

# **An Observed Performance Test of Medication Management Ability in HIV: Relation to Neuropsychological Status and Medication Adherence Outcomes**

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Neuropsychological assessment may identify mild deficits in HIV-infected persons, but it is sometimes unclear if such deficits compromise functional competencies, such as the ability to adhere to complex medication regimens. We examined the relationship between neuropsychological status (NP), observed performance on a medication management test (MMT), and antiviral medication adherence as elicited in a 3-day recall measure. Two samples of HIV+ subjects ( $n = 20$ ,  $n = 41$ ) were used to develop and validate the MMT. An additional 57 HIV+ patients taking antivirals were assessed to examine NP, MMT, and adherence outcomes. NP performance was scored according to age- and education-based norms. Adherence was assessed by comparing reported medication use to medication insert information. Poorer performance on the MMT was associated with scores  $< -1$  SD below norms in tests of memory (RAVLT), executive function (Odd Man Out), and psychomotor skill (Grooved Pegboard). Half the sample made  $>1$  adherence error, as reported in the recall measure. Number of errors was related to both NP and MMT performance. Deficits identified in NP assessment and captured in an observed performance test of medication management are related to HIV medication adherence.

**KEY WORDS:** HIV; cognitive impairment; medication adherence; function; antiviral medications.

## **INTRODUCTION**

The complexity of antiviral medication regimens in HIV and the significance of poor medication adherence for the efficacy of these therapies has generated new interest in measuring adherence. As Rabkin and Chesney (1999) point out, current highly active antiretroviral therapy (HAART) requires use of a protease inhibitor every 8 or 12 hr around the clock

(either with meals [saquinavir, zidovudine, zalcitabine, didanosine, zalcitabine, didanosine, zalcitabine, didanosine] or without [indinavir]), along with at least two additional antiviral medications that may have different schedules, for a total of up to 22 pills per day. People with HIV are often prescribed other medications as well, pushing the number of pills in a daily regimen even higher. Rabkin and Chesney (1999) conclude that "combination therapy for HIV illness is perhaps the most rigorous, demanding, and unforgiving of any outpatient oral treatment ever introduced."

The consequences of nonadherence to such therapies are severe. Blaschke and colleagues found rises in HIV RNA copy number following even a few days of missed doses of saquinavir (Blaschke, 1997). Similar results have been reported by other investigators (Condra *et al.*, 1995). Missed doses lead to drug resistance, which may compromise the effectiveness

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of an entire class of protease inhibitors (Deeks *et al.*, 1997).

For these reasons, research on adherence to antiviral regimens is critical. Such research has usually stressed patient characteristics, features of the treatment regimen itself (such as complexity), and the patient-provider relationship. However, HIV infection poses an additional complication for medication adherence. HIV-associated cognitive impairment occurs in about 20% of individuals who meet criteria for AIDS (Bacellar *et al.*, 1994; McArthur *et al.*, 1993). Its features have been well described (Academy of Neurology AIDS Task Force, 1991; Dana Consortium, 1996). It is likely that some of the low adherence reported for people with HIV (Alwood *et al.*, 1994; Galetko *et al.*, 1996; Muma *et al.*, 1995; Pablos-Mendez *et al.*, 1997; Samet *et al.*, 1992; Stall *et al.*, 1996; Wall *et al.*, 1995) may be due to such deficits. Prior research suggests that neuropsychological deficits affect daily performance, including work disability (Albert *et al.*, 1995) and alteration of daily activities (Albert *et al.*, 1994; Todak *et al.*, 1996), but we have been unable to identify studies that have examined the effect of cognitive deficit on adherence to HAART.

We undertook this research because providers, in our experience, are often unaware of the cognitive basis for patients' inability to comply with HAART. We wished to develop a simple test that might shed light on the ability of patients to adhere to such regimens. To this end, we devised an observed-performance test specifically tailored to antiviral medicines. The test identifies mistakes in dispensing prescriptions and assesses how well patients can calculate when a new prescription is needed, determine if pills have been missed over the prior week, and identify which medicines need to be taken with food or might make one drowsy. Test performance was examined relative to neuropsychological status and a recall measure of adherence.

## SAMPLE

We recruited three groups of HIV+ patients, two for development and testing of the medication management test (MMT), and one specifically to examine the extent to which the measures of medication management competence predict adherence. The test development samples consisted of 20 subjects recruited at Columbia University in a study of neurocognitive impairment in HIV and 41 subjects re-

cruited at Cornell University in a study of HIV and mental health. Subjects in the Columbia sample were required to have CD4 < 200, or CD4 < 300 and meet criteria for cognitive impairment (at least two tests with scores < -1 SD below norms, or one test < -2 SD below norms). Cornell subjects met criteria for AIDS. Both samples completed the MMT at a single assessment and were also assessed with a battery of neuropsychological tests.

The sample used to assess medication adherence consisted of an additional 57 HIV+ subjects recruited at Columbia for a study of cognitive deficits and the need for increased medication supervision. These subjects were required to be taking at least one antiviral medication.

All three samples were recruited through targeted advertisements, word of mouth, and clinic outreach. Subjects were reimbursed for travel costs to study centers. Both the Columbia University/Columbia-Presbyterian Medical Center and Cornell University Medical College Institutional Review Boards approved this research.

## METHODS

Standard sociodemographic information was collected. Blood was drawn from participants in the two test development samples for determination of CD4 counts. Subjects in the third sample provided documentation of their most recent CD4 count.

### Neuropsychological Battery

Subjects in the two Columbia samples completed the following neuropsychological tests: Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1941), Odd Man Out (Flowers and Robertson, 1985), Digit Symbol (Wechsler, 1981), FAS verbal fluency (Benton, 1951), grooved pegboard (Kløve, 1963), Rey Copy Figure-Copy and Recall (RCFT) (Rey, 1941), and CALCAP (Miller *et al.*, 1991). These tests are included in the AIDS Clinical Trials Group (ACTG) battery and cover the major domains of cognition, such as memory (RAVLT, RCFT), executive function and attention (Odd Man Out, Digit Symbol), discrimination and reaction time (CALCAP), psychomotor function (grooved pegboard), and language (FAS). A trained tester administered all tests. Subjects in the Cornell cohort completed a different neuropsychological battery, which included the

Grooved Pegboard and components of the California Verbal Learning Test (CVLT) (Delis *et al.*, 1983).

Performance on each test was scored against published age- and education-appropriate norms. For subjects who had attended college, we used norms derived from the MACS cohort (Selnes *et al.*, 1993). For less educated subjects, we used norms derived from the ALIVE cohort (Concha *et al.*, 1995). Performance on each test was scored as 0, 1, or  $\geq 2$  *SD* below the mean for the appropriate age and education group.

### Medication Management Test (MMT)

The MMT was newly designed for this research and adapts the medication component of an existing geriatric assessment instrument, the Observed Tasks of Daily Living (OTDL) (Diehl *et al.*, 1995). The OTDL was designed to assess "everyday problem-solving" in a variety of domains and has been shown to be related to cognitive status in the elderly, but has not been used to assess medication adherence. In adapting the instrument, we retained the basic format of presenting subjects with medication bottles and asking them to make inferences based on prescription label information. However, we altered the test by using antiviral prescription information and by refining the scoring procedure.

The MMT consists of two components, "pill dispensing" and "medication inference." In the pill component, subjects are observed and scored on their ability to dispense 1 day's dosage of five HIV medications. The "pills" (actually dried beans) are placed in five standardized bottles. "Medication A" is modeled on zidovudine, "medication B" on lamivudine, and "medication C" on saquinavir. The hospital pharmacy provided dosing information and appropriate labels. For this component of the test, subjects must transfer the right number of "pills" from the bottles to a compartmentalized box designed to hold 1 week's supply of pills. The fifth bottle states that it is a PRN medication, and subjects must recognize that this medicine should not be placed in the pill organizer. Subjects are scored on the percentage of prescriptions they correctly place in the box, ranging from 0% (all five wrong) to 100% (all five correctly placed). The number of beans in the box provides a behavioral record for scoring.

The medication inference component of the test consists of 15 items. These items require that subjects answer questions about the five medications and also

about information contained in an over-the-counter insert. For example, Questions 1 and 2 ask subjects how long a new prescription of Medication B will last. Subjects are scored on whether they correctly identify the right bottle (Question 1) and whether they correctly answer 15 days (Question 2); this requires recognition that 30 pills are in the bottle and that they should take 2 each day. Other items ask subjects to identify particular dosing instructions ("Take with food," "May cause drowsiness"). One set of items requires that subjects determine if they have missed a dose by examining labeling information, counting remaining pills in the bottle, and performing the appropriate arithmetic. Two questions require that subjects read a product insert (for aspirin) and make inferences from this information. The 15 items are scored dichotomously, and the total is expressed, for convenience, as percentage correct, ranging from 0% (none correct) to 100% (all 15 correct).

The current MMT takes 15–25 min to administer. A videotape was prepared to insure standardized administration of the test.

### Medication Recall

The Medication Recall measure uses a time budget format (Albert *et al.*, 1994) to elicit all antiviral medication use in the 3 days prior to the clinical assessment. Subjects begin with "yesterday," the day before their clinic appointment, and report when they woke up, when they went to bed for the night, and when they ate meals and snacks. These provide cognitive anchors for the day. They then report the actual time at which they took each of their antiviral medicines, along with the number of capsules or pills.

Subject reports of medication use were scored against product insert information. That is, we scored subject recall against clinical guidelines, rather than what their doctor may have recommended. Thus, the measure is really one of *adherence to clinical guidelines*, rather than adherence to what a doctor told a patient. A more ideal approach would be to score reported medication use against actual medication instructions, obtained from physicians, chart reviews, or pharmacy records. Because we did not have access to such information, we chose to score the recall measure against product insert recommendations.

With this limitation, subject adherence for each medicine was scored on three dimensions: correct number of pills, correct number of doses in a day, and

correct dosage interval. We defined correct interval liberally, so that a twice-a-day prescription would be scored correct if the interval between doses was  $12 \pm 3$  hr. Subjects taking three antivirals, then, could have 0–9 errors in medicines in a single day. Nine errors would summarize the experience of a subject who took the wrong number of pills and the wrong number of doses, and who also had incorrect intervals between doses (or who took none at all). More typical would be the subject who made only a single mistake in the dosing interval for one of the medicines. We calculated total errors and particular kinds of errors both in the day before clinic assessment and across the prior 3 days.

## ANALYSES

Because the MMT is a new instrument, reliability coefficients (Cronbach's alpha) were calculated for its two components. Two raters also scored the first 10 subjects to insure that the test could be reliably scored. The distribution of each item was also inspected. Validity was assessed by examining the percentage of items correct relative to neuropsychological performance.

Reliabilities were not calculated for the recall measure. However, a standardized guide for eliciting recall information and for scoring it against clinical guidelines was prepared.

Because the samples were small and the measures newly developed, analyses were limited to descriptive statistics, correlations, and tests of differences in means. In the test development samples, we determined whether NP-impaired subjects scored significantly worse on the MMT than nonimpaired subjects. Differences were assessed by *t* test and one-way analysis of variance. For the adherence outcomes, we examined the number of medication errors according to NP status and MMT score.

## RESULTS

### Samples

The Columbia and Cornell test development samples differed in education and age. Mean years of education was 13.7 in Columbia subjects and 16.0 in Cornell subjects. Columbia subjects were older (43.7 vs. 40.8 years). Six of the 20 Columbia subjects were women; the Cornell sample was exclusively

male. Half the Columbia subjects were infected through needle use, and a majority of the Columbia subjects were African-American. The Cornell sample was drawn from an exclusively gay/bisexual men's cohort. We do not present statistical tests comparing the samples because of the different selection factors used to recruit each sample (see above).

### Test Development/Validation

At the Columbia site, two raters scored the first 10 subjects, with almost identical scoring. Table I presents the range of scores for each component of the test, as well as scale reliabilities, for the two sites. As the table indicates, the two components of the MMT showed adequate variance and scale reliabilities in each sample. None of the Columbia subjects scored at the ceiling in the medication inference component of the test and only 7.3% of Cornell subjects did so. The more-educated Cornell subjects were more likely to score at the ceiling in the medication dispensing component of the test. Reliabilities (Cronbach's alpha) for the two scales were similar across the samples: .63–.74 for the medication inference component, .78–.84 for the pill dispensing component. In both samples, the correlation between the medication inference and pill dispensing components was similar ( $r = .72$ , Columbia;  $r = .76$ , Cornell).

### Relationship Between MMT and NP Status in Validation Samples

For both samples, poorer NP performance was associated with lower performance on both the medication inference and pill dispensing components of the test. These differences were most pronounced for

**Table I.** Medication Management Test: Scale Performance in Validation Samples

	Columbia sample ( <i>n</i> = 20)	Cornell sample ( <i>n</i> = 41)
Medication inference (15 items)		
Range, % correct	.21–.89	.47–1.00
Percent at ceiling	0.0	7.3
Scale reliability ( $\alpha$ )	.74	.63
Pill dispensing (5 items)		
Range, % correct	.00–1.00	.20–1.00
Percent at ceiling	40.0	63.4
Scale reliability ( $\alpha$ )	.84	.78

subjects scoring  $\leq -2$  *SD* below norms on both the psychomotor and memory tests. For example, Cornell subjects with this degree of impairment, on average, were likely to dispense only 60% of the pills correctly (three of the five medications), while less impaired subjects dispensed 80% of the pills correctly (four of the five medications).

### Adherence Sample

The 57 HIV+ subjects in the adherence outcomes study resembled the initial Columbia test validation sample. One third were women, and a majority were non-White (20% White, 60% African-American, 20% Hispanic or other). More than half reported IV injection as the source of HIV infection. The mean age was 44.0, and the mean reported education was 13.0 years. Sixty percent reported incomes below \$10,000 a year. The sample had tested positive for HIV a mean of 6.9 years, and the mean CD4 count at the time of evaluation was 199 (*SD* = 118).

In this sample, MMT reliabilities were roughly comparable to those obtained in the test validation samples. Cronbach's alpha was .82 for both the pill dispensing and medication inference components. Of the sample, 57.1% scored at the ceiling in the pill dispensing component, 3.6% in the medication inference test. The correlation between scores in the two components was .59 ( $p < .001$ ).

### NP and MMT Performance

Table II presents the mean percentage correct on the two MMT components according to NP performance on the full battery of eight tests. Because of the small sample, we summarized performance as either "no deficit" or scores  $\leq -1$  *SD* below age- and education-appropriate norms. Fifty-six subjects (in some cases, 55) completed the tests. The table shows that three NP tests were significantly associated with MMT performance. Poorer scores in executive function (Odd Man Out) and psychomotor skills (Grooved Pegboard) were significantly associated with poorer performance in pill dispensing, while poorer scores in memory (RAVLT) significantly predicted poorer performance on the medication inference component. It is notable that not all NP domains were associated with MMT performance and that different domains were related to the two components of the test.

**Table II.** Cognitive Performance and Medication Management Test

	Percent correct	
	Pill dispensing	Medication inference
<b>RAVLT</b>		
No deficit (23)	84.4	70.7
$\leq -1$ <i>SD</i> (33)	75.2	57.8*
<b>Odd Man Out</b>		
No deficit (41)	84.4	65.9
$\leq -1$ <i>SD</i> (14)	61.4*	54.3
<b>Digit Symbol</b>		
No deficit (38)	80.0	63.6
$\leq -1$ <i>SD</i> (16)	75.0	61.3
<b>Verbal Fluency</b>		
No deficit (41)	77.6	65.0
$\leq -1$ <i>SD</i> (14)	81.4	58.1
<b>Grooved Pegboard</b>		
No deficit (31)	86.5	63.9
$\leq -1$ <i>SD</i> (25)	69.6*	62.1
<b>RCFT Copy</b>		
No deficit (33)	77.6	64.2
$\leq -1$ <i>SD</i> (22)	80.0	60.1
<b>RCFT Recall</b>		
No deficit (34)	79.4	65.1
$\leq -1$ <i>SD</i> (21)	77.1	59.4
<b>CALCAP A,B</b>		
No deficit (26)	77.7	63.4
$\leq -1$ <i>SD</i> (29)	79.3	62.1
<b>NP Composite</b>		
No deficit (17)	82.4	67.1
Deficit (38)	76.8	61.1

Note: \* $p < .05$ ,  $n = 56$ . NP composite: No deficit: 2+ tests 1 *SD* or 1+ test 2 *SD* below norm.

The role of executive function is worth special notice. On average, subjects without impairment on the Odd Man Out test dispensed four of the five prescriptions correctly (84%); subjects scoring  $\leq -1$  *SD* below the appropriate norm dispensed, on average, only three prescriptions correctly (61%). Thus, a difference in executive function of this magnitude was associated with one less prescription correctly dispensed. Subdividing Odd Man Out performance by severity of deficit (0, 1–2 *SD*, or  $\leq -2$  *SD* below norms) showed that these deficits affected the ability to dispense pills only for the more severe level of deficit and were unrelated to medication inference.

### NP, MMT, and Adherence

Using the recall measure, nearly half the sample (49%) made at least one error in dosage, number of doses, or dose interval. This was true in both the 1-day and 3-day recall formats. Correlations between

error types across days were all  $>.50$ , indicating that subjects whose recall reports indicated errors on one day were likely to make errors on the other days as well. Similarly, correlations between different kinds of error were high, within and across days (in every case,  $r > .50$ ), indicating that subjects who made one kind of error were likely to make other kinds of errors as well.

We examined the extent to which NP deficit and MMT scores were related to errors in medication adherence in the 41 subjects taking three antivirals. Table III illustrates this relationship. Table entries are the percentage of subjects making at least one error over 3 days, as derived from the recall measure. Subjects with poorer memory performance ( $\leq -1$  *SD* below norm on RAVLT) and low scores on the MMT ( $\leq 60\%$  correct) were most likely to make errors; subjects with normal memory and better scores on the MMT were least likely to make errors. Within groups defined by NP status, the MMT helps identify subjects likely to make errors. For example, among subjects with normal memory, 60% of those with low MMT scores (medication inference component) made an error, compared to only 31% of those with high MMT scores.

The sample size is small; hence we did not test for interactions between NP and MMT in predicting medication errors. In a regression model that included memory and MMT performance as predictors, and errors in dose interval as the outcome (the most prevalent error), only NP status was significantly associated with number of errors ( $p < .03$ ,  $R^2 = .35$ ).

## DISCUSSION

Our results address an HIV+ patient's ability to follow a medication regimen that has been described as "complex, costly, and potentially toxic" (Carpenter *et al.*, 1997). Attention to a patient's ability to

adhere to such regimens was stressed by the International AIDS Society—USA Panel in their updated recommendations for antiretroviral therapy. The Panel recommended a detailed discussion between patient and physician to assess a patient's ability to follow such a regimen (Carpenter *et al.*, 1997). We have shown that one measure of medication adherence, derived from a recall measure, is related to neuropsychological status and scores on a performance test of medication management.

The MMT should not be seen as a replacement for patient–physician discussion, but rather as an adjunct. Results from prior studies suggest that querying patients about their adherence—at least with global self-report questions—is not likely to be useful (e.g., Geletko *et al.*, 1996), and therefore that accurate appraisals of patient ability will require more intensive contact with patients. In fact, good clinic practice already includes such contact, as when physicians and nurses explain medication use, devise dispensing schedules, and determine if patients can follow directions. The NP and MMT tests proposed here standardize this assessment and offer an objective scoring of ability.

Reliabilities for the MMT were stable and within acceptable limits over three different samples of people with HIV. Likewise, the relationship between NP and MMT performance (and the two MMT components themselves) was comparable in all three samples. An important finding was the importance of different cognitive domains for performance on the two MMT components. Executive function and psychomotor skill were significantly associated with pill dispensing, while memory was significantly associated with medication inference.

The adherence measure used in this study is limited by our scoring convention. We considered all departures from product insert guidelines as an error, when, in fact, one study showed that physicians did not follow insert guidelines for protease inhibitors in

**Table III.** Subjects (%) with Error in Recalled Medication Use, by Medication Management Test and Memory Status

Memory performance (RAVLT)	MMT: Pill dispensing		MMT: Medication inference	
	$\leq 60\%$ Correct	$> 60\%$ Correct	$\leq 60\%$ Correct	$> 60\%$ Correct
Normal	40% ( <i>n</i> = 5)	38% ( <i>n</i> = 13)	60% ( <i>n</i> = 5)	31% ( <i>n</i> = 13)
$< -1$ <i>SD</i> below norm	67% ( <i>n</i> = 6)	54% ( <i>n</i> = 17)	62% ( <i>n</i> = 13)	50% ( <i>n</i> = 10)

Note: *n* = 41 subjects on three antivirals; RAVLT: Rey Auditory Verbal Learning Test; total score entries are percentages of subjects with at least one error over 3 days before clinical assessment.

nearly 40% of prescriptions examined (Ungvarski and Rottner, 1997). Our measure of adherence must be interpreted in this light, especially the finding that nearly half of 57 subjects made one or more errors in dosage, number of doses, or dosing interval over 3 days. The recall measure may also be less reliable among subjects with memory deficits. We used a careful elicitation strategy to try to minimize this problem, but such confounding must be recognized as an additional potential source of error.

With these caveats, we did find that NP and MMT performance were related to adherence in the recall period. The sample size was too small to permit formal statistical tests of the interaction between MMT and NP in predicting error rates; however, descriptive analyses suggest that the two may help identify people most likely to make errors in taking medications. Adjusted analyses, with corrections for multiple tests, must await larger samples.

Perhaps the most important reason for developing the MMT is to give clinicians a tool for identifying patients who need support in taking antiviral medications. In a protocol currently underway, we have informed patients of test results and, with their consent, forwarded results to primary care physicians; the goal of this effort is to increase medication supervision for patients whose cognitive deficits are likely to interfere with adherence.

To conclude, our results suggest that the ability to follow complex medication regimens can be measured with the MMT and that measures of such ability are related to adherence behaviors. Utilization of these measurement tools, with appropriate intervention strategies, should facilitate appropriate prescribing practices and aid in progress against HIV.

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