Motor Function and Human Immunodeficiency Virus–Associated Cognitive Impairment in a Highly Active Antiretroviral Therapy–Era Cohort

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Background: Cognitive impairment has long been recognized as a manifestation of human immunodeficiency virus (HIV) infection. However, highly active antiretroviral therapy (HAART) has altered the neurologic manifestations of HIV.

Objectives: To develop a measure to quantify the motor abnormalities included in the original descriptions of HIV-associated dementia (HAD); to determine whether motor, affective, and behavioral dysfunction predict cognitive impairment; and to determine whether quantitative motor testing is a helpful adjunct in the diagnosis of HAD in a complex population from the HAART era.

Design: Neurologic and neuropsychological data were collected from the Manhattan HIV Brain Bank, a longitudinal cohort study of patients with advanced HIV. The HIV-Dementia Motor Scale (HDMS) was developed and validated and cognitive and affective or behavioral function was quantified using global neuropsychological T scores, the Beck Depression Inventory (BDI), and an independent assessment of apathy. Relationships among cognitive, motor, affective, and behavioral performance were examined using correlation, linear regression, and analyses of variance.

Setting: An urban AIDS research center.

Participants: A total of 260 HIV-positive, predominantly minority patients.

Main Outcome Measures: The HDMS scores and global neuropsychological T scores.

Results: The HDMS and BDI scores were independent predictors of cognitive impairment. Significant cognitive impairment was found in patients with motor dysfunction. Patients diagnosed as having HAD had a greater degree of motor impairment than those with other neurocognitive diagnoses.

Conclusions: Motor, affective, and behavioral abnormalities predict cognitive impairment in HIV-positive patients in this HAART-era cohort. The HDMS may be useful in the assignment of HIV-associated neurocognitive impairment in HIV populations in which normative data or neuropsychological test design is not optimal.

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Cognitive impairment has long been recognized as a manifestation of human immunodeficiency virus (HIV) infection. The original description of the AIDS dementia complex was published by Navia and colleagues in 1986. The authors described the cardinal features of the disorder: progressive dementia accompanied by motor and behavioral dysfunction. In 1991, the American Academy of Neurology (AAN) published diagnostic criteria for HIV-associated cognitive impairment using the terms HIV-associated dementia (HAD) and minor cognitive motor disorder (MCMD). Consistent with the description of the AIDS dementia complex, these criteria included motor, affective, and behavioral abnormalities.

Since these early definitions, highly active antiretroviral therapy (HAART) has altered the neurologic manifestations of HIV; however, neuropsychological impairment persists. The HIV-associated neurocognitive disorders (HAND) no longer display the virologic associations seen in pre–HAART-era cohorts. Furthermore, the epidemic has steadily shifted into populations with comorbidities that complicate cognitive assessment (eg, low literacy, sociocultural alienation, and substance abuse). In light of these changes, the National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke charged a working group with revising the AAN criteria. Three HAND diagnoses resulted: asymptomatic neurocognitive impairment (ANI), mild neuro-
cognitive disorder and HAD. Mild neurocognitive disorder and HAD were similar to the AAN definitions of MCMD and HAD. However, ANI was a new diagnostic category, defined as performance at least 1 SD below the mean in at least 2 cognitive areas, without abnormality in daily functioning. Motor, affective, and behavioral dysfunction were not included in the revised research criteria because “there is insufficient evidence that these symptoms are reliably associated with neurocognitive impairments.”8(p1797) The role of quantitative motor assessment in the diagnosis of HAND was also noted to need further exploration.8

In this study, we developed the HIV-Dementia Motor Scale (HDMS) to quantify the motor findings described in the early definitions of the AIDS dementia complex, HAD, and MCMD: slowed movements, gait abnormality, limb incoordination, hyperreflexia, hyper-tonia, and weakness.2 We then sought to determine whether motor, affective, and behavioral dysfunction were associated with cognitive impairment in a low literacy, predominantly minority cohort from the HAART era. We hypothesized that motor impairment would predict cognitive impairment and, thus, be a helpful adjunct in the diagnosis of HIV-associated cognitive syndromes in today’s complex populations.

METHODS

STUDY PARTICIPANTS

Data pertaining to motor and neuropsychological function for 260 HIV-positive patients and 18 HIV-negative controls were collected from the Manhattan HIV Brain Bank (MHBB). The MHBB is a longitudinal observational and tissue donation study that includes semiannual neurologic, neuropsychological, medical, and psychiatric evaluations of adults with late-stage HIV and HIV-negative controls. The MHBB enrollment criteria and assessment protocol have been described elsewhere.8

ASSESSMENT OF NEUROPSYCHOLOGICAL FUNCTIONING

Detailed components and normative standards for the MHBB neuropsychological evaluation have been described previously and include tests validated in the assessment of HAND.8,11 For this study, a global neuropsychological T score was calculated from 6 domain-specific T scores: memory encoding, memory retrieval, speed of information processing, working memory, verbal fluency, and abstraction or executive functioning. The motor domain T score was excluded to reduce the effects of motor dysfunction on the global neuropsychological T score.

HIV-ASSOCIATED NEUROCOGNITIVE DIAGNOSTIC PROCEDURES

Neurocognitive diagnoses were assigned during multidisciplinary consensus meetings. The criteria used to assign the diagnoses of HAD and MCMD were those described by the AAN, with the exclusion of motor abnormalities from the diagnostic algorithm. Diagnoses of subsyndromic impairment and neuropsychological impairment attributable to other causes (NPI-O) were assigned according to the algorithm described by Woods et al.12 Subsyndromic impairment was assigned to patients whose impairments did not affect their daily functioning and is equivalent to ANI as described in the revised research nosology.5

ASSESSMENT OF PSYCHIATRIC, AFFECTIVE, AND BEHAVIORAL FACTORS

Patients were assessed for symptoms of depression using the Beck Depression Inventory (BDI).13 In addition, patients were independently queried about symptoms of apathy and social withdrawal and were assigned a score of 0 through 4 (0 indicates normal or usual, as good as it has always been; 1, less interest in family or friends than usual; 2, spends less time with family or friends; 3, lost contact with some family or friends; and 4, little or no contact with others). The Psychiatric Research Interview for Substance and Mental Disorders was used to assess the presence of substance use disorders.14

ASSESSMENT OF MOTOR FUNCTIONING

All patients underwent standardized, comprehensive neurologic examinations. The United Parkinson Disease Rating Scale (UPDRS) was included in all assessments after 2004.15 To quantify the motor abnormalities described in the original descriptions of HAND, the HDMS was developed. Using the AAN definition as a guide, 5 motor domains were defined (strength, tone, reflexes, coordination, and gait), and elements of a standard neurologic examination were selected to represent them (Figure 1).

STATISTICAL ANALYSES

The internal consistency reliability of the HDMS was assessed by performing reliability statistical analysis on the individual HDMS domain scores. Test-retest reliability was not assessed because data from 2 motor examinations close together in time were not available. However, as an approximation, a correlation analysis between the HDMS score at entry and at 6 months was performed for all study participants with both available data points. The validity of the HDMS was judged based on the strength of its correlation to validated measures of motor function: the UPDRS and the motor domain T score derived from performance on the grooved pegboard. A subset of 108 patients was selected for these analyses (all patients with a UPDRS and with neurologic and neuropsychological evaluations). This subset was also used for a linear multiple regression analysis in which HDMS score, BDI score, and apathy were the independent variables used to predict the global neuropsychological T score.

A larger subset of 237 individuals (all participants with a complete neurologic and neuropsychological evaluation at the entry visit) was chosen for further analysis of cognition and motor function. The linear regression analysis was repeated with the HDMS score as the sole independent variable. This analysis was also performed on the 18 HIV-negative controls.

Study participants were then divided into 3 groups (no motor impairment, mild motor impairment, and severe motor impairment) based on the HDMS score. Scores used to determine the 3 groups were derived from a quartile structure; approximately 25% of patients earned an HDMS score of 0, approximately 50% had scores between 1 and 4, and approximately 25% had scores of 5 or greater. Accordingly, a score of 0 was considered no motor impairment; a score of 1 through 4, mild motor impairment; and a score of 5 or greater, severe motor impairment. Global neuropsychological T scores and demographic and virologic variables were compared between

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groups using analysis of variance (ANOVA) and the χ² test. Individuals were then divided into 5 groups based on neuropsychological diagnosis: neurocognitively normal, ANI (subsyndromic), MCMD, HAD, and NPI-O. The mean HDMS score was 3.24 (3.71) (range, 0.17). The internal consistency reliability of the HDMS met the criteria for acceptable reliability (Guttman split-half coefficient, 0.62; Spearman-Brown coefficient, 0.65; Cronbach α, 0.63). The correlation analysis between the HDMS score at entry and at 6 months demonstrated a significant positive correlation (r = 0.64, P < .001). The convergent validity analysis revealed significant associations between the HDMS and the UPDRS scores (r = 0.60, P < .001) and the HDMS score and the motor domain T score (r = -0.27, P = .007), both in the expected direction.

**PSYCHOMETRIC PROPERTIES OF THE HDMS: RELIABILITY AND VALIDITY**

The mean (SD) HDMS score for the sample was 3.24 (3.71) (range, 0-17). The internal consistency reliability of the HDMS met the criteria for acceptable reliability (Guttman split-half coefficient, 0.62; Spearman-Brown coefficient, 0.65; Cronbach α, 0.63). The correlation analysis between the HDMS score at entry and at 6 months demonstrated a significant positive correlation (r = 0.64, P < .001). The convergent validity analysis revealed significant associations between the HDMS and the UPDRS scores (r = 0.60, P < .001) and the HDMS score and the motor domain T score (r = -0.27, P = .007), both in the expected direction.

**COGNITION, MOOD, AND THE HDMS**

The multiple linear regression model with HDMS score, BDI score, and apathy as independent variables predicted the global neuropsychological T score (R² = 0.31, F₁,₂₃₅ = 14.80, P < .001). The BDI (B = -0.39, β = -0.41, t = -4.41, P < .001) and the HDMS (B = -0.89, β = -0.29, t = -3.44, P = .001) scores were significant predictors in the model. The apathy score was not (P = .41). The HDMS score was also a predictor of the global neuropsychological T score in the larger subset of 237 patients (R² = 0.11, F₁,₂₃₅ = 30.00, P < .001).

**COMPARISONS OF HDMS GROUPS**

The ANOVA and post hoc pairwise comparisons revealed significant differences in the mean global neuropsychological T scores among the motor groups (F₂,₂₃₅ = 12.05, P < .001) (Figure 2). No significant difference was found between motor groups in age, ethnicity, educational level, substance abuse history, positive urine toxicologic test results, head trauma, loss of consciousness, learning disability, use of HAART, CD4 cell count, CD4 cell count nadir, plasma viral load, or cerebral spinal fluid viral load (Table). The groups with motor impairment contained more men and more patients...
with focal brain lesions and seizures. Of these factors, focal brain lesions were of particular concern because they may affect both motor and cognitive function. The comparison of mean global neuropsychological T scores between motor groups was repeated excluding the 18 study participants with focal brain lesions. All results remained significant at \( P \leq .05 \).

**HDMS COMPARISONS IN NEUROCOGNITIVE GROUPS**

The study included 17 neurocognitively normal patients, 16 with ANI, 70 with MCMD, 46 with HAD, and 87 with NPI-O. The ANOVA and post hoc pairwise comparisons revealed a significant difference in the mean HDMS score among the neurocognitive groups \( (F_{2,232}=5.30, P<.001) \). The mean HDMS score was significantly higher in the HAD group than in any other group \( (P<.007 \text{ for all groups}) \), except NPI-O \( (P=.06) \). The HAD group also had the most patients with an abnormal HDMS score (36 patients [78%]), although differences were not statistically significant (neurocognitively normal group: 6 [33%] with an abnormal HDMS score, 9 [56%] with ANI, 52 [74%] with MCMD, and 61 [70%] with NPI-O; \( P=.22 \)). Significant pairwise differences were found in the mean HDMS score between the neurocognitively normal group and all cognitively abnormal groups except the ANI group (Figure 3).

**LONGITUDINAL ANALYSIS**

The Spearman rank correlation coefficient between the slope representing the change in the HDMS score and the slope representing the change in the HDMS score was \( -0.20 \) \( (P=.01) \). This finding suggests that over time worse motor performance correlated with worse neuropsychological test performance. Sample sizes at subsequent visits were substantially smaller than at entry. If this phenomenon represented a survivor effect, a correlation might be observed even if the HDMS score among the neurocognitive groups tended to be preserved over time.

**HIV-NEGATIVE CONTROLS**

A linear regression analysis revealed a trend for worsening of the global neuropsychological T score with worsening of the HDMS score \( (R^2=0.16, F_{1,16}=3.00, P=.10) \).

**COMMENT**

We undertook this study in the context of the recent publication\(^6\) of an updated research nosology that removes motor abnormalities from the definition of HAND and with the need for culturally less biased assessments of cognitive functioning in mind. We developed and validated the HDMS, the first quantitative measure of the motor abnormalities classically attributed to HAND: slowed movements, gait abnormality, limb incoordination, hyperreflexia, hypertonia, and weakness. We then used the HDMS, in conjunction with the BDI and an apathy score, in a multiple linear regression model to show that the combination of motor, affective, and behavioral abnormalities is predictive of cognitive impairment in HIV-positive patients in the HAART era. Although the triad of motor, affective, and behavioral, and cognitive abnormalities has been considered the hallmark of HAND since it was first described, the association has never before been rigorously demonstrated. We showed that motor impairment is worse in HAD than in other neurocognitive diagnoses. Finally, in a longitudinal analysis, we showed that the correlation between the HDMS score and the global neuropsychological T score tended to be preserved over time.

The significance of our findings is best understood in the context of the current HIV epidemic. In the United States, HIV infection is steadily shifting into populations with greater levels of socioeconomic deprivation, lower literacy, and nontraditional cultural backgrounds.\(^7\) In both nonmainstream US and developing world populations, the neuropsychological tests used to arrive at diagnoses of HAND continue to require adjustments and validation. For example, in our cohort, the impact of low literacy in biasing neuropsychological characterization toward diagnoses of impairment has previously been described.\(^8\) In addition, virologic markers no longer correlate with HAND in HAART-era cohorts, further complicating diagnosis.

In populations similar to ours, the HDMS may help establish the presence of HAND and distinguish it from pseudoimpairment, reflecting bias from a test unsuited to the individual or population under analysis. The relative insensitivity of motor testing to population bias has been noted in a prior study\(^9\) of HIV-associated dementia, in which premorbid and actual intelligence did not correlate with motor test results, such as rapid alternating movements and contraction times, but did correlate with more cognitively influenced HIV Dementia Scale scores. This prior study and the results we describe herein suggest that current recommendations to eliminate affective, behavioral, and motoric adjuncts to neurocognitive diagnosis should be carefully assessed when they are applied to nonmainstream populations. In our cohort, the only group that did not have a significantly dif-
different HDMS score from neurocognitively normal individuals was the group of functionally normal individuals with ANI. This finding may suggest that caution should be used in the assignment of ANI because it is currently unclear whether ANI represents a manifestation of brain dysfunction or a lack of suitability of testing modalities for nonmainstream populations.

The ability to distinguish the cognitive effects of HIV from other comorbidities has become one of the most pressing problems in the development of treatment strategies, particularly pertaining to the demonstration of efficacy in clinical treatment trials. Although, in our cohort, motor function was most severely abnormal in individuals with HAD, high levels of impairment were also seen in those with cognitive abnormalities attributable to other causes. The lack of specificity for motor phenomena to HIV underscores the need for continued analysis of culturally less biased, ancillary modalities in the diagnosis of HAND.

In summary, our study shows that, in the HAART era, motor and behavioral abnormalities are associated with and predict cognitive impairment in HIV-positive patients and may be important ancillary information in the assignment of cognitive impairment in marginalized populations. More work is needed to reliably distinguish HIV-associated cognitive impairments from those attributable to other causes.

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Author Contributions: Dr Robinson-Papp had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Robinson-Papp, Byrd, Rivera Mindt, Simpson, and Morgello. Acquisition of data: Robinson-Papp, Byrd, and Morgello. Analysis and interpretation of data: Robinson-Papp, Byrd, Oden, and

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**Table. Motor Group Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Motor Impairment Group (n=72)</th>
<th>Mild Motor Impairment Group (n=106)</th>
<th>Severe Motor Impairment Group (n=59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDMS score range</td>
<td>0</td>
<td>1-4</td>
<td>5-20</td>
<td>NA</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>49 (8.3)</td>
<td>51 (7.0)</td>
<td>51 (7.1)</td>
<td>.17</td>
</tr>
<tr>
<td>Male, No. (%):</td>
<td>42 (58)</td>
<td>74 (70)</td>
<td>47 (80)</td>
<td>.03</td>
</tr>
<tr>
<td>Ethnicity, No. (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (17)</td>
<td>29 (27)</td>
<td>19 (32)</td>
<td>.28</td>
</tr>
<tr>
<td>Black</td>
<td>37 (51)</td>
<td>54 (51)</td>
<td>23 (39)</td>
<td>.28</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22 (31)</td>
<td>22 (21)</td>
<td>17 (29)</td>
<td>.28</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>11.8 (2.8)</td>
<td>12.4 (2.8)</td>
<td>12.5 (2.8)</td>
<td>.23</td>
</tr>
<tr>
<td>CNS lesion, No. (%)</td>
<td>0</td>
<td>12 (11)</td>
<td>6 (10)</td>
<td>.01</td>
</tr>
<tr>
<td>Substance abuse by report, No. (%)</td>
<td>56 (78)</td>
<td>90 (85)</td>
<td>46 (78)</td>
<td>.39</td>
</tr>
<tr>
<td>Positive urine toxicologic test result, No. (%) a</td>
<td>38 (57)</td>
<td>58 (60)</td>
<td>35 (67)</td>
<td>.49</td>
</tr>
<tr>
<td>Receiving HAART, No. (%) a</td>
<td>57 (80)</td>
<td>80 (76)</td>
<td>41 (70)</td>
<td>.44</td>
</tr>
<tr>
<td>CNS trauma, No. (%)</td>
<td>33 (46)</td>
<td>37 (35)</td>
<td>22 (37)</td>
<td>.33</td>
</tr>
<tr>
<td>Loss of consciousness, No. (%)</td>
<td>25 (35)</td>
<td>37 (35)</td>
<td>27 (46)</td>
<td>.32</td>
</tr>
<tr>
<td>Seizures, No. (%)</td>
<td>6 (8)</td>
<td>28 (26)</td>
<td>19 (32)</td>
<td>.002</td>
</tr>
<tr>
<td>Learning disability, No. (%)</td>
<td>10 (14)</td>
<td>14 (13)</td>
<td>8 (14)</td>
<td>.99</td>
</tr>
<tr>
<td>CD4 lymphocyte count/µL, mean (SD)</td>
<td>319 (379)</td>
<td>271 (305)</td>
<td>247 (268)</td>
<td>.59</td>
</tr>
<tr>
<td>CD4 lymphocyte count nadir/µL, mean (SD) b</td>
<td>187 (279)</td>
<td>145 (221)</td>
<td>151 (179)</td>
<td>.48</td>
</tr>
<tr>
<td>Serum viral load, copies/mL c</td>
<td>3.6 (1.2)</td>
<td>3.8 (1.2)</td>
<td>4.1 (1.2)</td>
<td>.27</td>
</tr>
<tr>
<td>CSF viral load, mean (SD), copies/mL c</td>
<td>2.3 (0.80)</td>
<td>2.1 (0.72)</td>
<td>2.6 (1.20)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; HAART, highly active antiretroviral therapy; HDMS, Human Immunodeficiency Virus–Dementia Motor Scale; NA, not applicable.

a Percentages are not based on the totals given because of missing data.
b Lowest recorded value for the study participant, as reported either at entry or on subsequent visits.
c Log transformed (base 10).
Morgello. Drafting of the manuscript: Robinson-Papp, Byrd, and Rivera Mindt. Critical revision of the manuscript for important intellectual content: Robinson-Papp, Byrd, Rivera Mindt, Oden, Simpson, and Morgello. Statistical analysis: Robinson-Papp, Byrd, Rivera Mindt, and Oden. Obtained funding: Morgello. Administrative, technical, and material support: Morgello. Study supervision: Simpson and Morgello.

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