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Cocaine Use May be Associated with Increased Depression in Persons Infected with HIV

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Abstract

Background—HIV infection, depression, and cocaine use are independently associated with increased inflammatory signal production. There is increasing evidence about the role of inflammation in depression. In HIV disease, cocaine use may increase disease progression as well as alter T-cell functioning resulting in cytokine activation and thereby increasing susceptibility to depression.

Methods—We examined the association between cocaine use and depression among 447 African American persons infected with HIV who were frequent cocaine users or non-users, enrolled in an observational study in Baltimore, Maryland, between August 2003 and December 2012.

Results—The overall prevalence of depression was 40.9% (183 of 447) participants. Among persons who were depressed, the prevalence of cocaine use was 81.4% (149 of 183), compared to 69.3% among persons who were not depressed (183 of 264), *P*=0.004. Cocaine use was associated with nearly 2-fold increased odds of depression, unadjusted odds ratio (OR)=1.94, (95% CI: 1.23, 3.06); *P*=0.004, compared to never using cocaine, and OR=1.02, (95% CI: 1.10, 1.05); *P*=0.04 in adjusted analysis. A dose-response relationship between increasing duration of cocaine use and depression was observed.

Discussion—Frequency and duration of cocaine use may be associated with depression. We speculate that depression among cocaine users with HIV may involve an inflammatory component that needs further examination.

Keywords

HIV; Cocaine; Depression; Mental health

Introduction

Major depression is a common co-morbidity in persons with HIV and substance use disorders (1-3). This co-morbidity represents a multifactorial relationship. Whereas

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depression increases the risk of acquiring HIV and substance use disorders, both depression and substance use disorders are associated with increased progression and mortality in persons with HIV (3-7). Major depression, HIV infection, and cocaine use have all been independently associated with increased inflammation (8-12), and this convergence may result in increased medical comorbidity.

Depression is the most common psychiatric disorder associated with HIV/AIDS with a lifetime prevalence of 22-45% (13,14). Persons who are depressed are more likely to contract HIV through engaging in risky behavior than non-depressed individuals, including having sex for money or drugs, having sex when intoxicated by drugs or alcohol, having sex with intravenous drug users, and having a greater number of lifetime sexual partners (15).

Substance use and depression in persons infected with HIV are associated with increased likelihood of treatment non-adherence (16-21), which may result in antiviral drug resistance and poor HIV outcomes. In persons with comorbid HIV and depression, the use of stimulants such as cocaine may alter the biological pathways for both conditions (9,22-25).

Cocaine use is associated with increased T-cells susceptibility to HIV and increased rate of viral integration into host cells (26). A hypothesized pathway by which cocaine may affect T-cell functioning in the presence of HIV may be related to cytokine release from immune activation in response to cocaine use (23,26-28).

Cocaine use is associated with increased risk of HIV infection, decreased adherence to antiretroviral therapy (ART), lower CD4+ T-cell count, higher plasma HIV RNA and increased HIV disease progression compared with other substances of abuse such as marijuana and alcohol. This potentially bi-directional association between cocaine use and decreased ART adherence may increase HIV progression further worsening depression (29-32).

Recent findings have identified altered cytokine profiles, IL-4 and IL-10, to be positively associated with cocaine use in African American male cocaine users (33). Although Whites are more likely than African Americans to report a lifetime use of any cocaine use, African Americans are more likely than Whites to report lifetime use of crack cocaine (34), a more additive type of cocaine. The disparity of HIV infection continues to persist. The Centers for Disease Control and Prevention in 2010 reports a 7.9 fold higher rate of new HIV infections among African Americans compared with Whites (35). In 2010 although they made up only 12% of the United States population, African Americans experienced 44% of all new HIV infections compared with 31% new infections among White persons (36).

Because of increasing evidence supporting cytokine-induced depression (10,37-44), we examined the association between cocaine use and depression among African American persons infected with HIV who were on antiretroviral therapy (ART). An evaluation of the association between cocaine use and depression in persons with HIV would inform future research to identify inflammatory markers of depression in HIV. We hypothesized that cocaine use is associated with increased depression in persons with HIV. We also sought to evaluate how HIV treatment (duration of each ART drug use and duration of ART use for each ART class), viral control (CD4 cell count and HIV RNA quantification at study entry),

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cigarette smoking and alcohol use may modify the association between cocaine use and depression

Methods

Study Participants and Measures

Between August 2003 and December 2012, 447 African American persons infected with HIV who were frequent cocaine users or non-users, were enrolled in an observational study investigating the effects of cocaine use and antiretroviral regimens on subclinical atherosclerosis in Baltimore. The goal of the overall study was to investigate the association between cocaine abuse, antiretroviral therapy (ART), and other factors which might be associated with increased risk for subclinical atherosclerosis in African American men and women with HIV infection aged 25 years or older. All persons on ART were eligible to be included in these analyses. Exclusion criteria were any evidence of active clinical coronary artery disease at entry (CAD), any symptoms believed to be related to CAD at entry, glomerular filtration rate <60 mL/min/1.73 m^2, known allergy to the contrast used for the computerized tomography scan, and pregnancy. The study was restricted to non-cocaine users and chronic cocaine users defined as cocaine use at least 4 times a month for at least 6 months, by any route. We excluded infrequent cocaine users, persons who use cocaine fewer than 4 times a month, or for less than six consecutive months.

Clinical information including the diagnosis of major depressive disorder (MDD) was obtained from a database of abstracted medical history in medical charts, and medication information was obtained from medical records. A diagnosis of MDD by Diagnostic and Statistical Manual of Mental Disorder, 4^{th} Edition (DSM-IV) criteria within the last 6 months determined by Psychiatric providers who work closely with treating clinicians was recorded as depression. Persons with other mood disorders were not excluded. Persons identified with MDD included newly diagnosed and untreated MDD, and previously diagnosed but unresolved MDD regardless of treatment status. Interviews regarding sociodemographics and drug-use behaviors were conducted; clinical examinations, blood pressure (BP) measurement, echocardiography and 64-slice multidetector computed tomography coronary angiography (contrast-enhanced) were performed; and lipid profiles, vitamin D, and high sensitivity C-reactive protein (*hs*CRP) levels obtained. The Johns Hopkins Medicine Institutional Review Board approved the study protocol and all study participants provided written informed consent. All procedures used in this study were in accordance with Institutional guidelines.

Statistical analysis

Statistical analysis was performed using SAS (version 9.3, SAS Institute, Cary, NC). Continuous parameters were summarized by medians and interquartile ranges (IQRs), and categorical parameters were summarized as proportions. To compare between-group differences, the nonparametric Wilcoxon two-sample test was used for continuous variables and the Fisher's exact test was used for categorical variables.

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We fit logistic regression models to assess the association between cocaine use and depression. Univariate logistic regression models were fit to evaluate the crude association between each covariate and depression. Potential confounders and effect modifiers of the association between cocaine use and depression that were assessed in univariate analysis include age, sex, cigarette smoking, alcohol use, baseline CD4 cell count, baseline HIV RNA quantification, duration of each ART drug use, duration of ART use for each ART class [nucleoside reverse-transcriptase inhibitors (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (FI) or integrase inhibitors], duration of any ART use, and cocaine or other illicit drug use. We retained covariates that were significant at $P \leq 0.20$ level in univariate models for inclusion in multivariable logistic regression models. Covariates that ceased to make significant contributions to the model were eliminated in a stepwise backwards manner, yielding a final model. The *P*-values reported are two-sided and statistical significance was determined at $P < 0.05$.

Results

A total of 447 participants were included in these analyses. Mean age was 46 years, 38.6% were female and prevalence of cocaine use was 74.3% (*Table 1*). The overall prevalence of depression was 40.9% (183 of 447) participants. Among persons who were depressed, the prevalence of cocaine use was 81.4% (149 of 183), compared to 69.3% among persons who were not depressed (183 of 264), $P=0.004$ (*Table 1*). Persons who were depressed had a longer duration of HIV infection, were more likely to be on protease inhibitor based ART regimen, and were more likely to have longer duration and higher frequency of cocaine use. There was no difference in *hs*CRP levels among cocaine users and non-users

In univariate analysis, any use of cocaine was associated with approximately 2-fold increase in odds of depression, compared to never using cocaine, OR=1.94, (95% CI: 1.23, 3.06); $P=0.004$), *Table 2*. The odds of depression was increased regardless of ART use, OR=2.16; (95% CI: 1.32, 3.52); $P=0.002$. Among persons on protease inhibitor-based ART the odds of depression was increased by 2.75, (95%CI: 1.87, 4.14); $P<0.0001$. Persons on NRTI based regimen also had an increased odds of depression, OR=1.80, (95% CI: 1.16, 2.80); $P=0.009$ *(Table 2)*. Female sex was associated with a 1.5 fold increase in odds for depression. There was no association between alcohol use, cigarette smoking, use of other drugs and depression.

When adjusted for sex, duration of cocaine use, years of HIV infection and Protease inhibitor use, each year of cocaine use was associated with a 2% increased odds of depression, adjusted odds ratio =1.02, 95% CI: 1.01, 1.05); $P=0.04$ *(Table 3)*. Each year of HIV infection was associated with a 5% increase in odds of depression and a protease inhibitor-based ART regimen was associated with a more than 2-fold increase in odds of depression. *Figure 1* shows a dose-response relationship between increasing duration of cocaine use and increasing depression. After 5 years of cocaine use the prevalence of depression among persons with HIV was at least 45% compared to 28% among persons who had never used cocaine.

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Discussion

We determined that cocaine use, duration and frequency of use, were associated with increased odds for depression. On the other hand alcohol use, cigarette smoking and use of other drugs were not associated with increased depression in this study population. Our study population has been previously studied with findings to support that cocaine use is associated with the development of soft and hard plaque in cardiac blood vessels (45,46), suggesting an association between cocaine use and chronic inflammatory damage. Under the inflammatory model for depression, cocaine use may increase depression in persons with HIV by inducing chronic inflammatory changes rather than acute inflammation, suggested by normal hsCRP levels which showed no difference by depression status.

African Americans are disproportionately affected by HIV and substance use disorders, compared with Whites. Disparities concerning access to health care persist for African Americans (47), which places them a higher disadvantage of experiencing the untoward effects of HIV including comorbid HIV infection, substance use and depression. Because HIV increases the risk of MDD and substance use, our finding that frequent cocaine use may be associated with MDD in African Americans has implication for HIV care and psychiatric care.

Protease inhibitor use was associated with increased odds of depression. A number of explanations remain for this observation. The association between protease inhibitors and increased odds for depression may be a result of confounding by indication. Protease inhibitors by themselves may have good CNS penetration and therefore reduce the CNS HIV reservoirs (48). However because protease inhibitors have been associated with decreased depression scores (49), persons with depression or at increased risk for depression may be assigned treatment with protease inhibitors. As such, protease inhibitors may be used at higher rates with patients likely to exhibit higher symptoms of depression, representing confounding by indication. Also protease inhibitors have a higher threshold for resistance compared to (50), therefore persons more likely to be non-adherent may be assigned this class of drugs. Protease inhibitors have been associated with endoplasmic reticulum stress (51,52), which may lead to activation of proviral HIV particles and increased CNS inflammation, which may precipitate depression.

For each year a person is infected with HIV, the odds of depression increases. This may suggest an ongoing pathogenic role of the virus in developing depression. Our findings are consistent with prior reports of increased depression among females (53). We did not observe associations between alcohol and cigarettes use and depression. Previous reports support an association of increased depression among smokers and persons and alcohol use (54,55). Our observed lack of association could be due to the fact that cocaine use in this population may be a stronger predictor of depression than alcohol or cigarette use.

Because the current work evaluates depression diagnosis within the last 6 months including previously diagnosed but unresolved depression regardless of treatment status, our findings may represent an underestimation of the true association between cocaine use and depression. Furthermore among persons with HIV, depression may be under diagnosed and

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undocumented in as many as 45% or persons with HIV (56,57). This may additionally support an underestimated of the reported association between cocaine use and depression.

A limitation in these analyses is the cross-sectional study design. We are therefore unable to ascertain a causal association between cocaine use and depression. However our findings provide basis for this association to be further evaluated. By including persons who used cocaine for more than 6 months in these analyses, cocaine use was assessed to precede a diagnosis of depression among persons without a prior depression diagnosis. We did not account for depression treatment received which could affect the observed association. This may translate into our results being conservative estimates. We also did not account for hepatitis C viral (HCV) infections or treatment for HVC. HCV is a frequent comorbidity in persons with HIV and is associated with high depression rates (58-60). The dose-dependent association we observed between duration of cocaine use and depression strengthens our findings. Future studies need to evaluate a temporal association and the mechanisms by which cocaine use may increase depression in persons with HIV. Because infrequent cocaine users (persons who used cocaine fewer than 4 times a month or for less than six consecutive months) were excluded from these analyses, we reduced the possibility of misclassifying cocaine use. This approach may limit interpretation and comparison of our findings to prior research. By excluding infrequent users however, we increased the likelihood that persons captured in these analyses are cocaine abusers or dependent on cocaine. These findings may therefore not be generalizable to infrequent cocaine users. However our approach is relevant to frequent cocaine users and the observed dose-response association between frequent cocaine use and depression may suggest a potential association even among infrequent cocaine users, a hypothesis that needs further exploration. These findings are not intended to make an inference regarding all cocaine users but instead about frequent cocaine users.

Our findings among African American men may not be completely generalizable to the general population without understanding trends in depression among races, male and female sex, and substance differences between genders. Generally depression rates in females are higher compared with males (53), with Whites reporting higher depression rates than African Americans (61), and observed racial differences in substance abuse across populations (62,63). Race, sex and drug substance abuse rates may be effect modifiers of this association between cocaine use and depression which future research could help to understand better.

Conclusion

In conclusion, cocaine use, frequency and duration, may be associated with depression. Alcohol use, cigarette smoking and abuse of other substances were not associated with depression in our study population. We speculate that depression among cocaine users with HIV may involve an inflammatory component that needs further examination of CSF and plasma inflammatory signals.

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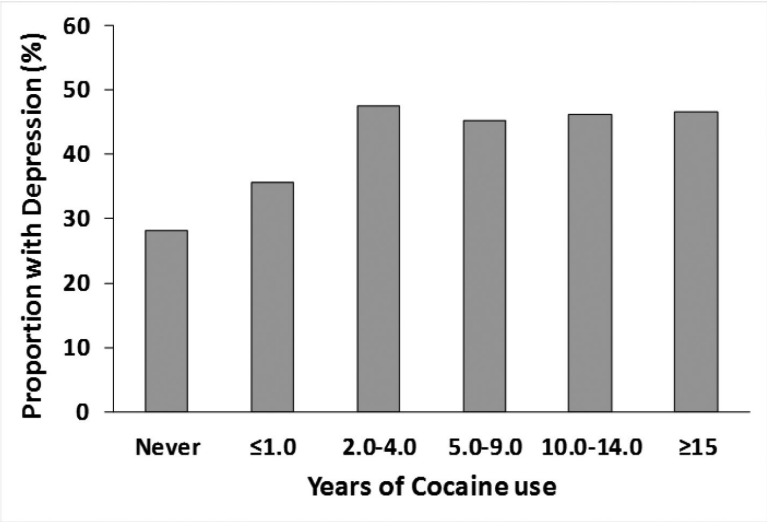

Figure 1.
Prevalence of Depression by Duration of Cocaine Use Among Persons with HIV

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Table 1

Characteristics[a] of Study Participants, by the Presence of Depression

Characteristic	Total (N = 447)	Depression		*P*-value
		No (N = 264)	Yes (N = 183)	
Age (year)	46 (41-51)	46 (41-52)	46 (42-50)	0.74
Female (%)	38.6	34.3	44.8	0.025
Cocaine use (%)	74.3	69.3	81.4	0.004
Years of cocaine use	8 (0-18)	6(0-15)	10 (3-19)	0.001
Times of cocaine use per day	2 (0-4)	2 (0-4)	2 (1-4)	0.03
Cigarette smoking (%)	82.6	82.3	83.1	0.83
Years of cigarette smoking	21 (7-30)	21 (7-31)	22 (9-30)	0.83
Alcohol use (%)	87.5	87.9	86.9	0.74
Years of alcohol use	16 (5-27)	15 (5-25)	18 (4-28)	0.49
Heroin use (%)	50.2	48.3	53.0	0.33
Marijuana use (%)	72.1	72.5	71.6	0.84
Speedball (%)	32.7	30.2	36.3	0.17
Amphetamine (%)	4.5	4.5	4.4	0.94
Methadone (%)	19.2	16.7	23.0	0.10
hsCRP ≥2 mg/dL (%)	49.2	47.7	51.4	0.45
hsCRP (mg/dL)	2.0 (0.6-5.0)	1.9 (0.6-4.8)	2.1 (0.6-5.1)	0.94
BMI (kg/m^2)	25.0 (22.1-29.3)	25.0 (22.2-28.9)	25.2 (22.0-29.9)	0.95
CD4 ($cells/mm^3$)	462(284-686)	463 (274-702)	461 (302-669)	0.90
HIV Viral load (c/mL)	34(20-400)	48(20-400)	23 (20-114)	0.12
Years of HIV infection	12.4 (6.6-17.6)	10.4 (4.5-16.2)	14.4 (10.0-18.7)	<0.0001
NRTI use (%)	72.5	67.9	79.2	0.008
NNRTI use (%)	34.6	35.5	33.3	0.64
PI use (%)	60.0	50.6	73.8	<0.0001
ART use (%)	77.9	72.8	85.3	0.0018

Abbreviations: hsCRP: high-sensitivity C-reactive protein; BMI: body mass index; ART: antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

[a]Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

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Table 2

Unadjusted Odds Ratios for the Association between Demographic, Laboratory, and Clinical Factors and Clinical Depression by Logistic Regression Analysis

Covariate	Crude OR (95% CI)	*P*-value
Age	1.00 (0.98-1.02)	0.87
Sex		
Male	1.00	
Female	1.55 (1.06-2.28)	0.03
Cigarette smoking		
Never	1.00	
Ever	1.06 (0.64-1.74)	0.83
Alcohol use		
No	1.00	
Yes	0.91 (0.52-1.60)	0.74
Cocaine use		
Never	1.00	
Ever	1.94 (1.23-3.06)	0.004
Duration of cigarette smoking (year)	1.00 (0.99-1.01)	0.81
Duration of alcohol use (year)	1.01 (0.99-1.02)	0.47
Duration of cocaine use (year)	1.03 (1.01-1.05)	0.004
Years of HIV infection	1.06 (1.04-1.09)	<0.0001
hsCRP>2 mg/dL		
No	1.00	
Yes	1.16 (0.79-1.69)	0.45
BMI (kg/m^2)	0.99 (0.97-1.03)	0.71
NRTI use		
No	1.00	
Yes	1.80 (1.16-2.80)	0.009
NNRTI use		
No	1.00	
Yes	0.91 (0.61-1.35)	0.64
PI use		
No	1.00	
Yes	2.75 (1.83-4.14)	<0.0001
ART use		
No	1.00	
Yes	2.16 (1.32-3.52)	0.002

OR: odds ratio; hsCRP: high-sensitivity C-reactive protein; BMI: body mass index (kg/m^2); NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; ART: antiretroviral therapy.

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Table 3

Adjusted Odds Ratios for the Association between Demographic, Laboratory, and Clinical Factors and Clinical Depression by Logistic Regression Analysis

Covariate	Adjusted OR (95% CI)	*P*-value
Sex		
Male	1.00	
Female	1.60 (1.06-2.41)	0.03
Duration of cocaine use, years (continuous)	1.02 (1.01-1.05)	0.04
Years of HIV infection	1.05 (1.02-1.08)	0.001
Protease Inhibitor use	2.22 (1.43-3.45)	0.0004

OR: odds ratio; Adjusted for sex, duration of cocaine use, years of HIV infection and Protease inhibitor use.