

Chronic Obstructive Pulmonary Disease in People with HIV: an Evidence-Based Review

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Abstract: HIV co-infection is a risk factor for the development of COPD. HIV enhances the deleterious effects of exposures such as tobacco smoking, as well as interacting with other drivers of COPD such as pulmonary tuberculosis, air pollution and biomass fuel burning. Recent work demonstrates that HIV also contributes independently to COPD pathogenesis by promoting oxidative stress, chronic inflammation, abnormal innate and adaptive immune responses, microbial dysbiosis, and epigenetic alterations within the lung. Consequently, people with HIV develop COPD younger, more often, and with faster rates of lung function decline compared to seronegative individuals. They may also have distinct patterns of lung function abnormalities compared to other etiologies of COPD. Understanding the natural and pathogenetic history of HIV-associated COPD is important as its assessment, prevention and treatment are currently extrapolated from the general population. Whilst smoking cessation remains vital, further understanding may help guide unique management strategies for HIV-associated COPD. In this review, we explore its epidemiology and pathophysiology and discuss prevention and treatment approaches in this increasingly common disease.

Keywords: smoking, emphysema, lung function, airflow obstruction, air pollution, antiretroviral therapy

Introduction

Effective antiretroviral therapy (ART) has moved the focus of HIV care away from acute, opportunistic infections, towards chronic, age-associated comorbidities. Of these, people with HIV appear particularly susceptible to the development of Chronic Obstructive Pulmonary Disease (COPD).^{1–5}

COPD is defined as a “heterogeneous lung condition characterised by chronic respiratory symptoms due to abnormalities of the airway and/or alveoli that cause persistent, often progressive, airflow obstruction”.⁶ COPD accounted for 3.3 million deaths globally in 2019⁷ and is one of the top three causes of death worldwide.⁸ The global prevalence of COPD is increasing, driven by a complex interaction of different risk factors which, in general, represent systemic disadvantage across the life-course.⁷ Traditionally, at least in high-income settings, tobacco smoking is regarded as the most important risk factor and is still the most prevalent.⁷ However, in 2023 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy proposed a new taxonomy for COPD based on the contribution of multiple factors driving disease pathogenesis.⁹ The development of these “etiologies” (that is, the primary cause of the resulting COPD) importantly emphasises the heterogeneity of COPD, and highlights the influence of other risk exposures on the lung, such as infections (Table 1).

More recently, HIV co-infection has been recognised as a novel risk factor for COPD. People with HIV develop COPD younger, more often, and with faster rates of lung function decline than seronegative individuals.^{3,5,10–12} HIV-associated COPD may be associated with distinct lung function abnormalities, compared to other “etiologies” of COPD,¹³ and with significant gas exchange impairment.¹⁴ Even in the setting of suppressive ART, HIV persists within the lung.¹⁵ By promoting immune senescence and impairing epithelial integrity, HIV augments the effects of other drivers such as tobacco smoke to promote oxidative stress and low-grade inflammation in the alveolar compartment.¹⁶

Table 1 Proposed Taxonomy (Etiotypes) of COPD

Classification (Etiotype)	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with similar effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD • Cigarette smoking (COPD-C) • Biomass and pollution exposure (COPD-P)	Exposure to tobacco smoke, including in utero or via passive smoking; vaping or e-cigarette use; cannabis use Exposure to household air pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

Notes: Adapted with permission from GOLD guidelines. *Global Initiative for Obstructive Lung Disease 2025 Report*. 2025:1–193. Available from: https://goldcopd.org/wp-content/uploads/2024/11/GOLD-2025-Report-v1.0-15Nov2024_WMIV.pdf.⁶

Understanding the relationship between HIV and the other exposures that contribute to COPD pathogenesis is key to the development of specific strategies to mitigate these risks. This review will summarise recent advancements in our understanding of the epidemiology of COPD and HIV co-occurrence in different settings. It will explore the interaction between HIV and different risk factors, how HIV infection contributes to COPD pathogenesis, the emerging paradigm of HIV-associated COPD as an independent “etiotype” of COPD, and the approaches that can be taken to impact this.

Methodology

Our goal was to review the epidemiology of COPD in people living with HIV in different settings, to discuss the interactions between HIV and other drivers of COPD, to highlight pathways by which HIV may influence the development and natural history of COPD and discuss interventions that clinicians may use now or in the future, to mitigate the effects of HIV on the development of COPD. The broad nature of the review precluded the use of systematic review methods, and our findings are presented as a narrative review.

References for this review were identified through searches of PubMed articles published from January 1st, 2020, to February 28th, 2025, containing the terms “HIV and COPD” and “HIV, COPD and smoking” yielding 280 results. Articles were screened by title and abstract and, if felt relevant to the above broad themes, read in more detail before being included. Studies were excluded if felt not relevant to the research themes above. Other publications were subsequently identified through cited reference searching and papers known to authors.

The Epidemiology of the Co-Occurrence of HIV and COPD in Different Settings

For people with HIV, COPD is one of the most common co-morbidities.^{1,17} The prevalence is higher than in the general population, though estimates vary widely amongst different cohorts.^{1,3,12} A recent meta-analysis estimated the global prevalence of COPD in people with HIV as 10.5% (95% CI: 6.2–15.7%),³ with highest prevalence in northern Europe and populations with higher incomes – although this likely reflects significant under-diagnosis of COPD in many global south settings.¹⁸

Depending on geographical location, cohort, and study design, prevalence estimates of HIV-associated COPD range from 3.4% to over 40%.¹² This may reflect the variation in methods used to establish COPD diagnoses: self-reporting, International Classification of Disease-9 (ICD-9) coding, computed tomography (CT)-proven emphysema and spirometry have all been used in different studies.¹² Generally, self-reporting of symptoms and radiological methods find higher rates of obstructive lung disease than spirometry,¹² which is obligatory for the diagnosis of COPD.⁶

Most prevalence studies have been conducted in high-income countries (HICs),³ where tobacco smoking is the predominant risk factor for the development of COPD. Here, longitudinal analysis of large cohorts of people with HIV has helped estimate COPD incidence and prevalence. The biggest of these to date was the Veteran Ageing Cohort Study (VACS), where health records of over 33,000 military veterans with HIV were compared to demographically matched seronegative controls.¹ ICD-9 codes were extracted from health records to analyse the co-occurrence of HIV with COPD. Veterans with HIV were significantly more likely to have incident diagnoses of COPD than those without HIV. HIV infection was associated with a greater incident risk of COPD in veterans under the age of 50 (Incident Risk Ratio [IRR] 1.17; 95% CI: 1.11–1.24), than those over the age of 50 (IRR 1.08 95% CI: 1.01–1.15), with the prevalence of COPD gradually increasing with age amongst both veterans with and without HIV. These effects were independent of smoking status.

It is imperative to understand how trends in the prevalence and incidence of obstructive lung disease in people with HIV develop over time. In a recent study by Rowell Consola et al, administrative health records from three hospitals in greater New York were retrospectively analysed for data on inpatient admissions over a 10-year period. Amongst >19,000 people with HIV, chronic lung diseases were the most prevalent recorded co-morbidity (25.3%), significantly higher than in the HIV negative population (14.0%; Prevalence Ratio [PR] 1.8; 95% CI: 1.8–1.8).⁴ Between 2006 and 2016, the prevalence of chronic lung diseases in people with HIV increased from just over 20% to nearly 35%. The study did not delineate between different forms of chronic lung diseases but suggests the burden of non-communicable lung disease is rising for people with HIV.

The development of COPD in people with HIV is a heterogeneous process and will depend on the interaction of different risk exposures and different HIV-related factors in different settings. Most people with HIV reside in African countries,¹⁹ where rates of tobacco use are rising,²⁰ but where tuberculosis (TB) and biomass fuel burning also markedly contribute to COPD development.²¹ Across the African continent, prevalence estimates of HIV-associated COPD vary, for example, from 3.7–10.4% in Uganda²² to 15.4%–22.2% in Nigeria.²³ Generally, studies report HIV-associated COPD prevalence at a lower frequency in LMICs than HICs,¹² though this may reflect reduced access to CT imaging or spirometry. Interestingly, a recent meta-analysis found the odds of developing obstructive lung disease for people with HIV were higher in Africans (Odds Ratio [OR]: 1.56, 13 studies), than Americans (OR: 0.93, 15 studies) or Europeans (OR 1.36; $p < 0.01$, 10 studies), though studies in Africa lacked gas exchange and CT scan data, and there was significant inconsistency between study design.⁵

Most reports have assessed COPD in men with HIV, though recent work has explored the impact of biological sex. In the general population, being female has been associated with the development of more severe, early onset COPD,²⁴ and females may be more susceptible than men to harmful effects of smoking.²⁵ Analysis of the Women's Interagency HIV study found that women with HIV have lower baseline forced expiratory volume in one second (FEV₁) and diffusing capacity for carbon monoxide (DL_{CO}) than seronegative women.²⁶ However, subsequent studies have failed to demonstrate an association between airflow obstruction and HIV status in women.²⁷ Interestingly, a US study suggests women with HIV may have lower baseline DL_{CO} and slower rates of decline of FEV₁ than men with HIV,¹³ though this may be a reflection of the equations used to calculate lung function values in people of different sex and ethnicities.

Differences between sexes are also reported in studies from African countries with high HIV prevalence, where the leading risk factor for the development of obstructive lung disease in women is exposure to household air pollution.²¹ In a cohort of non-smoking women with HIV in Uganda, faster rates of FEV₁ decline were noted compared to male counterparts and individuals without HIV.²⁸ These differences may be due to cultural behaviours that result in different exposures to indoor cooking fumes: in Ugandan women with HIV but not men, higher exposure to carbon monoxide (CO) was associated with increased odds of reporting respiratory symptoms.²⁹ However, this may not explain the entire association. In a cohort of Ugandan adults with HIV who had recently completed treatment for pneumonia, women with HIV had 3.44 increased odds of obstructive lung disease on spirometry than men (95% CI: 1.1–12.0; $p = 0.04$), a result that persisted when adjusted for exposure to TB and biomass fuel burning.³⁰ Whether sex-based differences in immune responses help to explain these differential patterns of lung function abnormalities in women with HIV is under investigation.

Risk Factors for COPD in People with HIV

Smoking

Globally, smoking is the most prevalent risk factor for COPD.²¹ In the US, up to 40% of people with HIV smoke compared to 21% of the general population.³¹ In China, studies suggest that over 50% of people with HIV are cigarette smokers,³² increasing to 65% in men with HIV who have sex with men.³³ In LMICs, tobacco consumption is less prevalent but is still statistically higher than in people without HIV.¹⁹ Cultural practices contribute to differences between sexes: in an analysis of tobacco use in people with HIV in 28 LMICs, 24.4% of men with HIV were active tobacco smokers, compared to just 1.3% of women with HIV.³⁴ In a recent prospective cohort study of over 500,000 adults in China, 74.3% of men had ever “smoked regularly” compared to just 3.2% of women.³⁵

Despite declining smoking rates in people with HIV in the US (from 37.6% to 33.6% between 2009 and 2014), rates remain almost twice as high when compared to seronegative individuals, and people with HIV are less likely to quit compared to the general population.³⁶ In China, rates of tobacco use remain high,³⁵ and in many African countries, prevalence of tobacco use is rising.¹⁹

Tuberculosis

Previous pulmonary TB is an independent risk factor for the development of COPD.³⁷ This is particularly significant considering an estimated 10 million people develop TB annually, and in 2020, there were over 150 million people who had survived TB.³⁸ A recent meta-analysis including 23 studies³⁷ found that TB increases the odds of developing fixed-airflow obstruction, meeting the spirometry criteria for COPD (by 2.59 CI: 2.12–3.15; $P < 0.001$).³⁸ The risk is also higher for people with HIV on ART. In a Ugandan population of people with well-controlled HIV, pulmonary tuberculosis was the strongest predictor of COPD risk and reduced lung function.³⁹ This association was also seen in a study of urban centres in Uganda, where the prevalence of COPD in people with HIV was associated with previous tuberculosis and a BMI of $< 21/\text{Kg}/\text{m}^2$.⁴⁰

Biomass Fuel Burning

Approximately 3 billion people around the world cook and heat their homes by burning solid fuels in open fires and stoves.⁴¹ In a recent report from the Global Burden of Disease collaborators, household air pollution from the burning of solid fuels was the primary risk factor responsible for disability adjusted life years from chronic respiratory diseases in southern Africa.²¹ A recent meta-analysis estimated exposure to burning of solid biomass fuels increased the risk of COPD by 2.65 (95% CI: 2.31–3.31) compared to the use of non-biomass fuels.⁴² COPD from household air pollution may differ from tobacco-related COPD in several ways, including greater airway involvement but less emphysema.⁴² Understanding how this relates to or differs from HIV remains under investigation.

Ambient Air Pollution

Air pollution is second only to tobacco smoke as globally the most attributed risk factor for deaths and disability adjusted life years lost from chronic respiratory disease.²¹ The development of COPD has been directly linked to exposure to air pollutants,⁴³ with recent estimates suggesting as much as 50% of the total attributable risk of COPD may come from exposure to gaseous and particulate components of air pollution.⁴⁴ There is no safe “threshold” for air pollution; the relationship between respiratory events and air pollution is supra-linear: there are more adverse effects per unit change in air pollution at lower concentrations, compared to higher concentrations.⁴⁴ High levels of air pollution increase the risk of COPD exacerbations, hospitalisations and death.⁴⁵ People with HIV may be particularly susceptible to the effects of air pollution: in a cohort study of > 250 adults in rural Uganda, people with HIV were more likely to report chronic cough, dyspnoea or wheeze when exposed to unsafe levels of CO measured by 48-hour ambulatory CO monitoring, compared to adults without HIV.²⁹ In people with HIV, elevated concentrations of ambient air pollutants are associated with suppressed antibody responses to *Pneumocystis jirovecii* surface glycoproteins in serum and bronchoalveolar lavage (BAL), though so far no correlation with adverse clinical outcomes has been demonstrated.^{46,47}

HIV as an Independent Risk Factor for Lung Disease

In meta-analyses, after adjusting for cigarette smoking, the prevalence of COPD is significantly higher in people with HIV than in those without HIV,³ suggesting an independent effect of HIV on lung health. In people with HIV, CD4⁺ T-cell counts <200 cells/ μ L are associated with reduced pulmonary diffusing capacity.⁴⁸ Low nadir CD4⁺ cell count is independently and negatively correlated with the development of COPD,⁴⁹ and with gas exchange impairment in people with HIV.⁵⁰ In the AIDS linked to the Intravenous Experience (ALIVE) cohort in the US, (a cohort of people who inject drugs) people with an HIV load of >75,000 copies/mL and CD4⁺ T cell counts <100 cells/mm³ had faster FEV₁ and FVC declines compared to individuals without HIV.⁵¹

The impact of HIV control on lung function decline is not completely understood. In the AGE_{HIV} study, a longitudinal cohort study which followed over 900 people in Amsterdam with virally suppressed HIV over almost 8 years, treated HIV infection was associated with greater adjusted yearly declines in FEV₁ and FVC over time compared to those without HIV: even in the setting of viral control, lung function decline is faster than in the general population.⁵² Although rates of FEV₁ and FVC decline between people with HIV and the general population were even faster in smokers, these changes persisted after controlling for smoking and other risk behaviours. Statistically higher C-reactive protein (CRP) concentrations during follow-up were associated with accelerated declines in FEV₁ and FVC among those with HIV, but not in participants without HIV, suggesting low-grade inflammation could be contributing to this.

Moreover, in the VACS cohort, ART use was not associated with a lower incidence of COPD after adjusting for smoking status.¹ To specifically examine the impact of ART on lung function decline, the Strategic Timing of Antiretroviral Treatment (START) trial enrolled ART-naïve adults with HIV who had CD4⁺ T-cell counts >500 cells/mm³ and a median time since HIV diagnosis of 1.2 years. Participants were randomised to begin ART immediately or deferred until CD4⁺ T-cell counts were <350 cells/mm³ or AIDS developed. After nearly 4 years of follow-up, there was no difference between immediate or deferred ART initiation on rates of post-bronchodilator FEV₁ decline or incident COPD risk.⁵³ This suggests that at least for those early in their disease course with CD4⁺ cell counts >500 cells/mm³, use of ART does not affect FEV₁ decline. However, this study did not assess other lung function measures (eg DL_{CO}) or radiographic markers of COPD, and the effects of HIV control on the development of COPD may become apparent after a longer follow-up period.

HIV Acts Synergistically with Other Risk Exposures

As well as causing an independent effect on lung health, HIV interacts with and augments other risk exposures to contribute to COPD pathogenesis (Figure 1). Perhaps, the most important of these is the synergistic effect of HIV and tobacco smoke on the lung. Smokers living with HIV are more susceptible to the development of emphysema than seronegative smokers.⁵⁴ A recent prospective matched cohort study of >1000 people in Denmark and the US with virally suppressed HIV found an 8.5mL/year faster decline in FEV₁ for people with HIV compared to those without. This effect was augmented by smoking: smokers with HIV experienced 16.8mL/year faster decline in FEV₁ than smokers without HIV.¹⁰

Tobacco smoking appears to impair the effectiveness of ART: smoking is associated with a greater risk of virological rebound in women with HIV on ART and a higher risk of developing AIDS when adjusted for other confounders.⁵⁵ Moreover, in a cohort of ART-naïve men living with HIV in South Africa, current smokers had 3 times higher odds (95% CI: 1.3–7.9, P = 0.01) for developing pulmonary tuberculosis than non-smokers,⁵⁶ suggesting smoking and HIV combine to enhance susceptibility to other infections. Smoking is also a risk factor for the development of bacterial pneumonia, an effect that is reduced when people stop smoking.⁵⁷ Given the synergistic effect of HIV and tobacco smoke on the lungs, understanding how to address tobacco dependence in people with HIV is critical.

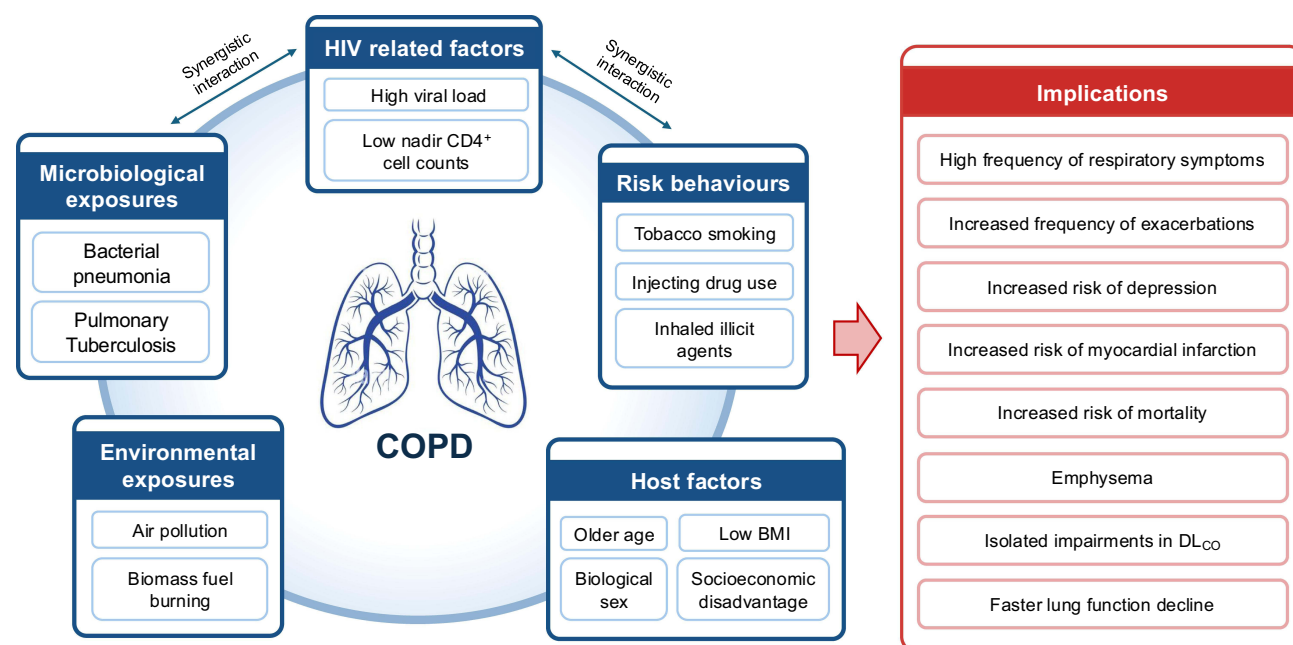


Figure 1 Drivers and implications of HIV-associated COPD. HIV interacts directly and indirectly with different factors to contribute to COPD pathogenesis with negative implications for patients.

How Does HIV Co-Infection Influence the Natural History of COPD?

The recent proposal of a new taxonomy for COPD, with “etiotypes” of COPD grouped by underlying causative factors reflects the observation that some disease entities show distinct clinical features.⁹ Although there are many cross-sectional studies reporting the prevalence of COPD among people with HIV,^{40,41,48,58,59} our understanding of the natural history of HIV-associated COPD is more limited. HIV infection accelerates lung function decline but may also contribute to impaired gas exchange before, or independently of airflow obstruction developing (Figure 1).

Effects on Gas Exchange

The diffusing capacity of the lungs for carbon monoxide is a measure of the ability of gas to transfer from the alveoli into red blood cells. People with HIV have a higher risk of gas exchange impairment,⁵ with reduced DL_{CO} measurements among the most prevalent findings on lung function testing in people with HIV.^{14,26,48} Low DL_{CO} is associated with low nadir $CD4^+$ T cell counts and detectable viraemia.^{50,60} Importantly, both impairments of DL_{CO} and FEV_1 have been identified as independent risk factors for mortality in people with HIV.^{13,61}

Discerning which factors contribute to lung function and gas exchange impairment, and the relationship between these measures in HIV-associated COPD is complex. Analysis of the Pittsburgh HIV Lung Cohort found that older age, male sex and GOLD stage 1 COPD at baseline were all associated with faster rates of decline of post-bronchodilator FEV_1 & FVC.⁶² Interestingly, viral load, $CD4$ T⁺ cell levels and ART use were not associated with rates of decline. In a separate analysis of the same cohort, measurements of DL_{CO} , FEV_1 and FVC were recorded in conjunction with symptoms and serum immune markers. Specific patterns of lung function decline were associated with specific symptoms. Elevated serum CRP & endothelin-1 (ET-1) levels were associated with faster rates of decline in FEV_1 and the FEV_1/FVC ratio.¹³ Detectable viraemia, however, was associated with impaired DL_{CO} at baseline. This might suggest that distinct mechanistic pathways lead to airflow obstruction or gas exchange impairment in people with HIV.

In one of the largest reported studies recording lung function in men with HIV (The Multicenter AIDS Cohort Study), HIV status was not correlated with impaired FEV_1 .⁵⁰ However, men living with HIV had a 1.6x increased risk of DL_{CO} <80% predicted (95% CI: 1.18–1.28, $p=0.002$), and a 3.0x increased risk of DL_{CO} <60% predicted (95% CI: 1.36–6.47, $p=0.006$) compared to men without HIV. Lower DL_{CO} was associated with lower nadir $CD4^+$ counts. Isolated impairments in DL_{CO} in the presence of normal spirometry (iso $\downarrow DL_{CO}$) have also been reported in cohorts of women living

with HIV,^{26,27} where they were again associated with lower nadir CD4 counts. Iso↓DL_{CO} is associated with worse ratings on health quality of life indexes,⁶³ and worse respiratory symptom scores, an association which strengthens as gas exchange worsens.¹⁴

If specific immunological mechanisms drive iso↓DL_{CO}, they are not well understood. Lower DL_{CO} levels are associated with increased CD25⁺/CD4⁺ and CD25⁺/CD8⁺ T cells, as well as higher IL-6 and CRP levels in people with HIV that have high rates of concurrent tobacco use.⁶⁴ This suggests that adaptive immune activation may contribute to gas exchange impairment, though the relative contribution of regulatory CD4⁺ T cells was not assessed. Perturbations in innate immunity may also contribute. In longitudinal analyses, reduced DL_{CO} in people with HIV was associated with elevated plasma markers of monocyte/macrophage activation such as Interleukin-2 (IL-2) and soluble CD163 (sCD163) as well as markers of endothelial dysfunction such as ET-1.⁶⁵

In the Inflammation, Ageing, Microbes and Obstructive Lung Disease (I AM OLD) Study, done in two US cities, elevated plasma levels of the pneumoproteins pulmonary and activation-regulated chemokine (PARC)/CCL-18 and Clara cell secretory protein (CC-16) were more strongly associated with low DL_{CO} than low FEV₁ in people with HIV.⁶⁶ Further work by the same group characterised biomarkers specifically associated with an iso↓DL_{CO} phenotype in people with HIV, including soluble CD14 (sCD14), sCD163, interferon gamma-induced protein 10 (IP10), soluble tumour necrosis factor (TNF) receptors sTNFR-I, and sTNFR-II.⁶⁷ In addition, two studies demonstrate that people with HIV with low DL_{CO} preferentially express different genes compared to people without HIV or those with normal gas exchange. Impairments in DL_{CO} are associated with activation of processes involved in inflammation, immunity, apoptosis⁶⁸ and interferon signalling.⁶⁹ Understanding the mechanisms by which HIV causes distinct abnormalities in lung function and gas exchange is imperative to understanding HIV-associated COPD as its own etiology. However, DL_{CO} impairment is non-specific and can be the result of infections;⁷⁰ abnormalities in lung structure such as emphysema or fibrosis; pulmonary vascular disease such as pulmonary hypertension or congestive cardiac failure.⁷¹ Further studies which control for these co-morbidities are required to delineate the significance of impaired gas exchange in people with HIV.

Emphysema

Emphysema on chest imaging is common in people with HIV, with a recent systematic review estimating a weighted average prevalence of emphysema in those with HIV of 23% (95% CI: 16–30%).⁷² High rates of tobacco and marijuana use are associated with the development of emphysema in people with HIV,⁷³ but HIV infection is a risk factor for the development of emphysema independent of smoking.^{54,74} In a single centre study from Italy, emphysema was reported in 18% of people with HIV that had never smoked.⁷⁵ Emphysema in people with HIV is often more diffuse on chest imaging than in those without and has been independently associated with CD4⁺ cell counts <200/mm³, high sCD14 levels,⁷⁴ high TNFα and IL-1B levels,⁷⁶ and low CD4⁺/CD8⁺ T cell ratios.⁷⁷ For people with HIV, radiological emphysema is associated with worse symptoms such as cough and mucus production and shorter six-minute walking distances, compared to those without HIV.⁷⁷ An emphysema burden of >10% on CT also carries a 2.4x increased risk of mortality (95% CI: 1.1–5.5), compared to people with ≤10% emphysema, an effect which is independent of smoking pack-years.⁶¹

Identifying people with HIV at greatest risk for progressive emphysema is therefore important, as it offers the possibility of intervening early, ie prior to significant morbidity and mortality occurring. Low DL_{CO} and a combination of CT-proven centrilobular and paraseptal emphysema have been identified as factors associated with radiological progression of emphysema in people with HIV.⁷⁸ Interestingly, a recent prospective cohort study from Atlanta of more than 160 people with HIV followed up over a 6-year period, found that traditional metrics of airflow limitation (FEV₁/FVC ratio <0.7) were not the most effective measures with which to predict the presence of radiological emphysema.⁷⁹ In this cohort, these were a FEV₁/FVC cut-off of 0.78 and a residual lung volume of 116% predicted.

Further work is required to determine the optimal thresholds for identifying patients with HIV associated emphysema. Although emphysema and COPD often coexist, one does not necessarily imply the other; airflow limitation on spirometry is required for a diagnosis of COPD. While high rates of emphysema may in part explain the high frequency of gas exchange impairment in people with HIV, in the multi-center study of HIV in the Etiology of Lung disease (SHIELD) the

association between HIV and low DL_{CO} were independent of emphysema severity, suggesting that this relationship is complex.⁸⁰

Symptom Burden, Morbidity & Mortality

People with HIV may report more respiratory problems than their seronegative counterparts (Figure 1). Even in individuals without overt lung disease, HIV infection is associated with reduced exercise tolerance and worse respiratory symptoms reported by questionnaire.⁸¹ Independent of the effect of antiretroviral therapy, people with HIV are more likely to have respiratory symptoms,⁸² and these are likely to be more severe and result in healthcare seeking behaviour.⁸³

People with HIV-associated COPD may be particularly affected. In the ALIVE cohort, HIV was an independent risk factor for moderate breathlessness on the MRC scale, and when HIV and COPD were present together, this association was worse than with either disease alone.⁵⁸ In other cohorts, more chronic cough and decreased exercise tolerance are present in people with HIV compared to negative individuals.⁸⁴ Moreover, people with HIV who have a diagnosis of COPD are more likely to report depressive symptoms and have a lower quality of life than those without COPD.⁸⁵

HIV has also been identified as an independent risk factor for exacerbations of COPD. In the ALIVE cohort, HIV was associated with 2.47 increased odds of COPD exacerbation (95% CI: 1.22-5.00).⁸⁶ How this relates to CD4⁺ cell count and immune function is not clear. The ALIVE study found there was an increased risk of COPD exacerbation for people with HIV with undetectable viral loads, and CD4⁺ cell counts >350 cells/mm³, but this was not seen with CD4⁺ counts <350 cells/mm³. By contrast, in the VACS study, lower baseline CD4⁺ cells counts, higher HIV RNA levels and lack of ART were all associated with increased risk of acute exacerbation.⁸⁷ While these observations may in part be explained by differences in how COPD exacerbations are reported or differences in health seeking behaviours between the two cohorts, the relationship between viral control and exacerbation risk requires further clarification.

Perhaps most importantly, the presence of COPD increases risk of death for people with HIV: airflow obstruction, gas exchange impairment and emphysema are all independently associated with increased risk of all-cause mortality.^{61,88} The negative implications of HIV-associated COPD are outlined in Figure 1.

How Does HIV Influence the Development of COPD?

In individuals without HIV, COPD is typically the result of a genetic susceptibility to a modified inflammatory response to chronic irritants such as cigarette smoke, though the mechanisms that cause this are not fully understood.⁶ HIV infection contributes to COPD pathogenesis by further modifying the alveolar immune response to noxious stimuli.

HIV Persistence within the Lung

HIV can directly infect a range of cell types within the lung. These include bronchial epithelial cells⁸⁹ and, when blood CD4⁺ T cell levels are low, alveolar macrophages.⁹⁰ Alveolar macrophages are the most plentiful cells within bronchoalveolar (BAL) fluid, and the primary innate cells within the lung. In the presence of CD4⁺ T cells in vitro, HIV infection of alveolar macrophages isolated from BAL fluid is enhanced, and HIV may be transmitted from infected CD4⁺ T cells to alveolar macrophages via direct contact.⁹¹

HIV infection alters the immune response of alveolar macrophages, impairing phagocytic activity^{92,93} and skewing macrophages towards a pro-inflammatory, protease producing phenotype. In vitro, monocyte-derived macrophages infected with HIV demonstrate activation of pathways associated with the pathogenesis of COPD such as activation of the NLRP3 inflammasome.⁹⁴ HIV therefore appears to promote lung inflammation by influencing the ability of alveolar macrophages to respond to external stimuli.

As described in other anatomical sites within the body,⁹⁵ HIV may persist within cellular reservoirs in the lung. As long-lived cells, tissue macrophages represent a compelling cellular reservoir for HIV. Initial studies demonstrating in vivo infection of alveolar macrophages from BAL fluid samples were complicated by the fact that donors were not treated with ART and may subsequently have had co-existent inflammatory processes occurring within their lungs.⁹³ It is therefore difficult to understand if the infected macrophages isolated represent recruitment of short-lived inflammatory

cells rather than chronic immune reservoirs within the lung. HIV nucleic acids have, however, been isolated from the BAL fluid alveolar macrophages of individuals on ART with undetectable plasma viral loads.⁹²

Further evidence for a cellular reservoir within the lungs is provided by animal models. Cellular labelling experiments in rhesus macaques demonstrate infection and destruction of short-lived interstitial macrophages but reduced cell death of longer-lived HIV-infected alveolar macrophages.⁹⁶ In murine models, HIV infection of tissue macrophages is rapidly suppressed by ART, but delayed viral rebound occurs in around one-third of animals, suggesting persistence of HIV infection within macrophages.⁹⁷

In lung samples from people with HIV who died and were on ART, significant levels of viral DNA were regularly isolated at post-mortem suggesting viral persistence despite ART.⁹⁸ It is unclear if this represents replication competent virus. Further studies suggest that bronchial epithelial cells,⁸⁹ CD4⁺CD8⁺ T cells,⁹⁹ and bronchial pericytes¹⁰⁰ may contribute to a cellular reservoir for HIV in the lung. The contribution of such reservoirs to the pathogenesis of COPD is likely indirect, though HIV persistence within the lung may contribute to chronic, low-grade inflammation within the alveolar space.

Altered Adaptive Immune Responses

The lung is continually exposed to inhaled pathogens, allergens and toxins. To counter these, a robust adaptive immune response requires a broad population of CD4⁺ and CD8⁺ T cells. HIV infection may reduce the effectiveness of the adaptive response by inducing immune senescence, and the recruitment of terminally differentiated exhausted cells into the alveolar compartment.

For example, chronic HIV infection results in the accumulation of CD8⁺ T cells exhibiting high levels of exhaustion markers, such as programmed cell death protein-1 (PD-1), and low proliferative capacity.¹⁰¹ In people with HIV not on antiretroviral therapy, there appears to be a profound influx of dysfunctional CD8⁺ T cells into the lung, with a resulting lymphocytic alveolitis.¹⁰² These cells again demonstrate decreased proliferation markers and higher expression of PD-1. People with HIV also appear to have low CD4⁺/CD8⁺ T cell ratios in peripheral blood even after CD4⁺ T cell population recovery following ART.¹⁰³ High levels of terminally differentiated, activated CD8⁺ T cells may represent a marker of persistent immune dysfunction in the T cell compartment, even after viral suppression.

HIV infection may also induce senescence of CD4⁺ T cells. Cell sorting studies comparing peripheral blood and lung mucosal T cell populations in HIV positive and negative individuals with COPD demonstrated qualitative and quantitative lung mucosal CD4⁺ T cell depletion in people with HIV, which was not replicated in peripheral blood, or people without HIV.¹⁰⁴ This was again associated with raised levels of exhaustion markers Fas-1 and PD-1. People on long-term ART also experience persistent depletion in the diversity of their T-cell receptor repertoire.¹⁰⁵ Thus, the inflammation associated with chronic HIV infection may result in immune senescence of the adaptive response and deplete the diversity of the response to external stimuli.

Changes to the Airway Epithelium

HIV infection reduces the integrity of the airway epithelium, the main physical and immunological barrier protecting the lung from external insults. HIV can infect bronchial epithelial cells which express HIV co-receptors CD4, CCR5 and CXCR4.¹⁰⁶ Following infection, HIV decreases expression of E-cadherin, an adhesion molecule produced by airway epithelial cells which is important for barrier function,¹⁰⁷ thus increasing epithelial cellular permeability to harmful inhalants.

The cystic fibrosis transmembrane regulator protein (CFTR) is a key component of airway clearance, ciliogenesis and epithelial cell differentiation. In vitro, the HIV protein *Tat* impairs transcription of CFTR,¹⁰⁶ and cigarette smoke acts synergistically with *Tat* to impair both CFTR transcription and mucociliary clearance.¹⁰⁸ In the macaque model, Simian adapted HIV (SHIV) infection results in goblet cell metaplasia and loss of tight junction proteins in the airway epithelium.¹⁰⁹ SHIV infection generates significant numbers of HIV-gp120⁺ epithelial cells in small airways, an effect doubled when macaques are exposed to cigarette smoke regularly.

HIV also promotes cellular senescence in airway epithelial cells. Small airway epithelial cells taken from people with HIV have shorter telomere lengths compared with HIV-negative controls even after accounting for cigarette smoke

exposure and age.¹¹⁰ These changes are also seen in basal progenitor cells, the multipotent progenitor cells that regenerate the airway epithelium following damage. HIV infection results in the expression of higher levels of matrix metalloproteinase-9 (MMP-9),¹¹¹ decreased differentiation capacity and shortened telomere length in these cells.¹¹²

HIV and Smoking Act Synergistically within the Lung

HIV infection may render cells more susceptible to the harmful effects of cigarette smoke by increasing the expression of pro-inflammatory mediators that cause lung damage. In alveolar macrophages taken from BAL fluid of HIV-1 transgenic rats, exposure to cigarette smoke increases expression of MMP-9, and this is increased further when cells are exposed to the HIV protein *Tat* in vitro.¹¹³ Alveolar macrophages taken from BAL fluid of people with HIV more frequently exhibit pro-inflammatory markers of differentiation (CD163⁺ CCR7⁺), compared to seronegative controls. In smokers, these macrophages also have increased expression of the HIV co-receptor CXCR4, and Toll-like receptor-4 (TLR-4).¹¹⁴

By inducing expression of HIV co-receptors on alveolar macrophages, smoking may potentiate HIV infection within cells of the lung. Cigarette smoke enhances HIV entry into bronchial epithelial cells in vitro, via up-regulation of CCR5.¹⁰⁸ Also, exposure of alveolar macrophages in vitro to the carcinogen benzo(a)pyrene, a component of cigarette smoke, enhances HIV-1 replication in these cells.¹¹⁵

Synergistic effects may also occur via modulation of miRNA pathways. The lactoperoxidase system (LPO) is an important part of the innate immune response, mitigating oxidative stress in the lung by reducing levels of hydrogen peroxidase (H₂O₂). Bronchial epithelial cells exposed to TGF-β1, which is upregulated in COPD and HIV infection, and cigarette smoke express decreased LPO levels via transcriptional silencing of miRNAs. Decreased LPO led to increased H₂O₂ expression, and a subsequent oxidative stress response.¹¹⁶ In vitro, *Tat* also impairs mucociliary clearance by modulating the miRNAome in the presence of cigarette smoke.¹¹⁷

Few studies have linked immunological changes with radiographic or spirometric outcomes. Corleis et al found increased numbers of CD8⁺ T cells in the airway mucosa of smokers with HIV, and these were inversely correlated with lung aeration measured by CT imaging, suggesting smoking may cause recruitment of CD8⁺ T cells which results in structural changes within the lung.¹¹⁸ In a retrospective study of 82 people from the Pittsburgh Lung HIV study cohort who were virally suppressed on ART, both current smoking and intensity of smoking were correlated with higher HIV DNA and cell-associated RNA levels in peripheral blood mononuclear cells (PBMCs). Whilst this may suggest that smoking promotes HIV persistence despite systemic viral suppression, there was no relationship between these markers of HIV persistence and impairments in FEV₁ % predicted, FVC % predicted, FEV₁/FVC or DL_{CO} % predicted.¹¹⁹

Dysbiosis in the Lung Microbiome

The effects of HIV on the gut microbiome are well-established,¹²⁰ though its impact on the lung microbiome is less so. Compared to other mucosal surfaces, the lungs must maintain a relatively lower bacterial burden to effectively facilitate gas exchange at the alveoli.¹²¹ HIV driven perturbations in lung microbial populations, resulting in an overabundance of pathogenic species, may contribute to COPD pathogenesis.

Pneumocystis jirovecii is disproportionately found in airways of people with HIV with COPD, regardless of CD4⁺ T cell count.¹²² A multicentre study identified bacterial gene sequences representing the gut pathogen *Tropheryma whippelii* more frequently in BAL fluid of some individuals with HIV compared to seronegative controls.¹²³ However, this has also been demonstrated in BAL fluid taken from healthy smokers and non-smokers so may not be unique to the HIV population.¹²⁴ Other studies conducted as part of the Lung HIV microbiome project failed to identify a significant difference in bacterial populations in BAL fluid between people with HIV on ART, and those without HIV, though changes have been demonstrated at the level of the oral mucosa.¹²⁵

Microbial dysbiosis may be exaggerated in advanced HIV infection as immunosuppression limits the ability of the immune system to restrict colonisation of the respiratory tract. Twigg et al took BAL samples from 30 people with HIV with a baseline mean CD4⁺ T cell count of 262 cells/mm³.¹²⁶ The relative abundance of *Prevotella* and *Veillonella*, species previously associated with lung inflammation, was higher in people with HIV than seronegative controls. These differences reduced but did not completely resolve after a year on ART. In a UK cohort study, there was no difference in the core airway microbiome depending on HIV status, but pathogenic respiratory taxa such as *Staphylococcus*,

Pseudomonas and *Klebsiella* were significantly more frequent in sputum samples of people with HIV, and this was correlated to the duration of HIV infection, and the timing of ART introduction.¹²⁷

Airway inflammation may result from translocation of oral bacteria into the lung. Alterations in the oral microbiome have been associated with increased airflow obstruction and lower DL_{CO} in people with HIV but not negative controls.¹²⁸ Detection of supraglottic taxa of bacteria in BAL fluid is correlated with detection of proinflammatory cytokines and deficits in lung function in people with HIV,¹²⁹ linking micro-aspiration of bacteria from the oral cavity to COPD pathogenesis. However, multiple studies have also demonstrated enrichment of the lung microbiome by commensal gut bacteria.^{123,126–128} In the setting of advanced HIV infection, breakdown of the gut mucosal barrier may result in translocation of bacteria from the gut, resulting in alteration of the lung microbiome.

A recent study compared respiratory microbiota between virologically suppressed adults in Uganda and the United Kingdom, stratified by HIV and COPD status.¹³⁰ Reduced bacterial diversity and significant enrichment of induced sputum samples with *Campylobacter* species was found in people with both HIV and COPD, compared to people with just one of these conditions. Comparisons between the two groups revealed significant differences in the sputum microbiome composition, irrespective of viral suppression, suggesting geographical differences may also play a role.

Oxidative Stress

HIV infection promotes oxidative stress within the alveoli by disturbing the normal oxidant/antioxidant balance.^{15,16} HIV indirectly inhibits synthesis of the compound glutathione, the main endogenous antioxidant.¹³¹ Glutathione protects alveolar cells by reducing reactive oxygen species. Non-smokers with HIV on ART have significantly higher glutathione levels in BAL than those not taking antiretroviral therapy,¹³² suggesting ART may protect the lung from oxidative stress. Smoking in people with HIV is associated with lower glutathione levels than non-smokers,¹³³ and smokers with HIV experience falling glutathione levels over time.¹³⁴ Decreased glutathione means that lung defence against oxidative species is impaired. Data suggest that this is the case even for people with HIV taking ART.^{132,135} Compared to uninfected controls, alveolar macrophages isolated from people with HIV on ART have higher levels of H₂O₂, and the proteins Nox1, Nox2, Nox4 and TGF-β1, proteins that contribute to oxidative stress and immune dysfunction.¹³⁶

Developments at the Epigenetic Level

DNA methylation regulates gene expression by recruiting or inhibiting proteins involved in transcription. Recent epigenome-wide association studies have investigated whether differential DNA methylation influences lung function variability in people with HIV. People with HIV in the START trial underwent annual spirometry testing over a median 5-year period. Airflow obstruction (FEV₁/FVC <0.7) in these people was associated with almost 1400 differentially methylated positions in DNA isolated from peripheral blood samples. These methylation signatures were enriched for biological pathways associated with chronic viral infections. Individuals with airflow obstruction were globally hypomethylated compared to those without.¹³⁷ Subsequent studies have also identified distinct DNA methylation profiles in bronchial epithelial cells in people with HIV with COPD and higher levels of epigenetic biomarkers associated with ageing.¹³⁸ Epigenetic changes that result in ageing of the airway epithelium in people with HIV may contribute to the heightened risk of COPD in this population.

Even with HIV suppression, infection with HIV promotes low level chronic inflammation in the lung. Impairments in, and senescence of, innate and adaptive immune cells, oxidative stress, dysbiosis of the lung microbiome and disordered epithelial barrier integrity may all contribute to increased susceptibility to environmental exposures such as cigarette smoke, and subsequent COPD pathogenesis.

How Might We Influence the Development and Natural History of COPD? Screening & Case Finding

Studies suggesting that lung function declines fastest in the incipient stages of COPD¹³⁹ highlight the importance of early diagnosis and raise questions about optimal approaches for early COPD detection in HIV clinics. This is particularly

complicated given the heterogeneity of COPD, where the presence of symptoms and objective lung function changes do not often correlate.¹⁴⁰

Screening, the process of identifying asymptomatic participants who have an increased risk of developing a disease, for COPD in the general population is controversial. The US Preventative Services Task Force currently recommends against screening asymptomatic people for COPD on the basis that early detection does not affect disease course and has no treatment other than exposure reduction, which should proceed irrespective of COPD status.¹⁴¹ GOLD, however, argues that this should not apply to high-risk populations⁶ and advocates for case finding, ie performing spirometry in patients with respiratory symptoms or risk factors, in the general population.⁶ The European AIDS Clinical Society¹⁴² also advocates for case finding of COPD in people with HIV.

The best way to do this is not yet determined. Lambert et al employed a questionnaire-based screening tool in an outpatient HIV clinic to screen over 1500 people with HIV for COPD.¹⁴³ Only 64% of participants successfully completed the questionnaire. Two hundred and four participants met criteria for spirometry, but it was performed in only 64, resulting in just 5 people with objective evidence of COPD.

In an urban HIV clinic in New York, Shirley et al screened all people aged >35 with same day peak flow measures and a respiratory symptom questionnaire.¹⁴⁴ Those with either abnormal questionnaire responses or abnormal peak flow (<70% predicted), as well as one-third of people with normal screens were offered spirometry. Five of 89 (6%) who completed spirometry were diagnosed with COPD. In this study, abnormal peak flow was more sensitive (sensitivity of 80%) than either the questionnaire or a combination of both peak flow and questionnaire, in the diagnosis of COPD.

A single centre study in Italy combined a questionnaire approach with hand-held spirometry in over 1450 participants.¹⁴⁵ Twenty percent (282) qualified for same day spirometry based on questionnaire scores, and of the 190 who completed it, 65 (34%) had impaired spirometry. They were referred for formal lung function testing, which was completed in only 33 people. Twenty-two (67%) had COPD. In each of these studies, large dropout rates, poor attendance at spirometry appointments, and/or the low specificity of tools for the detection of COPD highlight the difficulty of creating a screening tool for HIV-associated COPD in an outpatient setting.

Formal spirometry-based techniques may not be applicable for use in LMIC where access is often limited, or for the screening of large cohorts of people in outpatient settings. In LMICs, micro-spirometers may be useful and are generally more sensitive than questionnaire-based approaches.¹⁴⁶ Novel methods that incorporate questionnaires combined with peak flow, such as the COPD Assessment in Primary care To identify Undiagnosed Respiratory disease and Exacerbation risk (CAPTURE) tool, are currently being evaluated, though not specifically in people with HIV.¹⁴⁷ To date, this has demonstrated only limited sensitivity in the diagnosis of COPD,¹⁴⁸ though this may improve in patients who require treatment because of increased risk of exacerbations or hospitalisation.¹⁴⁹ Techniques that also incorporate clinically relevant exposures to particular risk factors have been tested in Uganda.¹⁵⁰ Studies that validate the CAPTURE tool and other such techniques in HIV populations are required. Currently, no conclusive recommendations on screening and case-finding can be made.

The Timing & Type of Antiretroviral Therapy

Work identifying low nadir CD4⁺ T cell counts and high HIV RNA levels as risk factors for impaired lung function^{48,51} contributed to the hypothesis that early initiation of ART may reduce the rate of lung function decline in people with HIV. However, in the START trial, after a median of 3.9 years follow-up in a relatively young population (median age 36 years; IQR 30–44), there appeared to be no difference in rates of decline of airflow obstruction, or COPD incident risk, whether ART were started immediately or deferred.⁵³

Conversely, data from early observational studies suggested that ART use may be associated with an increased risk of COPD.^{151,152} This led to the hypothesis that certain subtypes of ART could have a direct toxic effect on the lung. However, in the sub-group analysis of the START trial, different drug classes of antiretroviral therapy had no clear effect on declines in lung function, even though only small numbers of people were taking integrase inhibitors – which limits what we can conclude about this particular drug class.¹⁵³

Key Considerations When Managing COPD in People with HIV

People with HIV have been historically excluded from large, randomised controlled trials of treatments for COPD. Management strategies for COPD in HIV populations are extrapolated from the general population. However, there are a few specific areas of note when considering treatment for COPD in people with HIV (Figure 2).

Initial COPD strategies including exposure reduction, vaccinations and pulmonary rehabilitation are important irrespective of HIV status. Recent guideline updates in chronic pharmacological COPD management promote the use of inhaled therapies with dual bronchodilators (LABA-LAMA) as the background therapy recommended for all but those with minimal symptoms and low exacerbation risk.⁶ Inhaled corticosteroids are also recommended for people with relatively higher blood eosinophilia (≥ 300 cells/ μ L) and/or more than two COPD exacerbations per year. This is

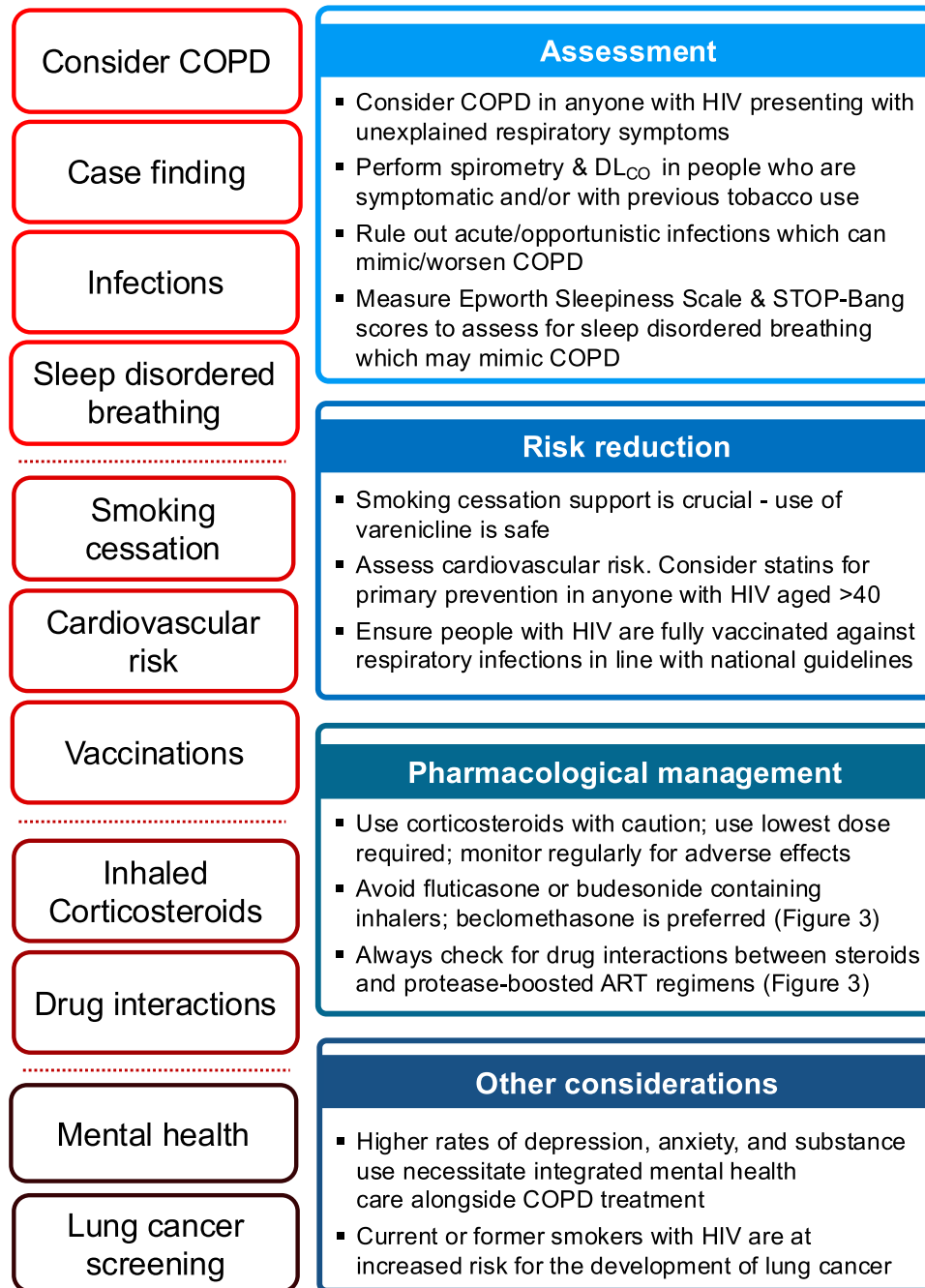


Figure 2 Key considerations in the assessment and management of HIV-associated COPD.

Class		Drug	ATV/rit	ATV/cob	DRV/rit	DRV/cob	LPV/rit	EFV	ETR	NVP	RPV	CAB/RPV	EVG/cob	FTR	LEN
LAMA	Preferred	Acridinium bromide	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
		Glycopyrronium bromide	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
		Tiotropium bromide	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
		Umeclidinium bromide	↑	↑	↑	↑	↑	NII	NII	NII	NII	NII	↑	NII	NII
SAMA	Preferred	Ipratropium bromide	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
LABA	Preferred	Indacaterol	NII	NII	NII	NII	NII	↓	↓	NII	NII	NII	NII	NII	NII
		Olodaterol	↑	↑	↑	↑	↑	NII	NII	NII	NII	NII	↑	NII	NII
	Caution	Formoterol	↑	↑	NII	NII	↑	Long QT	NII	NII	Long QT	Long QT	NII	Long QT	NII
		Salmeterol	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	↑
		Vilanterol	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	NII
SABA	Preferred	Salbutamol	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
		Terbutaline	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
MX	Caution	Aminophylline	↓	NII	↓	NII	↓	NII	NII	NII	NII	NII	NII	NII	NII
		Theophylline	↓	NII	↓	NII	↓	NII	NII	NII	NII	NII	NII	NII	NII
PDE4	Caution	Roflumilast	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	NII
ICS	Preferred	Beclomethasone	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII	NII
	Caution	Ciclesonide	↑	↑	↑	↑	↑	NII	NII	NII	NII	NII	↑	NII	↑
		Budesonide	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	↑
	Avoid	Fluticasone	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	↑
		Mometasone	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	↑
OCS	Caution	Prednisolone	↑	↑	↑	↑	↑	↓	↓	↓	NII	NII	↑	NII	↑

Figure 3 Clinically relevant drug interactions between COPD medications and selected antiretrovirals. For detailed drug interactions, dose adjustments, and alternative options, refer to the Liverpool HIV Drug Interactions Database: <https://www.hiv-druginteractions.org>.

Other ARTs: There are no known clinically relevant drug interactions between any of the COPD medications listed in the table and the following antiretrovirals: ABC, FTC, 3TC, TAF, TDF, ZDV, DOR, MVC, BIC, Oral CAB, DTG & RAL.

Notes: ↑: increased serum concentration of COPD medication; ↓: decreased serum concentration of COPD medication; **Long QT:** drug combination may prolong QT interval; **Green:** Preferred drug combination – No significant interactions; **Yellow:** Potential weak interaction – No additional monitoring and/or dose adjustment required; **Orange:** Likely interaction – Monitor carefully, consider alternatives or dose adjustment; **Red:** Significant interaction – Avoid drug combination. Use alternatives.

Abbreviations: **LAMA**, Long-acting muscarinic antagonists; **LABA**, Long-acting β agonists; **SABA**, Short-acting β agonists; **MX**, Methylxanthines; **PDE4**, Phosphodiesterase 4 inhibitors; **ICS**, Inhaled corticosteroids; **OCS**, Oral corticosteroids; **ABC**, Abacavir; **ATV**, Atazanavir; **BIC**, Bictegravir; **CAB**, Cabotegravir; **Cob**, Cobicistat; **DOR**, Doravirine; **DRV**, Darunavir; **DTG**, Dolutegravir; **EFV**, Efavirenz; **ETR**, Etravirine; **EVG**, Elvitegravir; **FTC**, Emtricitabine; **3TC**, Lamivudine; **FTR**, Fostemsavir; **LEN**, Lenacapavir; **LPV**, Lopinavir; **MVC**, Maraviroc; **NVP**, Nevirapine; **RAL**, Raltegravir; **Rit**, Ritonavir; **RPV**, Rilpivirine; **TAF**, Tenofovir Alafenamide; **TDF**, Tenofovir Disoproxil; **ZDV**, Zidovudine.

particularly important in the context of HIV, where co-infection increases the risk of exacerbations. Long-term inhaled corticosteroid use in COPD is associated with modest but increased risk of fractures,¹⁵⁴ bacterial pneumonia¹⁵⁵ and tuberculosis,¹⁵⁶ conditions for which HIV co-infection also confers a heightened risk.

Another consideration is the interaction between protease inhibitor-boosted ART regimens, such as those containing ritonavir or cobicistat, and inhaled steroid therapies. Ritonavir and cobicistat both inhibit the hepatic CYP3A4 isoenzyme, resulting in increased concentrations of corticosteroids. There are numerous reports of the development of hypercortisolism (Cushing’s syndrome) due to co-administration of ritonavir and inhaled fluorinated corticosteroids.¹⁵⁷ Beclomethasone is considered to have the lowest adverse effect profile of inhaled steroids,¹⁵⁸ and European HIV guidelines recommend against the co-administration of steroid inhalers with some boosted ART regimens.¹⁵⁹ Key clinically relevant drug interactions between COPD medications and ART are outlined in Figure 3.

Smoking Cessation

Smoking cessation is vital for people with HIV given their disproportionately high rates of tobacco use,^{31,36} and the fact smoking cessation reduces the risk of subsequent bacterial pneumonia,⁵⁷ myocardial infarction,¹⁶⁰ lung cancer and strokes¹⁶¹ in people with HIV.

How to promote smoking cessation in this setting is an active area of research. Mobile phone-based approaches and interventions administered at clinic level, such as training staff to administer smoking cessation advice or electronic processes that result in automatic referral to smoking cessation clinics, are generally more effective at achieving cessation than patient-level interventions such as counselling and pharmacotherapy.¹⁶² However, these may only achieve short-term cessation.¹⁶³ A recent Cochrane review assessing the effectiveness of different smoking cessation techniques in

people with HIV found that the nicotinic receptor agonist varenicline likely helps people stop smoking for at least 6 months more effectively than other methods, with no evidence of serious adverse events.¹⁶⁴ This conclusion was only based on two studies. A systematic review found no increase in neuropsychiatric events associated with varenicline use, other than sleep disorders.¹⁶⁵

Even when smoking cessation is achieved in people with HIV, there are high rates of relapse.^{31,166} This may be due to more withdrawal symptoms and co-consumption of alcohol and illicit drugs.¹⁶⁶ Other barriers to cessation include lower rates of employment causing financial instability, significant lifetime psychiatric diagnoses and the fact that peer support networks for people with HIV often include other smokers.^{36,167} Randomised controlled trials specifically comparing smoking cessation interventions in people with HIV are required.

Modulation of Non-Tobacco Related Risk Factors

Globally, 97% of major cities currently fail to meet the WHO's recommended annual concentrations of ambient air pollution levels.¹⁶⁸ This highlights the size and global nature of the challenge required to reduce environmental exposures that contribute to COPD. Change is required at every level from individual protective methods and the modification of cultural practices to population level policy-based approaches. New technologies such as high efficiency portable air cleaners, which when placed in people's houses reduce respiratory symptoms and risks of moderate exacerbations of COPD,¹⁶⁹ must be combined with global initiatives such as the Clean Cooking Alliance that aims to make clean cooking practices accessible in LMICs.¹⁷⁰ Further research is needed to address gaps in our understanding of how to best reduce risk exposures in those with HIV, particularly in LMICs.

Modulation of Chronic Inflammation

HIV increases COPD risk through activation of inflammatory pathways. The exact pathways by which this happens are not fully elucidated and there are no current HIV specific strategies to modulate chronic inflammation to mitigate HIV-related COPD risk. Nevertheless, several trials have looked at interventions that may reduce inflammation in the lung to slow rates of lung function decline.

TGF- β is implicated in the development of emphysema in murine models.¹⁷¹ In the general population, use of angiotensin receptor blockers (ARBs) has been associated with slower emphysema development, potentially due to effects on TGF- β .¹⁷² However, in a randomised controlled trial of people with HIV, the use of the ARB losartan was not associated with decreased levels of lung inflammation compared to placebo.¹⁷³

The use of statins has also been investigated given their pleiotropic effects as potent systemic immune modulators. In a small pilot study of 22 people with HIV, participants were randomised to receive placebo or 24 weeks of daily rosuvastatin therapy, and lung function was recorded over time. People receiving rosuvastatin demonstrated stability in serial FEV₁ measurements and improved DL_{CO}, compared to people who received placebo, but this effect was not statistically significant.¹⁷⁴

Pharmacological therapies aiming to reduce lung inflammation have also been studied in paediatric populations with HIV. In the double blinded Bronchopulmonary Function in Response to Azithromycin Treatment for Chronic Lung Disease in HIV-Infected Children (BREATHE) trial, 347 children and adolescents from Zimbabwe and Malawi were randomised to receive either weekly azithromycin or placebo for 48 weeks.¹⁷⁵ Azithromycin use was associated with reduced rates of exacerbation of respiratory symptoms, but in subsequent analysis at 72 weeks, there was no observed effect of azithromycin on FEV₁ decline.¹⁷⁶

Other Co-Morbidities

Key considerations regarding the investigation, management and risk mitigation of HIV-associated COPD as previously discussed are outlined in [Figure 2](#). Further consideration should be given to the fact that HIV-associated COPD almost always exists in conjunction with other co-morbidities, many of which are also related to tobacco smoking. Cardiovascular risk assessment is vital given HIV confers an increased risk of cardiovascular disease,¹⁷⁷ and COPD in people with HIV has been shown to increase the risk of both type 1 and type 2 myocardial infarction by 2.5–3x, after adjusting for smoking and other typical cardiovascular risk factors.¹⁷⁸ Statins reduce the risk of major adverse

cardiovascular events even in people with HIV with low-to-moderate cardiovascular risk,¹⁷⁹ and are now recommended by the British HIV Association (BHIVA) for all people with HIV over the age of 40 irrespective of lipid profile or cardiovascular risk.¹⁸⁰

Compared to seronegative individuals, the incidence of lung cancer may be twice as high for people with HIV.¹⁸¹ It may also present at a younger age and be less curable.¹⁸² Current or former smokers with HIV should be considered a target population for lung cancer screening.^{183,184} Sleep disordered breathing is also common in people with HIV,¹⁸⁵ and may present with symptoms that mimic COPD.

What are the Key Research Policy Questions for Now and in the Future?

Whilst there have been recent advances in our understanding of HIV-associated COPD as its own etiology, there needs to be wider recognition among the global scientific community of the independent risk HIV poses to the lung. HIV should be considered as an independent risk factor for obstructive lung disease in screening tools. This would improve identification of HIV-associated COPD as well as related co-morbidities such as cardiovascular disease and lung cancer. People with HIV should be included in major clinical trials for the treatment of COPD, including assessment of non-pharmacological measures, exercise and pulmonary rehabilitation. Heightened surveillance of respiratory problems in people with HIV is also needed irrespective of smoking status.

Like other etiologies of COPD, HIV-associated COPD rarely exists in isolation. Further prospective longitudinal cohort studies that control for different risk behaviours and measure symptoms, lung function, imaging, and inflammatory and immune activation biomarkers will help us better understand the natural history of HIV-associated COPD, and the relative contributions made by the different (often interacting) risks. These studies must occur in a variety of different settings and involve populations with different risk exposures including occupational exposures, for example silica dust exposure in miners living with HIV, which may be associated with development of both COPD and TB.¹⁸⁶ This will help to better understand the synergistic effect HIV has with other drivers of COPD. Understanding how these factors together impact on lung function and gas exchange will guide future diagnostic technologies and management strategies, which in turn need to be easily deployable in LMICs where the burden of HIV-associated COPD is often under appreciated.

Ultimately, a better understanding of the molecular mechanisms that allow HIV persistence and subsequent inflammation in the lung, and the contribution of HIV-related factors such as immune reconstitution and timing of ART may further the development of HIV-specific strategies to mitigate COPD risk and improve outcomes for the increasing number of people with HIV-associated COPD.

Disclosure

The authors report no conflicts of interest in this work.

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