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Risk Factors Associated with Acute Exacerbation of Chronic Obstructive Pulmonary Disease in HIV-infected and Uninfected Patients

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Abstract

Objective—To determine the association between HIV infection and other risk factors for acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Design—Longitudinal, national Veterans Aging Cohort Study (VACS) including 43,618 HIV-infected and 86,492 uninfected Veterans.

Methods—AECOPD was defined as an inpatient or outpatient COPD ICD-9 diagnosis accompanied by steroid and/or antibiotic prescription within 5 days. We calculated incident rate

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ratios [IRR] and 95% confidence intervals (CI) for first AECOPD over 2 years and used Poisson regression models to adjust for risk factors.

Results—Over 234,099 person-years of follow-up, 1,428 HIV-infected and 2,104 uninfected patients had at least one AECOPD. HIV-infected patients had an increased rate of AECOPD compared with uninfected (18.8 vs. 13.3 per 1000 person-years, p<0.001). In adjusted models, AECOPD risk was greater in HIV-infected individuals overall (IRR 1.54; 95% CI 1.44 – 1.65), particularly in those with more severe immune suppression when stratified by CD4 cell count (cells/mm^3) compared to uninfected (HIV-infected CD4<200: IRR 2.30, 95% CI 2.10-2.53, HIV-infected CD4 ≥200-349: IRR 1.32, 95% CI 1.15-1.51, HIV-infected CD4≥350: IRR 0.99, 95% CI 0.88-1.10). HIV infection also modified the association between current smoking and alcohol-related diagnoses with risk for AECOPD such that interaction terms for HIV and current smoking or HIV and alcohol-related diagnoses were each significantly associated with AECOPD.

Conclusions—HIV infection, especially with lower CD4 count, is an independent risk factor for AECOPD. Enhanced susceptibility to harm from current smoking or unhealthy alcohol use in HIV-infected patients may also contribute to the greater rate of AECOPD.

MESH Terms

Chronic Obstructive Pulmonary Disease; COPD; Acute Exacerbation; AECOPD; AIDS/HIV; Cigarette smoking; Tobacco use; Unhealthy alcohol use

Introduction

Chronic obstructive pulmonary disease (COPD) affects at least 6.5% of the US population[1] and is a leading cause of morbidity and mortality in the US, with annual cost estimated at $60-70 billion[1, 2]. Individuals with acute exacerbations of COPD (AECOPD) not only have decreased quality of life[3, 4], but also increased morbidity and healthcare expenditure[5-9].

While the HIV-infected population has experienced increased survival during the era of combination antiretroviral therapy (ART)[10], they have also experienced increased prevalence of chronic diseases such as COPD [11-22]. Previous studies have shown an increased prevalence of COPD among those with HIV, even after controlling for smoking history[3, 18, 23], but these earlier studies did not investigate whether HIV was associated with greater rates of AECOPD. A recent study demonstrated an increased risk for AECOPD associated with HIV infection in a study of 167 patients in the AIDS Link to Intravenous Drug Use (ALIVE) cohort[24]. However, while risk factors have been characterized for AECOPD in HIV-uninfected (uninfected) individuals[25], they have not been well characterized in the HIV-infected population. Understanding AECOPD risk factors in HIV-infected persons is important to improve detection of disease, ensure appropriate care in the acute setting, develop strategies for prevention and to tailor long-term disease management, all of which may differ compared to uninfected persons. Decreasing the rate of AECOPD could improve patient quality of life[3], influence the rate of change in lung function, as well as decrease health care expenditures[2].

Although many factors can impact the development and outcomes of COPD[26-38], smoking and other substance use, such as unhealthy alcohol[39] and drug use, are modifiable factors that are prevalent among HIV-infected individuals and can potentially impact the outcomes of COPD[40, 41]. While smoking is an established risk factor for AECOPD in uninfected patients, it is not known whether HIV-infected patients might have an enhanced susceptibility to the harms of smoking given underlying oxidative stress that may be present in the HIV lung[42]. Whether unhealthy alcohol use apart from smoking may have a deleterious effect on pulmonary function remains unclear[41, 43, 44], and has not been examined as a risk factor for AECOPD in HIV-infected patients[24]. While some studies show an adverse effect of alcohol on lung function over time, a recent large scale study demonstrated a protective effect of moderate drinking on lung health[45]. Previous research has also demonstrated increased lung oxidative stress with alcohol use and HIV [5, 43, 44, 46-55], and negative effects of alcohol on macrophage activation, ciliary clearance, and increasing susceptibility to infection[44, 52, 53, 56, 57]. We hypothesized that both alcohol and smoking may play a more significant role in impacting lung health and risk for AECOPD among HIV-infected than in uninfected individuals.

Therefore, in this study, we sought to compare incidence rates of AECOPD among HIV-infected and uninfected patients and to examine the influence of modifiable and non-modifiable risk factors for AECOPD using data from the Veterans Aging Cohort Study (VACS). We hypothesized that the incidence of AECOPD is higher among HIV-infected patients and that HIV-related immune suppression and modifiable tobacco and unhealthy alcohol use increase risk for AECOPD.

Methods

Design and Subjects

We used administrative, clinical, and pharmacy data from the Virtual Cohort in the Veterans Aging Cohort Study (VACS-VC)[58]. The VACS-VC has been described previously[59]. In brief, VACS-VC makes use of several nationally available Department of Veterans Affairs (VA) databases to longitudinally follow and evaluate all Veterans with HIV who receive care in the VA system. VACS-VC accesses datasets maintained at the Austin Automation Center (AAC, Austin, TX), Pharmacy Benefits Management Program (PBM, Hines, IL), VA Information Resources Center (VIReC, Hines, IL), and the Decision Support System (DSS). For VACS-VC, HIV-infected participants are identified by HIV International Classification of Diseases, 9th Edition (ICD-9) codes, a process validated against the VA Immunology Case Registry[59]. Using the VA computerized medical record system at the VA Automation Center in Austin, Texas, we identified the first HIV ICD-9 code within the VA as the index date and, for each HIV-infected participant identified, selected two uninfected participants in care at the same time to match the HIV-infected participant on age, race, gender, and Veterans Integrated Service Network (VISN) or region. Because of the limited sample size of HIV-infected women Veterans, we identified up to ten age-, race-, and region (VISN)-matched female controls. In these analyses, we used data from 43,618 HIV-infected Veterans identified from 1996 to 2010, and 86,492 age-, race-, gender-, and region-matched uninfected Veterans included in VACS-VC, with last follow-up through October 17, 2010.

The Institutional Review Boards of the VA Connecticut Healthcare System and Yale University School of Medicine have approved the VACS-VC study.

Primary outcome

Our primary outcome was time to AECOPD occurring within 2 years of index date. We constructed an algorithm to identify incident AECOPD using the electronic medical record. Similar to other studies,[41] we defined AECOPD as an inpatient or outpatient COPD ICD-9 diagnosis (codes 491.x, 492.x, 493.2, 496.x) within the VA accompanied by prescription dispensed through the VA pharmacy for oral or parenteral steroids or antibiotic within five calendar days of the ICD-9 code. We searched for all antimicrobial classes within the VA; the most frequently identified in these analyses were fluoroquinolones (20%), followed by penicillins (13%), macrolides (13%), sulfa drugs (12%), and cephalosporins (12%). In sensitivity analyses to assess the impact of our outcome definition, we also conducted analyses for an AECOPD definition that: 1) did not limit follow-up time to two years; 2) required prescriptions for both steroids and antibiotics; and 3) restricted the cohort to those individuals enrolled after 2000 in order to examine a more recent era.

Risk factors and covariates

Smoking status was obtained from the VA Health Factors database and was categorized as never, past, or current based on most frequent Health Factors smoking data, a method we have previously validated against self-reported data[60]. Diagnosis of unhealthy alcohol use was determined by the presence of one inpatient or two outpatient ICD-9 alcohol-related diagnoses in the baseline window, defined as twelve months prior to and up to 6-months after index date, in VACS-VC[61]. We used the same method to identify drug use disorders. Race was categorized as white, black, Hispanic, or other/unknown based on administrative information, from which we also obtained gender and age. Laboratory (CD4 cell counts and HIV viral load) and other pharmacy data (antiretroviral therapy [ART] use) were obtained from VA administrative databases, using results obtained closest to index date.

Statistical Methods and Analysis

Patients were followed from index date (i.e. date of entry into the VACS-VC) until time of first AECOPD, death, or last known follow-up within two years of the index date, whichever came first. As the study set out to determine risk factors for AECOPD and not COPD itself, patients with a diagnosis of COPD prevalent at baseline were included in analyses. Patients were not, however, required to have known COPD at baseline to be included and considered at risk for an AECOPD event. We excluded 2430 patients due to having no follow-up time after baseline.

We compared the incidence rates of first AECOPD by HIV status and HIV-related risk factors (namely CD4 cell count, HIV viral load, and ART use), and calculated the unadjusted incidence rate per 1,000 person-years and used Poisson regression models to determine the unadjusted incidence rate ratio (IRR). Poisson regression is appropriate to use in time to event analysis to generate IRRs. For large samples with low event rates, Poisson models are more efficient to run than Cox Proportional Hazard models and provide similar estimates. We used multivariable Poisson regression models to determine the independent

effect of HIV infection on the risk for AECOPD, first comparing all HIV-infected to uninfected individuals, and then stratifying HIV-infected individuals by CD4 cell count, adjusting for race, sex, smoking status, and alcohol-related diagnoses. We evaluated whether HIV modifies the relationship between current smoking and AECOPD, and/or the relationship between alcohol use and AECOPD, by evaluating interaction terms in two separate Poisson regression models with all patients. Given significant interaction effects, we also present models stratified by HIV status. All analyses were performed using STATA 13.0. Statistical tests were two tailed, and we considered p values < 0.05 to be statistically significant.

Results

Baseline characteristics of cohort

The analytic sample consisted of 43,618 HIV-infected and 86,492 uninfected patients, who were mostly male, and largely of black or white race, with a minority of Hispanic and other constituent groups (Table 1). The majority were current smokers, with fewer past smokers than never smokers. A diagnosis of COPD was prevalent at baseline in 1,919 (4.4%) of HIV-infected and 3,461 (4.0%) of uninfected patients in the sample.

Incidence rate of AECOPD according to HIV

Among VACS-VC participants, 1,428 HIV-infected and 2,104 uninfected patients had at least one AECOPD over 234,099 person-years of follow-up, with incident rates of 18.8 per 1000 person years for HIV-infected and 13.3 per 1000 person years for uninfected, p<0.001. The unadjusted rate of AECOPD was significantly higher amongst HIV-infected patients compared with uninfected (IRR 1.41; 95% confidence interval [CI] 1.32 - 1.51) (Table 2). Overall, 1750 (50%) of patients with AECOPD had a baseline diagnosis of COPD.

Next, we evaluated the effect of HIV-related risk factors on risk for AECOPD in unadjusted analyses restricted to HIV-infected patients. Decreasing CD4 cell count was associated with a significantly greater risk for AECOPD (CD4<200 cells/mm^3: IRR 2.12, 95% CI 1.86-2.42; CD4 ≥200-349: IRR 1.31, 95% CI 1.11-1.54, compared to CD4 >350) as was HIV RNA level above 500 copies/ml (IRR 1.29, 95% CI 1.13-1.47). Conversely, those prescribed ART at baseline had a significantly decreased risk of AECOPD (IRR 0.73, 95% CI 0.64-0.83).

Independent risk factors for AECOPD

Overall, HIV-infected patients had increased AECOPD risk (IRR 1.54; 95% CI 1.44 – 1.65) compared with uninfected in an adjusted model (Table 3A). Given the strong association with CD4 cell count, we then categorized patients according to HIV status and CD4 cell count in the same model (Table 3B). When compared to uninfected patients, we found that AECOPD risk in HIV-infected was greatest in those with lower CD4 cell count: HIV-infected, CD4 cell count <200: IRR 2.30; 95% CI 2.10-2.53; HIV-infected, CD4 cell count 200-349: IRR 1.32; 95% CI 1.15-1.51; HIV-infected, CD4 cell count ≥350: IRR 0.99; 95% CI 0.88 -1.10. Additional independent risk factors for AECOPD in this model included current smoking, past smoking, and alcohol-related diagnoses. Although significantly associated with AECOPD in bivariate analyses, a diagnosis of drug use disorders was not

statistically significantly associated with AECOPD in the multivariable analyses and was therefore not included in the final models.

In models to test for effect modification, we found statistically significant interactions between current smoking and HIV (IRR 1.18, 95% CI 1.03-1.35, p=0.021), and alcohol-related diagnoses and HIV (IRR 1.22, 95% CI 1.04-1.44, p=0.017) with risk for AECOPD. Thus, we also stratified models by HIV status, in order to evaluate risk factors for AECOPD within each group (Table 4). Age, race, smoking, and alcohol-related diagnoses remained significant risk factors for AECOPD in both HIV-infected and uninfected patients. Consistent with the significant interaction terms, smoking and alcohol-related diagnoses imparted greater risk for AECOPD among the HIV-infected patients. Lower CD4 cell count, HIV viral load >500 copies/ml, and lack of ART each remained independently associated with greater risk of AECOPD in those with HIV infection when input together in the multivariable model (Table 4a).

Sensitivity Analyses

In sensitivity analyses (see Supplementary tables), results were overall similar. In models containing the variables shown in Table 3b without limiting follow-up time to two years, the IRR for AECOPD was significantly greater for HIV-infected at all CD4 count strata compared to the uninfected, including those with a CD4 cell count ≥350 (eTable 1). When requiring both antibiotics and steroids to meet a definition of AECOPD, the IRRs were generally higher and were significantly greater for HIV-infected with CD4<200 or CD4 200-350 compared to uninfected (eTable 2). Finally, incidence rates were slightly higher when restricting the cohort to the year 2000 and later, but overall adjusted IRR were similar and inferences were not changed (data not otherwise shown).

Discussion

In this study, we sought to compare incidence rates of AECOPD in HIV-infected to uninfected patients, and to assess risk factors for AECOPD. We found that HIV was independently associated with an increased risk of AECOPD, and that immune suppression, reflected by a lower baseline CD4 cell count, was associated with a greater risk of AECOPD. HIV RNA levels above 500 copies/ml and lack of ART in the baseline window were also significantly associated with AECOPD in HIV-infected patients. In addition, AECOPD was strongly associated with current smoking, as well as past smoking, alcohol-related diagnoses, white race, and female gender in both the HIV-infected and uninfected patients. Finally, we found a significant interaction between HIV infection and current smoking, and HIV infection and alcohol-related diagnoses with greater risk for AECOPD. These findings support that severity of immune suppression increases risk for AECOPD, likely through greater risk of infection. Of significant clinical relevance, these data also suggest that the increased risk of AECOPD in HIV may be related to enhanced susceptibility to harms from the modifiable risk factors of smoking and unhealthy alcohol use.

Findings in this study corroborate and extend those of previous studies that have shown a greater prevalence of COPD among the HIV-infected population,[23, 62-64] although we are among the first to investigate risk factors for AECOPD in HIV-infected patients. One

prospective, smaller study from the ALIVE cohort showed an increased risk of AECOPD[24].. Similarly, we found that HIV was a risk factor for AECOPD in our cohort, but in contrast to the ALIVE study, we found that a lower CD4 cell count at study baseline among HIV-infected individuals, rather than a higher CD4 count (>350), was an important risk factor for AECOPD. One reason for this difference could be if there were differential rates of misclassification between AECOPD events and pneumonia or other infections in the two studies. However, this possibility is difficult to evaluate as the ALIVE study also did not require chest radiographs to detect AECOPD, but relied on patient self-report of breathing problems requiring an antibiotic or steroid prescription. While we might have misclassified pneumonia or other infections as AECOPD using administrative data, our sensitivity analyses that required both prescription for steroids and antibiotics in conjunction with a COPD ICD-9 code demonstrated a greater risk for these events in association with HIV infection. As steroids are not part of the routine management of community acquired pneumonia or most other infections, this supports that AECOPD was likely to be also present in these patients. Nonetheless, because 12% of cases were treated with sulfa drugs that can be used for *Pneumocystis* pneumonia as well as for AECOPD, this might have contributed to finding a greater risk of events in patients with HIV, particularly in those with CD4 cell counts below 200.

In this study we also tested the hypothesis that alcohol use is a risk factor for AECOPD, and might confer greater risk in those with HIV. Unhealthy alcohol use and alcohol-related diagnoses are associated with significantly increased risk of hospitalization in HIV-infected compared to uninfected patients, with HIV and alcohol-related diagnoses having additive effects on risk[65]. Previous studies have produced conflicting information as to the relationship between unhealthy alcohol use and COPD, some suggesting a relationship and others none[40, 41, 54, 57]. In contrast to a previous study[41], we found that alcohol-related diagnoses were significantly associated with AECOPD even after controlling for cigarette smoking. Furthermore, the magnitude of risk associated with alcohol-related diagnoses for AECOPD was greater in HIV-infected compared to uninfected individuals, and we found a statistically significant interaction between alcohol-related diagnosis and HIV for risk of AECOPD.

Biological data support that there may be a greater role for alcohol in impacting lung health and risk for AECOPD among HIV-infected than uninfected individuals. Both alcohol and HIV increase lung oxidative stress, which is associated with increased pulmonary disease[5, 43, 44, 46-55]. At the same time, alcohol inhibits macrophage activation, increases reactive oxygen species, increases apoptosis, affects ciliary clearance, and increases susceptibility to infection[44, 52, 53, 56, 57]. From a pathophysiologic perspective, infection with HIV coupled with alcohol use could serve as a ‘double-hit’ to increase susceptibility to exacerbations of lung disease in the setting of systemic inflammation[44, 55], apart from the known interactions of smoking. Similar effects related to smoking, which is known to increase oxidative stress in the lung, could be contributing to enhanced susceptibility to AECOPD in the setting of HIV infection. While residual confounding from pack-years of smoking and drug use could explain these associations, alcohol may nonetheless have an independent effect on COPD-related medication adherence or risk for infections that can trigger AECOPD, and requires further investigation.

This is one of the first studies to examine risk factors for AECOPD in HIV-infected compared to uninfected patients and to do so in a national cohort. Our study has several strengths. The VA healthcare system provides care to the largest population of HIV-infected persons in the United States, and the VACS-VC is the largest such study of HIV-infected individuals with demographically and behaviorally similar uninfected controls. As COPD and other chronic diseases continue to increase in the combination ART era, this is a robust environment for analyzing risk factors for AECOPD. The cohort is geographically diverse with multiple sites across the country, and is racially and ethnically diverse. This allowed us to detect a significantly decreased risk of AECOPD in patients of non-white race, a finding that is consistent with other work.[66] However, our current analyses do not allow us to conclude whether non-white race is truly protective against AECOPD or whether the relationship between race and AECOPD may be complicated by under-diagnosis and/or competing risk of mortality; additional investigations to understand the relationship between race, ethnicity and manifestations of COPD are required.

Our study also had certain limitations. Pharmacologic and administrative data to detect AECOPD may result in misclassification, as noted above. However, even with full access to chart data, misdiagnosis remains possible as other diseases such as pneumonia or congestive heart failure can present similarly, antibiotics are not always correctly prescribed, and often patients are treated for multiple conditions simultaneously. To comprehensively capture cases of AECOPD, our primary definition of AECOPD required a COPD ICD-9 code in combination with antibiotic or steroid prescription within five days. This approach is similar to other work[41], although we allowed a five day window rather than two for the medication prescriptions, because we have found in chart review work within VACS that ICD-9 codes are not necessarily coded on the exact same date in the administrative files as when events occur in the medical record, but are generally more accurate within a three to five day window. Our approach of using antibiotics or steroids is also supported by data evaluating the quality of care delivered for AECOPD, which finds that many patients do not receive both antibiotics and steroids despite recommendations. Only about 60% of patients have been shown to receive optimal quality of care for AECOPD, with 80-85% receiving antibiotics and 80-85% receiving steroids[67-69]. To evaluate the robustness of our approach, we evaluated alternative definitions, including requiring both steroids and antibiotics to be prescribed, increasing follow-up time, and limiting our cohort to a more recent era. Our associations with AECOPD were generally similar and showed a consistent association between HIV infection and greater risk for AECOPD, with a significantly greater risk of AECOPD in the HIV-infected when both steroids and antibiotics were required, and a significantly great risk in the HIV-infected with CD4 cell counts>350 cells/mm^3 with longer follow-up time.

Other limitations of the VACS-VC include a predominantly male composition with underrepresentation of women, whose AECOPD risk-profile may have significant differences from men. Although the data we used included smoking, using a validated method from VA Health Factors data[60], we were not able to evaluate for other forms of smoking such as marijuana, second-hand smoke, or pipe-tobacco. To determine drug use, we used diagnoses of drug use disorders, which would miss individuals with lower levels of use or who had not been identified as having such a disorder; we thus have likely underestimated

the frequency of drug use. While we have attempted to control for confounding variables, we cannot rule-out residual confounding to explain the association between HIV and AECOPD. Additionally, we may have missed episodes of AECOPD if patients received care outside of the VA; in prior work, we have found that the likelihood of receiving care outside the VA is generally similar by HIV status and thus is less likely to bias our results finding an association between HIV infection and AECOPD. Finally, we used baseline measures of risk factors and did not include time-updated variables. However, we truncated our follow-up interval to two years to address this limitation. Analyses where we did not truncate follow-up to two years demonstrated a similar association, with an IRR that was larger for the HIV-infected with higher CD4 cell counts when compared to the models limited to two years of follow-up.

In summary, we found that the incidence of AECOPD was increased in HIV-infected compared to uninfected patients. Among HIV-infected individuals, a lower CD4 cell count was associated with greater risk of AECOPD. Current smoking and unhealthy alcohol-related diagnoses substantially increased the risk of AECOPD, particularly in HIV-infected individuals. Thus, modifiable risk factors to target in future trials to decrease AECOPD in HIV-infected patients include current smoking and unhealthy alcohol use. Improved detection of COPD, earlier recognition of AECOPD, and optimizing maintenance therapy for COPD are also potential targets to explore in future studies that could result in better control of COPD and decreased risk for AECOPD. Intervening on these contributing factors may decrease morbidity and costs associated with COPD, particularly in a vulnerable HIV-infected population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Baseline characteristics of VACS Virtual Cohort participants

	Total (N = 130,110)	HIV-infected (N = 43,618)	HIV-uninfected (N = 86,492)	p-value
Demographics				
Age, mean years (SD)	48 (10)	47 (10)	48 (10)	
Sex				0.9
Female	3,139 (2.4)	1,055 (2.4)	2,084 (2.4)	
Male	126,971 (98)	42,563 (98)	84,408 (98)	
Race				<0.001
White	50,865 (39)	16,683 (38)	34,182 (40)	
Black	61,777 (48)	21,262 (49)	40,515 (47)	
Hispanic	9,851 (7.6)	3,106 (7.1)	6,745 (7.8)	
Other/Unknown	7,617 (5.9)	2,567 (5.9)	5,050 (5.8)	
Health Behaviors				
Smoking History				<0.001
Never	30,815 (24)	9,090 (21)	21,725 (25)	
Past	18,183 (14)	5,033 (12)	13,150 (15)	
Current	59,295 (46)	20,404 (47)	38,891 (45)	
Unknown	21,817 (17)	9,091 (21)	12,726 (15)	
Alcohol Related Diagnosis				<0.001
No	110,920 (85)	36,681 (84)	74,239 (86)	
Yes	19,190 (15)	6,937 (16)	12,253 (14)	
Drug Related Diagnosis				<0.001
No	111,720 (86)	35,616 (82)	76,104 (88)	
Yes	18,390 (14)	8,002 (18)	10,388 (12)	
HIV-related variables				
CD4 Cell Count (cells/mm3), median (IQR)	-	303 (132-501)	-	
CD4 cells/mm^3	-			
350+		16,318 (44)		

	Total (N = 130,110)	HIV-infected (N = 43,618)	HIV-uninfected (N = 86,492)	p-value
200-349		8,079 (22)		
<200		13,010 (35)		
HIV Viral Load (copies per mL), median (IQR)	-	6,174 (400-62,763)	-	
HIV Viral Load<500 copies/ml		25,597 (68)		
Prescribed Antiretroviral Therapy	-	10,746 (27)	-	
Baseline diagnoses				
COPD	5,380 (4.1)	1,919 (4.4)	3,461 (4.0)	0.001
Cardiovascular Disease	458 (0.35)	127 (0.29)	331 (0.38)	0.008
Hypertension	32,138 (25)	8,167 (19)	23,971 (28)	<0.001
Diabetes Mellitus	14,198 (11)	3,295 (7.6)	10.903 (13)	<0.001
Cirrhosis	1,239 (0.95)	649 (1.5)	590 (0.68)	<0.001
Hepatitis C Infection	26,815 (21)	14,496 (33)	12,319 (14)	<0.001
Cancer	2,029 (1.6)	654 (1.5)	1,375 (1.6)	0.2

Values shown in data fields are N (%) except for age, CD4, and viral load. Baseline CD4 count and HIV viral load were missing in 14% of patients. P-value is for comparison of HIV-infected to uninfected.

T-tests were used to compare normally distributed continuous variables, Wilcoxon rank-sum tests were used to compare non-normally distributed continuous variables, and chi-square tests were used to compare categorical variables.

Abbreviations: Standard deviation (SD), Interquartile range (IQR)

Table 2

Unadjusted rates of AECOPD within 2 years of study baseline by HIV status

	HIV-infected (N = 43,618)	HIV-uninfected (N = 86,492)
Patients with exacerbation, N	1,428	2,104
Time Observed (person-years)	75,924	158,175
Incidence Rate per 1000 person-years	18.8	13.3
Incidence Rate Ratio	1.41 [95% CI 1.32 -1.51]*	Referent

Abbreviation: Confidence interval (CI)

Unadjusted rates of AECOPD were compared between HIV-infected and uninfected using Poisson regression.

*p<0.001

Table 3

Multivariable Poisson regression model for AECOPD within 2 years of index date

A. All patients by HIV status (N = 130,110)		
Risk Factor	**IRR**	**95% CI**
Age, per year	1.06*	1.06 - 1.06
Female	1.37*	1.09-1.73
Race (Referent: White)		
Black	0.70*	0.65 - 0.75
Hispanic	0.56*	0.48 - 0.66
Other/Unknown	0.56*	0.46 - 0.67
Smoking Status (Referent: Never)		
Current	2.49*	2.24 - 2.76
Past	1.75*	1.55 - 1.98
Unknown	1.29*	1.12 - 1.47
Alcohol-related diagnosis	1.55*	1.42 - 1.68
HIV status (Referent: Uninfected)	1.54*	1.44 - 1.65

B. All patients by HIV status and CD4 cell count (N = 123,899)		
Risk Factor	**IRR**	**95% CI**
Age, per year	1.06*	1.06 - 1.06
Female	1.39*	1.08-1.78
Race (Referent: White)		
Black	0.69*	0.64 - 0.74
Hispanic	0.54*	0.46 - 0.64
Other/Unknown	0.61*	0.51 - 0.74
Smoking Status (Referent: Never)		
Current	2.47*	2.22 - 2.75
Past	1.67*	1.47 - 1.90
Unknown	1.21*	1.05 - 1.39
Alcohol-related diagnosis	1.54*	1.41 - 1.68
HIV status (Referent: Uninfected)		
HIV-infected, CD4 ≥350 cells/mm^3	0.99	0.88-1.10
HIV-infected, CD4 200-349 cells/mm^3	1.32*	1.15 - 1.51
HIV-infected, CD4 <200 cells/mm^3	2.30*	2.10 - 2.53

Abbreviations: Incidence rate ratio (IRR); Confidence interval (CI)

* $p<0.05$

Poisson regression models were used to compare the IRR for AECOPD within 2 years of index date. Models were adjusted simultaneously for all risk factors presented in Table 3A or in 3B.

Table 4
Multivariable Poisson regression model for AECOPD stratified by HIV status

	HIV-infected (N=34,319)		HIV-uninfected (N=86,492)	
Variable	**IRR**	**95% CI**	**IRR**	**95% CI**
Age	1.07 *	1.07 - 1.08	1.05 *	1.05 - 1.06
Female Gender	2.08 *	1.46 - 2.96	1.02	0.72 - 1.44
Race/Ethnicity (Referent: White)				
Black	0.68 *	0.60 - 0.77	0.66 *	0.61 - 0.73
Hispanic	0.54 *	0.40 - 0.73	0.54 *	0.44 - 0.66
Other/Unknown	0.76	0.55 -1.05	0.53 *	0.42 - 0.68
Smoking Status (Referent: Never)				
Current Smoker	2.86 *	2.33 - 3.50	2.22 *	1.95 - 2.52
Past Smoker	1.78 *	1.38 - 2.29	1.62 *	1.39 - 1.88
Unknown	1.25	0.97 - 1.61	1.23 *	1.03 - 1.46
Alcohol-related Diagnosis	1.75 *	1.51 - 2.03	1.39 *	1.24 - 1.56
CD4 Cell Count (Referent: ≥ 350 cells/mm^3)			-	-
200-349	1.33 *	1.12 - 1.58		
<200	2.19 *	1.89 - 2.53		
HIV Viral Load ≥ 500 (Referent: <500 copies/ml)	1.26 *	1.09 - 1.45	-	-
Prescribed Antiretroviral Therapy	0.84 *	0.74 - 0.97	-	-

Abbreviations: Incidence rate ratio (IRR); Confidence interval (CI), Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

* $p<0.05$

Poisson regression models were used to compare the IRR for AECOPD within 2 years of index date. Models were adjusted simultaneously for all risk factors listed and were restricted to either HIV-infected only (left hand columns) or uninfected only (right hand columns). CD4 cell count, HIV viral load, and antiretroviral therapy use were not included in the model for uninfected.