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HIV Infection is Associated with Increased Risk for Acute Exacerbation of COPD

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Abstract

Background—Poorly controlled HIV infection is associated with increased risk for chronic obstructive lung disease (COPD). Acute exacerbations of COPD (AECOPD) are major contributors to morbidity and mortality. Little is known about the association between HIV infection and AECOPD.

Methods—We identified 167 individuals with spirometry-confirmed COPD from a longitudinal study of current or former injection drug users at-risk or with HIV infection. AECOPD, defined as self-report of worsening breathing requiring treatment with antibiotics or steroids, was assessed at 6-month study visits. Multivariable logistic regression identified factors associated with AECOPD.

Results—Of 167 participants, the mean age was 52 years; 89% were black, 30% female and 32% HIV-infected (median CD4 count: 312 cells/mL, 46% with detectable HIV RNA). After adjusting for age, gender, smoking history, comorbidity treatment, and airflow obstruction severity, HIV was independently associated with a 2.47 increased odds of AECOPD (95% CI 1.22, 5.00). Compared to HIV-uninfected persons, HIV-infected persons with undetectable (<50 copies/mL) HIV RNA levels and those with a CD4 count ≥350 cells/mm^3 demonstrated increased AECOPD (OR 2.91; 95% CI 1.26, 6.71; OR 4.16; 95% CI 1.87, 9.27, respectively). Higher AECOPD risk was observed with higher CD4 counts irrespective of treatment for comorbid diseases.

Conclusions—HIV infection is independently associated with increased odds of AECOPD, potentially due to differences in treatment access and to variable disease manifestation by immune status. Providers should be aware that HIV infection may increase risk for AECOPD and that symptoms may be more discernible with intact immune function.

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Keywords

HIV; Pulmonary disease; chronic obstructive; COPD exacerbation; Airflow limitation

Introduction

Chronic obstructive pulmonary disease (COPD), a predominantly tobacco-related lung disease characterized by fixed airflow obstruction, recently became the third leading cause of death in the United States.[1] Acute exacerbation of COPD (AECOPD) is distinguished by an acute worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations which leads to a change in medication (e.g., corticosteroids, antibiotics).[2] The health impact of AECOPD is considerable, with substantial associated morbidity, healthcare resource utilization, disease progression and mortality.[3-8] Among patients with COPD in the general population, factors such as reduced lung function and prior AECOPD are strongly predictive of subsequent AECOPD.[2,9]

HIV infection is a risk factor for myriad incident pulmonary diseases, in particular, COPD.[10,11] Furthermore, poorly controlled HIV infection, as marked by high viral load or low CD4 count, is independently associated with more rapid lung function decline.[12] However, HIV infected individuals receiving highly-active antiretroviral therapy (HAART) were less likely to be aware of their diagnosis than persons not in care, likely reflecting the severity of lung disease in persons on ART.[13] Given the increasing burden of COPD among aging HIV-infected patients, studies identifying risk factors for sequela of COPD are needed. To date, studies of AECOPD in the setting of HIV infection have not been reported. To address this gap, we sought to determine the risk factors for AECOPD in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort, a population at-risk and with HIV and COPD.[14] ALIVE is comprised of current or former injection drug users (IDUs) who undergo regular behavioral, clinical and spirometric measurement. The prevalence of tobacco use,[15] HIV and obstructive lung disease[13] within this cohort, along with thorough symptom and disease assessments, allow for the observation of incident AECOPD and the identification of sociodemographic, behavioral, and clinical risk factors for AECOPD. We hypothesized that specific clinical factors, including reduced FEV1 and HIV infection, would be associated with increased risk of AECOPD in this at-risk population.

Methods

Study Population

Briefly, ALIVE is an on-going prospective, community-based cohort that has followed persons with a history of injecting drugs in Baltimore, MD since 1988. Participants are seen every 6 months for the collection of clinical, demographic, behavioral, and laboratory data. Pre-bronchodilator spirometry was added to routine data collection at all ALIVE study visits in 2007. A complete description of the ALIVE study has been previously reported.[14,16,17] ALIVE study visits are conducted with trained personnel to enhance self-reported medical history and medications. Participant encounters with the healthcare system are identified and medical record review with systematic data abstraction is performed. For this study, COPD

was defined using modified GOLD classification of forced expiratory volume in 1 second / forced vital capacity (FEV1/FVC) <0.70.[2,18] Participants in this analysis included 167 ALIVE participants who met COPD criteria at each spirometry measurement performed between January 2007 and December 2010. This selection criterion was used to exclude participants with asthma, which is characterized by variable airflow obstruction over time. This study was approved by the IRB of Johns Hopkins University and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. All participants provided written informed consent.

Data Collection

Demographic and clinical characteristics were collected using standardized study questionnaires; comorbidities were gathered through self-report and standardized medical record review. Specifically, smoking patterns, IDU status and antiretroviral use were gathered through self-report. HCV serology testing was performed at the first study visit after 2006 (Ortho Diagnostics; Rochester, NY). HIV serology status was confirmed at each study visit (for HIV-uninfected persons); CD4 count and HIV RNA testing (Roche Molecular Systems, Amplicor HIV-1 Monitor test version 1.5; Pleasanton, CA) were performed at each study visit (for HIV positives).

Pre-bronchodilator spirometry measurements, calculations and interpretation were conducted in accordance with ATS guidelines.[19] COPD disease severity was defined by FEV1 criteria: FEV1 ≥80% predicted (mild disease), FEV1 50-79% predicted (moderate disease), and FEV1 <50% predicted (severe disease).[18] AECOPD, assessed at each 6 month study visit, was defined as answering “yes” to the question “In the last 6 months, have you had a worsening of your breathing status requiring treatment with antibiotics or steroids?” Participants who answered “yes” to the any of the following questions “Have you received treatment for [diabetes, hypertension, hyperlipidemia, heart disease, renal disease, seizures disorder, stroke, or cancer] in the last 6 months?” were defined as having “comorbid disease.”

Statistical Analyses

Descriptive characteristics of the study population are presented as frequencies, mean (standard deviation) for normally distributed data and median (interquartile range) otherwise; comparisons were conducted using the *t* test, Wilcoxon rank-sum test or Pearson χ^2, as appropriate. A two-sided p-value ≤ 0.05 defined statistical significance. The outcome of interest was AECOPD as defined above. The 6 month study intervals were considered discrete units of analysis. Because participants contributed multiple visits to analysis, regression models with generalized estimating equations[20] were used to allow repeated measurements within the same individual. We first identified factors associated with AECOPD in univariable analysis. These factors, along with those determined to be of clinical relevance (i.e., age), had a p-value < 0.2, and were included in a multivariable model to determine independent association of each covariate. Self-reported sociodemographic and clinical measures (BMI, HIV and HCV serology) were obtained from the visit at which the outcome of interest was ascertained. In multivariable models, spirometric measurements were obtained from the study visit preceding the outcome of interest because AECOPD can

acutely lower FEV1. Comorbid disease status was also obtained from the study visit preceding the outcome of interest to reduce the ascertainment bias associated with these two measures. HIV-related variables were modeled separately and included HIV serostatus, HIV RNA categories (undetectable [<50 copies/mL] and detectable [≥50 copies/mL]) and CD4 count categories (defined as ≥350 cells/mm^3 and <350 cells/mm^3 based on exploratory data analysis and prior publications within this cohort).[21] Separate multivariable models included a prior episode of AECOPD were generated. All analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

Participant Characteristics

At baseline, the 167 ALIVE participants included in this study had a mean age of 52 years; 89% were black, 30% were female, 85% were HCV-seropositive and 32% HIV-infected (Table 1). The median CD4 count was 312 cells/mm^3 (IQR 193-454) among those with HIV infection, with 72% reporting HAART use within the past 6 months and 54% having an undetectable viral load (≤50 copies/mL). Among those with detectable HIV RNA, the median viral load was 4859 copies/mL (IQR: 1184-34350). The majority of participants were current smokers (90%) with a median of 24 pack-years smoked (IQR 15-38). According to modified GOLD criteria, participants predominantly had mild (41%) or moderate airflow obstruction (47%). A total of 82 (49%) of the participants reported receiving treatment for a comorbid disease in the past 6 months. Among participants with HCV antibody seropositivity, 83% of had detectable HCV RNA with a median HCV RNA level of 6.26 $\log_{10}$ copies/mL (IQR 5.87-6.70). Participants had a median of 3 visits (IQR: 2-5) during a median of 1.5 years of follow-up (IQR: 0.5-2.1). A total of 552 visits occurred during the study period with AECOPD occurring at 53 visits (9.6% of all person-visits). Of the 36 individual participants experiencing an exacerbation, 24 participants had one exacerbation, nine had two exacerbations, one had three exacerbations, and two had four exacerbations.

Univariable Associations with AECOPD

Univariable logistic regression analysis identified factors associated with increased odds of AECOPD (Table, Supplemental Digital Content 1), including female gender, receiving treatment for another comorbid disease, severity of airflow obstruction and HIV status. HIV infection was associated with increased odds of AECOPD (OR 2.18, 95% CI: 1.07, 4.44, p=0.032) in univariable analysis. Age, BMI, black race, smoking pack-years, and injection drug use status (current versus former) were not significantly associated with risk of AECOPD. Neither HCV antibody seropositivity nor HCV RNA levels were significantly associated with AECOPD risk.

Multivariable Associations with AECOPD

Multivariable logistic regression analysis incorporating significant variables identified from univariate analyses as well as clinically relevant factors were generated. HIV infection was modeled separately with HIV serostatus, viral load categories and CD4 cell count categories. Several factors were consistently associated with increased odds of AECOPD across

models, including female gender, treatment for comorbid disease, smoking pack-years and worsening airflow obstruction severity (Table 2). After adjusting for these factors and age, HIV infection was independently associated with a 2.47 fold increased odds of AECOPD (95% CI: 1.22, 5.00). In HIV viral load models with HIV-uninfected as the referent group, HIV-infected participants with undetectable HIV RNA (<50 copies/mL) had increased odds of AECOPD (OR 2.91, 95% CI 1.26, 6.71), while persons with detectable HIV RNA levels (≥50 copies/mL) were no longer significantly different from HIV-uninfected persons (OR 1.82; 95% CI 0.70, 4.78). When modeling HIV infection based on CD4 count, participants with a CD4 count ≥350 cells/mm^3 had increased odds of AECOPD as compared to HIV-uninfected (OR 4.16, 95% CI: 1.87, 9.27). HIV-infected participants with a CD4 count <350 cells/mm^3 did not demonstrate elevated odds of AECOPD as compared to HIV negatives (OR 1.17, 95% CI: 0.41, 3.31). Including HAART status in either the HIV RNA or CD4 multivariable models did not alter the primary findings. To account for potential ascertainment bias, we performed stratified analysis by whether persons had received treatment of other comorbid conditions or not. Irrespective of the marker examined (HIV status, HIV RNA level, CD4 count), the observed risk estimates for AECOPD were similar to those in the primary analysis albeit with less precision due to smaller strata (data not shown). Higher CD4 cell counts (>350 cells/mm3) were notably associated with higher AECOPD risk both in persons receiving treatment (adjusted OR 4.36; 95% CI: 1.37, 13.84) for a comorbid disease other than COPD and in person not on such treatment (adjusted OR 4.72, 95% CI: 1.48, 15.02).

Role of Prior AECOPD

Because a history of AECOPD is a risk factor for future exacerbations,[9] we evaluated the association between AECOPD in the visit immediately before the visit where the outcome was analyzed. Prior exacerbation was strongly associated with future exacerbation (OR 4.46, 95% CI 1.99, 10.00) in univariate analysis. Inclusion of prior AECOPD into multivariable models demonstrated that prior AECOPD was independently associated with increased occurrence of AECOPD, after adjusting for age, gender, comorbid disease, smoking pack-years and severity of airflow obstruction (OR 3.76, 95% CI: 1.57, 8.97; Table 3). Inclusion of prior AECOPD into our models attenuated the increased odds of AECOPD observed with HIV serostatus and undetectable viral load; however, HIV participants with CD4 count ≥350 cells/mm^3 remained at increased odds of AECOPD compared to HIV uninfected participants (OR 3.23, 95% CI 1.29, 8.12, p=0.12; Table 3).

Discussion

HIV infection has become increasingly recognized as a risk factor for the development of COPD,[11,22-24] yet little is known about the association between HIV infection and AECOPD. In this study of 167 ALIVE participants with COPD, HIV infection was independently associated with increased odds of AECOPD, even after adjusting for other AECOPD risk factors. AECOPD has been variably defined in prior studies[25]; our method relying on self-report of change in respiratory symptoms requiring treatment has been widely applied in major COPD trials.[26-28] AECOPD was most common in persons receiving treatment for other comorbid disease and among HIV-infected participants with well-

controlled HIV disease as measured by CD4 count and viral load, indicating increased ascertainment of AECOPD among persons engaged in regular care for HIV and comorbidities. However, compared to HIV-uninfected persons, those persons with HIV and higher CD4 cell counts had a greater than four-fold higher likelihood for AECOPD irrespective of whether they were engaged in care for comorbidities other than COPD or not. These data highlight the complicated relationship between HIV infection and AECOPD risk, and draw attention to the need for HIV care providers to consider AECOPD across the spectrum of HIV disease severity.

To our knowledge, this is the first report to describe an independent association of HIV infection with AECOPD. Several biological mechanisms may contribute to the increased risk of AECOPD observed among those with HIV infection. First, HIV infection has long been known to increase the incidence of lower respiratory tract infections (LRTIs),[29,30] and these LRTIs in turn may provoke an AECOPD.[31,32] Second, in addition to increasing risk of respiratory infections through impaired immune function, HIV also paradoxically causes chronic, though aberrant, immune activation.[33,34] Third, the lymphocytic alveolitis[35,36] implicated in COPD pathogenesis among HIV-infected persons may contribute to increased AECOPD risk. Finally, systemic inflammation and risk for AECOPD has been shown to exist within the general COPD population[37] and could be enhanced among those with comorbid HIV and COPD. Persons living with HIV infection suffer increased age-associated non-AIDS-related morbidity and mortality thought to be due to persistent inflammation caused by viral replication, viral expression and loss of immunoregulatory cells.[38] Increased levels of inflammatory biomarkers have been shown to correlate with all-cause mortality;[39] however the specificity of these biomarkers for respiratory disease incidence, morbidity and mortality remains unclear.

In addition to biological mechanisms for higher AECOPD risk with HIV infection, our data also suggest an increased recognition and management of AECOPD in persons effectively engaged in HIV care with higher CD4 cell counts or with virological suppression. This finding is not surprising considering that our AECOPD definition requires appropriate recognition and management of worsening respiratory symptoms. Participants with controlled viremia and higher CD4 cell counts may be more likely to regularly see a physician for their HIV care and thereby also more likely to be diagnosed and treated appropriately for AECOPD, as compared to HIV-infected persons not engaged in care or to HIV-uninfected persons in our cohort with limited access to care.

However, our data also suggest that access to appropriate care is unlikely to fully account for all of the observed association between HIV and AECOPD. First, other risk factors for AECOPD identified in this cohort including severity of airflow obstruction and prior AECOPD history are strongly consistent with those from general population studies, providing some face validity.[2,9] Second, using self-reported treatment of comorbidities other than COPD as a surrogate marker for having access to care, we analyzed whether HIV status, viral load and CD4 count remained associated with AECOPD. Irrespective of comorbidity treatment, HIV infection and related markers were consistently associated with AECOPD to a similar degree as in the primary analysis. Notably, the increase in AECOPD risk observed among HIV-infected participants with higher CD4 counts was >4-fold higher

than in those without HIV infection irrespective of comorbidity treatment. Based on limited clinical data from disparate populations, it has been hypothesized that manifestations of obstructive lung disease may more apparent with more intact immune function, such as in the setting of immune reconstitution with HAART. We have previously found that markers of more advanced HIV disease are associated with the severity of airflow obstruction and with declines in lung function over time,[12,19] findings which differ from the relationship between intact immune status and AECOPD observed here. There are several potential explanations for these observations. From an analytical perspective, participants in this analysis included those with established COPD, compared to inclusion of all ALIVE participants (the majority without pre-existing lung disease). Levels of HIV immunosuppression may differentially impact those with and without established disease. In this manuscript, we adjusted for current FEV_1 in our models in order to isolate the HIV effect upon AECOPD risk from the impact of severity of airflow obstruction, whereas prior analyses incorporated FEV_1 as an outcome of interest. These differing findings may represent a reporting bias in the structure of this analysis. The definition of AECOPD in this analysis required access to health care to be diagnosed with AECOPD, and that access to health care is associated with improved markers of immune function. However, we attempted to account for this bias by incorporating a variable of comorbid disease as a marker of access to care. From a biological perspective, AECOPD is classically characterized as a robust inflammatory and immune-mediated response[40] that may be more likely to occur among HIV-infected individuals with well controlled disease with an intact immune system. This is in contrast to FEV1 decline over time, which may be mediated by chronic low grade inflammation[41] as is observed in HIV-infected individuals with poorly controlled disease.[33,42] Further, the importance of the level of CD4 cell counts in the lung mucosa may be more relevant than the CD4 count in the peripheral compartment.[43-45] We have recently reported that persons with COPD and HIV exhibit profound $CD4^+$ T-cell depletion with reduced CD4/CD8 T-cell ratios in the bronchoalveolar lavage as compared to the periphery and compared to those with COPD alone. Moreover, HIV infection results in an altered respiratory microbiome which may contribute to the increased AECOPD risk.[46-48] The findings presented here offer additional insight into the complicated relationship between HIV-related immunosuppression and different lung outcomes.

Within the general COPD population, severity of airflow obstruction and prior AECOPD history have been consistently reported as the most important risk factors for future AECOPD.[37,49,50] Specifically, a history of frequent AECOPD (>2 per year)[4,49] and lower FEV1[49,51] have been shown to increase risk for future AECOPD and hospitalization for AECOPD. Our findings were consistent with these data from the general population, with a dose-response relationship between AECOPD risk and severity of airflow obstruction as measured by FEV1. In our analysis, prior AECOPD was the strongest factor associated with current AECOPD risk, attenuating the FEV1, HIV serostatus and viral load, but not CD4 count, associations in adjusted models. This observation is consistent with studies of the general COPD population[9] and highlights that, regardless of HIV control, providers should recognize the impact of past AECOPD events upon the future COPD course. We hypothesize that HIV infection may increase risk for incident AECOPD which leads to a pathway of repeated AECOPD.

Previously, we have shown a substantial burden of respiratory symptoms among both HIV-infected and uninfected persons with a history of injecting drugs.[52] Despite these respiratory symptoms and a high prevalence of tobacco exposure, approximately half of participants with spirometry-defined obstructive lung disease were unaware of their diagnosis.[19] These findings along with our observations linking engagement in care to appropriate diagnosis and management of AECOPD and of the impact of prior AECOPD upon risk for future AECOPD emphasize the critical need to consider the diagnosis of COPD and occurrence of AECOPD within at-risk HIV populations. Unrecognized COPD can lead to misclassification of AECOPD as acute respiratory infections, thereby missing an opportunity to appropriately treat an AECOPD.

This study has limitations. Our cohort includes urban dwelling, African-American current and former IDUs, which limits the generalizability of our results to other HIV-infected and at-risk populations. However, the IDU population with high smoking prevalence represents the group of individuals at greatest risk for COPD. We do not have post-bronchodilator spirometry to ensure the presence of fixed airflow obstruction seen in COPD; however we required participants to have airflow obstruction at every spirometric measurement thereby reducing the likelihood of persons having primarily reversible airflow obstruction (i.e., asthma). Lastly, we do not account for the treatment of COPD within our analysis, which may have reduced the risk for AECOPD and potentially impacted our results. Data regarding inhaled medications was not regularly collected in ALIVE, so we are unable to fully assess the impact of medications on AECOPD outcomes.

In conclusion, HIV was significantly associated with AECOPD, even after accounting for factors such as comorbid disease, smoking pack-years and severity of airflow obstruction. The increased risk of AECOPD observed among HIV-infected participants with intact CD4 counts and viral suppression may reflect the multiple ways HIV infection imparts upon AECOPD risk. HIV care providers should consider a diagnosis of AECOPD in HIV-infected patients at-risk for COPD given the association between these two disease processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Sociodemographic, Behavioral and Clinical Characteristics at Baseline

Number of Participants	167
Age, years	52.4 (8.1)
Female, n (%)	50 (30)
Black race, n (%)	148 (89)
BMI, kg/m^2	24.2 (21.4-27.1)
Smoking Status, n (%)	
Current	151 (90)
Former	13 (8)
Never	3 (2)
Smoking, pack years	24 (15-38)
FEV1	
Absolute, L	2.29 (0.84)
% Predicted	74.0 (21)
FVC	
Absolute, L	3.74 (1.2)
% Predicted	96.5 (20)
FEV1/FVC	
Absolute	0.61 (0.9)
Severity of Airflow Obstruction	
Mild (FEV1 ≥80% predicted), n (%)	68 (41)
Moderate (FEV1 50-79% predicted), n (%)	79 (47)
Severe (FEV1 <50% predicted), n (%)	20 (12)
Current IDU, n (%)*	60 (36)
Comorbid Disease*†	82 (49)
Hepatitis C antibody seropositive, n (%)*	142 (85)
Undetectable HCV RNA	23 (17)
HCV RNA level, $\log_{10}$ copies/mL ‡	6.26 (5.87-6.70)
HIV-infected, n (%)	53 (32)
CD4+ cell count	
Median (IQR)	312 (193-454)
<350 cells/mm^3, n (%)	29 (55)
HIV-1 RNA viral load §	
Median (IQR)	4858.5 (1184-34350)
Undetectable (<50 copies/mL), n (%)	28 (54)
Recent HAART use, n (%)*	38 (72)

Values presented as mean (Standard Deviation, SD) or median (Interquartile Range, IQR) unless indicated otherwise.

*In previous 6 months.

†Self-reported treatment for [diabetes, hypertension, hyperlipidemia, heart disease, renal disease, seizures disorder, stroke, or cancer] in the last 6 months

‡Among HCV seropositive participants with detectable HCV RNA.

§Among HIV-infected participants with detectable HIV RNA.

Abbreviations: BMI, Body Mass Index; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HAART, Highly Active Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; IDU, Injection Drug Use; L, liter; n, number; RNA, ribonucleic acid

Table 2

Multivariable Models of AECOPD

	HIV Serostatus Model		HIV RNA Model		CD4 Count Model	
Covariate	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Age, per 10 year increase	0.60 (0.36, 1.03)	0.063	0.57 (0.33, 0.98)	0.041	0.55 (0.32, 0.95)	0.031
Female	2.55 (1.25, 5.21)	0.010	2.41 (1.17, 4.96)	0.017	2.22 (1.08, 4.58)	0.031
Comorbid disease†	2.88 (1.37, 6.04)	0.005	2.97 (1.40, 6.30)	0.005	2.91 (1.38, 6.16)	0.005
Smoking pack-years	1.02 (1.00, 1.04)	0.026	1.02 (1.00, 1.04)	0.031	1.02 (1.00, 1.04)	0.057
Airflow Obstruction*						
Mild (FEV1 ≥80% predicted)	Reference		Reference		Reference	
Moderate (FEV1 50-79% predicted)	2.52 (1.09, 5.82)	0.031	2.38 (1.02, 5.52)	0.044	2.34 (1.01, 5.43)	0.047
Severe (FEV1 <50% predicted)	6.79 (2.53, 18.27)	<0.001	6.45 (2.39, 17.46)	<0.001	7.09 (2.63, 19.11)	<0.001
HIV Status						
HIV-Uninfected	Reference		Reference		Reference	
HIV-Infected	2.47 (1.22, 5.00)	0.012				
HIV RNA Undetectable (<50 copies/mL)			2.91 (1.26, 6.71)	0.012		
HIV RNA Detectable (≥50 copies/mL)			1.82 (0.70, 4.78)	0.221		
CD4 count ≥350 cells/mm^3					4.16 (1.87, 9.27)	<0.001
CD4 count <350 cells/mm^3					1.17 (0.41, 3.31)	0.766

*In previous 6 months

†Self-reported treatment for [diabetes, hypertension, hyperlipidemia, heart disease, renal disease, seizures disorder, stroke, or cancer] in the last 6 months

Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; CI, Confidence Interval; FEV1, Forced Expiratory Volume in 1 second; HAART, Highly Active Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; OR, Odds Ratio; RNA, ribonucleic acid;

Table 3

Multivariable Models of AECOPD with Inclusion of Prior AECOPD

	HIV Serostatus Model		HIV RNA Model		CD4 Count Model	
Covariate	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Age, per 10 year increase	0.58 (0.31, 1.06)	0.078	0.51 (0.27, 0.98)	0.042	0.51 (0.27, 0.97)	0.039
Female	2.68 (1.16, 6.23)	0.022	2.50 (1.06, 5.92)	0.037	2.32 (0.98, 5.51)	0.055
Comorbid disease†	2.94 (1.21, 7.15)	0.017	2.95 (1.19, 7.31)	0.019	2.70 (1.10, 6.64)	0.031
Smoking pack-years	1.03 (1.01, 1.06)	0.001	1.04 (1.01, 1.06)	0.001	1.04 (1.01, 1.06)	0.001
Airflow Obstruction*						
Mild (FEV1 ≥80% predicted)	Reference		Reference		Reference	
Moderate (FEV1 50-79% predicted)	1.85 (0.71, 4.82)	0.208	1.75 (0.66, 4.61)	0.260	1.65 (0.63, 4.35)	0.311
Severe (FEV1 <50% predicted)	3.82 (1.21, 12.05)	0.022	3.69 (1.16, 11.77)	0.027	4.02 (1.25, 12.95)	0.020
Prior AECOPD*	3.76 (1.57, 8.97)	0.003	3.67 (1.53, 8.80)	0.004	4.00 (1.64, 9.76)	0.002
HIV Status						
HIV-Uninfected	Reference		Reference		Reference	
HIV-Infected	1.86 (0.80, 4.30)	0.148				
HIV RNA Undetectable (<50 copies/mL)			2.37 (0.89, 6.34)	0.084		
HIV RNA Detectable (≥50 copies/mL)			1.19 (0.36, 3.92)	0.774		
CD4 count ≥350 cells/mm^3					3.23 (1.29, 8.12)	0.012
CD4 count <350 cells/mm^3					0.63 (0.15, 2.56)	0.515

*In previous 6 months

†Self-reported treatment for [diabetes, hypertension, hyperlipidemia, heart disease, renal disease, seizures disorder, stroke, or cancer] in the last 6 months

Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; CI, Confidence Interval; FEV1, Forced Expiratory Volume in 1 second; HIV, Human Immunodeficiency Virus; OR, Odds Ratio; RNA, ribonucleic acid;