Published in final edited form as:

Curr Opin HIV AIDS. 2014 January ; 9(1): 27–33. doi:10.1097/COH.0000000000000018.

“Will expanded ART use reduce the burden of HIV-associated chronic lung disease?”

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Abstract

Purpose of Review—The pulmonary complications of chronic HIV infection have shifted from infectious complications towards non-infectious pulmonary complications, predominantly chronic obstructive pulmonary disease (COPD). While the best-established COPD risk factor is cigarette smoking, emerging data suggest HIV infection also independently increases COPD risk. The purpose of this article is to review these data and the conflicting data regarding the role of antiretroviral therapy (ART) in modifying COPD risk.

Recent Findings—Observational studies favor HIV as an independent risk factor for COPD, particularly when viral load is high. The mechanisms underlying these associations are unclear, but untreated HIV infection is associated with pulmonary inflammatory responses similar to those seen in non-HIV COPD. ART reduces this pulmonary inflammation, but the clinical benefit of such reduction is unknown. Some observational studies suggest that ART users are at lower risk of COPD, while other studies suggest the opposite.

Summary—The effect of ART in causing COPD or reducing COPD risk is unknown, but is currently being tested in a randomized trial. Smoking cessation should remain of high priority.

Keywords

HIV; Pulmonary disease; chronic obstructive; Antiretroviral therapy; highly active

INTRODUCTION

The early days of the HIV/AIDS epidemic were marked by frequent and often deadly infectious pulmonary complications. Antiretroviral therapy (ART) has greatly improved life expectancy and decreased the incidence of *Pneumocystis pneumonia*¹ and bacterial

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Conflicts on interest: I declare that I have no conflicts of interest relevant to this article.

Disclaimer: The views expressed in this article are those of the author and do not necessarily represent the views of any of the author's affiliated governmental, academic, or funding institutions.

pneumonia², but newer data suggest that chronic, non-infectious lung diseases, especially chronic obstructive pulmonary disease (COPD), are emerging problems. This review focuses on HIV-associated COPD in the ART era and reviews the conflicting data regarding the potential role of ART in increasing or decreasing the risk of HIV-associated COPD. The topic of ART's role in COPD pathogenesis or protection is particularly relevant in light of ongoing current debates regarding whether or not to start ART at high CD4+ counts.

TEXT OF REVIEW

COPD is a major cause of global death and disability

In 2010, COPD was the third leading cause of global death³, trailing only ischemic heart disease and stroke; COPD was the fifth leading cause of global years lived with disability⁴.

The underlying pathophysiology of COPD is complex, but ultimately characterized and defined by expiratory airflow limitation, such that patients with COPD have impaired ability to exhale gas from their lungs. Airflow limitation can be quantified by spirometry, which measures the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC). Patients with COPD have a reduced FEV₁/FVC ratio, and the clinical effect of this is most commonly seen during exertion, when exhalation cannot be completed before the next inhalation cycle begins. As this process repeats itself, the lungs become progressively hyperinflated, leading to inefficient mechanics and eventual termination of exertion due to dyspnea⁵. As COPD worsens, this process can severely limit daily function and quality of life.

COPD is typically a problem of increasing age. As part of the normal aging process, FEV₁ declines by approximately 25-30 mL/year⁶, whereas smokers and persons with COPD experience a faster annual rate of FEV₁ decline of 35-45 mL/year^{7, 8}. COPD therefore typically develops insidiously over decades and often presents in later adulthood. HIV-infected patients are aging, with nearly one-third of all persons living with HIV being >50 years old in the U.S. in 2009; this percentage is expected to exceed 50% by the year 2020⁹. Therefore, one might reasonably expect to see COPD prevalence increase in HIV clinics as the mean age in such clinics continues to rise.

COPD is a common condition among HIV-infected individuals

Spirometry studies show that COPD is a common condition in cohorts of HIV-infected patients, with a prevalence between 3%-23% (Table 1)¹⁰⁻¹⁶. Most of these studies were small, single-center, cross-sectional studies, and most found that the COPD diagnosed was generally quite mild and in early, often asymptomatic, stages. One study was prospective and found that the 10% prevalence of COPD at baseline increased to 19% at 4.4 years of follow-up¹⁶. This finding suggests that as patients with HIV infection continue to live longer, COPD will begin to emerge as a major co-morbidity and mild asymptomatic COPD may progress to more severe forms of symptomatic disease.

HIV infection appears to increase COPD risk

The most common cause of COPD is cigarette smoking, and smoking cessation reduces both the rate of FEV₁ decline and the risk of death from COPD^{17, 18}. While the prevalence of cigarette smoking is typically much higher in HIV clinics compared to the general population^{19, 20}, emerging data suggest that HIV infection is another COPD risk factor, independent of smoking. Among ART-era studies examining HIV as a COPD risk factor, two of the largest have been conducted in the Veterans Aging Cohort Study (VACS). In a cross-sectional analysis of VACS data (n=1014 HIV-infected and 713 uninfected), the presence of HIV infection was associated with higher odds (adjusted for age and smoking history) for COPD by both self-report (OR 1.58; 95%CI: 1.14-2.18; p=0.005) and by ICD-9 coding (OR 1.47; 95%CI: 1.01-2.13; p=0.04)²¹. In a prospective analysis using administrative data (n=33,420 HIV-infected and 66,840 uninfected), HIV infection was independently associated with incident COPD in those <50 years old (incidence rate ratio [IRR] 1.25; 95%CI: 1.08-1.43) and was borderline in those ≥50 years old (IRR 1.11; 95%CI: 0.96-1.29)²². A limitation of both of these studies is their reliance on self-reported or administrative data, rather than spirometry, to assign a COPD diagnosis. Administrative data are not very reliable in accurately diagnosing COPD, as compared to the gold standard of spirometry^{23, 24}.

The AIDS Linked to the Intravenous Experience (ALIVE) cohort study from Baltimore (USA) has been measuring spirometry in individuals with and without HIV infection since 2007. In their initial cross-sectional analysis of data through 2009, among 1077 participants (303 with HIV infection), HIV infection overall was not associated with spirometry-confirmed COPD (OR 1.05; 95%CI: 0.74-1.50)²⁵. However, when HIV-infected patients were stratified by viral load within 6 months prior to spirometry, those with viral load ≥200,000 copies/mL had a significantly elevated odds of COPD compared to uninfected patients (OR 3.41; 95%CI: 1.24-9.39), whereas those with viral loads below this threshold had no observed difference in COPD odds compared to uninfected patients (OR 0.85; 95%CI: 0.56-1.29). Prospective, longitudinal spirometry data from the ALIVE cohort have also shed light on lung function decline in HIV infection.

Among 1064 ALIVE participants followed for a median of 2.75 years, the annual rate of FEV₁ decline in HIV-infected patients was -35.8 mL/year compared with -23.6 mL/year among uninfected participants, with a non-significant difference of 12.2 mL/year (95%CI: -28.1 to 3.78 mL/year; p=0.135)¹⁰. Similar to their cross-sectional analysis, when viral load was accounted for, those with viral loads >75,000 copies/mL experienced a faster rate of FEV₁ decline compared to uninfected controls (-99.1 vs. -23.5 mL/year, respectively; p=0.004), a striking difference of 75.6 mL/year (95%CI: 23.8 to 127 mL/year). Among HIV-infected patients with viral load ≤75,000 copies/mL, the rate of FEV₁ decline was not different from uninfected patients (-29.9 vs. -23.5 mL/year, respectively; p=0.44).

Limitations of the ALIVE analyses include their single-center and observational designs. Although many covariates were included in these analyses, high viral load may still be a marker for other unmeasurable factors that might explain the faster rate of FEV₁ decline. The differing viral load thresholds in the cross-sectional and prospective studies (200,000

copies/mL vs. 75,000 copies/mL, respectively) are also of unclear significance. Nevertheless, the spirometry data from ALIVE have provided further observational evidence that HIV infection (particularly with poor HIV control) may increase the risk for COPD.

One other notable study was an analysis of data from the Multicenter AIDS Cohort Study (MACS), a large cohort following men who have sex with men, both with and without HIV infection. This cohort collected self-reported COPD data in the ART era (n=3,480, 49% with HIV infection, median follow-up of 6.5-8.5 years) and there was no association between HIV infection and self-reported COPD. However, the confidence interval was very wide (OR 1.61; 95%CI: 0.36–7.19), largely due to only 10 MACS participants who self-reported COPD (6 HIV-infected and 4 uninfected). This analysis had no spirometry results and the cohort was notably quite young with a mean age of 34 years at cohort entry. COPD is typically not diagnosed until later adulthood, so MACS participants may be too young to rely on self-report of COPD, as opposed to the analysis of self-reported COPD in VACS, where the mean age was over the age of 50 years²¹.

Mechanisms of COPD development in persons living with HIV

The mechanisms by which HIV might increase COPD risk remain quite unclear. Postulated mechanisms include respiratory infections, abnormal inflammatory responses, oxidative stress, and HIV treatment with ART.

Prospective cohort data from the pre-ART era demonstrated permanent declines in the FEV₁/FVC ratio following both *Pneumocystis* and bacterial pneumonia²⁶. In the ART era, several studies have analyzed the effect of bacterial pneumonia on COPD risk, with some studies suggesting an association between bacterial pneumonia and COPD^{11, 25}, while others have found no such association^{12, 21}. A better understanding of the contribution of pneumonia to COPD in HIV-infected patients will require prospective spirometry studies with longer follow-up times. Other hypothesized infectious etiologies of HIV-associated COPD include *Pneumocystis jiroveci* colonization and/or an altered respiratory microbiome.

Pneumocystis jiroveci colonization in the lungs can be shown in 46%-69% of HIV-infected patients^{27, 28}. Interestingly, patients with non-HIV COPD often have *Pneumocystis jiroveci* colonization, and those with more severe COPD have a higher frequency of colonization²⁹. Due to the cross-sectional nature of these studies, directional causality cannot be assigned, but *Pneumocystis jiroveci* can induce matrix metalloproteinase activity, thus potentially causing lung tissue destruction and contributing to COPD pathogenesis in HIV infection. Prospective studies investigating the respiratory microbiome in HIV infection have begun and more results are anticipated in the next several years³⁰.

The Global Initiative for Chronic Obstructive Lung Disease includes in its definition of COPD the statement that COPD is “associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.”³¹ A common inflammatory pattern seen in the lungs of patients with COPD involves an abnormal accumulation of CD8+ T-cells, which then interact with macrophages and neutrophils to release chemokines, cytokines, and growth factors in the lungs³². Patients with HIV infection also display a similar abnormal accumulation of CD8+ T-cells in lung lavage

fluid³³ and this lymphocytic alveolitis correlates to the degree of viral RNA one can demonstrate in the lavage fluid³⁴. These studies did not include spirometry, so the correlation between HIV-associated lymphocytic alveolitis and COPD remains unclear.

HIV-infected patients, even those effectively treated with ART, also commonly display abnormal systemic inflammatory responses such as elevated blood C-reactive protein and interleukin-6 levels³⁵. Such elevations in HIV-infected patients predict poor clinical outcomes, including bacterial pneumonia³⁶ and death³⁷. Similar elevations have been observed in non-HIV COPD cohorts³⁸ and such elevations similarly predict poor non-HIV COPD outcomes such as exacerbations of disease³⁹ (which are often triggered by bacterial infections) and death⁴⁰. Mechanisms linking heightened systemic inflammation in HIV infection and in non-HIV COPD will require further research to understand.

Oxidative stress, like systemic inflammation, is another common link between HIV infection and non-HIV COPD. Studies on lung lining fluid and blood from patients with HIV infection have shown low levels of glutathione, the most abundant intracellular free radical scavenger^{41, 42}. Similarly low glutathione levels have been seen in patients with non-HIV COPD⁴³. A transgenic mouse model of HIV has shown that HIV proteins alter lung oxidative stress and cause lung epithelial dysfunction⁴⁴. The relevance of these findings to HIV-associated COPD in humans requires further study.

Finally, another postulated mechanism of COPD development in HIV infection relates to use of ART.

Studies of ART effects on HIV-associated COPD

Since patients with HIV infection display an abnormal CD8+ T-cell alveolitis in the lungs and CD8+ T-cells are felt to play an important role in COPD pathogenesis, this mechanistic pathway might explain the observed heightened risk for COPD in patients with HIV infection. Furthermore, interventions to reduce or eliminate the CD8+ T-cell accumulation might then reduce the risk of HIV-associated COPD.

In an important prospective, observational study of 40 HIV-infected, ART-naïve patients, 24 weeks of ART resulted in a significant reduction in viral load and normalization of CD8+ T-cell counts in lung lavage fluid⁴⁵. This study did not include spirometry (and would likely have been underpowered for spirometry outcomes), so the clinical impact of this reduction of CD8+ T-cells in the lung remains unknown⁴⁶.

The prospective observational study of FEV₁ in ALIVE suggests that reduction in viral load may reduce COPD risk¹⁰. Viral load is typically most impacted by ART, but in this analysis, ART use was not associated with differences in FEV₁ decline. Potential explanations for this discrepancy include reliance on self-report for ART use and changes in ART use over time, especially in this urban cohort of patients with a history of intravenous drug use and varying adherence to ART.

The prospective VACS analysis found ART use was associated with a lower incidence of COPD in unadjusted analysis (incidence rate ratio [IRR] 0.90; 95%CI: 0.82-0.99), but when smoking was adjusted for, the association was no longer significant (IRR 0.93; 95%CI:

0.73-1.18)²². Limitations of this analysis include its lack of spirometry and its use of administrative data to assign smoking status.

While the ALIVE and VACS data seem to favor a reduction in COPD risk with use of ART, other studies suggest that ART has either no effect on COPD risk or may even increase COPD risk. In one single-center cross-sectional study (n=111), ART use was not associated with COPD, although the 95% confidence interval was very wide (OR 0.59; 95%CI: 0.06–5.93), making any conclusions difficult¹⁴. In another single-center, cross-sectional study (n=215) a lower FEV₁/FVC ratio was associated with increasing age, more pack-years of smoking, a history of bacterial pneumonia, and use of ART¹¹. Similarly, another single-center, cross-sectional study (n= 167) showed that COPD was associated with more pack-years of smoking (OR 1.03 per pack-year; 95%CI: 1.01-1.05), a history of intravenous drug use (OR 2.87; 95%CI: 1.15-7.09), and ART use (OR 6.22; 95% CI: 1.19-32.43)¹². While ART use may reflect longer duration of HIV and/or more severe HIV such as lower nadir CD4+ T-cell count or previous pneumonia, the results presented were adjusted for these variables and still suggest ART increases COPD risk.

Of important note, the numbers of patients not on ART in all of the above observational studies is quite small (Table 2). Excluding the VACS analysis, which relied on administrative data rather than spirometry or clinical study visits, the total number of patients not on ART in the above cross-sectional studies was 20¹¹, 24¹⁴, 33¹², and 134²⁵, for a total of 211 patients. The observational design of these studies also makes them susceptible to unknown confounders that might relate to both lack of ART use and increased COPD risk. A randomized trial is the best way to truly determine the effect of ART on COPD risk.

The START Trial Pulmonary Substudy

The Strategic Timing of Antiretroviral Treatment (START) Trial is testing the hypothesis that among HIV-infected patients naïve to ART with CD4+ counts >500cells/mL, immediate initiation of ART will improve clinical outcomes, compared to deferral of ART until CD4+ counts are <350 cells/mL (NCT00867048)⁴⁷. A nested pulmonary substudy within START has enrolled over 1000 participants (from 80 sites in 20 countries) who will perform annual spirometry during their trial participation (NCT01797367). The primary outcome of the substudy is a comparison of annual rate of FEV₁ decline over 3 to 5 years between the immediate and deferred ART arms. Results are expected in early 2017.

Conclusions

COPD is a major global public health problem that is increasingly common among persons living with chronic HIV infection. Although the high rates of smoking observed in many HIV clinics indicate a need for improved smoking cessation strategies in such clinics, data also suggest that HIV infection itself independently contributes to COPD pathogenesis. The mechanisms to explain this relationship remain unclear. Some observational data suggest ART reduces both lung inflammation and COPD risk, while other data suggest that ART may actually propagate and worsen COPD risk. The nested randomized substudy within START should resolve this question for HIV-infected patients with high CD4+ counts.

Additionally, most existing data come from cohort studies in Western countries, so more research on HIV-associated lung disease is needed from developing countries, where ART use is increasing, smoking rates are often increasing, and concurrent pulmonary infections such as tuberculosis are often more prevalent.

Acknowledgments

I thank Dennis Niewoehner and Chris Wendt for feedback on earlier drafts of this manuscript. I thank the leadership of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) for its continued support of lung research in HIV.

Study supported by a grant from the National Institutes of Health, National Heart, Lung and Blood Institute (R01 HL096453) and Division of AIDS, National Institute of Allergy and Infectious Diseases (U01 AI068641)

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KEY POINTS

- COPD is a major global health problem, is a common condition among persons living with chronic HIV infection (affecting between 3% to 23%), and HIV appears to independently increase the risk for COPD.
- High viral load is associated with a fast rate of lung function decline.
- ART reduces HIV viral load and CD8+ T-cell accumulation in lung lavage fluid, but observational studies of ART effects on lung function and COPD diagnosis have produced conflicting results, with some suggesting ART increases COPD risk, while others suggest ART reduces COPD risk.
- An ongoing randomized controlled trial has completed enrollment in a pulmonary substudy and aims to resolve this conflict.

Table 1
Prevalence estimates of chronic obstructive pulmonary disease (COPD) in HIV-infected populations in the current antiretroviral era, listed in order of descending sample size

Studies included are those that used spirometry to define COPD (not self-report or administrative data). Spirometry-based definitions of COPD vary, with most guidelines suggesting use of post-bronchodilator spirometry (e.g. at least 15 minutes after inhalation of 360-400 mcg of albuterol/salbutamol), although practical concerns such as time, training, and contraindications to bronchodilators can make such studies more challenging. A FEV₁/FVC ratio of <0.7 is a commonly used definition, but may underdiagnose COPD in younger patients and overdiagnose COPD in older patients. As such, some have advocated for use of a lower limit of normal (LLN) definition, which adjusts for variables such as age and gender, then defines COPD as those with a FEV₁/FVC ratio <5th percentile adjusted for these clinical variables. Specific definitions used in each study are detailed in this table.

Author	n	Study years	Setting	% of current / former cigarette smokers	COPD definition and prevalence
Drummond ¹⁰	316	2007 - 2010	USA	85% / 10%	Pre-bronchodilator FEV ₁ /FVC <0.7 present in 16% at baseline
George ¹¹	234	2003 - 2004	USA	37% / 23%	Pre-bronchodilator FEV ₁ /FVC<0.7 present in 6.8% (<LLN in 8.6%)
Gingo ¹²	167	2007 - 2009	USA	53% / 23%	Post-bronchodilator FEV ₁ /FVC <0.7 present in 21% (<LLN in 19%)
Cui ¹³	119	n.r.	Canada	44% / 19%	Post-bronchodilator FEV ₁ /FVC <0.7 present in 3%
Madeddu ¹⁴	111	2006 - 2007	Italy	57% / n.r.	Post-bronchodilator FEV ₁ /FVC<0.7 present in 23%
Hirani ¹⁵	98	2008 - 2009	USA	21% / 34%	FEV ₁ /FVC (bronchodilator use not reported)<0.70 and FEV ₁ <80% of predicted present in 16%
Kristoffersen ¹⁶	63	2000 - 2001	Denmark	48% / n.r.	Post-bronchodilator FEV ₁ /FVC <0.7 present in 10% at baseline, 19% at 4.4 years of follow-up

FEV₁: forced expiratory volume in one second

FVC : forced vital capacity

LLN: lower limit of normal

n.r.: not reported

Table 2
Studies examining effects of antiretroviral therapy on risk of chronic obstructive pulmonary disease among patients with HIV infection

All studies adjusted for smoking variables.

Author	Setting	On ART (n)	No ART (n)	Design	Conclusions
George ¹¹	USA, single center (Los Angeles, CA)	195	20	Cross-sectional study	ART use associated with lower FEV ₁ /FVC ratio in linear regression analysis (β coefficient -3.2; p=0.04).
Gingo ¹²	USA, single center (Pittsburgh, PA)	134	33	Cross-sectional study	ART use with higher odds COPD (OR 6.22; 95% CI: 1.19–32.43)
Crothers ²²	USA, national healthcare system database	~21,700	~11,700	Prospective, administrative data analysis	ART use with lower incident COPD without smoking adjustment (incidence rate ratio [IRR] 0.90; 95% CI: 0.82–0.99). Smoking adjustment resulted in wider CI (IRR 0.93; 95% CI: 0.73–1.18)
Drummond ²⁵	USA, single center (Baltimore, MD)	169	134	Cross-sectional study	ART use not associated with COPD (OR 0.60; 95%CI: 0.29 – 1.22). However, viral load >200,000 copies/mL associated with COPD (OR 3.41; 95%CI: 1.24–9.39)
Drummond ¹⁰	USA, single center (Baltimore, MD)	172	144	Prospective, observational cohort	ART use not associated with differences in FEV ₁ rate of decline. However, viral load >75,000 copies/mL associated with faster rate of FEV ₁ decline compared to viral load <75,000 copies/mL (69 mL/year faster decline; 95%CI: 15.3–123.0 mL/year; p=0.012).
Madeddu ¹⁴	Italy, single center (Sassari, IT)	87	24	Cross-sectional study	ART not associated with COPD, but CI very wide (OR 0.59; 95%CI: 0.06–5.93)

ART: antiretroviral therapy

CI: confidence interval

COPD: chronic obstructive pulmonary disease

FEV₁: forced expiratory volume in one second

FVC : forced vital capacity

OR: odds ratio