

HIV and Lung Disease: What Every Clinician Should Know



Volume 3 Issue 1

In this Issue...

While people living with HIV/AIDS (PLWH) are living longer because antiretroviral medications are powerful and well-tolerated, the causes of morbidity and mortality in this population are increasingly related to noninfectious lung diseases, including lung cancer and chronic obstructive pulmonary disease. Treatment of lung disease in PLWH can be complex because of medication interactions, structurally abnormal lungs from history of infections, and reluctance to extrapolate lung-related treatment algorithms developed for people without HIV infection.

In this issue, Dr. Alysse Wurcel from Tufts Medical Center in Boston reviews recent publications on issues specific to the epidemiology, clinical presentation, pathophysiology, and treatment of lung disease in PLWH, including:

- the effects of alcohol use
- smoking cessation
- the effectiveness of pulmonary function tests
- potential interactions between HIV protease inhibitors and intranasal and inhaled corticosteroids
- the benefits of CT scanning for lung cancer screening

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Length of Activity

1.0 hour Physicians

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LEARNING OBJECTIVES

- Identify differences in prevalence, clinical presentations, and risk factors for pulmonary comorbidities in PLWH vs HIV-uninfected people.
- Describe the impact of smoking cessation on life expectancy in PLWH and the evidence for CT scans for lung cancer screening in PLWH.
- Discuss the clinical presentations of interactions between inhaled/intranasal corticosteroids and HIV medications and strategies to minimize medication interactions when treating PLWH for lung disease.

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Commentary & Reviews



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Guest Faculty Disclosure

Dr. Wurcel has disclosed that she is a site principal investigator for a ViiV Healthcare study.

Unlabeled/Unapproved uses

Dr. Wurcel has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

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COMMENTARY

The assessment of lung diseases in people living with HIV/AIDS (PLWH) has evolved dramatically over the past 30 years. Scanning the literature on lung disease in HIV from the 1980s reveals a plethora of manuscripts on bacterial, viral, mycobacterial, and fungal pathogens leading to hospitalization and death. Fortunately, with the advent and continued improvements of antiretroviral treatments targeting HIV, the incidence of opportunistic infections in PLWH living in resource-rich countries like the United States has dramatically decreased. Non-AIDS defining illnesses, such as cardiovascular diseases, liver diseases, malignancy, and chronic obstructive pulmonary disease (COPD) are increasingly recognized as causes of morbidity and mortality in PLWH.¹

PLWH develop emphysema at younger ages and with lower tobacco exposures.² The pathophysiology of lung disease in HIV is complex and likely related to several factors including alterations in the lung microbiome, decreased CD4+ cell function, and increased oxidative stress, as well as comorbid tobacco and substance abuse.³ The studies by Depp and Triplette (reviewed in this issue) highlight the complexity in interpreting radiography, exercise function tests, and pulmonary function tests in PLWH and COPD. The increased association of alcohol abuse with acute COPD exacerbations in smokers with HIV, but not in uninfected smokers, highlights interesting synergies between substance use and immunology.

As clinicians caring for PLWH, we can greatly impact the lives of our patients through discussions of smoking cessation, minimization of drug interactions, and appropriate cancer screening. Over 40% of PLWH in the US smoke cigarettes and another 20% are former smokers.⁴ The proportion of smokers who want to quit is similar among PLWH and those without HIV (about two-thirds), but PLWH have been less likely to quit smoking than the general US population.⁵ Surveys have shown that HIV providers believe that smoking cessation is important but report time pressures to address other issues. Providers also report limited training or clinical education on tobacco treatment and counseling methods as barriers to discussing smoking cessation with PLWH.⁶ The article by Reddy et al (reviewed in this issue) highlights the potential impact of smoking cessation for PLWH and underscores the importance of inquiring about and addressing smoking cessation at every visit. Hopefully there will be more interventional research about targeted smoking cessation counseling techniques and medications to help PLWH stop smoking.

While newer classes of agents are increasingly being used, many patients remain on protease inhibitors. Drug interactions between protease inhibitors and corticosteroids remain relevant and are important to recognize because of the potentially devastating and irreversible physiologic consequences of adrenal suppression. The most recent review of interactions between protease inhibitors and inhaled and/or intranasal corticosteroids was in 2013 by Saberi and colleagues (reviewed in this issue). These investigators performed a comprehensive review of the English-language literature for case reports, which reported that patients on coadministered protease inhibitors and inhaled or intranasal corticosteroids developed symptoms even several years after being on the medications. The review of



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preferred corticosteroids when managing lung disease in PLWH was useful, as well as methods to distinguish lipodystrophy from adrenal insufficiency. The authors comment on, but do not review, the adverse effects of intraarticular injections that can occur in PLWH on boosted-protease inhibitors, as reported in one case report.⁷ While this article recommends NNRTIs and raltegravir to manage HIV in people with comorbid lung disease, these drugs are becoming outdated. The article was published before the wide dissemination of powerful daily medications that use cobicistat, which is also a CYP3A4 inducer but with lower potency than ritonavir.⁸ There is a case report of interactions between cobicistat and fluticasone nasal spray leading to adrenal suppression.⁹ There is still a data-free zone as to whether low dose corticosteroids can be used with integrase inhibitors.

The article by Makinson et al (reviewed in this issue) provides reassurances that even in a cohort of PLWH who were at high risk for having infectious lung diseases leading to increased number of procedures and potential complications, CT scans were useful in detecting lung cancers. Based largely on a multicenter trial,¹⁰ the US Preventative Services Task Force (USPSTF) recommends annual screening for lung cancer with low-dose CT scan in adults aged 55 to 80 who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 years. Knowing that PLWH are at increased risk for multiple malignancies and already trying to juggle the burden of cancer screening with colonoscopies, mammograms, and liver ultrasounds, the task of screening for lung cancer in PLWH can seem daunting. In my practice, I have found that when I recommend CT scan for lung cancer screening, my patients are shocked and uncomfortable with even the possibility of lung cancer. Talking with patients about CT scans to screen for cancer may motivate patients to think more seriously about smoking cessation. Fortunately, most insurance and health care systems have evolved to make this type of screening easy to facilitate.

In summary, we are fortunate to be treating PLWH in this day and age with an incredible arsenal of HIV medications. The challenge now is to prevent, identify, and manage chronic diseases, with smoking and chronic lung diseases rising to the top of the priority list.

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Alcohol Use and Acute COPD Exacerbation

Depp TB, McGinnis KA, Kraemer K, et al. Risk factors associated with acute exacerbation of chronic obstructive pulmonary disease in HIV-infected and uninfected patients. *AIDS*. 2016 Jan 28;30(3):455-63.



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While chronic obstructive pulmonary disease (COPD) is prevalent in people living with HIV (PLWH),¹ the impact of HIV on the development of acute COPD exacerbations is not well studied. The authors of this manuscript sought to compare risks for acute exacerbations of COPD between HIV-infected and uninfected patients and examine the relative impact of modifiable and nonmodifiable risks using the Veterans Aging Cohort Study. The study queried administrative, clinical, and pharmacy data to create a cohort of 43,618 HIV-infected veterans who received care between 1996 and 2010; and 86,492 uninfected veterans matched for age, race, sex, and US region. Each HIV-positive participant was matched with two HIV-negative participants. The primary outcome was time to acute COPD exacerbation within two years of index date, defined as the first date that the HIV ICD-9 (International Classification of Disease, 9th Edition) code was used within the Veteran's Affairs (VA). Acute exacerbations were identified by ICD-9 code, as well as prescriptions dispensed (steroids or antibiotics within five days of the ICD-9 code). Risks and covariates in the analysis included smoking status, alcohol, and drug-related diagnoses before and after the index date, race, CD4, and HIV viral load. Incidence rates for acute exacerbations were compared between HIV- infected and uninfected patients, and Poisson regression models were used to determine unadjusted incidence rate ratios (IRRs).

Four percent of HIV-uninfected and 4.4% of HIV-infected subjects had COPD. Smoking prevalence, the strongest risk factor for acute exacerbation of COPD, was similar between groups. There was a higher incidence of acute COPD exacerbations in HIV-infected than in uninfected subjects (18.8 per 1000 person years and 13.3 per 1000 person years, respectively). HIV-infected patients had increased acute exacerbation risk (IRR = 1.55) compared to HIV-uninfected patients when adjusting for multiple confounders, including smoking- and alcohol-related diagnoses. The group at highest risk was HIV-infected patients with CD4 count < 200 (IRR = 2.30, compared to uninfected patients). White race and male gender were both associated with increased risk of acute exacerbations. Interestingly, illicit drug use disorders were not associated with acute COPD exacerbations and were not included in the multivariable modeling. Within the HIV group, decreasing CD4 count and HIV RNA > 500 copies/ml were associated with increased risk of acute exacerbation, while antiretroviral prescription decreased the risk by about 25%. Alcohol use associated with a greater increased risk of acute COPD exacerbation in PLWH than in people without HIV.

Sensitivity analyses that necessitated prescription of antibiotics and steroids in addition to the presence of ICD-9 code for definition of acute COPD exacerbation showed even higher incidence rate ratios for HIV-infected than in HIV-uninfected subjects.

The authors conclude that the severity of immune suppression increases risk of COPD in HIV, and this risk is further increased by the modifiable risk factors of smoking and unhealthy alcohol use. In comparison to previous work, the authors highlight the association of alcohol use with acute COPD exacerbations and hypothesize that alcohol use may synergize with HIV, leading to increased lung oxidative stress and inhibition of immune response. The authors note the limitations of using a veteran-based cohort, noting the underrepresentation of women, who may have different risk profiles for acute COPD exacerbation. They suggest increased focus on potentially modifiable factors such as smoking and unhealthy alcohol use to decrease acute COPD exacerbations in PLWH.

References:

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Cigarette Cessation and Life Expectancy of PLWH

Reddy KP, Parker RA, Losina E, et al. Impact of Cigarette smoking and smoking cessation on life expectancy among people with HIV: A US-based modeling study. *J Infect Dis*. 2016 Dec 1;214(11):1672-1681.



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Cigarette smoking is the leading cause of preventable death in the US. Before the discovery and wide dissemination of antiretroviral treatment for HIV, cigarette smoking was not an important driver of mortality in people living with HIV (PLWH). Benefiting from reconstituted immune systems, PLWH are facing morbidity and mortality from non-AIDS diseases like cardiovascular diseases, malignancies, and COPD. More than one-half of PLWH either previously or currently smoke cigarettes, a prevalence much higher than in the general US population.¹ Previous research has found that prevalence of smoking in PLWH spans evenly through age groups, gender, and race.¹

The impact of smoking cessation on life expectancy of PLWH was unknown, prompting Dr. Reddy and colleagues to use a mathematical model to approach this question. Using a validated Monte Carlo microsimulation of HIV disease and treatment, virtual patients passed through a monthly framework with potential events including AIDS and non-AIDS morbidity. Smoking was stratified into groups/categories: current, former, never. Factors impacting the risk of events included age, CD4 count, adherence to HIV medications, viral loads, and smoking. The model specifications were based on previously published and validated studies, which are described extensively in the article and supplementary appendices. The authors compared life lost from smoking with life lost from HIV. To derive the number of years of life that could be gained from smoking cessation at the population level, they compared life expectancies of former, current, and never smokers.

The authors found that among PLWH in the US who adhere to ART, the life expectancy loss from smoking is almost double that from HIV. When accounting for typical rates of nonadherence to HIV treatment and loss to follow-up, loss of life from smoking was similar to that from HIV. Factors associated with greater benefits from smoking cessation included younger age, higher CD4 count, and ART adherence. Smoking cessation five or 10 years after entering HIV care still resulted in substantial life expectancy gains. The authors compared the impact of smoking cessation to other treatments using the measurement of per-person survival gain. Smoking cessation in a 40-year-old HIV-positive man led to 68 months gain in per-person survival, compared to primary prevention with statins (2 months), clopidogrel for secondary prevention of cardiovascular events (1 month), and hepatitis C treatment (34 months).

A major limitation of this article was authors' inability to examine the impact of amount of tobacco on the outcome. Additionally, the modeling was done assuming that non-AIDS related mortality like suicides and trauma-related deaths were equal in PLWH and HIV-noninfected people; however, given the high prevalence of substance use disorders and mental illness in PLWH, this assumption may not be true. The authors did an analysis incorporating higher non-AIDS related mortality in PLWH, and the results of years lost and gained from smoking and smoking cessation remained the same.

The key take-home point from this article is that smoking cessation can greatly improve life expectancy of PLWH. Dr. Reddy and colleagues point out that PLWH in the US have been less likely to quit smoking than HIV-uninfected people, and there are few studies examining smoking cessation interventions in PLWH. Providers may not discuss smoking for several reasons, such as competing screening and harm-reduction priorities; however, the findings show that smoking cessation will have the biggest impact on life expectancy. The authors suggest that providers caring for PLWH should address smoking during every patient encounter.

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HIV and Emphysema: Airflow Obstruction Measurements

Triplette M, Attia E, Akgün K, Campo M, et al. The differential impact of emphysema on respiratory symptoms and 6-minute walk distance in HIV infection. *J Acquir Immune Defic Syndr*. 2017 Jan 1;74(1):e23-e29.



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Emphysema is more prevalent and develops earlier in people living with HIV (PLWH) than in HIV-uninfected populations, even when controlling for differences in smoking behavior.¹ Respiratory symptoms are more common in PLWH with emphysema, independent of impairment in pulmonary function when compared with HIV-uninfected populations.² The goal of this 2017 paper was to investigate the impact of emphysema on pulmonary symptoms and functional limitations and compare this impact between groups of patients with and without HIV.

The authors did a cross-sectional analysis of 170 PLWH and 153 HIV-uninfected people enrolled in a substudy of the Veterans Aging Cohort Study. The study enrolled all types of participants, including people without known COPD or emphysema. All participants had a baseline CT scan, and emphysema was characterized by radiologists blinded to the participants' HIV status. Emphysema severity was characterized on a scale of 0 (no emphysema) to 5 (> 75% emphysema), and for the analysis the variable was dichotomized as either greater or less than 10% emphysema. Validated questionnaires for assessing shortness of breath were used. Airflow obstruction was measured by diffusion capacity (DLCO) on all participants, as well as the distance walked in six minutes (6MWD), a standardized measurement of functional capacity. In the analysis, the main stratifications were by percentage of emphysema (greater or less than 10%) and HIV status. A regression model was created to include demographics and risk factors.

HIV-positive and HIV-negative subjects had similar racial, age, ethnic, and comorbid disease proportions. HIV-positive subjects were more likely to be men, have a history of pulmonary infection, and have a history of injection drug use. Despite similar rates of airflow obstruction, radiographic evidence of emphysema was twice as common in HIV-positive subjects compared to HIV-negative subjects. In HIV-uninfected subjects, there was no association between emphysema, pulmonary symptoms, and 6MWD. In comparison, in the HIV-positive groups, subjects with emphysema had four times greater odds of chronic cough and walked an average of 60 meters less than HIV-positive people without emphysema. Limiting the analysis only to people without airflow obstruction ($FEV_1/FVC > 0.75$) did not change the dramatic impact of emphysema on chronic cough or limited functional capacity.

This study has two important take-home messages. First, radiographic evidence of emphysema is more strongly associated with respiratory symptoms and exercise limitation in PLWH than in HIV-uninfected people. Second, limited functional capacity and symptoms related to emphysema were present in people with HIV, even in the absence of airflow obstruction. The authors speculated that emphysema in HIV-positive people may have pulmonary and extrapulmonary impact through poorly understood chronic inflammatory pathways. The authors suggest that airflow obstruction tests be interpreted with caution because spirometry may not adequately capture pulmonary function.

References:

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Interactions Between Corticosteroids and Protease Inhibitors

Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV Med*. 2013 Oct;14(9):519-529.



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Ritonavir is a potent inhibitor of the hepatic cytochrome P450 (CYP450) 3A4 isozyme. Ritonavir used to be prescribed for its antiviral properties, but in resource-rich settings its only use currently is in low doses (usually 100 mg) as a “booster” to enhance the effect of protease inhibitors, allowing for reduction in pill burden, dosing frequency, and food restrictions. With the shift in management from acute infectious disorders to chronic diseases like asthma and chronic obstructive pulmonary disease, the authors were interested in reviewing pharmacokinetics of protease inhibitors (PIs) and inhaled corticosteroids. They reviewed published case reports on patients who had consequences of interactions between ritonavir and other PIs and inhaled corticosteroids.

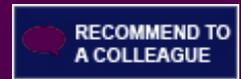
They found 51 case reports in English between 1999 and 2012 about the adverse effects of inhaled (n = 45), intranasal (n = 2), and inhaled and intranasal (n = 4) corticosteroids. Some of the cases used ritonavir as an antiviral medication rather than as a booster. The most commonly used inhaled and/or intranasal corticosteroid was fluticasone (91%) and less frequently budesonide, mometasone, and beclomethasone. The mean daily dose of fluticasone in adults was 400 µg/day (range 200 µg/day-800 µg/day.)

Symptoms associated with adrenal insufficiency typically developed a range of 10 days to 5 years (mean 7.1 months) following coadministration of the corticosteroid and PI. Symptoms were typical of Cushing syndrome, including facial swelling, facial hirsutism, central obesity and weight gain, dorsocervical fat pad, striae, and easy bruising. Once recognized, patients were tapered off the corticosteroids or changed to a different non-PI containing regimen. Five percent of people did not have normalization of the cortisol or adrenocorticotrophic hormone (ACTH) levels.

The authors discuss the importance of distinguishing between lipodystrophy and iatrogenic Cushing because of overlapping symptoms and recommend diagnosis of adrenal insufficiency through early morning plasma cortisol, followed by 30-minute ACTH or cosyntropin simulation test. They point out that the interactions are not limited to intranasal or inhaled corticosteroids but can also occur with topical and injectable steroids, though this was not their focus.

The authors suggest that if a patient with HIV needs corticosteroids, it may be preferable to switch to an antiviral agent that does not inhibit the CYP3A4, use a less potent corticosteroid (inhaled beclomethasone or flunisolide rather than fluticasone), or consider a noncorticosteroid alternative like a leukotriene receptor antagonist (eg, montelukast). They also note the paucity of research on this area. They provide a useful table with the pharmacokinetic properties of inhaled/intranasal corticosteroids that may be useful to HIV providers who are deciding on safe ways to treat chronic lung diseases. [See table 1](#)

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Chest CT Scans for Lung Cancer Screening

Makinson A, Eymard-Duvernay S, Raffi F, et al; ANRS EP48 HIV CHEST study Team. Feasibility and efficacy of early lung cancer diagnosis with chest computed tomography in HIV-infected smokers. *AIDS*. 2016 Feb 20;30(4):573-82.



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In light of updated guidelines for lung cancer screening with CT scans for smokers based on results from the National Lung Screening Trial, the authors of this study sought to understand the utility of CT scans in people living with HIV (PLWH).¹ PLWH have a high prevalence of other pulmonary comorbidities including infections, COPD, and emphysema, so many clinicians were concerned that screening tests may lead to false positive nodules and inappropriate invasive diagnostic procedures. In this study, a prospective cohort of PLWH was recruited for lung cancer screening. Participants were considered high risk for lung cancer as defined by at least 20-pack years smoking (including people who had stopped smoking), at least 40 years old, and current CD4 count > 100. Notably, the age and pack-year criteria were more liberal than those in the large National Lung Screening Trial in the US general population (30+ pack-years, age 55+). To ensure inclusion of PLWH with history of severe immunocompromise, all subjects had to have CD4 nadir of less than 350 cells/ μ l. All subjects had a single CT scan and a follow-up visit two years after the CT scan. One nonblinded radiologist from each participating center read all of the CT scans, and if the CT scan was positive an established algorithm (Early Lung Cancer Action Program) was followed to determine timing and need for follow up CT scans. The definitions of “positive” CT scans are outlined extensively in the paper and include at least one solid, noncalcified nodule, > 5 mm, one nonsolid nodule > 8 mm, solid endobronchial nodule, or significant adenopathy. The primary outcome of interest was number of histologically proven lung cancers found by CT scan, and the secondary outcome was the stage of diagnosis of the lung cancers that were found.

Between February 2011 and June 2012, 442 PLWH had a CT scan as part of this study. The mean age was 50 years, 98% were on HIV medications, and 90% had undetectable viral loads. Median smoking history was 30 pack-years and 368 (91%) were active smokers at study entry. Ninety-four patients (21%) had at least one positive image on baseline CT scan. From this group, nine people had diagnoses of lung cancer—eight by biopsy and one by clinical suspicion when biopsy was contraindicated. Only one lung cancer was found in the group of subjects that did not have original CT scan findings of concern for lung cancer. The incidence of lung cancer was 2.03%, which was high compared to other studies in smokers. Eight of the 10 cancers occurred in people younger than 55 years who, based on age, would not qualify for screening according to current US guidelines. Importantly, nearly all of the detected lung cancers were early stage and potentially curable. The authors comment that that high incidence may be related to decreased tumor suppression in the setting of HIV-related inflammation and repeated clinical or subclinical infections.

Addressing the concern for false positives, in the 94 patients with abnormal CT scans, 54 had a second CT scan, 5% a third, 4% a fourth or fifth, and 0.5% had a sixth. Eighteen diagnostic procedures were performed in 15 patients. Apart from the eight proven lung cancers, there was one lymphoma, one benign granular cell tumor, and one atypical mycobacterial infection. Four invasive procedures revealed no pathology. None of the diagnostic procedures had any serious adverse events. Interestingly, and unrelated to the primary or secondary outcome, at the two-year follow-up visit, 20% of the smokers had stopped smoking.

The authors acknowledge limitations including inability to assess for marijuana use and the impact of impact of concerning CT images on anxiety. They also comment that the relationship between increased lung cancer risk in the setting of frequent radiation, though low dose, could not be assessed. They conclude that their study is a powerful addition to the literature in support of lung cancer screening for PLWH at high risk, with a limited number of false positive results or adverse events.

References:

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KEY TAKEAWAYS

- Smoking cessation in PLWH dramatically increases life expectancy and should be prioritized.
- Radiographic, clinical presentation, and lung function tests may differ in PLWH and HIV-uninfected people.
- It is possible to avoid adverse events like the development of adrenal insufficiency through minimizing drug interactions and careful comanagement of HIV and COPD.

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