T-cells isolated from BAL[111,112]. Similarly, other work has observed an overall decrease in the abundance of regulatory MΦ phenotypes and an increase in inflammatory subsets among PWH[86,87]. Together, these findings indicate that HIV and COPD are associated with a dysregulated pulmonary immune environment. Understanding these differences and the role of specific immune subsets will be critical in defining the mechanisms that govern the development and progression of COPD and may offer novel therapeutic targets.

4. Changes in lung structure and function in PWH

HIV infection causes chronic changes in pulmonary structure and function that are not accounted for by smoking, intravenous drug use or pulmonary infections alone[7,9,13,28,84,113,114]. Several types of lung abnormalities have been observed in PWH, including emphysema, airflow obstruction, bronchiectasis, diffusion impairment and pulmonary hypertension[10,115].

4.1 Changes on imaging in PWH

4.1.1 Imaging findings pre-ART—Early imaging studies of patients with AIDS showed a high burden (42%) of bullous disease on CT, especially in patients with prior lung infections[116] (Figure 1). Even in AIDS patients without history of lung infection, CT scans showed changes in lung structure which were concerning for early emphysema[117] regardless of smoking status[118]. Other pulmonary abnormalities such as bronchial dilation have also been noted on imaging in HIV-infected patients without history of pulmonary infection[119].

4.1.2 Imaging findings in the ART era—Imaging findings from PWH in the ART era show that about a quarter of HIV-infected individuals have at least trace level emphysema[26,28,34,120]. Emphysema findings on imaging correlate with HIV status[28], age[34,120], smoking history[26,34,120], intravenous drug use[26], history of pneumonia[120] and lung function but not CD4 count. Not all patients with emphysema on imaging have obstructive disease on spirometry[13,25,34] despite being statistically more likely to have evidence of obstruction[120] or decreased diffusion capacity [26,120], which suggests that changes on imaging often pre-date functional decline.

4.2 Changes in lung function of PWH

4.2.1 Lung function findings pre-ART—In the pre-ART era much of the pulmonary morbidity and AIDS-related mortality was attributed to PCP and other bacterial respiratory infections[121]. Early studies of lung function were performed in the context of AIDS-related opportunistic infections and noted that patients' DLco, FEV1 and FVC are reduced

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acutely after episodes of PCP and bacterial pneumonia[55,121–123]. Additional studies with long-term follow-up of HIV-infected patients with pulmonary infections have shown persistent decline in FEV1, FVC, FEV1/FVC and DLco[55]. Even in HIV-positive individuals without history of pulmonary infections, complaints of dyspnea, combined with emphysematous changes on CT scans and obstructive defects on spirometry, were noted and were not explained by smoking, intravenous drug use or other non-HIV risk factors alone[13,117]. Smoking and other non-HIV-related risk factors such as drug use and prior respiratory infections did not fully account for the increase in incidence, as well as earlier age of onset, of emphysema in PWH compared to HIV-negative controls[124]. Instead, it appears that HIV and smoking have a synergistic effect, which may accelerate emphysema progression[13] and lung function decline[125].

4.2.2. Lung function findings in the ART era—Studies examining pulmonary function in the ART era show that pulmonary abnormalities and respiratory symptoms remain common despite antiretroviral treatment. COPD prevalence in HIV-infected populations remains higher (10–23%) than in non-infected populations (7–10%) [7,16,25,84], as do the burden of symptoms, diffusion impairment and emphysema on imaging, despite most patients being well-controlled on antiretroviral treatment [16,25].

Similar to HIV-negative individuals, PWH have increased COPD prevalence and abnormal FEV1/FVC ratio with increasing age and greater smoking history [30,125]. In places with a low smoking prevalence, tuberculosis (TB) remains a key infectious cause of faster FEV1/FVC decline in PWH compared to HIV-negative individuals[53]. Other factors associated with higher risk of developing obstructive airway disease in this patient population include intravenous drug use[5,16], and possibly antiretroviral therapy based on two observational studies[14,16]. More recently, however, a large multinational randomized controlled trial with 1026 participants looked at the timing of ART initiation and did not find a significant effect of immediate compared to delayed ART initiation on the rate of lung function decline, suggesting that ART does not have any significant detrimental short-term effects on FEV1 trajectory in early HIV infection[83].

4.3 DLco

A reduction in diffusing capacity is one of the most consistent findings in PWH. It is non-specific and can be attributed to a number of lung conditions. For example, early observations showed that DLco is reduced acutely after episodes of PCP and bacterial pneumonia, together with FEV1 and FVC[55,121,122,126]. Decline in spirometric values and DLco persists even on long-term follow-up after resolution of pulmonary infections [55,126].

DLco decline in PWH does not only stem from prior history of pulmonary infections, however. Patients with HIV and no history of pulmonary infections also have decreased DLco[19,20,46,122,127–129] and a higher risk of developing diffusion impairment compared to HIV-negative controls[46], suggesting that HIV is an independent risk factor for low DLco. While decrease in DLco is not specific to COPD, in smokers with HIV, diffusion impairment correlates with obstruction and emphysema rather than with other

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cardiopulmonary conditions such as interstitial lung disease or pulmonary hypertension[130]. In addition, low DLco without airflow obstruction can be seen in patients with radiographic evidence of emphysema, and thus it may be an early manifestation of emphysema[26,117,120,131].

Given the high prevalence of diffusion abnormalities in PWH, decline in DLco may also be considered a unique HIV lung function phenotype. This has direct clinical relevance because lower DLco is associated with lower CD4 count[19,20,46,132], as well as with increase in respiratory symptoms such as cough, shortness of breath and phlegm production[19]. Some studies have noted that DLco decline is an indicator for faster progression to AIDS[133], and that history of AIDS, CD4<200 and/or presence of viremia all correlate with lower DLco[132]. Finally, low DLco also correlates with higher mortality in PWH[40]. Further studies are therefore needed to better understand the role and importance of diffusion impairment in PWH.

5. Role of HIV in progression/clinical course of COPD in the current ART era

5.1. PWH have frequent respiratory symptoms and decreased exercise capacity

PWH develop cardiopulmonary dysfunction earlier than HIV-negative persons and they have higher morbidity even in the absence of predisposing cardiac or lung risk factors[134]. Chronic conditions such as COPD are associated with increased frailty in any population, but especially in HIV-infected men and women[35]. Compared to HIV-negative controls, PWH with known emphysema have significantly higher odds of chronic cough and shorter 6-minute walk distance; even individuals with only radiographic emphysema and no obstruction on spirometry have similar functional findings[124]. In individuals without overt lung disease, HIV status was associated with shorter 6-minute walk distance (431m vs 462m) and worse respiratory symptoms based on a St George's Respiratory Questionnaire (SGRQ) score, and HIV was also found to be an independent predictor of lower 6-minute walk test result[135].

Self-reported respiratory symptoms are significantly more prevalent in HIV-positive individuals even without any history of prior pulmonary infections and regardless of HIV viral load[14,136–139]. Dyspnea, cough and phlegm production are the most common symptoms [136], and they can occur independent of abnormal lung function as noted on spirometry[31,137], but are more likely in patients with underlying lung disease[137]. PWH with respiratory symptoms also have worse mental health and quality of life scores[140].

5.2. HIV, COPD and smoking

Cigarette smoking is the dominant risk factor for COPD. In 2016, smoking prevalence was an estimated 16% in the US general population[141] but, among PWH, studies estimate smoking prevalence of 30–90% depending on the cohort[5,16,114,139,142–146]. Early studies showed that emphysema found on imaging was much more prevalent in HIV-positive compared to HIV-negative participants, and the numbers were even greater among HIV-positive smokers compared to their HIV-negative counterparts[13]. From a functional

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standpoint, smokers with HIV have a faster rate of decline in their FEV1 compared to non-smokers with HIV[125]. PWH on ART who smoke may experience more years of life lost from smoking than from chronic HIV infection[147,148], are more likely to carry a diagnosis of COPD and have respiratory symptoms compared to non-smokers[30,149], as well as a suffer from higher overall cardiopulmonary morbidity and mortality[149] due to co-morbid diseases such as lung cancer[150], bacterial pneumonia[151], and cardiovascular disease[147].

5.3. HIV, COPD and respiratory infections

Acute respiratory infections are more common and more severe in PWH, even when they are on antiretroviral therapy[152]. Pulmonary infections such as PCP, bacterial pneumonia and TB are well-known risk factors for COPD in PWH[49,51,53,153]. The added lung function deficit due to COPD subsequently contributes to further increased incidence of pulmonary infections such as influenza, community acquired pneumonia (CAP), PCP and TB[48,154,155], and increased risk of hospitalization for these conditions[154].

5.4. HIV, COPD and air pollution

Given the existing data on the adverse additive effect of smoking and HIV on COPD development and progression, it is tempting to postulate similar effects of air pollution in this population. To our knowledge, there are no published studies that directly assess the associations between these triple scourges (HIV, COPD and air pollution). However, outdoor air pollution is a risk factor for COPD, COPD exacerbations and COPD-related mortality globally[156–160]. Indoor air pollution and biomass smoke exposure in general have similarly been shown to lead to COPD development, as well as to increase risk of COPD exacerbations[161]. Studies of the effect of air pollution on HIV-positive populations have been extremely limited. In adults, data have shown that ambient air pollution levels of nitrogen dioxide and PM10 (particulate matter 10 microns in size or less) were associated with suppressed serologic responses to PCP infection[162] and higher rates of hospitalization[163,164]. Children living with HIV were found to have worse neurocognitive deficits with increasing exposure to household air pollution as measured by personal carbon monoxide (CO) monitoring devices[165]. More recently, North *et al* compared respiratory symptoms as a result of indoor air pollution from biomass fuel burning in HIV-positive and HIV-negative participants using personal CO meters, and they found an association between CO and respiratory symptoms among women, as well as in PWH[166]. These data hint that air pollution may act as a modifier in PWH with COPD, leading to more severe COPD symptoms and more frequent exacerbations when compared to HIV-negative controls, through inflammatory pathways presumed similar to those triggered by smoking. Further studies are needed to assess this provocative hypothesis.

5.5. COPD exacerbations in PWH

HIV is independently associated with increased risk for acute COPD exacerbations[142]. As a result, PWH have a higher rate of acute COPD exacerbations compared to HIV-negative individuals[33]. Interestingly, studies have shown disagreement with regards to risk of exacerbation stratified by CD4 count- one study finding exacerbation is more common with CD4 counts >350 cells/mm3[142], and another- with CD4 counts <350 cells/mm3, likely

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attributed to differences in methods of reporting and confirming the diagnosis of COPD exacerbation[33].

5.6. HIV, COPD and cardiopulmonary comorbidities

HIV-positive patients with COPD or diffusion impairment often have other cardiopulmonary comorbidities[167]. For example, PWH with obstructive disease commonly have pulmonary hypertension, and worsening pulmonary pressures are often associated with worse airflow obstruction or diffusion impairment[115,167,168]. Notably, pulmonary hypertension in normoxemic PWH with COPD is often classified as HIV-associated group 1 pulmonary arterial hypertension, while in hypoxemic patients it can be Group 3 (due to COPD). There is also a correlation in PWH between emphysema and higher coronary artery calcium score on CT imaging[169], as well as between low DLco, odds of coronary calcifications, CAD and higher mortality[134].

5.7. Increased morbidity and mortality in PWH with COPD

Increased morbidity has been noted in HIV-positive individuals with COPD. A large study of a veteran cohort of HIV-positive and HIV-negative individuals showed that COPD was strongly associated with both frailty and functional limitations, especially in subjects who were HIV-positive[35,168]. COPD in PWH is an independent predictor of both obstructive lung disease-related mortality and all-cause mortality regardless of ART use[40,41,168,170].

6. COPD Management and Prevention

Given the burden and impact of COPD in PWH, preventing the development of COPD in the first place should be a high priority in HIV clinical care. Although clinical outcome disease prevention trials in HIV are largely lacking, surrogate outcome studies suggest several means to reduce the risk of COPD in PWH.

6.1. Smoking Cessation

Although data regarding COPD risk reduction from smoking cessation do not exist specifically for PWH, smoking cessation in PWH results in a significant decrease in subsequent risk of bacterial pneumonia[151,171] and in myocardial infarction[172], highlighting the clinical benefit of smoking cessation in this population.

Smokers with HIV commonly express significant interest in quitting smoking[145,173]. There have been few smoking cessation intervention studies in PWH, generally using non-randomized, open-label study designs, and they frequently showed no better cessation rates than usual care[174]. One meta-analysis of 12 studies of smoking cessation in PWH showed a pooled long-term abstinence rate of 8%[175]. Although smoking cessation rates are also low in HIV-negative populations, PWH may have additional factors contributing to low cessation rates such as social factors (e.g. poverty, stigma) and biological issues as suggested by data showing that PWH on ART may metabolize nicotine more rapidly than others[176]. In addition to counseling and nicotine replacement therapy, most guidelines in HIV-negative populations suggest addition of medications such as varenicline. Providers for PWH may have concerns about neuropsychiatric side effects of varenicline, but a meta-analysis of 39

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randomized trials (pooled n=10,761) found no evidence of suicide or depression with varenicline treatment in the general population[177]. In fact, in a small trial of varenicline in PWH (n=173, of whom 87 were randomized to varenicline and 86 to placebo), varenicline reduced anxiety symptom scores without affecting depressive symptom scores[178].

Further studies are clearly needed to identify optimal methods to support smoking cessation in PWH populations. However, despite the lack of robust evidence for the best available cessation strategy, clinicians should not delay discussing the importance of smoking cessation with PWH who smoke and tailoring available resources (e.g. counseling, nicotine replacement, varenicline) to individual patients.

6.2. Non-tobacco related COPD risk factors

Although cigarette smoking is the strongest risk factor for COPD in high-income settings, emerging data have also demonstrated the impact of other factors in the pathogenesis of COPD, especially in low to middle-income settings. These additional COPD risk factors include indoor air pollution from biomass fuel smoke, second-hand smoke exposure, outdoor air pollution, pulmonary TB, and poverty and may account for more than half of COPD cases in such settings [179]. Avoidance of these risk factors is more difficult to implement than smoking cessation, due to complex societal and economic interactions between factors such as biomass fuel use, poverty, and TB. Indoor air quality can be improved through seemingly simple methods such as using cleaner fuels (e.g. replacing wood-burning stoves with propane or electric stoves) or by venting cookstove smoke outside of the living space. However, these trials have often observed poor uptake of the new cooking methods. For example, in a randomized trial conducted in Mexico, 668 households were randomized to continue using their indoor open wood-burning fire versus using a wood-burning stove with a chimney vented to the exterior of the home [180]. The intention-to-treat analysis showed no difference in lung function decline between the two arms, but only 50% of the intervention households used the new stove system. When analyzed using as-treated analysis the rate of lung function decline was −31 mL/year in those who used the new stove and −62 mL/year in those who did not, which is nearly identical to the effect size of smoking cessation in smokers with COPD. These results suggest that improving indoor air quality might reduce COPD incidence, but trials looking at replacing long-standing traditional cooking practices often struggle to ensure reliable uptake of the new practices and thus require as-treated analyses of the data, which is prone to confounding.

6.3. HIV-specific strategies for COPD prevention

HIV increases COPD risk through derangements in immune activation, activation of pro-inflammatory pathways, and alterations in the respiratory microbiome though the precise pathways are not fully elucidated. As such, it is difficult to design specific intervention strategies for COPD prevention in PWH. The field awaits future intervention trials to alter such HIV-specific pathways and determine the impact of these interventions on modifying clinical risk of COPD in PWH. In the meantime, work has already focused on understanding whether HIV-specific treatments might affect the risk for lung disease development or progression.

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Several observational studies have identified lower nadir CD4 counts as a risk factor for COPD[19,37,49]. These data have led to the hypothesis that earlier treatment of HIV might reduce the risk for these adverse pulmonary outcomes. The Strategic Timing of AntiRetroviral Treatment (START) pulmonary substudy randomized trial (n=1026) tested this hypothesis, but found no difference in rate of lung function decline (primary outcome) or incident COPD risk between the immediate and deferred ART arms (which started ART at median CD4 counts of 648 and 482 copies/mm^3, respectively) over nearly 4 years of follow-up[83,181]. The trial enrolled only ART-naïve individuals with CD4 >500 cells/mm^3, so results may not be generalizable to those who present later in their HIV course.

ART medications can have end-organ toxicities such as bone density loss seen with tenofovir disoproxil fumarate[182,183]. However, studies have not identified any particular ART medications that affect risk of accelerating lung function decline or developing COPD. The START trial pulmonary substudy evaluated ART drug class effects on lung function decline and found no difference amongst non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors, though the small number of persons on integrase inhibitors (n=82) precluded precise estimates for potential lung function effects of that drug class[181].

6.4. COPD Screening and Case-Finding in PWH

The terms ‘screening’ and ‘case-finding’ are related but distinct. Screening for disease is intended to detect early disease in asymptomatic at-risk populations (e.g. colonoscopy in all adults over 50 years of age), while case-finding seeks to test individual patients based on clinical suspicion of disease, often due to certain the presence of signs and/or symptoms (e.g. colonoscopy in those with iron deficiency anemia or hematochezia).

The US Preventive Services Task Force recommends against screening asymptomatic individuals for COPD[184]. This decision is based on the assessment that early detection of asymptomatic COPD does not alter the course of COPD or improve patient outcomes. However, the joint American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society clinical practice guideline recommends spirometry testing to evaluate for airflow obstruction in patients with respiratory symptoms—essentially advocating for case-finding in symptomatic individuals[185]. Hence, the presence or absence of respiratory symptoms could and should be used to guide decisions about referral for spirometry testing.

Compared to HIV-negative individuals, PWH are more likely to report respiratory symptoms such as cough and dyspnea, as discussed above. This high prevalence of respiratory symptoms, along with the high prevalence of smoking and COPD in PWH, suggest that COPD case-finding approaches are in needed in HIV clinics. Large-scale studies of screening and case-finding for lung disease in PWH are rare, but several studies provide important preliminary insights into the observed prevalence of COPD in clinic populations, as well as into the challenges faced when implementing screening programs on a large scale.

Three studies have approached case-finding strategies in an HIV clinic. In one single-center study (New York/USA, 2012–2103), 235 PWH were assessed with the COPD Population

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Screener questionnaire and expiratory peak flow measurements[186]. Thirty-six patients (15%) met criteria for spirometry referral; of those, 33 completed spirometry, and 4 of these 33 (12%) had confirmed COPD. Results also showed that peak flow measurements outperformed the questionnaire. This raises questions about pragmatic approaches to implementation, as a simple approach using patient-completed questionnaires was not sufficient in this study, but many HIV clinics do not routinely have available peak flow meters (or spirometry).

An additional single-center study (Baltimore/USA, 2013) employed a similar questionnaire assessing PWH in a large multi-provider HIV clinic for respiratory symptoms, age, and smoking history[187]. This study did not assess peak flow. Spirometry was suggested for those who met all three criteria of: 1) age >40 years, 2) >100 lifetime cigarettes smoked, and 3) regular occurrence of symptoms of cough, phlegm, wheezing, or dyspnea when walking up a slight hill. The study found significant losses at each step of the assessment process due to provider factors and delays. From 889 unique questionnaires completed, 204 patients (23%) met criteria for spirometry referral. However, only 64 (31%) of these patients had a spirometry order placed by their provider, and of these 64, only 19 (30%) completed a spirometry test. Among those who completed the entire pathway, 5 (26%) had spirometry evidence of COPD.

Lastly, a single-center study (Brescia/Italy, 2015–2016) implemented a similar case-finding program into their HIV clinic[188]. They administered the same questions (symptoms, age, smoking history) and performed office handheld spirometry in those meeting criteria. From 1435 persons completing the questionnaire, 282 (20%) qualified for same-day office spirometry by HIV clinic staff. Unfortunately, 32% of these patients declined spirometry for reasons not quantified. Of the 190 who completed same-day spirometry, 65 (34%) had impaired lung function (FEV1 <80% of predicted normal). These patients were referred for formal lung function testing in pulmonary clinics, where 22 (67%) had confirmed COPD.

Overall, these studies suggest that site-specific factors may play some role in the efficacy of case-finding approaches. Loss to follow-up and scheduling delays lead to patients being lost at each step. By implementing same-day spirometric testing, the Italian study prevented loss to follow-up, providing key insight for designing much needed further studies of different case-finding strategies.

6.5. COPD Treatment in PWH

Goals of COPD treatment include reduction in risk of death and COPD exacerbations, while also improving exercise capacity and quality of life. Although large clinical trials focused on PWH with COPD are lacking, several important treatment considerations are worth noting when caring for PWH with COPD.

The most impactful COPD treatment is smoking cessation, as previously discussed. Along with smoking cessation[189], the other treatment with large effects on mortality reduction is chronic oxygen for persons with stable-state (i.e. not recently with an acute respiratory illness) resting chronic hypoxemia, defined by a resting room air PaO2 of ≤55mmHg or

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SpO2 ≤88% [190,191]. We do not expect that oxygen benefits would be any different in PWH from those in HIV-negative COPD populations in which it has been studied.

After smoking cessation and oxygen assessment and supplementation in those meeting criteria, inhalers are the other cornerstone of COPD treatment. Short-acting bronchodilators such as albuterol/salbutamol and ipratropium relieve acute dyspnea, while long-acting bronchodilators such as long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) inhalers reduce COPD exacerbation risk. LABAs and LAMAs are considered first-line inhalers in most COPD treatment guidelines[2], and we have no reason to suspect HIV-specific adverse effects of LABAs or LAMAs in PWH.

In contrast to LABAs and LAMAs, inhaled corticosteroid (ICS) prescribing in PWH should be carefully considered. Systematic reviews have concluded that ICS use in COPD has been associated with an increased risk for bacterial pneumonia[192] and bone fractures[193], which are two conditions that PWH are already at heightened risk for, even when on effective antiretroviral therapy. However, ICS also reduce COPD exacerbation risk and the absolute increase in pneumonia and fracture risk of ICS appears small and may be dose-dependent. Therefore, despite these known ICS risks, most COPD treatment guidelines would recommend ICS in those who have been hospitalized with COPD exacerbations, have frequent exacerbations or have an asthma component or peripheral eosinophils >300 eosinophils/mm3; and guidelines would also suggest avoidance of ICS in those with recurrent pneumonia[2]. In our view, these guidelines are reasonable to also apply to PWH with COPD, with special attention to avoiding ICS in PWH with a history of recurrent pneumonia despite good viral control or a history of significant osteoporosis or prior fractures.

The other major concern with ICS use with PWH is iatrogenic hypercortisolism. ART regimens frequently contain inhibitors of CYP3A4, such as ritonavir or cobicistat. ICS are metabolized through the same enzyme pathway, so when ICS are combined with CYP3A4 inhibitors, ritonavir or cobicistat, patients can develop significant hypercortisolism [194]. Therefore, we recommend that clinicians avoid ICS use in PWH treated with ritonavir or cobicistat. Options for the management of such patients would include an ART switch to a regimen not containing a CYP3A4 inhibitor. However, if ICS are immediately needed or ritonavir/cobicistat cannot be avoided, experimental data suggest that beclomethasone may be the least likely ICS to result in hypercortisolism[195]. In such cases, we would recommend close monitoring for signs and symptoms of hypercortisolism during inhaled beclomethasone treatment.

Vaccinations against respiratory pathogens such as *S. pneumoniae* and influenza virus have been shown to reduce the risk of COPD exacerbations and are therefore recommended for those with COPD[196,197]. We suggest following the national guidelines on vaccination of PWH against *S. pneumoniae* and influenza[198].

When acute exacerbations of COPD occur, treatment generally focuses on systemic corticosteroids and antibiotics, which have both been shown to hasten recovery[199]. Adjunctive supportive therapies include oxygen for associated hypoxemia and non-invasive

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ventilation for associated hypercarbia. Data about treatment of acute exacerbations specific to PWH are lacking, so we recommend following general guidelines about COPD exacerbation treatment. Although systemic corticosteroids such as prednisone and methylprednisolone should be used with caution in combination with ritonavir or cobicistat, as discussed in the ICS section above, the generally short courses (five days being typical) used for exacerbation treatment should not result in significant hypercortisolism. Hospital discharge bundles for COPD might include ICS, but these inhalers should not be prescribed to those on ART regimens containing ritonavir or cobicistat.

7. Conclusions

COPD is a highly prevalent pulmonary comorbidity in PWH, which is associated with additional cardiopulmonary complications, worse quality of life and overall higher mortality. The mechanism of COPD development in HIV is not fully elucidated but is related to increase of chronic inflammation at the lung mucosa, oxidative stress, dysregulation of local immune cells and susceptibility to external pathogens and environmental insults. Smoking remains the major risk factor for disease severity and progression in this population, and it has a synergistic negative effect with HIV on lung function and structure. Smoking cessation is therefore the cornerstone of COPD management and prevention in this population, as it is in the general patient population. Given worse outcomes in patients with HIV and COPD, case-finding and screening approaches are needed in the clinic to help identify and treat cases of COPD as early as possible and prevent downstream complications, poor quality of life and early death.

8. Expert opinion

Research on HIV-associated COPD has grown tremendously over the past two decades with the aging of HIV-positive populations and an increased recognition that HIV may uniquely predispose PWH to COPD. A PubMed search of the terms ‘HIV’ and ‘COPD’ retrieved one to five publications per year between 1990 and 2000, 26 results in 2010, and 69 results in 2018 (Figure 2). Despite these many advances, many important knowledge gaps remain.

Perhaps the most glaring knowledge deficit is that the field still lacks a precise understanding of how HIV predisposes to COPD. One should note, however, that the general field of COPD research has still not identified why only a minority of heavy smokers develops clinically significant COPD. As such, some of the challenges faced by investigators unraveling mechanisms of HIV-associated COPD may lie in the common challenge of understanding COPD heterogeneity and likely multifactorial pathways of disease pathogenesis.

Despite these challenges, we view this line of investigation as a critical piece to addressing the global burden of COPD. Although most COPD research focuses on more widely recognized COPD risk factors such as cigarette smoke or air pollution, understanding how a chronic viral infection like HIV can lead to a lung disease like COPD would provide important novel insights into COPD pathogenesis that may lead to new therapeutic interventions. Additionally, we need a better understanding of how HIV modifies known

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COPD risk factors to affect COPD disease progression, so we can develop targeted interventions to reduce these toxic exposures.

Most work to date on HIV-COPD has been conducted in high-income countries and much of our current knowledge stems from these settings. There is a growing body of literature on obstructive lung disease in PWH in Africa and other low- and middle-income countries (LMICs). Given that the majority of the PWH globally live in LMICs, where smoking rates are substantially lower but poor air quality is a major public health problem, it is imperative that we develop better understanding of the regional and population-specific risk factors that determine COPD prevalence and severity. For example, in PWH in high-income countries, PCP and bacterial pneumonia have well-established detrimental effects on lung function and COPD, but the effects of TB, the dominant opportunistic pneumonia in LMICs, on lung function and COPD in PWH are less well-studied. Efforts on understanding the interplay of pulmonary infections, air pollution, occupational exposures (such as mining in Southern Africa) will be key in designing targeted approaches for early case identification and risk mitigation in LMICs.

Beyond the important bench and translational science work, clinical intervention studies in HIV-associated COPD are also lacking, as alluded to in other sections of this review. The same search terms of ‘COPD’ and ‘HIV’ retrieve only two randomized trials—the START Pulmonary Substudy discussed above and a small randomized pilot trial of rosuvastatin (n=22) that suggested rosuvastatin might slow lung function decline in PWH[200]. While it may be logistically challenging to conduct randomized controlled COPD trials restricted to PWH, many COPD trials have excluded PWH, thereby precluding any extrapolation or meta-regression methods to allow an understanding of whether or not HIV affects response to COPD treatments. Reasons for these HIV exclusions are unclear, as HIV is now a chronic, manageable disease like diabetes. We firmly believe that, given the rising number of patients with comorbid HIV and COPD, the increased risk of COPD exacerbations and the more severe course of COPD in PWH, COPD studies should no longer exclude well-controlled PWH.

Finally, we want to briefly address the current COVID-19 pandemic and its effect on our population of interest. At present data on the clinical course and outcomes in PWH with COVID-19 infections are limited. Work is currently underway to address the short- and long-term clinical outcomes of this group compared to the general population. Given decrease in lung function after acute infection with PCP or bacterial pneumonia, and its contribution to development of obstructive lung disease over time, future work should address the possibility of accelerated respiratory decline among PWH who survive COVID-19 pneumonia, both in patients with known and ones without prior chronic lung disease.

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** of considerable interest

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Article highlights:

- HIV is an independent risk factor for obstructive lung disease. People with HIV develop comorbid chronic obstructive pulmonary disease at a younger age and at a higher rate than the general population, independent of cigarette smoking. The precise reason(s) for this are incompletely understood but are the subject of active scientific investigation.
- Infection with HIV and COPD share common pathological pathways that result in chronic inflammation and progression of obstructive lung disease. Higher levels of systemic markers of inflammation are associated with the progression of HIV-related COPD, even among virally suppressed patients on antiretroviral treatment (ART).
- Decreased DLco is a consistent finding in PWH that may indicate mechanisms of lung impairment specific to chronic HIV infection. Low DLco is associated with higher mortality and represents an important phenotype of lung impairment in this population.
- Compared to general COPD patients, PWH with COPD have a higher symptom burden and risk of COPD exacerbations, more cardiopulmonary comorbidities and higher mortality.
- Given high prevalence of COPD in PWH, case-finding strategies are needed for early recognition of disease. Strategies to implement COPD case-finding within HIV clinics are promising despite identified challenges.
- Medical management of COPD in PWH is similar to that in the general population, and smoking cessation is the cornerstone of COPD management and prevention.

  Inhaled corticosteroids should be used with caution in PWH with COPD, due to important drug interactions with ART and concerns about bacterial pneumonia risk in PWH.

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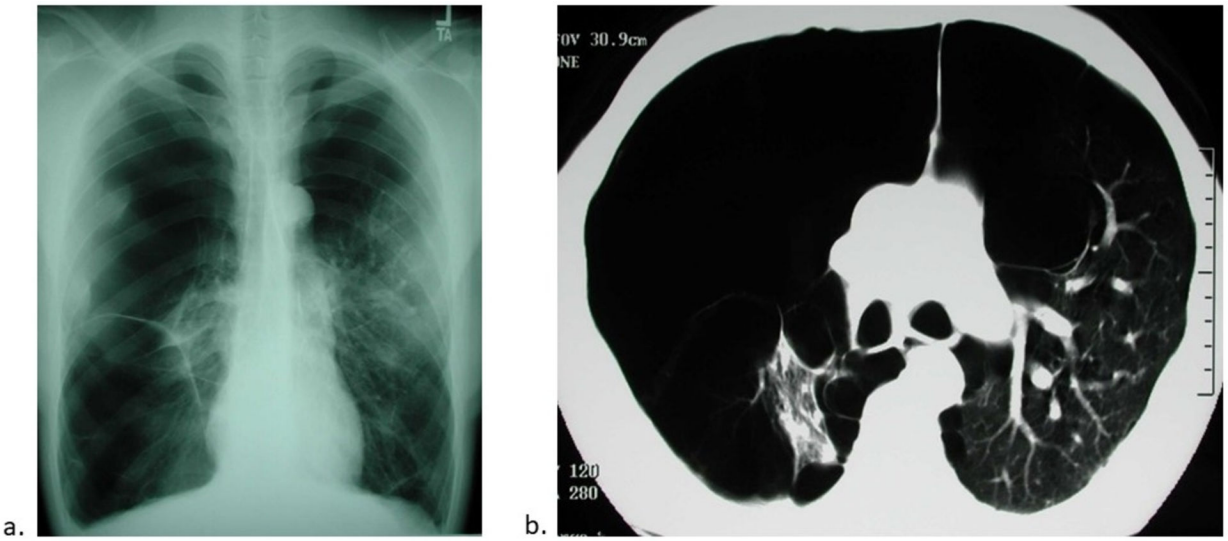

Figure 1:
Bullous emphysema on CXR (a) and CT chest (b) in patients with HIV. (Courtesy of Laurence Huang, MD)

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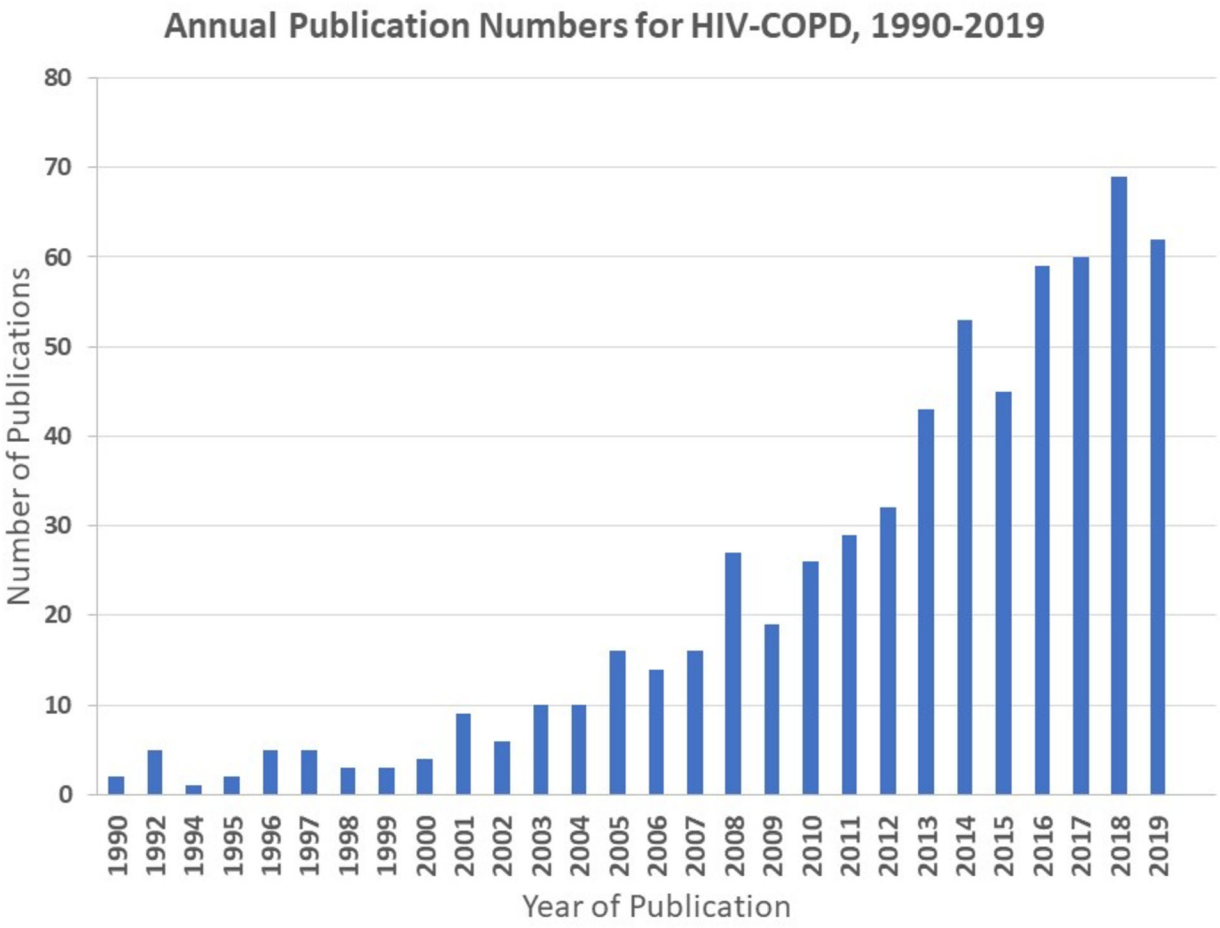

Figure 2:
Pubmed search results for ‘HIV’ and ‘COPD’ by year of publication

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Table 1.

COPD Prevalence among Adults with HIV in Era of Combination Antiretroviral Therapy[1]

Author (Year)	Country	Participants (Sites)	Age, Yrs.	Gender	Ever Smoker	Current Smoker	Prior Pneumonia	On ART	COPD Prevalence[2]
Diaz (2000) [13]	USA	114 (1)	34.1	89.5% M 10.5% F	60%		NA	NA	14.9% CT with emphysema
Crothers (2006) [5]	USA	1,014 (5)	50	100% M	75%	46%	NA	NA	10.3% (ICD-9) 15.2% (Self-report)
Magalhaes (2007) [4]	USA	162 (1)	NA	73.5% M 26.5% F	NA	NA	NA	72.2%	16.0% (Self-report)
George (2009) [14]	USA	234 (1)	44.1	82.5% M 17.5% F	59.8%	37.2%	BP: 27.4% PCP: 15.8%	83.3%	8.6% (LLN) 6.8% (Fixed)
Cui (2010) [15]	Canada	119 (1)	43.4	79.0% M 21.0% F	63.0%%	43.7%	NA	84.0%	3.4% (Fixed)
Gingo (2010) [16]	USA	167 (1)	46	73.7% M 26.3% F	76.1%	52.7%	BP or PCP: 44.3%	80.7%	21.0% (Fixed) 19.0% (LLN)
Crothers (2011) [10]	USA	33,420 (VA)	45	98% M 2% F	80%	NA	BP: 7.5% PCP: 5.3% TB: 2.0%	65%	4.6% (ICD-9)
Hirani (2011) [17]	USA	98 (1)	44.8	83.7% M 16.3% F	55.1%	21.4%	PCP: 22.4%	87.8%	16.3% (Fixed)
Kristoffersen (2012) [18]	Denmark	63 (1)	43.3	88.9% M 11.1% F	NA	47.6%	PCP: 12.7% TB: 1.6%	88.9%	9.5% (Fixed) at baseline; 19.0% at follow-up
Madeddu (2013) [7]	Italy	111 (1)	42.3	69.4% M 30.6% F	NR	56.8%	NA	78.4%	23.4% (Fixed)
Drummond (2013) [11]	USA	316 (1)	48.0	65.8% M 34.2% F	93.7%%	84.2%	BP: 23.4% PCP: 5.4%	54.4%	16.5% (Fixed)
Crothers (2013) [19]	USA	300 (2)	54	100% M	74%	47%	BP: 28% PCP: 10% TB: 6%	89%	18% (Fixed)
Fitzpatrick (2013) [20]	USA	63 (1)	49.1	100% F	74.6%	46.0%	BP: 17.5% PCP: 6.3%	81.0%	11.1% (Fixed)[3]
Kendall (2014) [21]	Canada	14,005	45.4	80.5% M 19.5% F	NA	NA	NA	NA	8.33% (Admin data)[4]
Campo (2014) [22]	USA	180 (4)	55	98.3% M 1.7% F	85.0%	64.4%	NA	88.9%	20.0 (Fixed)
Rahmanian (2014) [23]	USA	243 (1)	44.3	87.7% M 12.3% F	NA	64.6%	NA	NA	33.3%–45.8% CT with emphysema
Nakamura (2014) [24]	Japan	49 (1)	40	100.0% M	61.2%	44.9%	NA	98.0%	10.2% (Fixed)
Samperiz (2014) [25]	Spain	275 (1)	48.5	78.2% M 21.8% F	86.5%	61.5%	NA	95.6%	17.2% (Fixed)
Guaraldi (2014) [26]	Italy	1,446 (1)	48.4	71.2% M 28.8% F	NA	38.6%	BP: 11.0% PCP: 7.2% TB: 2.1%	100.0%	35.4% CT with emphysema; 9.6% (Fixed)[5]

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Author (Year)	Country	Participants (Sites)	Age, Yrs.	Gender	Ever Smoker	Current Smoker	Prior Pneumonia	On ART	COPD Prevalence[2]
Simonetti (2014) [27]	USA	184 (3)	53.1 (M) 49.1 (F)	65.8% M 34.2% F	78.5% (M) 80.9% (F)	30.6% (M) 44.4% (F)	BP/ PCP:33.1% (M)/22.2% (F)	86.0% (M) 81.0% (F)	13.2% (Fixed) (M) 11.1% (Fixed) (F)
Attia (2014) [28]	USA	114 (4)	55	85.1% M 14.9% F	86.0%	54.4%	BP: 17.5% TB: 7.0% PCP: <1.0%	81.6%	17.5% (Fixed) 33% >10% emphysema on CT
Makinson (2015) [29]	France	338 (14)	50	82.8% M 17.2% F	100%		PCP: 8.3%	NA	26.0% (Fixed) 22.2% (LLN)
Kunisaki (2015) [30]	Europe/ Israel/ Australia	298 (35)	38	91.7% M 8.3% F	58.1%	44.7%	NA	None	9.1% (Fixed) 9.1% (LLN)
	Mexico/ S.America	182 (10)	34	86.4% M 13.6% F	42.4%	28.3%	NA	None	3.3% (LLN) 2.7% (Fixed)
	Asia	102 (8)	36	73.8% M 26.2% F	30.1%	19.4%	NA	None	2.0% (LLN) 0% (Fixed)
	USA	85 (20)	36	90.1% M 9.9% F	46.2%	33.0%	NA	None	8.2% (LLN) 7.1% (Fixed)
Drummond (2015) [31]	USA	908 (9)	50	78.1% M 21.9% F	86.2%	67.6%	BP: 26% PCP: 11.1% TB: 4.3%	73%	26.9% (Fixed)
Nimmo (2015) [32]	UK	218 (1)	46.7	73.4% M 26.6% F	47.2%	22.9%	BP: 12.6% PCP: 12.6%	84.4%	6.8% (Fixed)
Depp (2016) [33]	USA	43,618 (VA)	47	97.6% M 2.4% F	73.7%	59.1%	NA	27%	4.4% (ICD-9)
Leader (2016) [34]	USA	510 (8)	48.9	80.8% M 19.2% F	84.9%	63.7%	BP: 27.1% PCP: 10.8%	68.6%	25.1% with trace or greater emphysema on CT
Akgun (2016) [35]	USA	3,538 (8)	44	97.4% M 2.6% F	77.4%	53.1%	NA	83.5%	4.4% (ICD-9, plus validation)
Ghadaki (2016) [36]	Canada	247 (1)	49	75.3% M 24.3% F	66.4%	37.3%	NA	92.3%	6.1% (Self report)
Risso (2017) [37]	France	581 (1)	48.3	73.8% M 26.2% F	71.8%	50.8%	NA	93.5%	9.0% (Fixed)
Triplette (2017) [38]	USA	190 (4)	55	98% M 2% F	84%	63%	NA	71%	31% with mild or greater emphysema on CT
Makinson (2018) [39]	France	351 (14)	50	82.6% M 17.4% F	100%		PCP: 8.8% TB: 4.0%	NA	19.3% (Fixed)
Gingo (2018) [40]	USA	396 (3)	49	68% M 32% F	74%		BP: 35% PCP: 6%	81%	17.1% (Fixed)
Triplette (2018) [41]	USA	196	55	98% M 2% F	85%	64%	TB: 3.9% PCP: 2.0%	NA	20% (Fixed) 17% (LLN)
Ronit (2018) [42]	Denmark	742 (1)	54.2	85.7% M 14.3% F	65.1%	26.3%	NA	98.4%	10.4% (LLN) 9.3% (Fixed) 21.2% with emphysema on CT
Li (2018) [43]	USA	285 (3)	47	67.7% M 32.3% F	73.4%	51.1%	BP: 34.7% PCP: 5.8%	78.5%	17.2% (Fixed)

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Author (Year)	Country	Participants (Sites)	Age, Yrs.	Gender	Ever Smoker	Current Smoker	Prior Pneumonia	On ART	COPD Prevalence[2]
Costiniuk (2019) [44]	Canada	503 (1)	52	70.8% M 29.2% F	52.5%	23.7%	PCP: 7.2% TB: 4.6%	96.0%	10.7% (Fixed)
Jeon (2019) [45]	USA	65 (1)	51	78.5% M 21.5% F	76.9%	NA	BP: 75.4% PCP: 38.5%	92.3%	35.4% (Fixed)
Kunisaki (2020) [46]	USA	591 (4)	55	100% M	67.9%	26.2%	PCP: 2.9%	90.3%	9.7% (Fixed) 6.8% (LLN)

[1] Individual publications may overlap. All studies that report spirometry adhered to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for standardization of spirometry.

[2] Prevalence was reported as self-report, International Classification of Diseases 9th edition (ICD-9) coding, administrative data, emphysema observed on chest computed tomography (CT), or by the gold standard of spirometry demonstrating a ratio of forced expiratory volume in 1s / forced vital capacity (FEV1/FVC) either <0.70 (fixed) and/or <lower limit of normal (LLN).

[3] Personal communication with Dr. Fitzpatrick.

[4] Administrative databases at the Institute for Clinical Evaluative Sciences.

[5] A subset of 264 of the 1,446 participants also underwent PFTs and 9.6% had COPD (Fixed).

Abbreviations: ART = Antiretroviral therapy; BP = bacterial pneumonia; PCP = *Pneumocystis* pneumonia; TB = pulmonary tuberculosis

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Table 2.

COPD Prevalence among Adults with HIV in Low- and Middle-Income Countries[1]

Author (Year)	Country	Participants (Sites)	Age, Yrs.	Gender	Ever Smoker	Current Smoker	Biomass Exposure	Prior Pneumonia	On ART	COPD Prevalence[2]
Onyedum (2010)	Nigeria[3]	100 (1)	30.1 F 38.2 M	51.0% F 49.0% M	None	None	None	No prior TB	None	3.0% (Fixed)
Pefura-Yone (2015)	Cameroon[4]	461 (1)	42.6	67.7% F 32.3% M	12.8%	5.0%	37.7%	TB: 42.1% BP: 12.4%	85.2%	5.2% (LLN) 2.2% (Fixed)
Akanbi (2015)	Nigeria[4]	356 (1)	44.5	59.0% F 41.0% M	17.1%	3.7%	37.9%	TB: 23.0%	97.5%	22.2% (LLN) 15.4% (Fixed)
Kunisaki (2015)	Nigeria[4], S. Africa[5], Uganda[3]	322 (7)	37	64.3% F 35.7% M	19.8%	14.0%	NA	NA	None	7.8% (LLN) 5.0% (Fixed)
Gupte (2017)	South Africa[5]	730 (1)	36	85.1% F 14.9% M	30.1%	8.4%	0%	TB: 7.1% PCP: 2.7%	24.7%	4.8% (Fixed)
North (2018)	Uganda[3]	143 (1)	52	53.8% M 46.2% F	42.7%	9.1%	100%	PNA: 12.6% TB: 12.6%	100%	5.6% (Fixed)
Attia (2018)	Kenya[4]	375 (1)	40	67.2% F 32.8% M	12.5%		84.3%	BP: 24.3% TB: 21.9%	85.1%	7.5% (LLN)
Varkila (2019)	South Africa[5]	84 (1)	42.4	70.2% F 29.8% M	32.1%	17.9%	6.0%	TB: 34.5% PNA: 9.5%	82.1%	9.8% (LLN) 7.3% (Fixed)
Kayongo (2020)	Uganda[3]	722 (4)	48.0	59.7% F 40.3% M	15.8%		88.5%	TB: 9.1% BP: 4.4%	90%	6.2% (LLN)

[1] Individual publications may overlap. All studies that report spirometry adhered to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for standardization of spirometry.

[2] Prevalence was reported as spirometry demonstrating a ratio of forced expiratory volume in 1s / forced vital capacity (FEV1/FVC) either <0.70 (fixed) and/or <lower limit of normal (LLN).

[3] Classified by the World Bank as low income country at time of study.

[4] Classified by the World Bank as lower middle income country at time of study.

[5] Classified by the World Bank as upper middle income country at time of study.

Abbreviations: ART = Antiretroviral therapy; BP = bacterial pneumonia; Pneumonia = Unspecified pneumonia; PCP = *Pneumocystis* pneumonia; TB = pulmonary tuberculosis