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Factors Affecting Cognitive Functioning in a Sample of Human Immunodeficiency Virus-Positive Injection Drug Users

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ABSTRACT

Injection drug users represent a major vector of human immunodeficiency virus (HIV) infection in the nation's inner cities, and are an important population for harm reduction treatment interventions to target. However, there has been relatively little research examining the specific contribution of the multiple factors contributing to cognitive functioning among injection drug users that may affect engagement in, and response to, addiction and HIV-related interventions. The current study examined the independent contributions to neuropsychological (NP) test performance of premorbid educational attainment, medical and psychiatric history, long- and short-term drug use, assessed by laboratory, observation, and self-report measures, and HIV disease, assessed by plasma HIV-1 RNA viral load and $CD4^+$ count, in a sample of 90 HIV-positive injection drug users dually addicted to heroin and cocaine. Fully 88% of the sample showed evidence of impairment (>1 standard deviation below the population mean) on an NP test battery selected to assess processes associated with successful engagement in the treatment of substance abuse and HIV, such as learning and memory of verbal information, capacity to solve new problems and deal with more than one stimulus at a time, visual-motor coordination, and visual tracking and cognitive flexibility. In addition to drug use, independent predictors of NP test performance were HIV viral load, educational attainment, and premorbid medical and psychiatric problems. Findings underscore the multiplicity of factors that contribute to cognitive impairment in HIV-positive drug-abusing individuals in addition to drug use. Clinical implications are discussed.

INTRODUCTION

HUMAN IMMUNODEFICIENCY VIRUS (HIV)-seropositive injection drug users represent a major vector of HIV infection in the nation's inner-cities, and have been recognized as constituting an important population for harm reduction programs to target.[1] As with most interventions, the effectiveness of these programs will be enhanced if they are designed to accommodate and address specific characteristics of the target population. Given that many of these programs are psychoeducational or cognitive-behavioral in orientation, it follows that cognitive functioning is an important patient characteristic to consider. However, there is

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currently incomplete, or inconsistent, information in the literature regarding the relative contributions of drug use, HIV, and other risk factors to cognitive impairment in HIV-seropositive, drug-abusing populations. Because drug use is viewed as a confound in neuropsychological (NP) studies, it is often an exclusion criterion in studies investigating the neurocognitive effects of HIV. Hence, much of the research in this area has been conducted with relatively well-educated, gay males, thus limiting generalizability of the findings. Several investigators have emphasized the need for NP research that includes drug users with HIV, women, ethnic minorities, and individuals who have had limited opportunity for educational attainment.[2–5] Although findings are accruing, a clear picture of cognitive functioning in HIV-positive drug addicted populations has not yet emerged.

Impairment in cognitive functioning may occur, not only in late stages of AIDS,[6–8] but also in milder forms during early stages of HIV infection. Compared to HIV-negative individuals, HIV-seropositive patients have shown impairment in information processing, verbal memory, motor speed, procedural learning, and problem solving.[9–18] Impairment in any of these domains has the potential to adversely affect learning or performance of the complex sequence of behaviors required for prevention of relapse to substance abuse, HIV harm reduction, or adherence to treatment recommendations.

Drug users infected with HIV show deficits similar to those found in HIV-infected non-drug–users.[3,10,19–27] However, NP assessment of drug users is complicated by multiple contributors to impairment,[28] such as the short- and long-term effects of illicit drug use, comorbid psychiatric and medical problems, and low educational attainment, or cognitive reserve.[29] For methadone-maintained patients, the potential effects of methadone, as well as the long-term effects of illicit opioid use, may also contribute to impaired cognitive ability.[30] Yet another complicating factor is cocaine abuse, which is prevalent in many methadone-maintenance programs (MMPs).[31] Cocaine abuse may be particularly problematic in the interpretation of NP test performance because it may hasten HIV disease progression,[32] as well as having lasting effects on cognitive functioning.[33–39] Thus, the etiology of cognitive deficits in HIV-seropositive drug abusers is extremely complex, and the field awaits a precise accounting of the relative contribution of drug use and other prominent cofactors, particularly HIV infection, to cognitive impairment in this population.

Misattribution by clinicians of what may in fact be the neurobehavioral effects of HIV disease and other risk factors, solely to unremitting illicit drug use has the potential to substantially influence the type of treatment received by HIV-positive drug users. For example, addiction treatment services may be adversely affected if drug counselors misattribute cognitive impairment as lack of motivation and, as a consequence, discontinue treatment, rather than providing appropriate cognitive remediation or compensation strategies.[40–43] In addition, as HIV-positive drug users are prescribed a wide range of medications,[44] some related to their addiction (e.g., opiate-substitution therapies, psychotropics), some to comorbid conditions found at high rates in this patient population (e.g., antihypertensives), and some to HIV, including, but not limited to, highly active antiretroviral therapies (HAART), their medical treatment could potentially be affected. Although there are conflicting findings in the literature regarding the influence of drug abuse on adherence to medical recommendations,[45,46] some health care providers may continue to be reluctant to prescribe medication regimens, such as HAART, to inner-city drug users because of the perception that poor adherence is due primarily to ongoing drug use.[47] However, access to these and other medications is extremely important, not only because they may slow HIV disease progression, but also because they may reverse or slow cognitive decline.[48]

The purpose of the current study was twofold: (1) to contribute normative data to the NP literature from a sample of HIV-positive cocaine- and opiate-dependent patients at different stages of HIV progression on a battery of NP measures for which there currently exists little or no comparison data and (2) to investigate the unique contribution of a number of co-

factors, linked in the literature to cognitive impairment, to performance on an NP test battery selected specifically to assess the capacity for new learning and retention. Patients in this study were entering an MMP with onsite psychological testing and primary medical facilities, presenting the opportunity to obtain thorough addiction, medical, and psychiatric histories, as well as laboratory measures of both drug use and HIV.

MATERIALS AND METHODS

Subjects

Participants were 90 HIV-positive injection drug users entering an MMP who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition* (*DSM-IV*) criteria for opioid dependence as well as for cocaine dependence or abuse. The samples was 70% (63/90) male; 30% (27/90) female; 48.9% (44/90) African American; 35.6% (44/90) white; and 15.6% (14/90) Hispanic. Mean age was 41 (± 6.5); 94% (85/90) were unemployed; 61% (55/90) had completed high school; all demonstrated fluency in written and spoken English. Number of years since testing HIV-seropositive was 8.00 (± 4.63) years. At entry into treatment, mean $CD4^+$ count and plasma HIV-1 RNA viral concentrations were 366 μL (range, 5 to 1477) and 55,273 copies per milliliter (range, 399–710,000), respectively; 13.3% (12/90) were asymptomatic; 55.6% (50/90) symptomatic, and 28% (31/90) met Centers for Disease Control (CDC) criteria for AIDS.[49]

Procedure

Methadone dose was initiated at 25 mg and increased by 5 mg every other day until individualized stabilization dose was reached (median, 85 mg/d). The NP battery was administered an average of 12.21 (+ 3.26) days after entry into the MMP (mean methadone dose at time of testing was 52.89 (+ 10.73) mg.). Although this dose was deemed medically sufficient to curb withdrawal symptoms, a 12-item (0 = not at all to 4 = extremely) self-report measure of opiate withdrawal symptoms (e.g., lacrimation, rhinorrhea, yawning, piloerection, sweating, muscle pain/spasm, vomiting) was administered prior to NP testing. To reduce between-subject variability caused by methadone effects, testing was conducted for all patients immediately after receipt of daily methadone dose. Recent use of alcohol or illicit drugs was determined by breathalyzer and urine toxicology conducted immediately prior to assessment. Signs of acute intoxication were assessed during administration of the NP battery by the technician using an 11-item measure developed for this purpose. An "under the influence" composite score was then computed as the absence or presence (0/1) of the following signs and symptoms: observed signs of intoxication, or self-reported symptoms of withdrawal, or self-reported drug or alcohol use in past 12 hours. NP tests were administered in fixed order by trained Master's degree-level technicians in a single testing session, with breaks provided to reduce fatigue. Patient's history of learning problems, head injury, and other medical conditions that could potentially influence NP test results was determined during a pre-NP assessment interview.

NP Battery

The battery consisted of tests selected to assess functioning in domains requisite for following treatment recommendations, as follows: (1) Processes and strategies involved in learning and memory of verbal information was assessed using the California Verbal Learning Test (CVLT).[50] Two scores were used for purposes of the current study—Learning = sum of List A Trials 1 through 5; and Memory = delayed recall of List A. (2) The capacity to solve new problems (fluid IQ) and to use acquired school-based concepts (crystallized IQ) was assessed with the Kaufman Adolescent and Adult Intelligence Test (KAIT).[51] (3) Visual-motor coordination and manual dexterity, using dominant and non-dominant hands, was assessed with the grooved pegboard task.[52] (4) Visual tracking ability and the ability to switch focus between cognitive sets, and to deal with more than one stimulus at a time was assessed with the Trail Making Tests A and B.[53] The number of standard deviations from the age, gender, and/or education adjusted population

means on each test[54] were summed to create an NP impairment summary score for each patient.

Because years of education may not reflect pre-morbid educational attainment in this patient population, and because lower cognitive reserve scores are independently associated with impairment,[4,5] the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[55] information subscale was administered as an additional indicator of premorbid educational attainment.

Laboratory measures

$CD4^+$ count and plasma HIV (RNA by polymerase chain reaction [PCR]) viral load was assessed by blood assay at entry into the study. Breathalyzer and urine toxicology screens were conducted immediately prior to administration of the NP battery. Opiate values greater than 200 were coded as positive for illicit opiates; cocaine metabolite (benzoylegonine) levels greater than 300 ng/mL were coded as positive for cocaine.

Measures of addiction and psychiatric severity

Severity of addiction and psychiatric problems (lifetime and past 30 days) was assessed with the Addiction Severity Index (ASI).[56] The ASI is a commonly used semistructured interview, with established validity and reliability. Symptoms of depression and anxiety at time of NP testing were assessed with the Beck Depression Inventory (BDI)[57] and the state-version of the State-Trait Anxiety Inventory (STAI).[58]

Data analytic strategy

Descriptive statistics were used to characterize the sample. To rule out alternative explanations for associations between HIV disease and cognitive functioning, patients at different stages of HIV disease (asymptomatic, symptomatic, AIDS) were compared on continuous and categorical sociodemographic and drug use variables using analyses of variance (ANOVA) and χ^2 analyses, respectively. We also examined the current sample relative to three drug-using samples described in the literature on a widely used NP measure reported to be sensitive to HIV disease progression—Trails B. Mean (+ standard deviation [SD]) scores provided in the literature[59–61] were used for comparison using independent sample *t* tests. Next, a correlational matrix was created to examine zero-order correlation among the variables. Last, a hierarchical multiple regression analysis (HMRA) was conducted, with simultaneous entry of variables in each block. HMRA was chosen because it can estimate how much each block adds to the variance in the dependent variable (i.e., NP performance) accounted for by the complete model, such that the variance accounted for by a given block is over and above that accounted for by all of the previous blocks in the model.

RESULTS

Rates of cognitive impairment and potential influences on NP performance

Rates of cognitive impairment. On the cognitive impairment summary score 55.6% (50/90) of the sample scored 2 SD or more below the normative mean; 87.8% (79/90) of the sample scored 1 SD or more below the mean; none scored above the mean.

Educational attainment. On the WAIS-R Information subtest (mean age adjusted scaled score = 7.03 [+2.60]), 43.3% (39/90) completed 12 or more years of education (mean, 11.18 [+2.10] years)], and 53.3% (37/90) scored more than 1 SD below the age-adjusted normative mean.

History of learning problems, head injury, and other medical conditions. A history of one or more medical conditions was reported by 52.2% (47/90) of the sample. Conditions reported were as follows: liver disease (28.9%); heart disease (13.3%); kidney disease (5.6%); diabetes (4.4%). Neurologically related conditions included stroke (3.3%), brain infection (3.3%), epilepsy (4.4%); head injury with loss of consciousness (31.1%); problems with vision, hearing, or speech (31.1%), and learning disability (12.2%). For purposes of providing a control for the influence of comorbid condition

on NP performance in the regression analysis, patients were classified as "with/without history of any comorbid condition" (1/0).

Psychiatric disorders and mood disturbance. On the ASI index of severity of psychiatric problems, lifetime and past 30 days, 34.4% (31/90) scored in the range of moderate to severe psychiatric problems (≥ 0.40). On measures of current mood disturbance, 43.3% (39/90) scored in the range of current clinical depression (≥ 17) on the Beck Depression Inventory (BDI), and 62.2% (56/90) scored in the range of moderate to high anxiety (≥ 40) on the STAI. Mean (SD) psychiatric severity, BDI and STAI scores were 0.30 (± 0.23), 16.68 (± 11.61), and 42.17 (± 12.01), respectively.

Severity of addiction and recent drug use. Patients had been using heroin and cocaine for an average of 18.24 (+ 9.47) and 15.6 (+ 7.71) years, respectively, and had a mean addiction severity score of 0.38 (+ 0.08) on the ASI. At time of NP assessment, there was no evidence of recent alcohol use by breathalyzer. However, the majority of patients did provide urine samples positive for either heroin (67.8%), or cocaine (68.9%), or both (55.6%). Illicit drug use within 12 hours of NP testing was self-reported by 20% (18/90). Signs of intoxication were observed by the interviewer in 18.9% (17/90) of the sample. Symptoms of opiate withdrawal (i.e., a mean of 1 (slightly) or more on the 0–4 point scales) were reported by 26.7% (24/90) of the sample, with a mean opiate withdrawal score of 0.70 (+ 0.74).

Comparisons by stage of HIV disease

Table 1 provides sample characteristics by stage of HIV disease.[49]

There were no significant differences on any measure by HIV stage, with the exception of $CD4^+$ count [$F(2,87) = 38.358$, $p = 0.001$], viral load [$F(2,87) = 18.96$, $p = 0.001$], and ethnicity [$\chi^2(2) = 6.98$, $p = 0.03$]. As anticipated, patients with AIDS had significantly lower $CD4^+$ counts and significantly higher viral load than did either asymptomatic or symptomatic patients (p values < 0.05). Consistent with the literature on HIV-infected drug users, patients with AIDS ($n = 28$) were also more likely to be ethnic minorities (82.1%) than white (17.9%).

Comparisons to normative data

Comparisons were made between Trails B means (± SD) for the current sample relative to those provided in three previously published studies. As described below, the current sample was generally comparable to other drug-using samples on Trails B; however, a diagnosis of AIDS in the current sample was associated with significantly poorer performance on Trails B. Comparison Study 1[61] provided log-transformed, age-adjusted, norms for a sample of 150 injection drug users (65% HIV-positive) collapsed across HIV-serostatus in presentation of the results. When comparisons were made to log-transformed Trails B data in the current sample, similarly collapsed across HIV-serostatus, there were no significant differences between the Trails B scores in the two samples (Comparison 1 = 4.52 [± 0.47]; Current Sample = 4.65 [± 0.57]; $t[163] = 1.61$, $p = 0.11$). Comparison Study 2[59] provided means (+ SD) for a sample of HIV-negative ($n = 39$) and asymptomatic HIV-positive ($n = 42$) injection drug users. Pairwise comparisons revealed that patients with AIDS in the current study had significantly higher Trails B scores (165.14 [± 127.15]) than did either HIV-negative (104.1 [± 35.0]; $t[29] = 2.47$, $p = 0.02$) or asymptomatic HIV-positive drug users (112.5 [± 0.40]; $t[30] = 2.12$, $p = 0.04$). Comparison Study 3[60] provided means (± SD) for HIV-negative ($n = 81$), asymptomatic HIV-positive ($n = 19$) and symptomatic ($n = 21$) HIV-positive methadone maintained drug users. Again, the only significant difference found between the two studies was the finding that patients who had progressed to AIDS in the current study had significantly higher scores (165.1 [± 127.1]) than did either HIV-negative (107.9 [+46.3]; $t[29] = 2.33$, $p = 0.03$) or symptomatic HIV-positive (101.4 [± 33.4]; $t[31] = 2.54$, $p = 0.02$).

Correlational analyses

As shown in Table 2, both HIV viral load and $CD4^+$ count were significantly correlated with KAIT crystallized IQ (p values = 0.01), peg-

TABLE 1. SAMPLE CHARACTERISTICS BY CDC STAGE OF HIV DISEASE

	Asymptomatic	*Symptomatic*	*AIDS*
Sociodemographic:			
Gender (*n*)			
Male	7/12 (58%)	35/50 (70%)	21/28 (75%)
Female	5/12 (42%)	15/50 (30%)	7/28 (25%)
Race:*			
White	7/12 (58%)	20/50 (40%)	5/28 (18%)
African American	4/12 (33%)	24/50 (48%)	16/28 (57%)
Hispanic	1/12 (8%)	6/50 (12%)	7/28 (25%)
Age	40.42 (± 8.78)	41.32 (± 6.76)	40.75 (± 4.93)
Education (# years)	11.42 (± 2.43)	11.26 (± 2.15)	10.93 (± 1.88)
WAIS Info raw score	14.42 (± 6.10)	13.58 (± 5.90)	10.64 (± 4.57)
Medical			
$CD4^+$ count (μL)**	698.5 (± 309.8)	422.2 (± 226.8)	116.1 (± 58.1)
HIV RNA (Log_{10})***	3.00 (± 0.54)	3.72 (± 0.77)	4.56 (± 0.91)
Any comorbid condition	9/12 (75.0%)	38/50 (76.0%)	18/28 (64.3%)
Psychiatric problems			
ASI psychiatric severity	0.38 (± 0.23)	0.28 (± 0.23)	0.32 (± 0.23)
Beck Depression Score	15.08 (± 13.47)	15.78 (± 10.43)	18.96 (± 12.85)
STAI anxiety score	38.02 (± 11.85)	41.24 (± 12.69)	45.61 (± 10.22)
Addiction-related			
Long-term			
Years using heroin	16.83 (± 12.42)	18.60 (± 9.58)	18.21 (± 8.08)
Years using cocaine	15.92 (± 7.38)	15.88 (± 8.41)	14.96 (± 6.70)
ASI addiction severity	0.39 (± 0.06)	0.40 (± 0.08)	0.35 (± 0.10)
Short-term			
Methadone dose (mg)	56.25 (+ 14.00)	52.50 (+ 11.03)	52.14 (+ 8.54)
"Under the influence"	4/12 (33.3%)	23/50 (46.0%)	16/28 (57.1%)
Opiate positive urine	6/12 (50%)	36/50 (72.0%)	19/28 (67.9%)
Cocaine positive urine	5/12 (41.7%)	35/50 (70.0%)	22/28 (78.6%)
NP Assessment (uncorrected, raw)			
Summary NP (*z* score)	−1.73 (± 1.12)	−1.95 (± 0.82)	−2.31 (± 0.90)
KAIT fluid IQ	87.33 (± 14.07)	81.46 (+ 9.36)	79.14 (+ 11.84)
KAIT crystallized IQ	88.25 (± 13.17)	84.24 (+ 10.97)	78.43 (+ 11.71)
Trails A	42.92 (± 32.67)	38.13 (+ 15.03)	50.04 (+ 44.54)
Trails B	101.75 (± 67.65)	110.27 (+ 77.54)	165.14 (+ 127.15)
Pegboard (dominant)	92.75 (+ 25.82)	97.31 (+ 28.83)	110.71 (+ 42.05)
Pegboard (non-dominant)	97.42 (+ 24.77)	106.43 (+ 30.11)	118.00 (+ 52.18)
CVLT-new learning	40.42 (+ 17.44)	36.90 (+ 12.50)	33.29 (+ 11.86)
CVLT-delayed recall	7.75 (+ 4.09)	6.64 (+ 3.01)	6.21 (+ 3.80)

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
CDC, Centers for Disease Control; HIV, human immunodeficiency virus; ASI, Addiction Severity Index; STAI, State-Trait Anxiety Inventory; KAIT, Kaufman Adolescent and Adult Intelligence Test; CVLT, California Verbal Learning Test.

board dominant hand (p values < 0.01 and 0.05, respectively), and Trails B (p values < 0.01 and 0.05, respectively).

Table 3 presents correlation coefficients among latent and observed measures.

Significant zero-order correlations were found between poor NP performance and the following variables: premorbid educational attainment, history of one or more medical conditions, severity of psychiatric problems, current symptoms of depression and anxiety, being "under the influence" and having a cocaine-positive urine at time of testing, $CD4^+$ count, and HIV viral load. Viral load and $CD4^+$

TABLE 2. ASSOCIATION BETWEEN NP RAW TEST SCORES AND HIV VIRAL LOAD AND $CD4^+$ COUNT

	Viral load	*$CD4^+$ count*
Learning and memory:		
CVLT List A trials 1–5	−0.16	−0.16
CVLT Long delay free recall List A	−0.18	−0.13
Capacity to solve new problems and use acquired school-based concepts:		
KAIT fluid IQ	−0.23*	−0.14
KAIT crystallized IQ	−0.26**	−0.26**
Visual-motor coordination:		
Pegboard dominant hand	0.27**	0.21*
Pegboard nondominant hand	0.30**	0.18
Visual-tracking and cognitive flexibility:		
Trails A	0.10	0.14
Trails B	0.28**	0.25*

*$p < 0.05$.
**$p < 0.01$.
NP, neuropsychological; HIV, human immunodeficiency virus; CVLT, California Verbal Learning Test; KAIT, Kaufman Adolescent and Adult Intelligence Test.

count were significantly negatively correlated; subsequent hierarchical analysis investigating the unique contribution of HIV serostatus to NP test performance therefore used viral load as the more specific measure of HIV disease progression.

Hierarchical multiple regression analysis

Entered simultaneously in Block 1 were sociodemographic variables: age, gender (0/1; female/male), ethnicity (0/1; minority/majority), number of years of education, and premorbid educational attainment (scaled score on the WAIS information subtest). Entered simultaneously in Block 2 were long- and short-term medical and psychiatric variables: history of one or more comorbid medical conditions (0 = absent; 1 = present), severity of psychiatric problems (ASI psychiatric composite score), and current symptoms of depression (BDI score) and anxiety (STAI score). Entered simultaneously in Block 3 were measures of long- and short-term drug use: severity of addiction (ASI severity of drug problems composite score); methadone dose received immediately prior to NP testing, being "under the influence" at time of testing (0 = negative; 1 = showed signs of intoxication, or reported symptoms of withdrawal, or reported drug or alcohol use in past 12 hours), and results of urine toxicology screens for opiates and cocaine (0 = negative; 1 = positive). Finally, to determine whether a biologic marker of HIV disease improved the fit of the model and predicted NP test performance in this patient population over and above the measures included in Blocks 1–3, plasma HIV RNA ($\log_{10}$) load was entered in the final block (Block 4).

Table 4 presents the results of the hierarchical regression analysis. The control variables entered simultaneously in Block 1 accounted for a significant proportion of the variance in cognitive functioning ($R^2 = 26$ (adj. = 0.21), $F[8,84] = 5.82$, $p = 0.001$]. The addition of medical and psychiatric variables in Block 2 accounted for a significant increase in variance (R^2 change = 0.12; Fchange$[4,80] = 3.77$, $p = 0.01$). The addition of long- and short-term drug use variables entered in Block 3 did not reach statistical significance, but did contribute an additional 8% of the variance over and over the effect of variables entered in Blocks 1 and 2 (Fchange$[5,75] = 2.21$, $p = 0.06$). The addition of HIV viral ($\log_{10}$) load in the final block accounted for a significant increase in the variance (R^2change = 0.03, Fchange$[1,74] = 3.94$, $p = 0.05$). The full model accounted for 48% (adj. 38%) of the variance in NP performance ($F[15,74] = 4.61$, $p = 0.001$). In addition to high

TABLE 3. CORRELATIONAL MATRIX OF VARIABLES IN HIERARCHICAL MULTIPLE REGRESSION ANALYSIS

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
1. NP summary score	1.00															
2. Age	0.06															
3. Gender (1 = male)	0.12	0.28**														
4. Ethnicity (1 = white)	0.20	−0.26**	−0.22*													
5. Education (yrs)	0.04	0.12	0.11	−0.02												
6. Education (WAIS info)	0.48***	0.30**	0.21*	0.26**	0.34**											
7. Other medical (1 = yes)	−0.26**	0.04	−0.03	0.20*	−0.09	−0.03										
8. Psychiatric severity	−0.28**	−0.10	−0.37**	0.14	−0.04	−0.03	0.29**									
9. Current depression	−0.26**	−0.08	−0.12	0.13	−0.06	−0.15	0.34**	0.51***								
10. Current anxiety	−0.18*	−0.02	−0.02	0.13	−0.17	−0.19	0.25*	0.34**	0.69***							
11. Addiction severity	0.09	0.11	−0.10	−0.09	0.21*	−0.04	−0.09	0.08	−0.06	−0.05						
12. Current methadone dose	0.01	−0.09	−0.07	0.14	0.05	−0.02	−0.10	0.14	0.11	−0.06	0.10					
13. "Under the influence"	−0.28**	−0.01	0.04	−0.01	0.02	−0.11	0.25**	0.26**	0.49***	0.44***	0.14	0.02				
14. Opiate-positive urine	−0.07	−0.09	0.07	0.01	−0.03	0.25**	−0.003	0.02	−0.03	−0.02	−0.19	−0.18	0.14			
15. Cocaine-positive urine	−0.20*	0.05	0.08	−0.30**	0.02	−0.09	−0.09	0.13	−0.09	−0.09	0.01	−0.09	0.07	0.41***		
16. HIV viral load	−0.25**	0.03	0.26**	−0.22**	−0.04	−0.12	−0.02	−0.02	−0.09	0.20	0.04	−0.04	0.22*	0.09	0.11	
17. $CD4^+$ count	0.20*	−0.16	−0.04	0.24**	−0.05	0.12	0.16	0.10	−0.01	−0.08	0.05	0.03	−0.06	−0.16	−0.18*	−0.47***

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
NP, neuropsychological; WAIS, Wechsler Adult Intelligence Scale; HIV, human immunodeficiency virus.

TABLE 4. HIERARCHICAL MULTIPLE REGRESSION ANALYSIS OF NP TEST PERFORMANCE (n = 90)

Variable	*B*	*SE*	β	t	p
Block 1: Sociodemographics					
Age	−0.01	0.01	−0.04	−0.42	0.68
Gender (0 = female 1 = male)	0.14	0.19	0.07	0.71	0.48
Ethnicity (0/1)	0.25	0.20	0.13	1.23	0.22
Educational attainment:					
Years of education	−0.06	0.04	−0.15	−1.55	0.12
WAIS-R information	0.17	0.04	0.48	4.37	0.001***
Block 1 R^2 = 0.26, F(5,84) = 5.82, p = 0.001***					
Block 2: Medical and Psychiatric					
History of medical condition (0/1)	−0.56	0.19	−0.28	−2.97	0.01**
Severity of psychological problems (ASI)	−0.90	0.46	−0.23	−1.97	0.05*
Depressive symptoms (BDI)	0.001	0.01	0.001	0.01	0.99
State anxiety (STAI)	0.01	0.01	0.09	0.71	0.48
Block 2 R^2 change = 0.12, Fchange (4,80) = 3.77, p = 0.01**					
Model R^2 = 0.375, F(9,80) = 5.33, p = 0.001***					
Block 3: Addiction					
Severity of drug problems (ASI)	1.97	1.01	0.18	1.95	0.06
Current methadone dose	−0.002	0.01	−0.02	−0.21	0.84
"Under the influence" composite	−0.27	0.19	−0.15	−1.43	0.16
Urine toxicology:					
Opiate positive	−0.32	0.21	−0.17	−1.56	0.12
Cocaine positive	−0.04	0.21	−0.02	−0.17	0.85
Block 3 R^2 change = 0.08, Fchange (5,75) = 2.12, p = 0.06					
Model R^2 = 0.45, F(14,75) = 4.48, p = 0.001***					
Block 4					
HIV viral load ($\log_{10}$)	−0.18	0.09	−0.18	−1.98	0.05*
Block 4 R^2 change = 0.03, Fchange (1,74) = 3.94, p = 0.05*					
Overall model R^2 = 0.48 (Adj. = R^2 = 0.38), F(15,75) = 4.61, p = 0.001					

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
NP, neuropsychological; WAISR, Wechsler Adult Intelligence Test-Revised; ASI, Addiction Severity Index; BDI, Beck Depression Index; STAI, State-Trait Anxiety Inventory; HIV, human immunodeficiency virus.

HIV viral load (β = 0.18), other significant independent predictors of poor NP performance were low educational attainment (0.52), having a history of one of more medical conditions (0.20), and more severe psychiatric problems (0.22).

DISCUSSION

The challenges of assessing cognitive functioning in this patient population are clearly demonstrated in this study of HIV-positive injection drug users entering methadone maintenance treatment. The preponderance of patients had been using heroin and cocaine for almost two decades and, at the time of NP testing, most provided a urine sample positive for heroin or cocaine. Furthermore, although the majority reported 12 or more years of education, scores on the WAIS-R information subtest suggested that premorbid educational attainment was generally below average. In addition, more than 50% had a history of one or more medical conditions that could potentially influence NP performance, such as prior traumatic brain injury, and more than one third had moderate to severe psychiatric problems and current symptoms of depression and anxiety.

As anticipated, and consistent with the literature, most of the variables assessed were associated with poor performance on the NP test battery.[61] Consistent with previous findings,[21,60,62] drug use was significantly related to NP performance, and remained marginally significant (p = 0.06) after controlling for other prominent cofactors in the hierarchical regression analysis. An effect of HIV disease, as mea-

sured by HIV-1 RNA viral load, could also be detected, even after accounting for all of the other cofactors in the model, including long- and short-term drug use. This finding thus lends support to the hypothesis that there is an effect of HIV disease over and above other cofactors contributing to cognitive impairment in HIV-positive, drug-abusing populations. Additional evidence in support of an association between NP impairment and HIV disease progression was provided by the finding that performance on Trails B was a sensitive measure of HIV disease progression in the current study, as it has been in previous studies.[60,63] Poor performance on Trails B was not only significantly associated with low CD4 count and high viral load, but when comparisons were made to Trails B performance of HIV-negative and HIV-positive drug using samples provided in the literature,[59–61] the current sample of patients who had progressed to AIDS had significantly poorer scores.

Findings from this study highlight a number of important clinical issues. For example, it was interesting to note that the classification "being under the influence" at the time of NP assessment was significantly related to viral load and to medical and psychiatric comorbidity, suggesting that both interviewers and patients may have misattributed signs and symptoms of distress as drug withdrawal or intoxication. Regardless of the etiology of cognitive impairment, it is clear that these patients enter treatment with impairments in domains that may influence their response to treatment. Almost 90% of this sample were in the below-average range of cognitive functioning ($>$ 1 SD below normative means), and more than 50% were in the range of moderate to severe cognitive impairment ($>$ 2 SD below normative mean). Although methadone maintenance provides numerous benefits, including reducing rates of HIV transmission through unsafe injection practices,[64] and increasing the HIV-positive patient's access to HAART,[47] impaired cognitive functioning may adversely affect learning, retaining, and enacting skills that are required for addiction recovery, HIV harm reduction, and medication adherence.[44] If cognitive impairment is mistaken for lack of motivation or treatment resistance by clinicians who treat these patients, the "window of opportunity" to intervene in these patients' lives that is provided by substance abuse treatment programs, such as methadone maintenance, may be prematurely closed. There is a need to educate clinicians to differentiate between cognitive impairment and lack of motivation in this patient population,[43] and to provide interventions that are sensitive to patients' cognitive status (M. Copenhaver, unpublished data). As we have reported elsewhere, integration of cognitive remediation strategies within methadone counseling shows promise not only with regard to reducing HIV risk reduction behavior and improving addiction-related outcomes, but also for improving medication adherence (A. Margolin, unpublished data).

A limitation of the current study should be noted. Significant associations in correlational analyses, including HMLA, do not demonstrate a causative relationship between the predictor variables and outcome variable. The utility of this type of analysis is that it may point to potential relationships among variables that can be used to guide future research. More definitive answers concerning specific contributions to cognitive impairment would require comparing samples of drug-abusing, HIV-positive individuals to matched samples of non-drug–using HIV-positive individuals, as well as drug-using HIV-negative individuals. However, the challenges involved in creating reliably matched samples drawn from drug-using and HIV-positive populations with numerous health and related problems should not be underestimated.

We also note that the current study had a number of strengths. These include use of a sensitive biological marker of HIV disease—plasma HIV-1 RNA viral load—multiple measures of drug use at the time of testing that included laboratory, observation, and self-report, and provision of an opiate agonist, methadone, to all patients at a known dose. To the best of our knowledge, this study is the first in the published literature to provide evidence of an association between HIV status, as assessed by viral load, and cognitive impairment in a sample of injection drug users. This study therefore provides additional evidence for a link between HIV disease and cognitive impairment

using a highly sensitive measure of HIV disease.

CONCLUSION

In conclusion, this study found that the preponderance of patients in our sample of inner-city HIV-positive injection drug users showed significant NP impairment, and that an effect of HIV viral load could be detected, over and above the influence of drug use and other known risk factors. Our findings reinforce the view that regardless of etiology, cognitive impairment in HIV-positive patients who are addicted to drugs is a complex, multifactorial phenomenon that goes beyond addiction, and that may affect domains that could impede these patients' ability to respond optimally to treatment recommendations. The careful NP assessment of injection drug users living with HIV may have numerous benefits, not only for increasing extant knowledge about the neurobehavioral effects of HIV disease progression in this typically understudied patient population, but also for guiding the development and evaluation of substance abuse and HIV treatment interventions that are sensitive to the cognitive difficulties experienced by many of these dually stigmatized patients.

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