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Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence

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Abstract

Cocaine abuse among HIV patients is associated with faster disease progression and mortality. This study examined the relationship between neurocognitive functioning and medication adherence in HIV patients with (n= 25) and without (n= 39) current cocaine dependence. Active users had greater neurocognitive impairment (mean T-score= 35.16 vs. 40.97, $p < .05$) and worse medication adherence (mean z-score= −0.44 vs. 0.27, $p < .001$). In a multiple regression model, neurocognitive functioning ($\beta = .33$, $p < .01$) and cocaine dependence ($\beta = -.36$, $p < .01$) were predictive of poorer adherence. There was a significant indirect effect of cocaine dependence on medication adherence through neurocognitive impairment (estimate= −0.15, $p < .05$), suggesting that neurocognitive impairment partially mediated the relationship between cocaine dependence and poorer adherence. These results confirm that cocaine users are at high risk for poor HIV outcomes and underscore the importance of treating both neurocognitive impairment and cocaine dependence among HIV patients.

Keywords

HIV/AIDS; cocaine dependence; antiretroviral therapy; medication adherence; neurocognitive functioning

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s was a major breakthrough in the treatment of HIV/AIDS. While newer regimens are more forgiving (Bangsberg, 2006; Shuter, Sarlo, Kanmaz, Rode, & Zingman, 2007), near perfect adherence remains the goal to optimize clinical outcomes (Liu et al., 2006). Yet nearly half of HIV patients living in North America are not perfectly adherent to their medication regimens (Mills et al., 2006). Patients who abuse drugs, particularly psychostimulants like cocaine and methamphetamine, are more likely to be non-adherent and thus at high risk for

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poor HIV outcomes (Arnsten et al., 2002; Hinkin et al., 2007; Hinkin et al., 2004; Tucker et al., 2004).

In a large, nationally representative sample of adults receiving HIV care in the United States, over half reported illicit drug use in the past year, and a quarter of drug users screened in for drug dependence (Bing et al., 2001). The most commonly abused drugs among HIV patients are cocaine and marijuana; only a small minority abuse opioids (Cook et al., 2007; Korthuis et al., 2008; Kuo et al., 2004). Opioid substitution treatment is associated with improved HAART adherence among injection drug abusers (Avants, Margolin, Warburton, Hawkins, & Shi, 2001; Clarke et al., 2003; Roux et al., 2008), but as of yet there is no effective pharmacologic treatment for cocaine dependence. Existing substance abuse treatments are generally insufficient for improving HIV clinical outcomes, and many substance users are not even engaged in treatment (Palepu, Horton, Tibbetts, Meli, & Samet, 2004).

Drug dependence and HIV infection both cause neurocognitive impairment. Within days of infection, HIV can infiltrate the central nervous system, causing direct and indirect damage to brain structure and functioning (Anthony & Bell, 2008; Hult, Chana, Masliah, & Everall, 2008). If untreated, HIV patients may experience severe cognitive impairments (Sacktor, 2002). Since the introduction of HAART, milder cognitive disorders with more gradual and fluctuating courses are increasingly common (Antinori et al., 2007; Brew & Gonzalez-Scarano, 2007). Immunosuppression and disease progression are generally associated with greater neurocognitive impairment, but patterns are variable (Dawes et al., 2008). HIV infection most prominently affects attention, processing speed, motor abilities, memory, and executive function (Heaton et al., 1995; Moore et al., 2006; Reger, Welsh, Razani, Martin, & Boone, 2002). HIV-associated cognitive impairment is associated with declines in social and occupational functioning and difficulty with activities of daily living (Benedict, Mezhir, Walsh, & Hewitt, 2000; Heaton, Marcotte et al., 2004; Rabkin, McElhiney, Ferrando, Van Gorp, & Lin, 2004). It may also lead to poorer HAART adherence. A recent systematic review of the literature found that impairments in executive function, memory, attention, and global cognition were generally associated with poorer adherence (Lovejoy & Suhr, 2009).

Drug dependence also disrupts brain circuitry, with reduced activity in frontal cortical regions in response to non-drug stimuli (Volkow, Fowler, Wang, & Swanson, 2004). During decision making tasks, psychostimulant abusers have less activation in the prefrontal cortex, orbitofrontal cortex, anterior cingulate, and posterior parietal regions (London, Bonson, Ernst, & Grant, 1999; Monterosso et al., 2007; Paulus et al., 2002). They also generally perform worse than controls on neurocognitive tasks of verbal memory, executive function, processing speed, and visuospatial construction, but not on verbal fluency and motor speed (Ardila, Rosselli, & Strumwasser, 1991; Beatty, Katzung, Moreland, & Nixon, 1995; Hoff et al., 1996; Medina, Shear, & Schafer, 2006; Rippeth et al., 2004; Rosselli, Ardila, Lubomski, Murray, & King, 2001; Simon et al., 2000; Verdejo-Garcia & Perez-Garcia, 2007). One study found that methamphetamine use and HIV infection had additive deleterious effects on global cognition (Rippeth et al., 2004), but the effects of psychostimulants, particularly cocaine, on neurocognitive functioning in HIV patients remains largely understudied.

In sum, HIV patients with co-occurring cocaine dependence may be at increased risk for neurocognitive impairment, and neurocognitive impairment may partially explain the lower rates of medication adherence observed in cocaine users. This hypothesis has not been systematically tested in prior studies examining the relationship between neurocognitive impairment and medication adherence. The majority of extant studies did not assess (or at least report) substance abuse (Albert et al., 2003; Hinkin et al., 2002; Solomon & Halkitis, 2008; Wagner, 2002) or did not account for it in analyses (Ammassari et al., 2004; Hinkin et

al., 2004; Levine et al., 2005). Four studies have examined neurocognition and HAART adherence among injection drug users (Applebaum, Reilly et al., 2009; Avants et al., 2001; Waldrop-Valverde, Jones et al., 2009; Waldrop-Valverde, Osborn et al., 2009), but none included a comparison group of non drug users or focused on cocaine use.

Building upon this literature, the present study examined the relationship between neurocognitive functioning and HAART adherence in HIV patients with and without current cocaine dependence. Our comparison group of non cocaine users included individuals with no history of substance dependence and with lifetime cocaine dependence in sustained full remission; this allowed us to test the hypothesis that the deleterious effects of cocaine dependence are due to active cocaine use. Specifically, we hypothesized that: (1) active cocaine users would have greater neurocognitive impairment and worse medication adherence compared to non cocaine users; (2) neurocognitive impairment would be associated with worse medication adherence; and (3) neurocognitive impairment would mediate the relationship between current cocaine dependence and medication adherence.

METHOD

Participants and procedures

Inclusion criteria were HIV infection, current antiretroviral therapy, and 18–59 years of age. Participants were recruited for one of two groups based on current drug abuse. Active cocaine users met DSM-IV diagnostic criteria for current cocaine dependence, had used cocaine in the past month, and reported cocaine as their drug of choice. Because polysubstance use is common in the United States, co-occurrence of other substance use disorders was acceptable for inclusion in the current study, but cocaine had to be the principal diagnosis. Non cocaine users did not meet criteria for any current alcohol or drug use disorders and had not used any substances other than occasional marijuana or moderate alcohol in the past year. Within this group, 49% had a lifetime history of cocaine dependence in sustained full remission (recovered), and the rest had no history of any substance use disorder (naïve). Participants who were in early recovery from cocaine (< 1 year), used cocaine sporadically without meeting criteria for dependence, or had principal substance dependencies other than cocaine were excluded to ensure sufficient differentiation between the active and non cocaine groups. Exclusion criteria were lifetime psychotic or bipolar disorder, acute psychiatric distress (e.g., suicidal ideation, severe depression), loss of consciousness of ≥ 30 minutes and requiring medical intervention, impaired mental status, any conditions incompatible with MRI scanning (e.g., ferromagnetic implants, pregnancy) due to a neuroimaging component, and illiteracy and/or lack of fluency in English.

Participants were recruited from the community through advertisements in local newspapers and websites, flyers posted and brochures distributed at clinics and nonprofit organizations serving persons with HIV/AIDS, and participant referrals. Interested individuals called into the study and completed a structured telephone screen to assess preliminary eligibility (i.e., HIV infection, antiretroviral medication use, psychiatric diagnoses, drug use history, MRI incompatibilities, and literacy). If eligible, callers were invited to the hospital for a full screening.

At the screening visit, participants provided written informed consent and then completed a set of clinical interviews and questionnaires. They also provided a urine sample for drug and pregnancy screening and brought in pill bottles for verification of their HAART regimen. Participants were paid $50 for this visit regardless of eligibility. Eligible participants returned on another day to complete additional clinical interviews and questionnaires, a battery of neurocognitive tests, and an MRI brain scan. Participants were paid $85 for this assessment visit.

Measures

Screening measures—Module E of the Structured Clinical Interview for DSM-IV was used to identify current and lifetime cocaine dependence and other substance use disorders (First, Spitzer, Gibbon, & Williams, 1996). The Addiction Severity Index-Lite was administered to assess lifetime substance use and impairments associated with drug and alcohol abuse (McLellan et al., 1992). Timeline Followback methodology was used to assess frequency of substance use in the past month (Sobell & Sobell, 1996). At both visits, self-report of recent drug use was corroborated with a urine toxicology screen that tested for cocaine, marijuana, amphetamine, methamphetamine, oxycodone, methadone, other opioids, and benzodiazepines. A breathalyzer was used to ensure that participants were sober at the time of assessment. The Mini International Neuropsychiatric Interview was used to identify other Axis I psychiatric disorders, including mood, anxiety, and psychotic disorders (Sheehan et al., 1998). The Mini Mental State Examination was used to rule out impaired mental status (score ≤ 23) (Folstein, Folstein, & McHugh, 1975). Finally, participants completed a questionnaire documenting their medical history and provided a blood sample to test for current CD4 lymphocyte count.

Medication adherence—Multiple self-report measures were used to evaluate HAART adherence. In all cases, a 1-month recall period was used because it has been found to be more strongly associated with objective measures of adherence than 3- or 7-day periods (Lu et al., 2008). Participants completed the Medication Use and Adherence Questionnaire developed by the AIDS Clinical Trials Group Study 359 (Chesney et al., 2000; Fletcher et al., 2005). This is a widely used measure that is predictive of HIV viral load (Fletcher et al., 2005; Reynolds et al., 2007). Participants reported when they last missed a medication dose (< 1 week, 1–2 weeks, 2–4 weeks, 1–3 months, > 3 months, never), yielding a dichotomous variable indicative of perfect adherence in the past month (0= no, 1= yes). They also reported on a 5-point scale how easy/difficult it was to always take HIV medications as prescribed (1= very difficult, 5= very easy) and how closely they followed their specific medication schedule (1= never, 5= all of the time). Participants used a visual analogue scale (VAS) to record percent adherence (0–100%) (Giordano, Guzman, Clark, Charlebois, & Bangsberg, 2004). This tool asks participants to “put a cross on the line below the point showing your best guess about how much of each medication you have taken in the last 4 weeks.” A mean percentage across all medications was computed. The VAS tool obtains estimates that parallel unannounced pill counts and predicts HIV viral load (Giordano et al., 2004; Kalichman et al., 2009). Finally, participants used a 6-point scale to rate their ability to take all medications as prescribed (1= very poor, 6= excellent) (Lu et al., 2008). This rating scale has been found to validly assess adherence relative to a medication event monitoring system (Lu et al., 2008). As in previous studies (Lu et al., 2008; Reynolds et al., 2007), a combined adherence variable was created by standardizing the five adherence items (perfect adherence, ease of adhering, closeness of schedule, VAS percent adherence, and adherence rating) and then computing a standardized mean score (α= .81).

Neurocognitive functioning—A battery of measures was used to assess neurocognitive functioning. The entire battery took about 30 minutes to administer. For all tests, raw scores were converted to demographically corrected T-scores (M= 50, SD= 10) using published norms (i.e., correcting for age, gender, education, and race whenever possible) (Brandt & Benedict, 2001; Heaton, Miller, Taylor, & Grant, 2004; Meyers & Meyers, 1995; Smith, 2007).

The Hopkins Verbal Learning Test – Revised (HVLT-R) measured verbal memory (Brandt & Benedict, 2001). A list of 12 words was read aloud three times. After each reading, participants recalled as many words as they could. Unbeknownst to them, they would recall

the words again 20–25 minutes later. The number of words correctly recalled after trial 4 was scored.

The Trail Making Test measured executive function, including cognitive flexibility, attention, and planning (Lezac, 1995). Trails B requires participants to connect 25 numbered and lettered circles in order as quickly and accurately as possible, alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc). Time to completion was recorded, with a maximum of 300 s.

The Symbol Digit Modalities Test (SDMT) measured information processing speed (Smith, 1973). Participants paired specific numbers with specific symbols using a reference key. The number of correct pairings made in 90 s was scored.

The Controlled Oral Word Association Test (COWAT) measured verbal fluency (Benton, Hamsher, & Sivan, 1983). Participants were asked to rapidly retrieve and verbally report from memory words beginning with F, A, and S in 60 s for each letter. The number of words correctly retrieved across the three trials was recorded.

The Rey Complex Figure Test (RCFT) measured visuospatial constructional ability (Meyers & Meyers, 1995). Participants copied a target figure that was presented in a standardized manner. Eighteen distinct figural elements were scored for accuracy and organization of reproduction.

A global score of neurocognition was created by taking the average of the T-scores on each test: HVLT-R, Trails B, SDMT, COWAT, and RCFT. This method is commonly used as an indicator of overall neurocognitive functioning in HIV patients (Applebaum, Otto, Richardson, & Safren, 2009; Brew et al., 2007; Clifford et al., 2002; Schifitto et al., 2007).

Data analysis plan

First, descriptive statistics were used to characterize the sample in terms of demographics and HIV disease. Preliminary analyses were conducted to confirm that recovered and naïve cocaine users performed similarly on neurocognitive and adherence measures, thus justifying combining them into a single comparison group of non cocaine users. To test hypothesis 1, active and non cocaine users were compared on neurocognitive functioning and medication adherence using t-tests and chi-square tests. To test hypothesis 2, Pearson correlation was used to assess the association between neurocognitive functioning and medication adherence. To test hypothesis 3, a mediation model was tested to determine whether neuropsychological impairment accounted for the relationship between cocaine dependence and medication adherence (Baron & Kenny, 1996). In addition, we used a bootstrap approach to test the significance of this indirect effect (Efron & Tibshirani, 1993; Preacher & Hayes, 2004). The indirect effect of the independent variable on the dependent variable through the mediating variable (ab) is equivalent to the total effect of the independent variable on the dependent variable (c) minus its direct effect (c’). An estimate of the indirect effect was computed using a bias corrected bootstrap technique with 5,000 resamples and a confidence interval set at 95% (Mackinnon, Lockwood, & Williams, 2004; Preacher & Hayes, 2004). To account for the higher proportion of African-Americans in the cocaine-dependent group, the analysis was rerun controlling for race.

RESULTS

Participant characteristics

The sample included 64 HIV-positive adults on HAART medications. Table 1 shows their demographic and HIV disease characteristics. Overall, the sample was 72% male, 25–58

years old (M= 45.67, SD= 7.70), and ethnically diverse (30% Caucasian, 50% African-American, and 20% Hispanic). Nearly half reported being heterosexual (47%), and most were currently single (89%), had at least a high school education (82%), and had an annual income of less than $20,000 (66%). Participants had been diagnosed with HIV for 1–26 years (M= 12.86, SD= 6.98). Current CD4 cell counts ranged from 61 to 1,500 (M= 573.73, SD= 332.07). The groups did not differ on any of these characteristics, except that active cocaine users were significantly more likely than non cocaine users to be African-American (72% vs. 36%, p= .013).

Active users had been using cocaine regularly for a mean of 18.10 years (SD= 9.23) and had used cocaine on 6.64 days (SD= 6.41) in the past month. All had a principal diagnosis of cocaine dependence, and all but one had a positive urine screen for cocaine at one or both study visits. In addition, 68% had other lifetime substance dependencies (56% alcohol, 20% cannabis, 8% stimulants, 8% opioids) and 20% had other current substance dependencies (16% alcohol, 8% cannabis). Recovered users had used cocaine regularly for 13.53 years (SD= 5.54) and had been in sustained full remission for 10.26 years (SD= 6.13). All had a principal diagnosis of cocaine dependence, and 74% had other lifetime substance dependencies (53% alcohol, 42% cannabis, 32% opioids, 5% sedatives, 5% stimulants), all in sustained full remission. No recovered or naïve participants tested positive for cocaine at either visit. The only other illicit drug that participants tested positive for was marijuana (28% active, 16% recovered, 20% naïve).

Hypothesis 1: Do active cocaine users have greater neurocognitive impairment and worse medication adherence than non cocaine users?— Overall, participants demonstrated substantial impairment in neurocognitive functioning, with T-scores < 40 on HVLT-R, SDMT, and RCFT (Table 2). Active cocaine users had significantly poorer performance than non cocaine users on HVLT-R, SDMT, RCFT, and global neurocognition, but they performed equally well on Trails B and COWAT. This suggests that active cocaine users had greater overall neurocognitive impairment, with specific impairments in verbal memory, information processing, and visual construction.

As shown in Table 3, participants were on a mean of 2.67 (SD= 1.11) HAART medications with 4.50 pills/day (SD= 2.94) and 1.50 dosing times/day (SD= 0.56). There were no significant differences in the medication regimens prescribed to active and non cocaine users. Nevertheless, active users had significantly poorer adherence in the past month. Specifically, only 36% of active users were perfectly adherent compared to 74% of non users. Active users also did not adhere as closely to their medication regimen, took a lower percentage of their medication doses, were less able to take their medications as prescribed, and had a lower combined z-score. Given the consistency of these results, the combined adherence score was used in subsequent analyses.

Hypothesis 2: Is neurocognitive functioning associated with medication adherence?—There was a significant correlation between global neurocognition and medication adherence (r= .439, p < .001), suggesting that patients with greater neurocognitive impairment had poorer adherence. Specifically, poorer adherence was associated with lower scores on HVLT-R (r= .432, p < .001), SDMT (r= .388, p= .002), and RCFT (r= .305, p= .015); it was unrelated to Trails B (r= .112, p= .38) and COWAT (r= . 131, p= .30).

Hypothesis 3: Does neurocognitive impairment mediate the relationship between cocaine dependence and medication adherence?—First, we used the four-step, ordinary least square approach proposed by Baron and Kenny (Baron & Kenny, 1996). As indicated above, cocaine dependence was significantly associated with medication

adherence (β= −.467, p < .001; step 1) and neurocognitive functioning (β= −.304, p= .015; step 2). For step 3, a multiple regression model was run to test whether neurocognitive functioning was a significant predictor of medication adherence when controlling for cocaine dependence. Both neurocognitive functioning (β= .330, p= .004) and cocaine dependence (β= −.361, p= .002) were significant predictors of medication adherence, meeting the conditions for step 3. Step 4 tests for complete mediation, which occurs when the effect of the independent variable decreases to zero when the mediator is included in the model. In this study, cocaine dependence remained a significant predictor of adherence when adding neurocognitive functioning to the model, so the criteria for complete mediation were not met. However, the effect of cocaine dependence on adherence was reduced when neurocognitive functioning was added (from β= −.467 to −.361), indicating partial mediation. Table 4 summarizes the bootstrap analysis. There was a significant indirect effect of cocaine dependence on medication adherence through neurocognitive functioning [ab= −.150 (−0.330 to −0.051)], suggesting that neurocognitive functioning is a partial mediator. The model was rerun controlling for race, and results did not change [ab= −.158 (−.341, −.055)]. Race was associated with cocaine dependence (coefficient= −.290, p < .05) but not adherence (coefficient= −.092, p= .632).

DISCUSSION

This study is among the first to examine the association between neurocognitive impairment and HAART medication adherence in HIV patients with and without cocaine dependence. Overall, participants demonstrated substantial neurocognitive impairment, with mean T-scores under 40 on most measures. This is consistent with prior research findings that neurocognitive deficits are common in a majority of HIV patients, particularly as the disease progresses (Antinori et al., 2007; Tozzi et al., 2007). In our sample, all participants had a history of CD4 cell count < 500, reflecting disease progression; they had been diagnosed with HIV for a mean of 13 years, and 78% had a diagnosis of AIDS. Across the whole sample, neurocognitive impairment was associated with poorer HAART adherence, even after accounting for current cocaine dependence. However, active cocaine users had significantly greater neurocognitive impairment and poorer medication adherence, and neurocognitive impairment was found to partially mediate the relationship between cocaine dependence and medication non-adherence. That is, the higher rate of non-adherence in cocaine users was partially explained by the negative correlation between cocaine dependence and neurocognitive functioning. The degree of neurocognitive impairment and poor medication adherence among active cocaine users suggests that this is a population in need of more intensive interventions to optimize treatment outcomes.

Active cocaine users had greater overall neurocognitive impairments, with specific deficits in verbal memory, processing speed, and visuospatial construction. This is generally consistent with studies conducted among HIV-negative samples, which also found specific rather than global deficits (Beatty et al., 1995; Hoff et al., 1996; Medina et al., 2006; Rippeth et al., 2004; Rosselli et al., 2001; Simon et al., 2000; Verdejo-Garcia & Perez-Garcia, 2007). The effects of cocaine dependence on neurocognitive functioning may be particularly profound in HIV patients, given that HIV infection itself also causes impairments in many of the same neurocognitive domains, notably information processing, memory, and executive function (Heaton et al., 1995; Moore et al., 2006; Reger et al., 2002). Our results lend further support to the independent effect of current cocaine dependence on neurocognitive impairment in HIV patients, but further research is necessary to explore whether or not HIV infection and cocaine dependence have additive and/or synergistic effects on neurocognition.

Few studies have examined the association between cocaine use and neurocognitive functioning among HIV patients, and results have been variable, likely due to methodological differences. Durvasula and colleagues found that cocaine users had poorer performance on information processing but not in other domains (Durvasula et al., 2000). However, the use of a 12-month recall period meant that some of the "active" users could have been abstinent for several months, and the quantity of cocaine use in the sample was modest. Chang and colleagues also found no differences between HIV patients with and without cocaine dependence on verbal memory, psychomotor speed, and executive function, but the cocaine users in that sample had been abstinent for an average of 5 years (Chang et al., 2008). This is consistent with our finding that recovered cocaine users demonstrated no neurocognitive impairments relative to drug naïve participants. In contrast, Levine and colleagues found that participants who had used psychostimulants (cocaine or methamphetamine) in the past month, as verified by toxicology screen, had impairments in sustained attention relative to those who had not used in the past month (Levine et al., 2004). A major strength of our study was that participants were carefully assessed using several validated clinical interviews and urine toxicology screens to differentiate groups of active, recovered, and naïve cocaine users, enabling us to tease apart the effects of current versus past cocaine dependence. Furthermore, the active cocaine users in our sample were chronic users who met diagnostic criteria for cocaine dependence and used cocaine at least weekly, strengthening our ability to identify effects due to cocaine use. Cumulatively, findings from these studies suggest that neurocognitive deficits associated with cocaine dependence are due to the impermanent effects of active use, and that cocaine use may have to exceed a certain threshold before any measurable impact on neurocognitive impairment is observed.

Our results lay the groundwork to examine whether prolonged abstinence may reverse the neurocognitive impairments associated with cocaine dependence. The recovered group in our study met full diagnostic criteria for past cocaine dependence in sustained full remission, with a mean of nearly 14 years of regular cocaine use. They demonstrated no neurocognitive impairments relative to drug naïve participants and were equally likely to adhere to their HAART regimens. Evidence from HIV-negative samples supports the idea that drug-induced neurocognitive impairments can be reversed. In a study of twins with and without a history of heavy psychostimulant use, after 1 year of abstinence, deficits were evident only on motor skills; there were no differences in verbal learning, visuospatial construction, or executive function (Toomey et al., 2003). Another study found no difference between cocaine users who were abstinent for 1 month and controls on verbal memory, visuospatial construction, processing speed, verbal fluency, and executive function (Bolla, Rothman, & Cadet, 1999). A third study of veterans entering a 3-week substance abuse treatment program found significant improvements in memory, attention, motor skills, and executive function, but not in visuospatial construction or language (Schrimsher & Parker, 2008). Longitudinal studies that measure changes in neurocognitive functioning over the course of treatment and longer-term recovery (> 1 year) in HIV patients are needed to establish causality.

As expected, active cocaine users reported poorer HAART adherence compared to non users. Specifically, 64% of active cocaine users missed at least one dose in the past month compared to only 26% of non drug users. Our results support the hypothesis that neurocognitive impairments associated with cocaine dependence partially explain the higher rates of non-adherence in cocaine users. Cognitive remediation strategies may be helpful for improving medication adherence among HIV-positive cocaine users. However, given that neurocognitive functioning only partially mediated the relationship between cocaine dependence and medication adherence, further research is needed to identify additional mediators that may be amenable to intervention. For example, disruptions in sleep and eating patterns, increased environmental instability, and a generally chaotic lifestyle may

lead to poor adherence among psychostimulant users (Reback, Larkins, & Shoptaw, 2003; Tucker et al., 2004). Furthermore, many of the active cocaine users also abuse alcohol and marijuana, which may further impair neurocognitive functioning and ability to adhere to HIV medications. Ultimately, treatment for cocaine dependence and additional co-occurring substance use disorders may be critical for improving HIV clinical outcomes.

Results of this study should be interpreted in light of the following limitations. First, the cross-sectional design precludes any conclusions regarding causality. Differences in neurocognition may have preceded the onset of cocaine dependence and/or interfere with substance abuse treatment (Aharonovich et al., 2006; Aharonovich, Nunes, & Hasin, 2003; Fals-Stewart & Lucente, 1994; Fox, Jackson, & Sinha, 2009; Teichner, Horner, & Harvey, 2001). It is also likely that the relationship between neurocognition and medication adherence is bidirectional: neurocognitive impairment may limit a patient's ability to adhere perfectly to HAART, and poor adherence may lead to further declines in neurocognitive functioning (Lovejoy & Suhr, 2009). Clearly, longitudinal studies are needed to elucidate the temporal relationship between these variables. Second, this study relied on self- report of medication adherence. Self-report is the most practical means of collecting adherence data in cross-sectional studies, and it has been found to be a valid measure that is predictive of HIV viral load (Fletcher et al., 2005; Giordano et al., 2004; Lu et al., 2008; Reynolds et al., 2007). A notable strength of this study was the use of multiple adherence measures, with consistent results across measures. Nevertheless, results may have been biased by the poor neurocognitive functioning evidenced by the sample. Future studies may wish to combine self-report with objective measures of adherence, such as pill counts and pharmacy refills, given the high rates of memory impairment observed in our study (Lovejoy & Suhr, 2009). Third, global neurocognition variables have the potential to underestimate performance in specific domains (Lovejoy & Suhr, 2009). However, these are commonly used in neuroAIDS research (Avants et al., 2001; Barclay et al., 2007; Hinkin et al., 2002), and use of a global neurocognition variable allowed us to test a single regression model, minimizing the risk of a type I error. Fourth, the proportion of African-Americans was higher in the active versus non cocaine group. Whenever possible, we employed demographic connections that accounted for race when converting raw scores to T-scores, and results did not change when accounting for race in the regression models. A matched control study that ensures equal proportions of African-Americans across groups would help to eliminate potential confounding effects of race on neurocognitive functioning. Finally, this study utilized a convenience sample of patients receiving HIV treatment in the United States. Replication studies with larger sample sizes and in other regions of the world are needed to determine if results generalize to the broader population of HIV patients.

In conclusion, cocaine dependence among HIV patients is associated with suboptimal clinical outcomes, including higher viral loads, greater immune suppression, faster disease progression, and death (Baum et al., 2009; Chander et al., 2008; Webber, Schoenbaum, Gourevitch, Buono, & Klein, 1999), and poor medication adherence may be an important contributing factor. This study found that HIV patients with current cocaine dependence had greater neurocognitive impairment and poorer HAART adherence compared to non drug users, and that neurocognitive impairment associated with cocaine dependence partially explained the lower rates of medication adherence. Results underscore the importance of assessing and treating both neurocognitive impairment and cocaine dependence among HIV patients, including the development of empirically supported treatments. Further research is needed to identify potential additive and/or synergistic effects of HIV infection and cocaine dependence and their long-term effects on clinical outcomes.

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Table 1

Demographic and HIV disease characteristics of the sample

	Active cocaine n = 25	Non cocaine n = 39	Statistic
Male sex (%)	76.0%	69.2%	$\chi^2(1) = 0.35$
Age, years (M, SD)	46.44 (7.85)	45.18 (7.66)	$t(62) = -0.64$
Race (%)			$\chi^2(2) = 8.67^*$
Caucasian	12.0%	41.0%	
African-American	72.0%	35.9%	
Hispanic	16.0%	23.1%	
Heterosexual (%)	48.0%	46.2%	$\chi^2(1) = 0.02$
Currently single (%)	84.0%	91.7%	$\chi^2(1) = 0.85$
Years of education (M, SD)	13.60 (2.43)	14.08 (2.65)	$t(62) = 0.72$
Yearly income (%)			$\chi^2(2) = 2.92$
< $10,000	40.0%	22.2%	
$10–20,000	36.0%	36.1%	
> $20,000	24.0%	41.7%	
Years HIV infected (M, SD)	11.88 (7.47)	15.68 (4.99)	$t(62) = 1.92$
CD4 cell count (M, SD)	539.17 (306.24)	701.11 (364.47)	$t(62) = -1.58$

$^*p < .05$

Table 2

Neurocognitive functioning in active and non cocaine users

Measure	Domain assessed	Active cocaine n = 25	Non cocaine[1] n = 39	t-test	p-value	Cohen's d
HVLT-R	Verbal memory	27.77 (12.90)	40.82 (15.15)	t(61) = 2.89	.005	.928
Trails B	Executive functioning	43.75 (10.42)	44.64 (14.55)	t(61) = 0.26	.795	.070
SDMT	Processing speed	33.29 (17.14)	40.82 (12.99)	t(62) = 2.05	.051	.495
COWAT	Verbal fluency	46.00 (8.25)	45.15 (10.72)	t(62) = −0.34	.738	.089
RCFT	Visuospatial construction	25.77 (19.58)	35.70 (14.55)	t(61) = 2.30	.025	.576
Mean score	Global functioning	35.16 (7.77)	40.97 (9.76)	t(62) = 2.51	.015	.659

[1]There were no differences between recovered and naive participants, except that recovered participants performed better than naïve participants on COWAT [49.16 (10.60) vs. 41.35 (9.60); t(37) = −2.24, p = .021).

Table 3

Past month medication use and adherence in active and non cocaine users

	Active cocaine n = 25	Non cocaine n = 39	Statistic	p-value	Effect size
Medication use					
Number medications (M, SD)	2.52 (1.19)	2.77 (1.06)	t(62) = −0.87	.387	d = .222
Number pills/day (M, SD)	3.84 (2.63)	4.92 (3.09)	t(62) = −1.45	.153	d = .376
Number dosing times/day (M, SD)	1.36 (0.57)	1.59 (0.55)	t(58) = −1.61	.112	d = .411
Medication adherence					
Perfect adherence (%)	36.0%	74.4%	$\chi^2(1) = 9.29$	.002	φ = .381
Adherence rating (M, SD)	4.76 (1.01)	5.72 (0.61)	t(62) = −4.75	< .001	d = 1.151
Closeness to schedule (M, SD)	3.72 (0.46)	3.95 (0.22)	t(62) = −2.67	.010	d = .638
Percent adherence (M, SD)	91.80 (12.67)	97.95 (5.90)	t(62) = −2.63	.011	d = .623
Ease of adhering (M, SD)	4.16 (0.99)	4.54 (0.86)	t(62) = −1.63	.109	d = .410
Combined z-score (M, SD)	−0.44 (0.92)	0.27 (0.46)	t(62) = −4.10	< .001	d = .976

Table 4

Summary of the bootstrap analysis

	Estimates		Significance testing	
Direct effects	Coefficient	Standard Error	t-value	p-value
IV on MV (a)	−5.812	2.316	−2.510	.0147
MV on DV (b)	0.0265	0.009	2.958	.0044
IV on DV (c')	−0.5558	0.1715	−3.2402	.0019
Total effects	Coefficient	Standard Error	t-value	p-value
IV on DV (c)	−0.7099	0.1734	−4.0951	.001
Indirect effect	Coefficient	Standard Error	Bootstrap estimate	95% confidence interval
IV on DV through MV (ab)	−0.1541	0.0668	−0.1503	−0.3304, −0.0506

Model summary: R^2 = .311, adjusted R^2 = .289, F(2,61) = 13.808, p < .001

Independent variable (IV) = cocaine dependence; mediating variable (MV) = neurocognitive functioning; dependent variable (DV) = medication adherence