Longitudinal Modeling of Depressive Trajectories Among HIV-infected Men Using Cocaine

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Abstract

Cocaine use is prevalent among HIV-infected individuals. While cross-sectional studies suggest that cocaine users may be at increased risk for depression, long-term effects of cocaine on depressive symptoms remain unclear. This is a longitudinal study of 341 HIV-infected and uninfected men (135 cocaine users and 206 controls) ages 30 to 60 enrolled in the Multicenter AIDS Cohort Study during 1996–2009. The median baseline age was 41; 73% were African-American. In mixed-effects models over a median of 4.8 years of observation, cocaine use was associated with higher depressive symptoms independent of age, education level, and smoking (n=288; p= 0.02); HIV infection modified this association (p= 0.03). Latent class mixed models were used to empirically identify distinct depressive trajectories (n=160). In adjusted models, cocaine use was associated with 3-fold increased odds of membership in the class with persistent high depressive symptoms (95% confidence interval (CI) 1.38–6.69) and 8-fold increased odds (95% CI (2.73–25.83) when tested among HIV-infected subjects only. Cocaine use is a risk factor for chronic depressive symptoms, particularly among HIV-infected men, highlighting the importance of integrating mental health and substance use treatments to address barriers to well-being and successful HIV-care.

Keywords

HIV; cocaine; crack cocaine; depression; cognitive function

Background

Cocaine use is prevalent among HIV-infected populations and has been associated with lower rates of viral suppression, faster decline of CD4 cell counts, and increased AIDS-related morbidity (1–8). Among 3000 HIV-infected individuals receiving care in United

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CONFLICTS OF INTEREST

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States (U.S.) cities, 8.5% reported using crack cocaine and recent use was associated with detectable viral loads and nonadherence to antiretroviral therapy (ART) (4). While white Americans are more likely to report lifetime cocaine use (powder or crack cocaine) than black or Hispanic Americans, black Americans report more crack cocaine use than white or Hispanic Americans (9). The high reporting of crack cocaine use is particularly evident among impoverished black communities in the U.S. South (10, 11), an area that comprises a disproportionate share of new HIV infections and deaths among persons living with HIV (11–14). Moreover, crack compared to powder cocaine is specifically associated with an immediate euphoric effect, greater risk for dependence, compulsive use, and faster HIV disease progression (2, 15); controversial laws mandating unequal prison sentences for crack cocaine relative to powder cocaine use remain in place, and continue to impact black and economically disadvantaged Americans disproportionately (9).

Cocaine users, including individuals using crack cocaine, are more likely to engage in high-risk behaviors linked to increased HIV transmission rates including unsafe sexual and needle-sharing behaviors and ART non-adherence (4, 8, 16–21). Among HIV-infected cohorts, living alone or with someone other than a spouse or partner, was predictive of screening positive for drug dependence, which may result in part from factors that include difficulty sustaining relationships or successfully living with others (1); among crack users, homelessness was associated with reduced pharmacy refills for ART despite access to free medication (19). Cocaine use may influence behavior by increasing impulsivity and reducing inhibitory control, reasoning, planning, and emotional regulation (22–26), suggesting that understanding the effects of cocaine use, particularly crack cocaine, on mood and cognitive function in HIV-infected individuals is important for the development of policies and HIV-care programs that enhance access to appropriate care providers, improve prevention and disease management, and increase individual well-being (27).

Major depressive disorders and cognitive impairment are common co-morbidities in people living with HIV infection that have been associated with poor health outcomes (1, 4, 27–30). In a U.S.-based national survey, people living with HIV infection were five times more likely to report a diagnosis of major depression compared to similar survey responses in the general population; increased likelihood of screening positive for a psychiatric disorder was greater among persons who were unemployed, disabled, and living alone (1). Additionally, mental health, including depression, has a major influence on sexual risk behavior and HIV infection across several studies (31, 32), and is of particular concern among men who have sex with men (MSM), especially in racial/ethnic minority communities including black men (32, 33).

Chronic cocaine use has been associated with greater depressive symptoms (27, 34) and cognitive impairments in domains that include attention, executive function, and verbal learning/memory (23, 28, 35, 36). In the general population, cocaine users who report high depressive symptoms are also more likely to exhibit cognitive impairment and impulsivity (37), suggesting a multifaceted relationship between depression and cognitive function in the context of cocaine use. Chronic cocaine exposure has neurotoxic effects that include alterations in glutamate levels in brain regions such as prefrontal cortex, and mesolimbic structures such as ventral tegmentum and nucleus accumbens (38). Decreases in functional

connectivity between prefrontal cortex and underlying subcortical limbic structures among daily or weekly cocaine users suggests that neuroadaptive changes lead to large-scale alterations in brain circuits engaged in emotional regulation (39). While cross-sectional studies suggest that HIV-infected cocaine users may be at greater risk for depression and cognitive impairment, longitudinal studies using matched controls are limited (11, 28, 40–43).

The relative contributions of all factors including psychosocial and social contextual (including stigma), behavioral (including drug use), and HIV-related host factors in the pathogenesis of depression in HIV-positive persons require deeper understanding (44–46). Given the integrated prefrontal and limbic circuitry involved in both depression and neurocognitive impairment influenced by drug use and HIV infection, the purpose of the current study was to understand the influence of daily or weekly cocaine use and HIV infection on baseline and longitudinal reporting of depressive symptoms and cognitive trajectories. In a study of 341 HIV-infected and HIV-uninfected predominantly black men participating in the Multicenter AIDS Cohort Study (MACS) from 1996–2009, we used mixed-effects models to determine whether cocaine use (primarily crack cocaine) and HIV infection have independent effects on depressive symptoms based on the Center for Epidemiological Studies Depression Scale (CES-D) and cognitive scores over time. We then used latent class mixed models (LCMM) to empirically identify individuals with similar trajectories of depressive symptoms, and examined relationships between cocaine use, HIV infection, and persistently high depressive symptoms.

Methods

Participants and Data Collection

The MACS is an ongoing prospective study of the natural and treated histories of HIV infection in men who have sex with men. The study recruited men from four urban centers (Los Angeles, Chicago, Pittsburgh, and Baltimore/Washington D.C.) in three enrollment waves: 1984–1985, 1987–1991, and 2001–2003 with a focus on racial and ethnic minority recruitment during recruitment waves two and three; details of study design and enrollment patterns have been described elsewhere (47). The Institutional Review Board at each clinical site approved the study protocols, and informed consent was obtained from all participants. MACS participants return every six months for detailed interviews, physical examinations, and biological specimen collection. Interviews include questions about medical conditions and treatments, cigarette and alcohol consumption, and cocaine, marijuana, amphetamines/methamphetamine, heroin, 3,4-methylenedioxy-methamphetamine (MDMA)/3,4-Methylenedioxyamphetamine (MDA), and nitrite inhalant (poppers) use. Questions about sexual and drug use history are administered by audio computer assisted self-interview (ACASI). In 1988, the MACS began a neuropsychological substudy which includes neurocognitive tests evaluating multiple cognitive domains related to HIV-associated neurocognitive disorders; biannual testing for all parcipants began in 2005 (47). All data were obtained from the MACS public dataset (p23 release; http://www.ntis.gov/search/index.aspx) and translated to create a local SQL database.

Study Design

This longitudinal nested study was restricted to MACS participants ages 30 to 60, an age window with consistent data coverage for testing of depressive symptoms and cognitive performance, enrolled in the neuropsychological substudy between 1996 and 2009. Exclusion criteria included a diagnosis of central nervous system (CNS) toxoplasmosis or lymphoma, progressive multifocal leukoencephalopathy, or cryptococcal meningitis; participants who seroconverted during the study period were excluded. To evaluate cocaine-related effects on depression and cognitive performance, participants using daily marijuana, or daily or weekly amphetamine/methamphetamine, MDMA/MDA, or heroin were also excluded (n=38; 22% of heavy cocaine users). HIV-infected and HIV-uninfected cocaine users were matched to respective control groups (minimal or/no cocaine use) for baseline age, race, education level and hepatitis C virus (HCV)-antibody serostatus in a 1:2 ratio using the MatchIt package in R (Version 3.1); controls lacking cognitive test scores were excluded. The final cohort consisted of 341 men ages 30 to 60 years (n=135 cocaine users, n=206 controls).

Demographic and Clinical Covariates

Cocaine use was the primary exposure of interest. Subjects were classified based on self-reported frequency of cocaine use as heavy users (daily or weekly use for at least one year in the study interval) and compared to controls (monthly or no use at all visits). Eighty-four percent of heavy cocaine users reported crack cocaine use. Crack and powder cocaine were combined into a single cocaine exposure variable given insufficient statistical power to test their respective effects. Race and ethnicity was categorized as African-American/Black, White, and Other (Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native). Education was categorized as 12 or >12 years of education; HCV status was categorized as HCV-positive (detectable antibody and/or RNA) or HCV-negative. Self-reported alcohol consumption of more than 14 drinks/week or 5 drinks/day at two visits in the study interval was classified as heavy drinkers and compared to moderate/nondrinkers. Self-reported tobacco cigarette use of ½ pack/day or more on two visits during the study interval was classified as heavy smokers and compared to light/nonsmokers (0 to < ½ pack/day).

HIV-Related Characteristics

At each six-month visit, HIV-uninfected participants were tested for HIV seroconversion to validate continued enrollment in the uninfected group. HIV-infected participants were tested for T-cell subsets using standardized flow cytometry, and plasma HIV RNA was quantified using the Roche Amplicor RNA kit (detection limit <400 copies/mL) or the Roche Ultrasensitive RNA PCR assay (detection limit <50 copies/mL) (34). Self-reported ART adherence was measured at baseline and categorized at 95% of visits in study.

Depression and Neurocognitive Scores

The CES-D scale includes 20 items measuring frequency of depressive symptoms ranging on a four-point rating scale with maximum score of 60; higher scores indicate more frequent depressive symptoms. CES-D scores can be separated into four subscales assessing: (1)

depressed affect, (2) vegetative depression, (3) loss of wellbeing and (4) interpersonal relationships (48).

The neurocognitive battery included the Grooved Pegboard Test, Rey-Auditory Verbal Learning Test, Stroop Task, Trailmaking Test, Symbol-Digit Modalities Test, and California Computerized Assessment Package (49). Raw scores on neurocognitive tests were normalized by z-scoring, using the mean and standard deviation from education-matched HIV-uninfected controls aged 30 to 39 years from the MACS as the reference group. Reference norms from the MACS, as opposed to national reference norms, were used to account for biases typical for study recruitment procedures in HIV-seropositive cohorts (i.e. incentives may attract participants who are unemployed, have prior or current substance use, high prevalence of Hepatitis C or other coinfections) (50). The signs for some timed tests were transformed so that higher z-scores always denote better performance. Z-scores allow for neurocognitive tests to be on a common scale with approximately equal weighting for creation of composite domains and is a preferred method for examining longitudinal effects (51). The summary cognitive score (NPZ16) used to capture heterogeneity was derived from a battery of 16 individual cognitive tests testing verbal learning and memory, executive function, speed of processing and attention, and motor skills (Supplementary Table I).

Statistical Analyses

Simple univariate/bivariate tests were conducted using Wilcoxon Rank-Sum Test, paired *t*-test, Pearson χ^2, or analysis of variance (ANOVA) for cohort characteristic comparisons (Table I) and baseline depression and cognitive analyses (Supplementary Table II). Longitudinal analyses of depressive trajectories and cognitive decline were conducted in subjects with ≥2 CES-D evaluations (n=288, average 9 time points/participant [range 2–14]) or neurocognitive scores (n=242, average 3 time points/participant [range 2–9]), respectively. The association between heavy cocaine use, HIV-infection, and change in depression scores was examined using mixed-effects models with interaction terms for HIV-infection with time, cocaine use with time, and their joint interaction with time. Baseline age at study entry was treated as a continuous variable; education, HIV infection, cocaine, and smoking were analyzed as binary covariates. Baseline age was calculated based on year of birth and study visit at entry, providing only an approximate but reasonably accurate assessment of age. While using baseline age and year after study entry provides an indirect measurement of a subject's age (i.e. study increments occur in tandem with age within a subject), the age of each subject was not directly modeled. A backward elimination procedure (cutoff p< 0.05) was used on a large initial pool of fixed predictors and variances/ covariances of random terms, as described (52). The association between covariates and the summary cognitive z-score was analyzed in a separate mixed-effects model. Random predictors were correlated intercepts and linear slopes of time. Analyses were performed using SAS PROC MIXED version 9.3 (SAS Institute, Cary, NC).

Latent class mixed models (LCMM) is an analytical method that clusters subjects with similar trajectories into latent classes, maximizing homogeneity within and heterogeneity across groups (53–56). In LCMM, the latent variable represented the trajectory of depressive symptoms over six years. Optimal data coverage for LCMM was from participants between

ages 37–60 for CES-D. Model fit was determined by Bayesian Information Criterion (BIC), value of group membership probability and average posterior probability (entropy statistic), and distribution of subjects across latent classes. Each subject was assigned exclusively to the latent class for which the participant had the highest posterior probability of membership. Subjects with maximum posterior probabilities <0.65 were not classified into trajectory groups to maintain sufficient internal reliability (57); we set an *a priori* requirement for at least 5% of the total number of subjects to be classified in a trajectory group for inclusion in subsequent logistic regression analyses, a decision based on review of publications excluding minor groups not meeting an *a priori* population size estimate (58). The CES-D score, coded such that lower scores corresponded to worse depressive symptoms, was transformed by taking the square root of the score (to reduce skewness). Models were fit and trajectories for each latent class were plotted with 95% confidence intervals (CIs) using the lcmm package and supersmooth function in R.

The best-fitting model for the entire sample was determined to be a 5 class model. A logistic regression model and stepwise automated selection was then performed to assess significant clinical, demographic, and substance-related predictors associated with persistent high depressive symptoms versus low/moderate depressive symptoms class membership. Candidate variables were selected for multivariate analysis with p<0.2 (Wald test). Descriptive statistics and logistic regression was conducted in GraphPad Prism and SAS.

Results

Study Cohort

Clinical characteristics of study participants by HIV status and cocaine use are shown in Table I (n=341; 194 HIV-infected, 147 HIV-uninfected men). The median age was 42 years at study entry (IQR 37–45), and the majority were black (73.3%); HCV seropositivity was common (22%). After exclusions for using other drugs of abuse in subjects reporting daily or weekly cocaine use, crack cocaine was the most commonly used form of cocaine (84.8%). Cocaine use was associated with baseline heavy smoking and alcohol use (p<0.01). Groups were similar with respect to baseline age, race, education, HCV serostatus and length of follow up. While HIV-infected cocaine users had similar baseline CD4 cell counts, and CD4 nadir during follow-up compared to controls (Table I), users were more likely to have plasma HIV RNA 400 copies/mL (p=0.02) and report lower ART-adherence (p < 0.01).

Cocaine Use, HIV status, and Depressive Trajectories

HIV-infected cocaine users were more likely than HIV-infected controls to have CES-D scores 16, a cutoff suggestive of high depressive symptoms (p <0.01, Table I), and nearly half reported using an antidepressant at the baseline visit. Among all participants, HIV-infected cocaine users reported higher mean depression scores at baseline compared to any other group(p=0.03, Supplementary Table II). Using mixed-effects models, we investigated the association between cocaine use and HIV infection on baseline depressive symptoms and longitudinal depressive trajectories over an average of 4.8 years (±1.5 years) in participants with repeat CES-D scores (n=288; HIV+ cocaine nonusers n=125, HIV+ cocaine users

n=37, HIV− cocaine nonusers n=100, HIV− cocaine users n=26). While heavy cocaine use was associated with a small increase in baseline depressive symptoms compared to nonusers (estimate 0.4314, p= 0.02), the modifying effect of HIV infection was associated with substantially higher depressive symptoms in cocaine users (estimate 5.7119, p= 0.03), independent of age, education level and cigarette smoking (Table II). Model estimates for time-related effects predicted an annual worsening of depression scores among cocaine users (estimate 0.017, p=0.03), with relative improvement over baseline in depressive symptoms for HIV-infected cocaine users (estimate −1.101, p= 0.02). Older age correlated with lower depressive symptoms; higher depressive symptoms correlated with lower education (Table II).

Cocaine use, HIV status, and Cognitive Trajectories

Mean baseline raw scores for each cognitive test by group are listed in Supplementary Table II. There were no significant group differences observed in the z-scores for individual cognitive tests when all four groups were compared (HIV+ cocaine nonusers, HIV+ cocaine users, HIV− cocaine nonusers, HIV− cocaine users, two-way ANOVA and in pairwise comparisons between HIV− controls vs. HIV− cocaine users or HIV+ controls vs. HIV+ cocaine users; Supplementary Table II). In mixed-effects models among participants with at least two available neurocognitive tests (n=242; HIV+ cocaine nonusers n=101, HIV+ cocaine users n=35, HIV− cocaine nonusers n=83, HIV− cocaine users n=23, Table II) analyzed over an average of 4.1 years (± 1.7 years), cocaine use was marginally associated with worse neurocognitive summary scores at baseline (estimate − 0.28, p=0.07). While there was annual improvement in cognitive scores among HIV− uninfected controls, suggestive of a practice effect in this subgroup (estimate 0.04574, p <0.001), cocaine use was not associated with a change in cognitive performance over time (p=0.57). The annual improvement in cognitive scores observed in HIV− uninfected controls was attenuated among HIV-infected participants (estimate −0.03825, p= 0.02), and not further modified by cocaine use (p= 0.9).

Latent Class Analysis of Depressive Trajectories

Latent class analysis of longitudinal CES-D scores allowed for the examination of individual variability in depressive symptoms and potential identification of subgroups at high risk for persistent depressive symptoms. LCMM analysis clustered into five classes based on BIC and mean posterior probabilities; minor groups that did not meet the *a priori* defined population threshold (i.e. at least 5% of the original population) or posterior probability thresholds were removed from subsequent analysis (Supplementary Table III). Figure 1A shows the mean depressive trajectories and 95% confidence intervals of the remaining classes which made up 21%, 34%, and 37% of the total cohort analyzed (n=160). The largest cluster consisted of 66 subjects who exhibited persistently high depressive symptoms (*i.e.* CES-D 16) during the six years of follow up (Figure 1A and B).

Using univariate and multivariate logistic regression, we evaluated predictors of persistently high depressive symptoms versus the remaining two latent classes (HIV+ cocaine nonusers n=70, HIV+ cocaine users n= 26, HIV− cocaine nonusers n= 50, HIV− cocaine users n=14, Table III). In univariate analysis, cocaine use (OR 3.71 [95% CI 1.75–7.88]), lower

education (odds ratio (OR) 2.75 [95% CI 1.43–5.28]) and heavy drinking (OR 2.40 [95% CI 1.20–4.79]) were associated with high depressive symptoms among all participants. Cocaine use remained a predictor of high depressive symptoms after adjusting for lower education and heavy drinking (OR 3.04 [95% CI 1.38–6.69]). To investigate potential effects of HIV-disease characteristics on high depressive symptoms, we performed a secondary analysis among HIV-infected subjects only. In multivariate analysis, heavy cocaine use and baseline plasma viral load 400 copies/mL was associated with 8-fold [OR 8.41 (95% CI (2.73–25.83)] and 3-fold [OR 3.07 (95% CI (1.10–8.56)] higher odds of persistently high depressive symptoms, respectively. Figure 1B shows CES-D trajectories of individuals within these three latent classes, stratified by HIV and cocaine use, and illustrates the high prevalence of HIV-infected cocaine users in the predicted high depressive symptom group.

Discussion

In this study, we used a prospective design with matched controls to evaluate the longitudinal effects of cocaine use on depressive symptoms and cognitive trajectories in a cohort of predominantly black men who have sex with men ages 30–60 years old. Using both mixed-effects models and subject-centered latent class analysis, we show that longitudinal depressive symptoms are influenced by the combined effects of cocaine use (primarily crack cocaine) and HIV infection. Heavy cocaine use was the most likely predictor for HIV-infected men to be classified in the persistently high depressive symptom group, and was a stronger determinant of depressive symptoms than unsuppressed plasma viral load. Social determinants such as education level and heavy drinking were also associated with depressive symptoms in all participants. Together, these findings suggest that depression and cocaine use, along with other psychosocial health challenges, are interconnected in MSM populations and potentially exacerbated in people with HIV infection, highlighting the critical need for integrated mental health and substance use treatments to address barriers to successful HIV-related care.

Black race has been associated with greater illicit drug use, higher depressive symptoms, and reduced ART adherence in previous studies of HIV-infected participants in the MACS cohort (32, 34, 59–61). Stigma undermines the health of MSM populations and limits access to health care (62), an effect that may be particularly accentuated for black MSM given multiple types of discrimination faced including discrimination based on race, sexual orientation, gender identity, and HIV status (61, 62). A study in a young black MSM cohort showed that individuals who reported higher levels of HIV stigma also had more unprotected sex while under the influence of drugs or alcohol (62), while another study showed that moderate depressive symptoms were associated with unprotected anal intercourse with casual male partners among black MSM (32). While stigma was not formally assessed in this study, other syndemic conditions including substance use and depression, in socially marginalized MSM populations are known to increase risk of HIV-infection acquisition and transmission and can lead to additional health disparities (27). Findings in this study, in which the majority of participants were black MSM, are consistent with other cohorts that report an association between high depressive symptoms in HIV-infected black MSM (63), and consistent with cross-sectional studies suggesting that cocaine use influences depressive symptoms among HIV-infected cohorts (27, 59, 64, 65). Thus, the

co-occurrence of cocaine use and high depressive symptoms observed in this study provides further evidence of syndemic relationships that exist between depression and substance use (27), which may be amplified in black MSM (40, 59, 61, 66).

In this cohort, cocaine use was not associated with differences in baseline cognitive tests across multiple domains or cognitive decline after adjusting for other clinical covariates frequently associated with cognitive performance. While this finding was unexpected, our findings are consistent with previous longitudinal studies in the MACS and CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohorts that detected no differences in cognitive function associated with cocaine use (67, 68). In this study, we focused on the combined ART era, matched users to controls from the same cohort, controlled for differences in education level and other demographic covariates, focused on frequent cocaine users without polydrug use, and used mixed-effects models to isolate the independent effects of HIV infection and cocaine use on cognitive function. Despite these measures, we did not detect differences in individual baseline cognitive scores associated with cocaine use or cognitive decline in this cohort of 30–60 year old MSM. While depressive symptoms and cognitive impairment are common co-morbidities in HIV-infection (1, 28, 29, 45, 46), several studies suggest psychiatric and neurocognitive sequelae of HIV-infection are largely independent of each other (69–72). A recent report of depression in older people living with HIV on ART showed that despite greater overall depressive symptom burden among HIV-infected participants compared to HIV-uninfected controls, depressive symptoms were not associated with HIV-associated neurocognitive disorders, suggesting a disconnect between depressive and neurocognitive symptoms in HIV infection (72). Thus, findings in the present study along with studies from the literature highlight that in the context of HIV infection, etiological mechanisms underlying depressive symptoms may be distinct from mechanisms that influence cognitive decline. In contrast, findings in this study showed that HIV infection resulted in the attenuation of a practice effect observed in the control group in mixed-effects models, suggesting that HIV infection remains an important consideration when evaluating subtle changes in cognitive decline.

There are several key strengths of this study including longitudinal analysis with six years of follow-up data, stringent criteria to exclude subjects with polydrug use, and nested controls from a population with similar demographics, and psychosocial health factors. An additional strength is the focus on depressive trajectories in a predominantly black cohort, which stem from dedicated efforts of increased minority enrollment into the MACS. Black MSM are an underrepresented group in research studies, despite being disproportionately affected by HIV infection (14), and have the largest increases in rates of new HIV infection in the United States (13, 73), making findings in this study particularly relevant to a high-risk population for HIV-acquisition and critical for informing treatment interventions.

There are several important limitations in this study including those inherent to longitudinal observational studies such as selection, survivorship, and severity bias reflected in the MACS cohort. The study is restricted to men, predominantly with 12 years education, and requires replication in study populations with other demographic characteristics, including women. Longitudinal analyses were limited to visits within the last six years of enrollment in the study for maximal data coverage, restricting our ability to analyze longer follow-up

periods. Given the limited number of heavy cocaine users over age 50, findings in this study could underestimate cognitive decline among older people living with HIV infection due to survivorship bias. Additionally, logistic regression analysis was performed for participants classified into latent classes, not among participants who did not meet posterior probability thresholds of latent class selection, which may introduce unintended bias among those individuals who for unknown reasons were not classified. While we considered our analysis of heavy cocaine users without polydrug use a strength of the study, this strategy also limits these findings to a subset of cocaine users and should be taken into consideration in future studies on cocaine use and depression in HIV-infected cohorts. Finally, subjects in this cohort were linked to care as part of their participation in the MACS, and it is possible that these findings underestimate the impact of cocaine use on depression within the larger MSM population.

In summary, the findings in this longitudinal study highlight the importance of cocaine use on depressive trajectories in the context of HIV infection. In two different longitudinal analyses examining within-subject changes in depressive symptoms, heavy cocaine use was associated with high depressive symptoms and had a profound impact in HIV-infected MSM. Achieving durable ART-mediated viral suppression is a challenging task in populations experiencing psychosocial barriers that includes depression and substance use. Given high rates of ART adherence failure among cocaine users infected with HIV, this study underscores the critical importance of HIV-care models that integrate mental health and substance use treatments in efforts to minimize HIV acquisition and optimize well-being, HIV treatment, and medical care in MSM populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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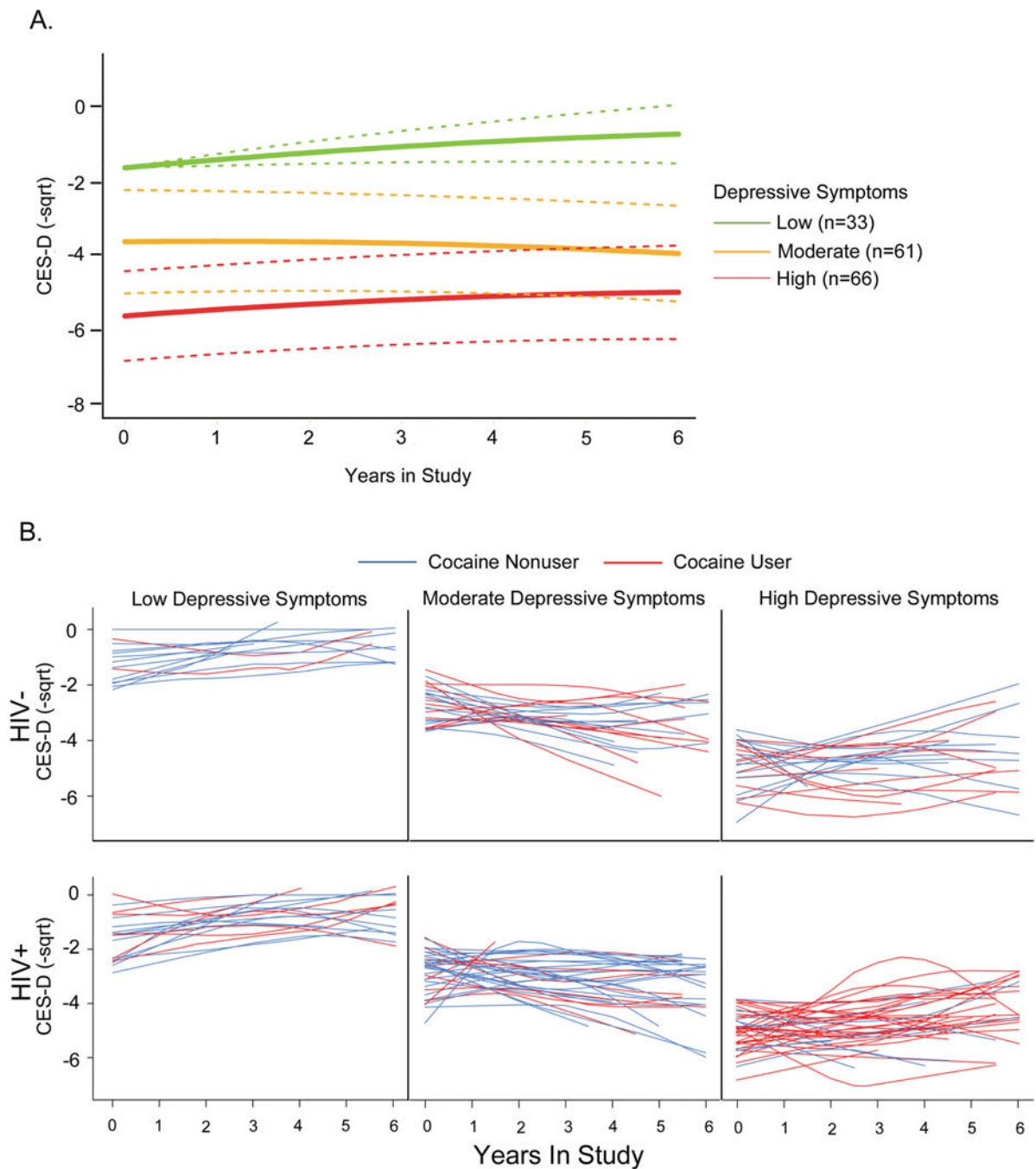
Figure 1. Trajectories of Depressive Symptoms in HIV-Infected and HIV-Uninfected Participants Using Latent Class Mixed-effects Models

CES-D scores were square-root transformed and sign changed to negative values, so lower scores indicate worse depressive symptoms (i.e. CES-D square root values closer to zero are indicative of less depressive symptoms), and LCMM trajectories were estimated for the last six years enrolled in study for ages 37–60. The three group trajectories of CES-D performance that passed the posterior probability and population size thresholds are shown

in Figure 1A. Individual depressive trajectories of cocaine users (red) and non-users (blue) are plotted, and separated by HIV-infection status (Figure 1B).

Table I

Cohort characteristics by HIV Serostatus and Cocaine use

	HIV− (n =147)		HIV+ (r=194)		p value[c]	
	Controls (n=94)	Cocaine[a] (n=53)	Controls (n=112)	Cocaine[a] (n=82)	HIV− controls vs. HIV− cocaine	HIV+ controls vs. HIV+ cocaine
Baseline Age (years; mean, SD)	41.8 (7.0)	39.8 (6.3)	39.0 (5.4)	39.1 (4.8)	ns	ns
Follow-up (years; mean, SD)	5.9 (3.1)	6.1 (2.5)	6.6 (3.7)	6.5 (3.3)	ns	ns
Demographic and Clinical Characteristics (%)						
Race					ns	ns
Black	79.8	67.9	72.3	70.7		
White, non-Hispanic	18.1	20.8	21.4	22.0		
Other	2.1	11.3	6.3	7.3		
Education < 12 years	40.4	45.3	47.3	42.7	ns	ns
HCV-antibody positive	20.2	32.1	21.4	18.3	ns	ns
Heavy Smoking[a]	25.0	50.9	17.7	52.4	**<0.01**	**<0.01**
Heavy Drinking[a]	19.1	47.2	18.1	42.7	**<0.01**	**<0.01**
Depression Profile						
Antidepressant use[a]	16.0	26.4	18.8	50.0	ns	**<0.01**
CES-D score > 16[b]	23.4	37.7	26.8	46.3	ns	**<0.01**
HIV-Related Characteristics (%)						
Baseline CD4 count (cells/mm^3)						
< 200	–	–	17.0	15.9	–	ns
< 350	–	–	33.0	30.5		ns
Baseline viral load (plasma HIV RNA, copies/mL)						

	HIV− (n =147)		HIV+ (r)=194		p value[c]	
	Controls (n=94)	Cocaine[a] (n=53)	Controls (n=112)	Cocaine[a] (n=82)	HIV− controls vs. HIV− cocaine	HIV+ controls vs. HIV+ cocaine
> 400	–	–	56.3	63.4	–	**0.02**
Self-reported antiretroviral therapy use						
Baseline	–	–	64.3	58.5	–	ns
> 95% of visits in study	–	–	42.0	26.8	–	**<0.01**

[a] - Reported heavy use at ≥ 2 visits in study (corresponding to at least one year); Cocaine use defined as daily or weekly; Smoking defined as ½ pack cigarettes/day; Drinking defined as >14 alcoholic drinks/week

[b] - Reported at > 50% of visits in study

[c] - Wilcoxon rank sum or paired t-test; p<0.05, significant

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; ns, nonsignificant; SD, standard deviation; HCV, Hepatitis C Virus.

Table II

Effect of Cocaine use and HIV infection on CES-D and Neurocognitive Scores

Fixed Effects	CES-D (actual score; n=288)			Neurocognitive Summary (NPZ16; n=242)		
	Estimate	SE	p-value	Estimate	SE	p-value
Baseline age	−0.2754	0.1052	**0.009**	−0.00250	0.006183	0.687
Education < 12 years	2.4459	1.1058	**0.028**	0.1064	0.08034	0.187
Cocaine Use	0.4314	2.0732	**0.018**	−0.2806	0.1435	0.069
HIV Infection	−0.6870	1.2460	0.105	0.08344	0.08905	**0.039**
Smoker	1.5933	1.1502	0.167	0.002895	0.08344	0.972
Cocaine * HIV Infection	5.7119	2.6552	**0.032**	0.2151	0.1836	0.243
Years in Study	−0.1792	0.1730	**0.004**	0.04574	0.01262	**<0.001**
HIV Infection* Years in Study	0.1884	0.2296	0.134	−0.03825	0.01655	**0.020**
Cocaine * Years in Study	0.01700	0.3755	**0.028**	0.01033	0.02730	0.570
Cocaine * HIV Infection * Years in Study	−1.1010	0.4823	**0.023**	−0.00163	0.03340	0.961

Negative years in study estimates indicate a steeper slope of cognitive decline.

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; SE, standard error; *, interaction term

Table III

Predictors of Depressive Trajectories in Latent Class Mixed Effects Models.

CES-D	All participants (n=160)		HIV+ participants (n=86)	
	Unadjusted OR (95%Cl), *p*-value	Adjusted OR (95%Cl), *p*-value	Unadjusted OR (95%Cl), *p*-value	Adjusted OR (95%Cl), *p*-value
Baseline Age	0.96 (0.89–1.03), 0.30		0.89 (0.79–1.00), 0.05	
Education[a]	2.75 (1.43–5.28), **<0.01**	2.50 (1.26–4.97), **<0.01**	2.32 (0.99–5.40), 0.05	
Cocaine use[b]	3.71 (1.75–7.88), **<0.001**	3.04 (1.38–6.69), **<0.01**	5.92 (2.17–16.14), **<0.001**	8.41 (2.73–25.83), **<0.001**
Heavy Drinking	2.40 (1.20–4.79), **0.01**	2.19 (1.04–4.59), **0.04**	2.56 (1.03–6.36), **0.04**	
HIV Infection	1.16 (0.61–2.21), 0.64			
Viral Load ≥ 400[c]			1.79 (0.77–4.17), 0.17	3.07 (1.10–8.56), **0.03**
CD4 count < 350[d]			1.06 (0.45–2.51), 0.88	

Unadjusted and adjusted odds ratio (OR) for predictors of membership in the latent class representing persistent high depressive symptoms versus low/moderate symptoms

[a]- OR for ≥ 12 years of education

[b]- Daily/weekly use reported at first 2 visits in study interval

[c]- Baseline viral load (plasma HIV RNA, copies/mL)

[d]- Baseline CD4 count (cells/mm^3)