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Neurocognitive Aspects of Medication Adherence in HIV-Positive Injecting Drug Users

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Cognitive deficits are associated with nonadherence to HIV medications. HIV-positive injecting drug users (IDUs) are at particular risk for nonadherence and cognitive barriers to adherence specific to this population should therefore be identified. The present study assessed the relation of three domains of cognitive functioning, executive functions, memory, and psychomotor speed, to self-reported antiretroviral adherence in a sample of HIV-positive IDUs. Depression, use of alcohol, heroin, cocaine/crack, or marijuana in the last week were also included in the models. Logistic regression analyses showed that only psychomotor slowing was significantly associated with nonadherence. Executive functions, memory, depression, and active alcohol and substance use were unrelated to adherence. No other studies to date have exclusively linked psychomotor slowing to nonadherence in HIV infection. Psychomotor slowing among our study sample was severe and suggests that when evident, such slowing may be a valuable determinant for antiretroviral adherence among IDUs.

KEY WORDS: adherence; HIV; cognition; neuropsychological; AIDS.

INTRODUCTION

The advent of highly active antiretroviral therapy (HAART) has provided unprecedented opportunities for the effective treatment of HIV-1 disease and has led to dramatic declines in HIV mortality (Karon *et al.*, 2001; Murphy *et al.*, 2001). It is now known that strict adherence to antiretroviral (ARV) regimens is necessary to achieve the clinical and virological benefits of HAART. Substantial proportions of HIV-infected individuals have shown viral suppression with adherence rates near 90% (Howard *et al.*, 2002) with several studies advocating adherence rates as high as 90–95% (Bangsberg *et al.*, 2000; Paterson *et al.*, 2000). Individuals with ≥95% adherence had significantly fewer hospitalizations and no opportunistic infections or deaths over the course of one study (Paterson *et al.*, 2000). Nonadherence can lead to multiple drug resistance and severe limitations on ARV treatment options (Liu *et al.*, 2001; Wainberg and Friedland, 1998).

Many studies have shown that HIV-positive individuals are often unable to maintain these high levels of adherence (Howard *et al.*, 2002; Mannheimer *et al.*, 2002; Montaner *et al.*, 1998; Paterson *et al.*, 2002), and that persons with a history of substance abuse are even less likely to achieve these levels (Arnsten *et al.*, 2002; Carrieri *et al.*, 2003). Active substance use is associated with lower levels of adherence in many studies (Carrieri *et al.*, 2003; Tesoriero *et al.*, 2003; Tucker *et al.*, 2003) and nonadherence contributes to poorer health outcomes and increased rates of medication resistance in injecting drug users (IDUs) (Lucas *et al.*, 2001).

Although active substance use is a recognized risk factor for nonadherence (Carrieri *et al.*, 2003; Tesoriero *et al.*, 2003; Tucker *et al.*, 2003), few studies

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have focused their efforts to understand nonadherence in this population specifically. Moreover, cognitive impairment associated with HIV infection itself is emerging as a risk factor for nonadherence. The neurocognitive complications associated with HIV-1 infection show subcortical and frontostriatal patterns of deficits, similar to those seen in other subcortical diseases such as Parkinson's and Huntington's Diseases (Cummings and Benson, 1992; Navia *et al.*, 1986). Earlier reports indicate that functioning in the domains of attention, memory, executive functioning, working memory, information processing speed, and psychomotor skills can be affected (Grant *et al.*, 1987; Grant and Martin, 1994; Wilkie *et al.*, 1990). Further, although it is known that substance users are often impaired in cognitive skills important for daily functioning (Ahmad *et al.*, 1989; Berry *et al.*, 1993; Meek *et al.*, 1989; Strickland, 1993), the relation of such impairments to nonadherence in HIV-positive substance abusers has been little studied.

Currently available research with nonsubstance users has consistently shown that poor performance on executive functioning tasks requiring attention, mental flexibility, and reasoning skills predicts lower levels of adherence (Albert *et al.*, 1999; Hinkin *et al.*, 2002; Wagner, 2002). Other areas of functioning, including memory, attention, and psychomotor speed, have also shown a relation to adherence, although with somewhat less consistency (Albert *et al.*, 1999; Hinkin *et al.*, 2004; Wagner, 2002). Those with global cognitive impairment have also been reported to have poorer adherence when the medication regimen is complex (Hinkin *et al.*, 2002) and when the individual is 50 years old or older (Hinkin *et al.*, 2004).

In the only study known to date that assessed cognitive predictors of adherence exclusively in substance users, Avants *et al.* (2001), in a sample of methadone maintained HIV-infected adults showed that executive functions were significantly correlated with adherence. However, analyses using a global cognitive impairment index along with other sociodemographic and mood measures did not show a relation between cognition and adherence in this population.

Substance users also have higher rates of mental health problems (Galea and Vlahov, 2002; Martens, 2001), particularly depression, and depression has been consistently linked to lower adherence (Arnsten *et al.*, 2002; Carrieri *et al.*, 2003; Catz *et al.*, 2000; Gordillo *et al.*, 1999; Turner *et al.*, 2003). Little is known about how depression, cognitive functioning, and active substance use affect adherence in HIV-positive IDUs. Identification of factors that contribute to nonadherence in substance users will aid in the design of targeted interventions to improve adherence in this high-risk group. The purpose of this study was to investigate the relation of executive functions, memory, psychomotor speed, and medication adherence in a sample HIV-positive injecting drug using (IDU) men and women. Based on findings from previous research, we hypothesized that these cognitive abilities would be significantly related with adherence. Since active drug and/or alcohol use and depression have also been consistently linked to nonadherence, we also hypothesized that these factors would be independently associated with adherence.

METHOD

Participants

Participants in this study were 57 HIV-positive men and women enrolled in a larger study (which also included HIV-positive participants who were not on ARV treatment, total $N = 94$) investigating the effects of ARVs on cognitive functioning; all were at least 18 years old. Participants were excluded if they reported ever having a head injury with loss of consciousness for more than 30 min, learning disability, or a history of major psychiatric illness such as schizophrenia or bipolar disorder. Individuals reporting depressive symptoms were included in the study, since depression was a variable of interest. However, to ensure that depressive symptoms did not interfere with participation in the study, if a participant became tearful during the interview plus showed other signs of depression (e.g., scored greater than 15 on the Beck Depression Inventory), a study psychologist further evaluated his or her ability to continue in the study based on clinical judgment. No participants became tearful during the interview and thus no one was dropped from the study based on these criteria. All participants gave informed consent at initiation of the study and were paid for their participation. All study procedures were completed in a single session.

Drug Use Inclusion and Exclusion Criteria

Men and women in this study were required to have injected drugs at least one time in the last 12 months. No exclusions were made based on the type of drug injected or whether noninjecting drugs had also been used at any time. All participants were required to have abstained from drugs and/or alcohol for at least 12 hr prior to assessment. This was verified by self-report and clinical evaluation. If a participant was acutely intoxicated (e.g., presented with lethargy and/or erratic behavior, smelled of alcohol, reported drug use within 12 h of the study), he or she was rescheduled for the study at a later date. Fifteen participants (26%) were found to be acutely intoxicated and were rescheduled. Only one of these participants failed to return for the rescheduled appointment.

Antiretroviral Medication Criteria

Participants were required to bring their ARV medications to the study in order to verify the type of medication and dosing schedule. Individuals who did not bring their HIV medications to the study were rescheduled for a later date.

Measures

All participants completed a neuropsychological evaluation, which consisted of questionnaires assessing drug and alcohol use, depression, and a battery of neuropsychological measures. All participants were English speaking.

Alcohol and Drug Use

A questionnaire, based on the Structured Clinical Interview for DSM-IV Axis I Diagnoses, Alcohol and Substance Abuse module (First *et al.*, 1995) ascertained drug use characteristics for the sample, although no diagnoses were made. Each participant provided self-report information on drug use patterns for marijuana, opiates, cocaine, crack-cocaine, and alcohol. Information on the frequency, duration, and time since last use for each of these substances was obtained.

Depression

Symptoms of depression were assessed using the Beck Depression Inventory (BDI) (Beck *et al.*, 1961). Scores were dichotomized at ≥ 15 to indicate the presence of depression (Bornstein *et al.*, 1993). Many participants in this study had low educational attainment and therefore, this scale was read aloud to any participant who had difficulty reading. The reliability of the scale in this study was excellent (Cronbach's $\alpha = .93$).

Neuropsychological Tests

The neuropsychological measures used in this study were chosen because of their established use with HIV-positive drug users and their sensitivity to detect cognitive deficits in this population (Basso and Bornstein, 2000; Bono *et al.*, 1996; Selnes *et al.*, 1997; Stern *et al.*, 1996).

The *Logical Memory* (LM) subtest of the Wechsler Memory Scale-III (WMS-III) (Wechsler, 1997) uses free recall of two brief stories. Participants were required to immediately recall as much detail as possible after each story was read aloud by the examiner. After a 30-min delay, participants were again asked to recall the details of each story. Total number of story units recalled correctly for the immediate (LM I) and delayed recall (LM II) trials were summed and used in analyses.

The *Visual Reproduction* subtest of the WMS-III (Wechsler, 1997) assesses visual memory and consisted of presentation of five novel visual designs in increasing complexity. After viewing the design for 10 s, each design was reproduced from memory by the participant. This test also has an immediate and 30-min delayed recall format. Total score from the immediate (VR I) and delayed formats (VR II) were summed and used in analyses.

Executive Functions: Color Trails Test (CTT 1 and 2) (D'Elia *et al.*, 1996). Both parts of this measure consist of numbered circles colored in vivid pink or yellow: in CTT 1, each number is represented by only one color, whereas, in CTT 2, each number is printed twice, once in pink and once in a yellow circle. In CTT 1, the task is to draw a line between the numbered circles one after the other, following the number sequence. In CTT 2, the task is to maintain the sequence of numbers and alternate between pink and yellow. The CTT measures processing speed, sequencing, mental flexibility, and visual search and motor function.

The *Digit Span* subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997) consists of two parts: Digits Forward requires the subject to repeat sequences of digits which are read aloud to them that increase in length from three to nine digits; Digits Backward requires sequences of two to eight digits to be repeated in reverse order. Digit Span measures attention and working memory, components of executive functions. The total score, based on the longest correctly repeated digit strings, was used for analyses.

Controlled Oral Word Association Test (COWAT) (Benton *et al.*, 1983) measures verbal fluency through self-initiated search and retrieval strategies. Participants are asked to generate as many words as possible (no proper names and no repetitions of words) that begin with the letters F, A, and S. Participants were given 60 s for each letter. The total number of words generated was used in analyses.

Motor: Purdue Pegboard Test (Tiffin, 1968) is a measure of fine eye–hand motor coordination and speed. This test consists of a board with two columns of holes and cups that hold metal pins, washers, and collars. The complete test includes four trials. The first trial requires participants to place pins in one of the columns of holes with their dominant hand as quickly as possible over 30 s. The same procedure is followed in trial 2 with the nondominant hand. The third trial asks that participants place pins in holes alternating their use of each hand to place pins in each of the columns of holes. The fourth trial is a more complex construction task. The person assessed must use continuously alternating movements of the right and left hands, picking up and placing a pin, a washer, a collar, and another washer into a small assembly. Participants complete as many assemblies as possible in 60 s. The total number of correctly placed pins or assemblies for each of the four trials was used in analyses.

Motivation, Fatigue, and Pain

Participants' level of motivation to complete testing and level of pain and fatigue were assessed using three separate visual analog scales. The fatigue scale consists of seven items and the pain and motivation scales consist of one item each. The line was anchored by two extremes of the condition. For example, persons were to mark their current level of motivation on the line between the anchors of "*not at all motivated*" and "*as highly motivated as I could be.*" The location of the participant's mark through the line is measured in cm, which constituted the score.

Adherence to HIV Medications

Self-report adherence to ARV medications was assessed by an interviewer-administered questionnaire for both 1 day and 1 week preceding the study visit (Arnsten *et al.*, 2001). The assessment of 1-day adherence was conducted because of its efficiency and feasibility (Arnsten *et al.*, 2001). One-week adherence was assessed in order to include medication-taking behavior on weekends since medication regimens may be disrupted during this time (Wall *et al.*, 1995). The 1-day adherence variable was defined as the percentage of medication doses taken as prescribed for all medications in the day preceding the interview. The 1-week adherence variable was defined as the percentage of medication doses taken as prescribed for all medications during the 7 days preceding the interview. The estimates of adherence did not include a measure of the proper timing of doses. Arnsten *et al.* (2001), using the same self-report indices of adherence with a sample of former and current drug users, found that both the 1-day and 1-week self-report adherence measures were significantly correlated with average viral load over a period of 6 months, (1-day self-report adherence, $r = .43$, $p < 0.01$, and 1-week self-report adherence, $r = .53$, $p < 0.01$).

For participants who had difficulty recalling their medication taking behavior in the preceding day, the study interviewers used medication charts that included pictorial representations of each pill as well as memory anchors such as recalling what the participant had for breakfast, lunch, and dinner as a cue to aid in recall. Participants were also asked to identify the primary reason they missed a dose from the following choices: (1) *Side effects/made me feel sick*, (2) *Away from home*, (3) *Forgot*, (4) *Sleeping through a dose*, (5) *Change in routine*, (6) *Too busy or Feeling down*, or (7) *Other*.

Disease Markers

Blood samples to measure plasma viral load using PCR amplicor method (Roche Diagnostics) and CD4 cell counts using flow-cytometry were obtained for all participants during the same single study session and were analyzed at the Clinical Immunology Laboratory in the Department of Medicine, the University of Miami School of Medicine.

Data Analyses

Data Management

Data were examined for outliers and influential data points via inspection of data distributions. Data values more than three standard deviations from the mean (Stevens, 1996) for those variables were considered potential outliers, and analyses were done both with and without the case including the outlying variable. In any case in which removing an outlying data point meaningfully changed results, the point was excluded from subsequent analyses. Three neuropsychological test scores were identified as potential outliers. Exclusion of these scores from data analysis did not change results. Therefore, these values were included in analyses.

Viral Load and CD4 Cell Count

Examination of the distribution of viral load and CD4 cell count values indicated that these values were not normally distributed. Values for viral load and CD4 cell counts were therefore log transformed; evaluation of distributions after transformation through inspection of plots of expected vs. transformed values in a normal distribution confirmed the resulting distribution was approximately normal.

Cognitive Domain Scores

In order to test our hypothesis that executive functions, memory, and psychomotor speed would significantly predict adherence, test scores were converted to demographically corrected *T*-scores, using published normative data (D'Elia *et al.*, 1996; Smith, 2000; Tombaugh *et al.*, 1996; Wechsler, 1997; Yeudall *et al.*, 1986), with a mean of 50 and a *SD* of 10. For each of the three cognitive domains, scores were created by averaging the *T*-scores from the following tests: *Executive functions*—CTT 1 and 2, Digit Span, COWAT; *Memory*—Logical Memory immediate (LM I) and delayed recall (LM II), Visual Reproduction, immediate (VR I) and delayed recall (VR II); and *Psychomotor Speed*—trials 1, 2, 3, and 4 of the Purdue Pegboard test. These three domain scores were used as predictors of adherence in analyses.

Drug and Alcohol Use

The literature suggests that current drug use, rather than a history of drug use, has the greatest impact on adherence (Carrieri *et al.*, 2003; Lucas *et al.*, 2001; Tesoriero *et al.*, 2003). Therefore, participants were grouped based on the use of illicit substances (opiates, cocaine, crack-cocaine, or marijuana) in the last week ("1" = *yes*; "0" = *no*) and based on the use of alcohol in the last week ("1" = *yes*; "0" = *no*). Drug use in the last week and alcohol use in the last week were used as predictors in analyses.

Adherence

We conservatively dichotomized adherence into ≥95% (coded "1") and <95% (coded "0") since this level has been associated with optimal clinical outcomes. Self-report adherence has been reported to overestimate adherence levels when compared to more objective measures such as electronic monitoring devices (Arnsten *et al.*, 2001). However, several studies have shown that self-report adherence is associated with viral outcome (Arnsten *et al.*, 2001; Bangsberg *et al.*, 2000). Therefore, to better estimate the validity of the 1-day and 1-week adherence measures, we used *t*-tests to compare the mean plasma viral load and CD4 cell counts between adherent and nonadherent participants based on the 95% adherence cutoff. We found that log transformed viral load values were significantly lower in those reporting 1-day adherence $t(55) = 2.034$, $p < .05$ but not in those reporting 1-week adherence, $t(55) = -.204$, $p > .05$. No differences in log-transformed CD4 cell counts were found for either 1-day or 1-week adherence. Based on this finding, we used one-day self-report adherence as the outcome measure in subsequent analyses. (However, this finding does not account for other possible explanations for mean differences in viral load between adherence groups, e.g., medication resistance). Although the literature supports adherence cutoffs typically between 90 and 95% (Bangsberg *et al.*, 2000; Paterson *et al.*, 2000) analysis of our data with 1-day adherence revealed that the highest level of adherence below perfect adherence (100%) in this sample was 86%. We therefore defined adherence in this study as 100% adherence, yes or no (100% coded—1 and <100% coded—0).

Hypothesis Tests

Bivariate analysis (*t*-test) was used to test for differences between adherent and nonadherent participants in age, years of education, and number of ARV medications taken per day. χ^2 analysis was used to test for differences in gender and ethnicity/race among adherent and nonadherent individuals. Age, gender, ethnicity/race, years of education, number of pills taken per day, motivation for testing, pain, and fatigue were examined in correlational analyses with the dependent variable. Only motivation for testing was significantly correlated with adherence, $r_s = .31$, $p < .05$, and was thus included in the final logistic regression analyses.

To test the hypothesis that specific domains of cognitive functioning would predict nonadherence independent of active drug and alcohol use and depression, three logistic regression analyses were conducted using each of the three cognitive domain scores (executive functions, memory, and psychomotor speed), active drug use, active alcohol use, and depression as predictors. Due to increased risk of Type I errors from multiple comparisons, we adjusted the α according to the method outlined by Sankoh *et al.* (1997), which takes into consideration the average correlation among dependent variables. The average correlation among our cognitive domain scores was $r = .228$, which adjusted our α level to $p < 0.017$.

RESULTS

Participants in this study included a total of 57 HIV-positive individuals who were mostly African American men (African American, $N = 51$; Hispanic, $N = 4$; White, $N = 2$; men, $N = 44$; women, $N = 13$). The average age of participants was 42.75 ($SD = 5.6$). Fifty-six percent of the participants had less than 12 years of education and a test of reading ability [the Reading Subtest of the Wide Range Achievement Test-3 (WRAT-3); Wilkinson, 1993] indicated the average reading skills of the sample to be at the 5th-grade level. Twenty-eight percent of the sample was homeless or living in a shelter at the time of the study. Clinically significant depression levels (≥15 on the BDI) were observed in 46% of the sample. Almost 50% had used opiates, cocaine, crack-cocaine, marijuana, or alcohol in the past week. Participants reported using heroin for an average of 13 years ($SD = 10.5$), cocaine/crack an average of 14 years ($SD = 8.5$), marijuana an average of 19 years ($SD = 10$), and alcohol an average of 19 years ($SD = 22.5$).

Forty-nine percent of participants were being treated with a combination of nucleoside reverse transcriptase inhibitors (NRTIs) and/or nonnucleoside reverse transcriptase inhibitors (NNRTIs) and 51% of participants were being treated with combination therapy of an NRTI, NNRTI, or both plus a protease inhibitor at the time of testing. Participants took ARV medications an average of about 41 months. Mean time since HIV diagnosis was almost 10 years. χ^2 analysis and *t*-tests revealed no differences between adherent and nonadherent individuals in age, gender, years of education, race/ethnicity, drug or alcohol use in the last week, duration of drug or alcohol use, housing status, time since HIV diagnosis, or number of ARV medications prescribed daily.

Twenty-four participants (42%) were classified as nonadherent (<100%) and 33 participants (58%) were classified as adherent (100%). The mean adherence rate for the entire sample was 71% for the preceding day. Thirteen participants took none of their prescribed medications the previous day.

Plasma CD4 cell counts for all participants ranged from 4 to 1093 cells/mm^3 and the plasma viral loads of all participants ranged from <400 (the lower limits of detection) to 750,000 HIV RNA copies/ml. Mean plasma CD4 cell counts and viral loads for those reporting 95% one-day adherence are presented in Table I.

In those instances where a participant reported missing a dose of medication, he or she was asked to indicate the reason for missing the dose. From a total of 60 responses, 22% forgot to take their medication, 13% slept through a dose, 8% were away from home, 7% did not take the medication due to side effects, 7% did not take a medication due to a change in routine, and 13% endorsed "other."

The mean *T*-scores for each test included in each of the three cognitive domains are included in Table II. Participants performed an average of 1 *SD* below the mean on the immediate recall of the Visual Reproduction I test and on all measures of psychomotor speed. Neither viral load nor CD4 cell counts were significantly correlated with the three cognitive domain scores (data not presented).

Table III presents the results of three logistic regression analyses for each of the cognitive domains. The first logistic regression model, which included the memory domain, alcohol use, drug use, and depression and controlled for motivation, was nonsignificant, $\chi^2(5, N = 57) = 7.7$, $p > 0.017$. The second logistic regression model that included

Table I. Mean (*SD*) Viral Load and CD4 Cell Counts for Adherent and Nonadherent Individuals

Adherence	Mean HIV RNA log-transformed copies (ml)	Mean CD4 log-transformed cells (mm^3)
100%	8.7 (2.5)	5.3 (1.2)
<100%	10.0 (2.16)	5.2 (1.2)
P	0.047	0.839

Table II. Mean *T*-Scores (*SD*) on Neuropsychological Tests and Cognitive Domains by Adherence Level

	<100% Adherence	100% Adherence
Logical memory I	41.39 (9.49)	42.29 (10.78)
Logical memory II	42.83 (9.94)	43.26 (11.18)
Visual reproduction I	33.74 (8.05)	33.94 (8.22)
Visual reproduction II	42.57 (6.03)	43.21 (7.67)
Memory domain	39.29 (6.15)	40.18 (7.75)
Color trails test 1	47.22 (13.50)	43.21 (17.45)
Color trails test 2	43.22 (17.96)	44.59 (17.20)
Digit span	42.04 (8.59)	42.35 (8.01)
Controlled oral word association test	39.09 (8.38)	41.85 (9.17)
Executive functions domain	42.89 (9.80)	43.00 (10.89)
Purdue pegboard—dominant hand	23.09 (8.85)	31.09 (10.03)
Purdue pegboard—nondominant hand	25.77 (11.85)	30.44 (11.55)
Purdue pegboard—both hands	25.59 (12.53)	32.21 (10.64)
Purdue pegboard—assembly task	23.05 (15.75)	33.61 (10.98)
Psychomotor skills domain	24.37 (10.83)	32.19 (8.44)

Note. *T*-scores are standardized scores with a mean of 50 and a standard deviation of 10.

executive functioning and the same variables above was also nonsignificant $\chi^2(5, N = 57) = 7.6, p > 0.017$. The final model that included psychomotor skills was significantly associated with 1-day self-reported adherence $\chi^2(5, N = 57) = 14.1, p < 0.015$. Of the variables included in this model, only psychomotor skill was significantly related to adherence. Every standard deviation increase in psychomotor performance (i.e., 10-point increase) was associated with a 10.90 times greater chance of reporting 100% adherence.

DISCUSSION

This study evaluated whether memory, executive functions, and psychomotor speed were related to ARV adherence in HIV-positive IDUs. We found only psychomotor slowing to be significantly related to nonadherence. Depression, active drug use, and active alcohol use in the last week were also unrelated to adherence in this study.

Two previous studies reported a relationship between psychomotor performance and adherence behaviors. Hinkin *et al.* (2004) found that impaired psychomotor speed was related to nonadherence as measured by electronic monitors. (The measure of psychomotor speed was not a pegboard but was a composite measure from the Trail Making Test A and Symbol Digit Modalities Test). Albert *et al.* (1999) found that HIV-positive individuals with a deficit (>1 *SD*) in psychomotor speed were significantly more likely to commit errors on the pill-dispensing portion of a medication management task which entails reading the label on a pill bottle (resembling that of common ARV medications) and

Table III. Logistic Regression Analyses of Cognitive Predictors of Adherence

Predictor	β	*SE*	Odds ratio	95% *CI* Lower	95% *CI* Upper
Logistic regression model 1					
Motivation	.021	.011	1.021	1.00	1.04
Active drug use	−.871	.816	.419	.085	2.074
Active alcohol use	1.209	.692	3.350	.864	12.99
Depression	−.547	.625	.579	.170	1.972
Memory	.013	.044	1.013	.930	1.105
$\chi^2(5, N = 57) = 7.748, p > .017$					
Logistic regression model 2					
Motivation	.021	.011	1.021	1.00	1.04
Active drug use	−.900	.806	1.245	.084	1.98
Active alcohol use	1.172	.685	3.228	.842	12.37
Depression	−.614	.636	.541	.156	1.88
Executive functions	−.004	.030	.996	.939	1.06
$\chi^2(5, N = 57) = 7.675, p > .017$					
Logistic regression model 3					
Motivation	.019	.012	1.019	.996	1.042
Active drug use	−1.114	.951	.328	.051	2.116
Active alcohol use	1.249	.772	3.488	.768	15.488
Depression	−.411	.675	.663	.177	2.488
Psychomotor skills	.086	.036	1.090	1.016	1.169
$\chi^2(5, N = 57) = 14.181, p < .017$					

correctly dispensing a week's supply of pills into a pill box.

Psychomotor slowing is a hallmark feature of HIV disease in the symptomatic stages (Navia *et al.*, 1986) and is included in the clinical diagnosis of minor cognitive motor disorder (MCMD) (The Dana Consortium, 1996). Selnes *et al.* (1997) found that with the occurrence of AIDS in infected individuals, performance declines in psychomotor speed tasks were more frequent in IDUs. Moreover, long-term opiate users appear to have sustained deficits in visuomotor skills (Grant *et al.*, 1978).

Both adherers and nonadherers performed poorly on the psychomotor speed task. Adherer's average performance was nearly two *SD*s below the normative mean and nonadherer's average performance was nearly three *SD*s below the normative mean. Additionally, the psychomotor skills test used in the present study was a more complex and difficult task than those used in previous studies (e.g., Grooved Pegboard). The test used in the present study required the coordinated use of both hands simultaneously plus an assembly task that required, in addition to complex motor coordination, constructional skills. It may be that the greater difficulty level of this test increased its sensitivity to deficits. Such severe deficits may have a marked impact on daily functioning. Difficulty manipulating pill bottles and the pills themselves may lead to frustration with medication taking in this population. Unfortunately, this was not directly assessed in the present study. Devices such as pillboxes or other tools that require less dexterity may improve adherence in persons with psychomotor deficits.

Furthermore, speed is a component of many cognitive tasks. It is unclear at this time whether a generalized cognitive slowing or psychomotor deficits *per se* were responsible for the present findings. The severe levels of psychomotor slowing noted in this study may reflect generalized cognitive slowing that could impede the ability to manage multiple daily obligations, leading to missed medication doses. Interventions such as cognitive rehabilitation or pharmacotherapy to improve psychomotor slowing may potentially be able to address the effect of slowed cognitive processing on the ability to effectively manage HIV medication regimens.

Our findings do not necessarily directly link psychomotor slowing as a *cause* of poor adherence because alternatively, poor adherence could lead to more severe motor deficits. Indeed, psychomotor speed impairment has been demonstrated across several studies to improve with HAART (Cohen *et al.*, 2001; Ferrando *et al.*, 1998; Sacktor *et al.*, 2002, 2003 Suarez *et al.*, 2001) and to be a primary area of cognitive improvement for HIV-positive IDUs. It is likely that there is a bidirectional relationship between adherence and cognitive functions. Taking ARV therapy may affect cognitive status, which, in turn, may affect one's ability to take the medications as prescribed. It was not possible to address this bidirectionality in this study, however current findings show that psychomotor deficits are related to adherence and may be a target for intervention.

It is interesting that active substance and alcohol use and depression were unassociated with adherence in our study. Earlier studies that have found depression and active substance use to predict medication adherence (Carrieri *et al.*, 2003; Tesoriero *et al.*, 2003; Tucker *et al.*, 2003) did not include cognitive measures. It may be that impaired cognitive skills such as slowed processing/psychomotor speed that often accompany depression and substance use accounted for the relationships reported earlier but were not directly tested.

In contrast to the present study, several previous studies found additional cognitive skills to predict adherence (Avants *et al.*, 2001; Hinkin *et al.*, 2002, 2004). This may be explained by differences in the measures used to assess these skills. For instance, we used recall for passages rather than the more commonly used list-learning tasks. Also, our executive function measures relied primarily on working memory and mental flexibility rather than reasoning and problem-solving skills typically evaluated earlier. Earlier studies also used objective measures of adherence such as electronic monitors. Whether the lack of association between executive functions, memory, and adherence in the present study was due to characteristics of the cognitive tests, the adherence measure, or the population under study requires further investigation.

Our finding that self-reported adherence for the previous day was significantly correlated with HIV virus load, whereas self-reported adherence for the previous week was not, suggests that the time frame for self-report adherence estimates in this population may need to be quite limited. In clinical practice, it is often not feasible to measure adherence objectively and clinicians are often forced to rely on self-report measures; however, use of self-report adherence measures may be problematic when memory and other cognitive problems are expected in a population. The very cognitive problems one is positing to be related to adherence may adversely impact recall of medication taking behavior, thereby resulting in a spurious relationship. In future studies that attempt to evaluate optimal time periods for self-report adherence measures, other potentially confounding factors such as medication resistance should be considered. Results of this study should be interpreted cautiously. Information on participants' medical history and complications associated with HIV infection were not available as part of this study. Therefore, complications such as peripheral neuropathy, which could affect psychomotor speed, are unaccounted for in this sample. The cross-sectional nature of the study precluded use of objective adherence measures in addition to self-report. Despite these limitations, the findings from this study demonstrate that HIV-positive IDUs with psychomotor slowing are significantly less likely to be adherent to ARVs. No other studies to date have exclusively linked psychomotor slowing to nonadherence in HIV infection. Psychomotor slowing among our study sample was severe and suggests that when evident, such slowing may be a valuable determinant for ARV adherence among IDUs.

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