Clinical trials in HIV-associated cognitive impairment: Cognitive and functional outcomes

Article abstract—Cognitive and functional outcomes are of primary interest in the design of efficacy trials in HIV-associated cognitive impairment. In a longitudinal cohort study, weak associations were found between measures of cognitive performance and commonly used measures of daily functioning (mostly self-report measures) in HIV-infected individuals. Modifications of current functional scales or new functional instruments are needed to assess the clinical relevance of cognitive changes in clinical trials of HIV-associated cognitive impairment.

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Cognitive impairment is a common sequela of HIV-1 infection[1] that continues to exist despite the current use of potent antiretroviral therapy. Clinical trials in HIV-associated cognitive impairment have been largely safety and tolerability studies, relatively short in duration.[2-4] However, as we move from these early phase studies to larger efficacy trials, cognitive and functional outcomes are of primary interest. Unfortunately, there are no available measures of function specifically designed to assess performance in HIV-infected subjects with cognitive impairment. Using data from the Dana cohort,[5] we investigated whether or not commonly used functional measures were associated with cognitive performance.

Design and method. The characteristics of the Dana cohort have been previously described.[5] Based on a modification of the American Academy of Neurology (AAN) recommendations[5] and previous clinical trials in HIV-associated cognitive impairment,[4] we defined mild cognitive impairment as performance that was 2 SD below the appropriate means on one test (which could not be timed gait) or 1 SD below the mean on at least two tests. Subjects having no test scores 2 SD below the mean and no more than one test score 1 SD below the mean were classified as not impaired (some of these subjects might have met AAN criteria for minor cognitive/motor disorder[5]). In this study, we classified the remaining subjects based only on the number of tests on which scores were 2 SD below the mean as moderately impaired (two or three tests 2 SD below thee mean) or as severely impaired (four or more tests 2 SD below the mean). It was felt that a test 2 SD below the mean would represent a definite abnormal result and that if 50% (four) or more of the neuropsychological tests were 2 SD below the mean the cognitive performance would be severely impaired.

Average *z* scores were created from the neuropsychological test battery with the aid of a principal component factor analysis using varimax rotation. Three factors were identified that accounted for 68.4% of the total variance: Attention/Memory (Rey Auditory Verbal Learning Test—total score, Trial 5 score, Recall after Interference, Delayed Recall, and Correct Recognition), Psychomotor Speed (Grooved Pegboard, dominant and nondominant hands, and Symbol Digit Modalities Test), and Executive Function (Rey Complex Figure Copy and Immediate Recall, Odd-Man-Out Test, and Verbal Fluency).

Functional measures included the Instrumental Activity of Daily Living (IADL) scales of Lawton and Brody,[6] the Katz ADL/Lawton Self-Maintenance scale (SMADL),[7] the Role Functioning items of the Medical Outcomes Study (MOS),[8] the MOS Physical Function Subscale,[8] and the Karnofsky Performance Scale.[9] In addition, the Center for Epidemiologic Studies–Depression Scale (CES-D) was used to assess mood.

A detailed description of the statistical methods used can be found on the web site. Brief descriptions follow in Results and the tables.

Results. Demographic and clinical characteristics of the participants at baseline are shown in table 1. Functional performance tended to decline with increasing degree of cognitive impairment at baseline (table 2), in particular with regard to Role Function, Physical Function, and Karnofsky Performance Scale score. These differences were attenuated after adjustment for other baseline covariates. The percentages of subjects demonstrating an IADL deficit were as follows: unimpaired, 40%; mild, 41%; moderate, 34%; severe, 56%. The percentages of subjects demonstrating an SMADL deficit were as follows: unimpaired, 10%; mild, 9%; moderate, 12%; severe, 20%.

Of the 270 subjects included in the baseline analyses, 138 had a 1-year follow-up visit, 102 did not return for the 1-year visit (46 due to death, 31 due to loss to follow-up, 11 due to withdrawal of consent, 11 for other reasons, and

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Table 1 *Demographic and clinical characteristics of subjects with and without cognitive impairment*

Characteristics	Normal, n = 83	Mild, n = 95	Moderate, n = 67	Severe, n = 25
Sex, % men	76	79	76	84
Ethnicity, white/black/Hispanic/others, %	59/34/5/2	48/40/7/4	49/39/10/1	36/60/4/0
Age, y, mean (SD)	38.8 (7.5)	40.7 (7.6) [0.11]	39.1 (7.5) [0.85]	40.6 (7.9) [0.30]
Education, y, mean (SD)	13.0 (2.6)	13.6 (2.8) [0.20]	14.0 (3.2) [0.04]	13.7 (3.8) [0.30]
UPDRS, mean (SD)	2.8 (5.3)	4.3 (5.2) [0.16]	5.9 (7.8) [0.01]	10.9 (12.3) [0.0001]
CES-D, mean (SD)	17.6 (9.6)	19.6 (11.4) [0.21]	22.0 (10.6) [0.01]	28.6 (12.0) [<0.0001]
$CD4^+$ T-cell count/mm^3, mean (SD)	211.2 (222.2)	143.7 (162.7) [0.02]	187.7 (155.4) [0.99]	183.6 (168.1) [0.83]
Hemoglobin, g/dL, mean (SD)	13.1 (1.6)	12.9 (1.8) [0.50]	12.6 (2.1) [0.09]	12.4 (2.0) [0.10]

Two-tailed *p* values for comparison between patients with normal cognitive performance and those with cognitive impairment are shown in brackets, as obtained from *t*-tests. *p* Values of <0.017 are considered to be significant, after Bonferroni adjustment for multiple comparisons.

UPDRS = Unified Parkinson's Disease Rating Scale (motor component); CES-*D* = Center for Epidemiologic Studies–Depression Scale.

three for unknown reasons), and 30 were enrolled into the study too late to have a 1-year follow-up visit. The dropout rates before 1 year were the following: unimpaired, 36%; mild, 39%; moderate, 53%; severe, 52%. As expected, those who dropped out before 1 year tended to have more advanced HIV infection and lower Physical Function scores than those who had a 1-year visit (additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for this issue to find the title link for this article). In terms of cognitive function, the two groups tended to differ only in average Psychomotor Speed *z* scores ($p = 0.07$; additional information related to this article can be found on the *Neurology* Web site) .

Cognitive and functional performance tended to be either stable or improved after 1 year of follow-up (table 3). Seventy percent (70%) of subjects changed by at most 1 point on the IADL scale, and 87% of subjects did not change at all on the SMADL scale. The improvement in Attention/Memory *z* scores tended to be more prominent for the groups with mild/moderate cognitive impairment, and the improvement in the Executive Function and Psychomotor Speed *z* scores tended to be more prominent for the groups with moderate/severe cognitive impairment. The improvement in Role Function was consistent across the cognitive impairment groups (additional information related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for this issue to find the title link for this article).

Overall, the correlations between the 1-year changes in function (Karnofsky Performance Scale, Role Function, Physical Function) and the 1-year changes in cognitive performance (domain *z* scores) were weak, with only one correlation (between Karnofsky Performance Scale score and the Psychomotor Speed *z* score, $r = 0.26$, $p = 0.003$) being >0.20. Within the subgroup of subjects with mild

Table 2 *Baseline functional performance in subjects with and without cognitive impairment*

Analyses	Normal, n = 83	Mild, n = 95	Moderate, n = 67	Severe, n = 25
Unadjusted analyses*				
Role Function	10.9 (2.2)	10.5 (2.3) [0.23]	10.1 (2.2) [0.06]	9.6 (2.5) [0.02]
Physical function	21.2 (4.9)	21.5 (4.2) [0.69]	19.8 (4.8) [0.08]	18.6 (6.0) [0.03]
Karnofsky	85.2 (12.5)	83.8 (12.0) [0.51]	83.1 (15.1) [0.34]	77.0 (16.8) [0.008]
Adjusted analyses†				
Role Function	11.0	10.9 [0.61]	10.7 [0.30]	10.6 [0.42]
Physical function	20.3	21.6 [0.05]	19.9 [0.57]	21.1 [0.49]
Karnofsky	84.6	84.2 [0.81]	85.0 [0.87]	80.7 [0.20]

* Values are expressed as means (SD) [*p* value]. *p* Values for comparison between patients with normal cognitive performance and those with cognitive impairment are shown in brackets, as obtained from *t*-tests. *p* Values of <0.017 are considered to be significant, after Bonferroni adjustment for multiple comparisons.

† Values are adjusted group means. Group comparisons were adjusted for age, sex, years of education, Center for Epidemiological Studies–Depression Scale, CD4 count (log transformed), hemoglobin level, number of medications (square root transformed), and number of AIDS diagnoses (dichotomized as 0–1 vs >1).

Functional score ranges: Role Function, 7–14; Physical Function, 9–27; Karnofsky, 0–100. A higher functional score indicates better performance.

Table 3 *One-year changes in cognitive domains and functional scores*

Parameter	One-year change, mean (SD)	*p* Value
Executive function, *z* score	0.14 (0.87)	0.09
Attention/memory, *z* score	0.30 (0.97)	0.0007
Psychomotor Speed, *z* score	0.15 (1.22)	0.17
Karnofsky	−0.7 (14.8)	0.58
Role Function	0.4 (2.0)	0.02
Physical Function	0.2 (4.2)	0.68

A positive sign indicates improvement from baseline assessment. *p* Values are from two-tailed paired *t*-tests of the null hypothesis of zero mean change.

cognitive impairment, the partial correlations (adjusted for CES-D, CD4 count, and hemoglobin) between the change in Executive Function *z* score and changes in the functional tests were as follows: 0.44 ($p = 0.007$) for Karnofsky Performance Scale score, 0.33 ($p = 0.05$) for Role Function, and 0.37 ($p = 0.02$) for Physical Function. For subjects with moderate cognitive impairment, significant partial correlations were observed between the change in Karnofsky Performance Scale score and both the Attention/Memory *z* score ($r = 0.52$, $p = 0.009$) and the Psychomotor Speed *z* score ($r = 0.54$, $p = 0.01$).

Discussion. In the current study, we investigated the relationship between the degree of HIV-associated cognitive impairment, as defined by neuropsychological test performance, and commonly used measures of daily function. Our results show that at baseline, IADL[6] and SMADL[7] had the weakest relationships with cognitive performance. The other three measures, Role Function,[8] Physical Function,[8] and the Karnofsky Performance Scale,[9] indicated that functional impairment tended to be present only in patients with severe cognitive dysfunction. However, when other factors such as age, education, mood, and immune function were taken into account, none of the functional measures showed a significant relationship with cognitive performance (see table 2).

A 12-month evaluation showed a weak association between changes in functional measures and changes in cognition. Conversely, the cognitive subgroup analyses showed some significant but nonuniform relationships between changes in cognition and changes in functional measures. For example, the Karnofsky Performance Scale was the functional measure that correlated best with Executive Function (mild cognitive impairment subgroup) and with Attention/Memory and Psychomotor Speed (moderate cognitive impairment subgroup).

The five functional measures used in this study, with the exception of the Karnofsky scale, are self-report measures. It may be anticipated that subjects with more severe cognitive impairment may not realize the extent of their functional decline. This may explain in part the results of the cognitive subgroup analyses, suggesting a better correlation between changes in some cognitive domains and changes in the Karnofsky score (scale scored by physician or nurse). Conversely, the premorbid functional status probably influenced the subject assessment of functional changes.

The longitudinal analyses were limited in part by an attrition of 42.5% at 1 year. The observed cognitive improvement may be a spurious result that could be explained by an enrichment of the cohort of subjects with better cognitive performance after the withdrawal of those with worse performance. Also, regression to mean may be responsible for the improvement. This questionable cognitive improvement may make it difficult to specify a reasonable effect size to try to detect when determining the appropriate sample size for a clinical trial.

Enrolling into trials HIV subjects with cognitive impairment based on neuropsychological test scores rather than the definition of dementia offers some advantages. Dementia, by definition, requires loss of function. Unfortunately, attribution of loss of function to cognitive impairment is a difficult task when applied to a systemic disease such as HIV infection. Furthermore, dementia scales may be prone to substantial variability.[10] In addition, subjects in earlier stages of cognitive impairment may be more likely to respond to therapy. Neuropsychological test batteries are well standardized, thus less prone to subjective interpretation, and can be easily used in multicenter studies. However, modification of current functional scales or new instruments that correlate better with cognitive performance are needed to assess the clinical relevance of impairment (and improvement) on neuropsychological tests.

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Neuro*Images*

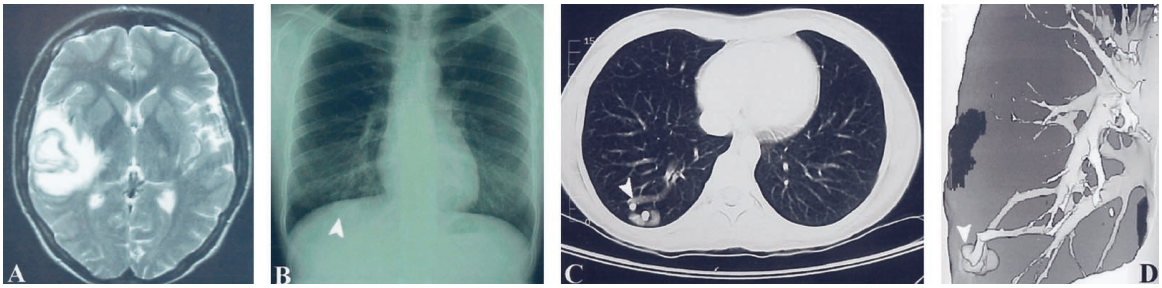

Figure. (A) Axial T2-weighted MRI—right temporal brain abscess with surrounding edema; (B) chest x-ray shows mass at right base; (C) axial chest CT—enhancing vascular mass at right base; (D) three-dimensional chest CT reconstruction demonstrates a right pulmonary arteriovenous fistula.

Pulmonary arteriovenous fistula and brain abscess

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A 23-year-old woman presented with 3 days of headache followed by complex partial seizures. Stereotactic aspiration of a large right temporal mass revealed purulent material with Gram-positive cocci (*Streptococcus millieri*). Chest radiograph and CT scan demonstrated a pulmonary arteriovenous fistula (PAVF). PAVF are low resistance, abnormal connections between a pulmonary artery and distended vein. They may occur as an isolated entity or associated with hereditary hemorrhagic telangiectasia (Osler Weber Rendu syndrome). PAVF often present with neurologic symptoms, usually stroke, TIA, or brain abscess from the right to left shunt that bypasses the normal filtering action of the lungs.

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