Published in final edited form as:

Subst Abus. 2019 ; 40(2): 256–261. doi:10.1080/08897077.2019.1576088.

Substance use is independently associated with pneumonia severity in persons living with the human immunodeficiency virus (HIV)

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Abstract

Background: Pneumonia is common in persons living with the human immunodeficiency virus (HIV) (PLWH). Alcohol, cocaine, and marijuana impact pneumonia pathogenesis. We hypothesized that substance use was independently associated with pneumonia severity in PLWH and modified the effect of alcohol on pneumonia severity.

Methods: Retrospective data analysis of PLWH admitted with a diagnosis of pneumonia was conducted. Alcohol use disorder was defined by the Alcohol Use Disorders Identification Test score ≥ 14 . Drug use was quantified by self-report. Pneumonia severity was defined by the pneumonia severity index (PSI). Multivariable linear regression was used to test independent associations with pneumonia severity and effect modification by sex.

Results: Of 196 PLWH, the mean age was 44 (SD = 9) years and the majority were men (71%). Ten percent ($n = 19$) of subjects met criteria for an alcohol use disorder (AUD). In subjects reporting alcohol use, 25% reported concomitant crack/cocaine use and 16% reported marijuana use. PSI scores were higher with lifetime use of crack/cocaine (mean PSI: 63.1 vs. 57.3, $P = .06$) and/or injection drug use (68.4 vs. 54.9, $P = .04$). PSI scores were lower with active marijuana use (51.5 vs. 62.2, $P = .01$). There was no significant difference in clinical outcomes. Sex modified the effect of drug use on PSI, with greater PSI scores in women with an AUD ($\beta = 58.1$, 95% confidence interval [CI]: 46.7 to 69.5, $P < .01$), whereas active marijuana use mitigated the effect of AUD on PSI in men ($\beta = -12.7$, 95% CI: -18.8 to -6.6 , $P < .01$).

Conclusions: Active alcohol and/or crack/cocaine use was associated with increased pneumonia severity in PLWH, with less severe pneumonia with marijuana use. Alcohol and marijuana effects on pneumonia severity differed by sex, with increased PSI in women and decreased PSI in men with concomitant marijuana and AUD.

Keywords

alcohol; cocaine; HIV; marijuana; pneumonia; severity of illness

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Author contributions

Both authors contributed to the study design. D.A.W. was responsible for the original data collection. S.E.J. performed the data analysis. Both authors contributed data interpretation and drafting of the manuscript.

Introduction

Community-acquired pneumonia (CAP) remains a frequent complication of human immunodeficiency virus (HIV) infection.^{1,2} Bacterial pneumonia rates are up to 25 times higher in patients living with HIV (PLWH) compared with the general community, with the incidence increasing with decreasing CD4 counts.¹ In developed countries, CAP represents one of the most frequent HIV-associated diagnoses and accounts for a large majority of HIV-related hospitalizations despite the availability of effective combined antiretroviral therapy (cART).³

Substance use is ubiquitous in the United States. Twenty-five percent of individuals over 12 years old report alcohol use, and 10% report use of illicit drugs.⁴ Alcohol use and other substance use account for \$249 and \$193 billion annually as a result of health care costs, lost productivity, and substance use-related crime.⁵ Substance use disorders frequently occur concomitantly with HIV, with up to 10% of new HIV infections attributable to injection drug use (IDU).⁶

Illicit drug use and alcohol use in PLWH are associated with increased complications, including increased risk of CAP.^{7,8} These complications may result from differing host immunologic responses or viral replication or may reflect differences in access to care, including decreased HIV adherence or social instability in patients with ongoing substance use.^{9–12} Alcohol use is independently associated with pneumonia severity in PLWH, with increasing pneumonia severity with escalating alcohol use.¹³ Similarly, cocaine use is associated with an increased incidence of pneumonia¹⁴ and worse outcomes in PLWH.¹⁵ Conversely, cannabis use reduces systemic inflammation and immune activation in PLWH on cART.¹⁶ In non-HIV-infected individuals, cointoxication is associated with increased incidence of pneumonia and greater pneumonia severity.¹⁷ Yet, there are few data examining the interaction between alcohol and substance use on pneumonia severity in PLWH. The goals of this study were to investigate whether substance use was independently associated with pneumonia severity in PLWH admitted for pneumonia and to determine whether active drug use modified the effect of alcohol on pneumonia severity.

Methods

Study design

We performed a retrospective data analysis of data collected from a clinical management pathway study enrolling PLWH admitted to the Interim Louisiana State University Public Hospital in New Orleans between 2007 and 2011 with a presumptive diagnosis of pneumonia. Presumptive pneumonia diagnosis required the following criteria: (1) clinical suspicion of lower respiratory tract infection by the primary health care provider and (2) either new or changing radiographic infiltrate or unexplained hypoxia in the absence of an infiltrate (defined by partial pressure of oxygen <70 mm Hg or oxygen saturation <90% or a drop in oxygen saturation >4% with exertion).

Alcohol exposure

The Alcohol Use Disorder Identification Test (AUDIT) questionnaire, previously validated in PLWH,¹⁸ was administered by interview at the time of enrollment. All subjects with available alcohol use data were included in the current analysis. Based upon published thresholds,^{19,20} an AUDIT score of ≥ 8 was defined as *hazardous* drinking and a score of ≥ 14 defined an *alcohol use disorder* (AUD). Biochemical data of alcohol use were not available in the study cohort.

Substance use

Subjects were questioned via face-to-face interview with a study coordinator regarding the type, quantity, and frequency of substance use. Specifically, subjects were asked to quantify cocaine, crack cocaine, marijuana, heroin, and other drug use. Subjects could report polysubstance use. The route of drug use was recorded, and all subjects were queried regarding any intravenous drug use. Active substance use (alcohol, marijuana, or crack/cocaine use) was defined as use in the month preceding hospital admission.

Pneumonia severity

Pneumonia severity was quantified using the pneumonia severity index (PSI). The PSI is a cumulative risk score composed of demographic, physiologic, and organ dysfunction variables. The PSI is a well-validated marker of pneumonia severity, with increasing scores indicative of an increased odds of 30-day mortality.²¹ The PSI has been validated in PLWH, with PSI risk groups predictive of pneumonia-related mortality.²² All variables contributing to the PSI were obtained at the time of presentation. There were no missing data. The PSI was used as a continuous variable in models exploring the interaction between alcohol use, substance use, and pneumonia severity.

Statistical analysis

Descriptive statistics included means for continuous variables, medians for nonparametric data, and proportions for categorical variables. Bivariate analysis was performed using Student's *t* tests for means, Wilcoxon rank-sum testing for nonparametric data, and chi-square testing for proportions, with Fischer's exact tests for samples with <5 observations. Multivariable linear regression was used to determine whether the presence of an AUD was an independent predictor of PSI when adjusted for active marijuana or crack/cocaine use. Models were adjusted for the following potential confounders chosen a priori based on clinical importance and known literature indicating their significance as CAP predictors in PLWH^{7,8,15}: sex, active crack/cocaine use (within the month preceding admission), active marijuana use (within the month preceding admission), homelessness, current smoking status (yes/no), most recent CD4 count, and self-report of cART adherence. We used interaction terms within our adjusted model to examine the interactions between alcohol and substance use (crack/cocaine and marijuana) and sex. All statistical analyses were performed using STATA software (version 13.0; StataCorp, College Station, TX), and a *P* value $< .05$ was considered statistically significant for bivariate analyses and multivariable models. Interaction terms were considered significant with *P* value $< .1$. The Louisiana State

University Health Sciences Center Institutional Review Board (IRB #5585) approved the parent study, and informed consent was obtained upon enrollment into the parent study.

Results

Cohort characteristics

Our cohort was composed of a total of 196 PLWH admitted for pneumonia between 2007 and 2011. Subjects were predominantly men (71%), with a mean age of 44 (SD = 9) years. Most subjects self-identified their race as African American (87%). A minority of subjects were on cART (30%), with median CD4 cell counts of 60 cells/mm³ (interquartile range [IQR]: 15–131 cells/mm³) and median viral loads of 79, 601 copies (IQR: 2364–258,452).

Substance use patterns

Most subjects (76%) reported a lifetime history of alcohol use. More than half (55%) reported alcohol use prior to hospital admission. Forty-eight subjects (24%) met criteria for hazardous drinking, with 19 subjects (10%) meeting criteria for an AUD. In subjects with active alcohol use (defined as use in the preceding month), 27% ($n = 54$) reported use 4 times weekly, with 12% reporting use 2–3 times/week (Table 1). Other substance use was common amongst PLWH admitted for pneumonia, with 77% of the cohort reporting a lifetime history of any illicit substance use and 6% ($n = 11$) reporting a history of IDU. More than half of the cohort reported a lifetime history of crack/cocaine use (55%, $n = 109$), with 16% ($n = 31$) of the cohort reporting a history of marijuana use and 9% ($n = 18$) reporting lifetime heroin use. In subjects with active alcohol use prior to admission, 25% reported concomitant crack/cocaine use and 16% reported marijuana use. In patients with active crack/cocaine use at time of hospital admission, 8% ($n = 16$) reported weekly use and 8% ($n = 15$) reported daily use. All subjects with crack/cocaine use reported inhalational use, whereas 23% ($n = 9$) reported intravenous and inhalational use. Amongst patients with active marijuana use, 5% ($n = 9$) reported weekly use and 4% ($n = 7$) reported daily use.

PSI scores

The average PSI score for the cohort was 61 (SD = 21). PSI scores were significantly higher for subjects who used alcohol at a high frequency (4 times weekly) (69.6 vs. 55.4, $P < .01$). PSI scores trended higher, on average, for subjects with reported lifetime history of crack/cocaine use (mean PSI: 63.1 vs. 57.3, $P = .06$), whereas there was no significant difference with active crack/cocaine use (61 vs. 55.4, $P = .23$) when compared with subjects without any lifetime substance use (Table 2). Subjects with everyday crack/cocaine use had higher PSI scores, on average, compared with less frequent use, although the difference was not statistically different (61.3 vs. 55.4, $P = .4$). Subjects with reported IDU of any drug had significantly higher PSI scores (68.4 vs. 55.4, $P = .05$). Conversely, subjects with active marijuana use had significantly lower PSI scores (51.5 vs. 62.2, $P = .01$) when compared with subjects with other substance use, but the PSI scores were not different when compared with subjects without any lifetime substance use (51.5 vs. 55.4, $P = .37$). Subjects with daily marijuana use had lower PSI scores than subjects with less frequent use, although the difference was not statistically different (49.1 vs. 55.4, $P = .33$).

Clinical outcomes

Seven subjects (4%) died during the study hospitalization. In-hospital mortality did not differ significantly in subjects who were actively using alcohol (2% vs. 6%, $P = .24$), crack/cocaine (3% vs. 4%, $P = 1.00$), or marijuana (3% vs. 4%, $P = 1.00$). Similarly, there was no difference in the frequency of readmission within 6 weeks of hospital discharge for subjects with active alcohol (18% vs. 27%, $P = .18$), crack/cocaine (23% vs. 20%, $P = .75$), or marijuana (11% vs. 23%, $P = .21$) use.

Interactions between alcohol and substance use

There was a significant relationship between alcohol, marijuana, and PSI. In adjusted models of alcohol and PSI, active marijuana use remained independently associated with decreasing PSI scores. For each point increase in total AUDIT, PSI scores decreased by 7.8 in subjects with concomitant marijuana use (95% confidence interval [CI]: -14.9 to -0.70 , $P = .02$) when compared with subjects without marijuana use. Homelessness and male sex remained independently associated with higher PSI scores (homelessness: $\beta = 6.9$, 95% CI: 0.65 to 13.1 , $P = .03$; male sex: $\beta = 13.9$, 95% CI: 8.0 to 19.8 , $P < .01$). There was no modification of the alcohol effect on PSI with active crack/cocaine use (interaction term P values $> .10$). There was a significant interaction between the presence of an AUD and female sex on PSI scores (interaction $P < .01$). PSI scores were, on average, 59.8 points higher for each point increase in AUDIT score for women with an AUD (95% CI: 53.1 to 66.5 , $P < .01$) (Table 3). There was a significant interaction between active marijuana use and sex on PSI scores ($P = .07$). PSI scores were, on average, 13 points lower for men with an AUD with active marijuana use (95% CI: -18.8 to -6.6 , $P < .01$) (Table 3).

Discussion

In this study, we found that substance use is common and is associated with differential pneumonia severity in PLWH. Increased frequency of alcohol use and injection drug use were significantly associated with more severe pneumonia, with higher PSI scores observed in female patients with AUDs. There was a trend towards increased pneumonia severity with a lifetime history of crack/cocaine use. Use of marijuana was associated with less severe pneumonia in patients with an AUD, and this association was mitigated in men. These findings did not correlate with clinical outcomes.

Our results support prior research demonstrating increased rates of substance use in PLWH.

Substance use may be overrepresented in our cohort, as studies suggest that patients with active substance use are often late HIV presenters and are more likely to undergo hospitalization at time of first acquired immunodeficiency syndrome (AIDS)-presenting diagnosis.²³ As all patients in our cohort were presenting for pneumonia, our cohort was potentially enriched for patients with a substance use disorder given the propensity towards acute illness.

Immunoregulatory effects of crack/cocaine and marijuana

Substance use and alcohol use are known risk factors for pneumonia in non-HIV-infected patients. We previously showed that alcohol use was independently associated with worse pneumonia severity in PLWH.¹³ Our current results demonstrate that there are differential effects of illicit drugs on pneumonia severity. In our cohort, crack/cocaine was associated with greater pneumonia severity whereas marijuana was associated with less severe pneumonia.

Crack/cocaine use is associated with increased incidence of pneumonia in HIV-positive and -negative cohorts.^{3,8, 14,15,24,25} Crack/cocaine is known to increase viral replication and worsen immune suppression in PLWH, providing a plausible mechanism for greater pneumonia severity.^{9,10,12} Further, patients who use crack/cocaine may be more reluctant to seek clinical care at illness onset and may experience greater social isolation limiting access to clinical care.¹⁵

Conversely, marijuana was associated with less severe pneumonia in our cohort. This could not be explained by differences in adherence, as marijuana-using patients were less adherent to cART and opportunistic infection (OI) prophylaxis than non-drug-using patients. Data on the effects of cannabinoids on host response to infection are conflicting. Murine models showed increased toxicity and tissue destruction when endotoxin was combined with cannabinoids, resulting in increased mortality.²⁶ In vitro experiments, however, demonstrate a microbiocidal effect of cannabinoids, particularly *Cannabis sativa*,²⁶ with improvement in bacterial clearance. *C. sativa* exerts direct immunomodulatory effects, resulting in decreased cytokine production and decreased lymphocyte proliferation or antibody formation.²⁷ Although decreased inflammation may lessen the severity of the acute illness, it may ultimately impair pneumonia clearance, leading to worse longer-term outcomes.

Impact of substance use on care engagement and pneumonia risk

Subjects with ongoing substance use with homelessness exhibited increased pneumonia severity in our cohort. It is likely that substance use contributes to social instability, thereby reducing access to care, increasing time to presentation for care, and reducing HIV adherence.^{11,28–30} Excessive alcohol, crack/cocaine, and marijuana use are all shown to reduce adherence to cART.^{11,29} Heavy alcohol use is shown to contribute to missing ART and stopping ART, whereas illicit drug use is significantly associated with missing ART.²⁹ Delays in care, uncontrolled comorbid disease, and greater immunosuppression due to lack of cART may explain the differential effects on pneumonia severity observed in our cohort of PLWH with ongoing substance use.

Differential sex responses to substance use

Interestingly, we found that the interactions between alcohol, illicit drugs, and pneumonia severity were differential by sex. Studies suggest that although women exhibit a lower prevalence of hazardous drinking, those who develop an AUD experience a greater burden of alcohol use sequelae and comorbid disease.^{31,32} A lower threshold for the toxic effects of alcohol may explain some of the differential effects we observed in pneumonia severity in women dependent drinkers.³¹ Additionally, studies demonstrate a greater reduction in

immune activation during acute illness in women with an AUD relative to men.³³ As previously mentioned, marijuana appears to have important down-regulatory effects on the acute immune response, but it is unclear why this response is more pronounced in men. Further, the downstream effects of this down-regulation are yet to be defined. Highlighting this differential response as evidenced by our results will hopefully spur additional investigation into the differential biological effects of substance use on host response by sex.

Limitations

There are notable limitations to our study. Our sample was small and from a single center with a population of predominantly African American HIV patients with severe immunosuppression and poor adherence overall. Therefore, our results may not generalize to all HIV patients. The low mortality and readmission rates within our cohort limited our inferences regarding the effect of substance use on hospital outcomes. Our sample may be underpowered to fully assess the interactions between alcohol use and particular drugs. Drug and alcohol assessment in our cohort was reliant on patient self-report, which may be subject to social desirability bias and subsequent misclassification. Face-to-face interview may underestimate actual drug use compared with anonymous reporting. Further, self-report of alcohol use via the AUDIT may not represent true alcohol use disorders, and future studies should aim to link objective biochemical tests of alcohol use with pneumonia severity.

Significant findings

Our results highlight 3 important clinical findings. First, active crack/cocaine use in PLWH was associated with increased pneumonia severity, whereas marijuana use was associated with less severe disease. Second, there was a significant interaction between active substance use and alcohol use in PLWH and pneumonia severity, with a differential response by sex. Finally, although active substance use was associated with more severe pneumonia in PLWH, there was no significant difference in clinical outcomes in a cohort of hospitalized patients.

Future directions

Future studies should focus on understanding the biological mechanisms contributing to increased pneumonia severity in PLWH with active substance use. These studies should examine the impact of active substance use on bacterial virulence factors and host susceptibility to disease in PLWH. Finally, studies are needed to understand the interplay between marijuana, alcohol, and host responses to pneumonia and the differential response by sex.

Conclusions

Use of crack/cocaine was associated with greater pneumonia severity in PLWH, with increasing illness severity for increasing alcohol use. Use of marijuana was associated with less severe pneumonia with concomitant alcohol use. There was a significant interaction between dependent drinking and sex, with greater pneumonia severity in HIV-positive women with dependent drinking. There was also an interaction between marijuana use and sex, with less severe pneumonia in men with active marijuana use. Further studies are

needed to understand the relationships between marijuana, patient sex, and other substance use disorder with pneumonia pathogenesis.

Acknowledgments

Funding

Dr. Welsh is supported by the NIH/National Institute of Alcohol Abuse and Alcoholism (NIAAA) Comprehensive Alcohol Research Center [P60 AA009803], the CoPARC Clinical Resource for Lung and Alcohol Investigations [R24AA19661], and UH2AA026226. Dr. Jolley is supported by NIH/NIAAA K23 AA026315-01A1. The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1.

Frequency of substance use in a cohort of HIV-infected patients admitted for pneumonia.

Substance use	% (n)
Cocaine	
Less than once per month	1 (2)
Greater than once monthly but less than once weekly	0.5 (1)
Greater than once weekly but less than everyday	1 (2)
Crack	
Less than once per month	1.5 (3)
Greater than once monthly but less than once weekly	5.6 (11)
Greater than once weekly but less than everyday	7.1 (14)
Everyday	4.1 (8)
Marijuana	
Less than once per month	1.5 (3)
Greater than once monthly but less than once weekly	5.6 (11)
Greater than once weekly but less than everyday	4.6 (9)
Everyday	3.6 (7)
Injection drug use	
Less than once per month	3 (1)
Greater than once monthly but less than once weekly	16 (6)
Greater than once weekly but less than everyday	9 (3)
Everyday	14 (5)
Alcohol	
Monthly or less more than 4 times per week	12.2 (24)
2–4 times per month	13.7 (27)
2–3 times per week	11.7 (23)
More than 4 times per week	27.4 (54)
Tobacco use	
Never smoker	21 (42)
Former smoker (quit >3 months)	15 (29)
Active smoker (quit <3 months)	64 (126)

Table 2.

Mean pneumonia severity index (PSI) scores by active substance use and frequency compared with subjects without substance use.

Substance use	Mean PSI with substance use	Mean PSI without substance use	P value
Active cocaine/crack	61 (20.1)	55.4 (18.5)	.23
Lifetime use	63.1 (20)	57.3 (22.9)	.06
Less than once per month	63.3 (19.8)		.32
Greater than once monthly but less than once weekly	62.7 (14.2)		.19
Greater than once weekly but less than everyday	56.3 (17.3)		.87
Everyday	61.3 (24.5)		.40
Active marijuana	51.5 (16.1)	55.4 (18.5)	.37
Lifetime use	60.9 (21.7)	59.7 (21.1)	.72
Less than once per month	51.3 (11)		.71
Greater than once monthly but less than once weekly	48.2 (10.6)		.18
Greater than once weekly but less than everyday	60.1 (17.3)		.45
Everyday	49.1 (15.2)		.33
Active injection drug use	68.4 (18.8)	55.4 (18.5)	.05
Lifetime use	68.9 (16.6)	59.3 (21.9)	.04
Less than once per month	90		
Greater than once monthly but less than once weekly	60.7 (16.2)		.52
Greater than once weekly but less than everyday	76.7 (24.5)		.07
Everyday	62.4 (12.9)		.42
Active alcohol use	62.1 (23.3)	55.4 (18.5)	.13
Lifetime hazardous drinking (AUDIT 8)	67.7 (23.7)	58.5 (20.5)	.01
Monthly or less	51.5 (24.4)		.50
2–4 times/month	64.6 (19.8)		.07
2–3 times/week	52.6 (16.6)		.57
4 or more times/week	69.6 (24.3)		<.01

Bolded values represent values less than the pre-specified significant p-value of <0.05

Table 3.

Patient sex modifies the effect of an alcohol use disorder and active marijuana use on pneumonia severity index (PSI) score.

Substance use	β	95% confidence interval	P value
Female sex			
Alcohol use disorder (AUD) ^a	58.1	46.7 to 69.5	<.01
Active marijuana use ^b	-3.7	- 17.7 to 10.3	.60
Active crack/cocaine use	-4.9	-16.3 to 6.5	.39
CD4 count	0.03	-0.01 to 0.06	.13
Homelessness	9.5	-0.04 to 19.1	.05
Smoking	2.0	-9.4 to 13.4	.73
cART ^c	3.9	-7.3 to 15.1	.48
Male sex			
AUD	5.3	-6.5 to 17.0	.37
Active marijuana use	- 12.7	- 18.8 to -6.6	<.01
Active crack/cocaine use	-3.9	-12.6 to 4.8	.38
CD4 count	-0.01	-0.03 to 0.01	.40
Homelessness	4.7	-3.1 to 12.4	.23
Smoking	5.1	-5.3 to 15.4	.34
cART	1.1	-7.3 to 9.4	.80

Bolded values represent values less than the pre-specified significant *p*-value of <0.05

^aAlcohol use disorder: total Alcohol Use Disorder Identification Test score ≥ 14 .

^bActive use: use <3 months prior to admission.

^ccART = combined antiretroviral therapy.