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Timing is everything: Antiretroviral nonadherence is associated with impairment in time-based prospective memory

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Abstract

Nonadherence to combination antiretroviral (ARV) therapies (cART) is highly prevalent and significantly increases the risk of adverse human immunodeficiency virus (HIV) disease outcomes. The current study evaluated the hypothesis that prospective memory—a dissociable aspect of episodic memory describing the ability to execute a future intention—plays an important role in successful cART adherence. Seventy-nine individuals with HIV infection who were prescribed at least one ARV medication underwent a comprehensive neuropsychological and neuromedical evaluation prior to completing a 1-month observation of their cART adherence as measured by electronic medication monitoring. Nonadherent individuals ($n = 31$) demonstrated significantly poorer prospective memory functioning as compared to adherent persons ($n = 48$), particularly on an index of time-based ProM (i.e., elevated loss of time errors). Deficits in time-based prospective memory were independently predictive of cART nonadherence, even after considering the possible influence of established predictors of adherence, such as general cognitive impairment (e.g., retrospective learning and memory) and psychiatric comorbidity (e.g., depression). These findings extend a nascent literature showing that impairment in time-based prospective memory significantly increases the risk of medication nonadherence and therefore may guide the development of novel strategies for intervention. (*JINS*, 2009, *15*, 42–52.)

Keywords: Human immunodeficiency virus, AIDS dementia complex, Neuropsychological tests, Cognitive science, Patient compliance, Time perception

INTRODUCTION

Medication nonadherence is a significant public health problem, particularly among persons living with chronic medical conditions. In fact, it has been estimated that as many as 50% of participants in clinical trials for chronic disorders may not adhere to their prescribed medication regimens (Osterberg & Blaschke, 2005). Medication nonadherence also presents a significant healthcare cost, accounting for estimated $100 billion in annual expenditures and 33–69% of medication-related hospital admissions (Osterberg & Blaschke, 2005). Adequate adherence to prescribed medication regimens is particularly important for persons infected with the human immunodeficiency virus (HIV), for which optimal disease outcomes are intricately tied to the efficacy of combination antiretroviral (ARV) therapies (cARTs). Over the past decade, cART has altered the landscape of HIV disease management in developed countries by dramatically reducing HIV-associated morbidity and mortality (Centers for Disease Control and Prevention, 2006) and also improving health-related quality of life (Liu et al., 2006). However, approximately 40–50% of patients are not adherent to their cART regimens (e.g., Nieuwkerk et al., 2001), which has led to adherence being branded as the "Achilles' heel" of HIV treatment (Simoni et al., 2003). Although there is variability among different classes of ARVs, the literature generally shows that adherence levels of 95–100% are needed to ensure optimal treatment

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effectiveness (Bangsburg, 2008). Nonadherence to cART (most commonly classified as less than 90% compliance) is associated with poorer HIV disease outcomes, including higher rates of virologic failure (Perno et al., 2002), the development of drug-resistant viral mutations (Harrigan et al., 2005), and an increased risk of mortality (Lima et al., 2007).

Considering the numerous adverse clinical outcomes associated with cART nonadherence, the importance of identifying salient risk factors to target for screening and remediation is readily apparent. Prior studies have identified a variety of factors that influence nonadherence, including demographics (e.g., age), psychiatric comorbidity (e.g., depression, substance abuse), psychosocial variables (e.g., attitudes and beliefs related to medications, familial support), and systemic factors (e.g., limited access to healthcare). HIV-associated neurocognitive impairment is also associated with increased risk of cART nonadherence, which is pertinent in that approximately 30–50% of HIV-infected persons demonstrate neuropsychological deficits (Heaton et al., 1995; Robertson et al., 2007). Although progress has been made toward simplifying cART regimens, successful medication management nevertheless remains a complex cognitive challenge that typically requires tracking multiple drugs (oftentimes including non-ARVs) with varying dosages, administration times, and special instructions. Supporting the hypothesized role of cognitive deficits in cART nonadherence, Chesney et al. (2000) found that nearly 70% of individuals who were nonadherent to cART reported that they "simply forgot" to take their medication. Subsequent research demonstrated that HIV-associated neuropsychological impairment is associated with poorer performance on laboratory medication management tasks (e.g., Albert et al., 1999, 2003; Heaton et al., 2004), higher rates of self-reported problems with medication management (e.g., Avants et al., 2001; Benedict et al., 2000; Waldrop-Valverde et al., 2006; Woods et al., 2008b), and nonadherence as measured by electronic medication monitors (e.g., Barclay et al., 2007; Hinkin et al., 2002, 2004). For example, Hinkin et al. (2002) reported that individuals with neuropsychological impairment experienced a twofold risk of nonadherence, even when the potentially confounding effects of demographic factors and psychiatric comorbidities were considered. Across this literature, the domains of episodic learning and memory, executive functions, and psychomotor speed have emerged as the most robust and reliable cognitive predictors of cART nonadherence.

It has been argued that HIV-associated impairment in the domain of prospective memory (ProM) may be a particularly strong risk factor for cART nonadherence (Carey et al., 2006; Martin et al., 2007; Woods et al., 2008b). ProM is a dissociable aspect of episodic memory that refers to the execution of a future intention in the face of ongoing distractions (i.e., "remembering to remember"). The cognitive aspects of medication adherence can be readily mapped on a conceptual framework of ProM. Specifically, successful independent medication adherence requires one to (1) encode an intention to take a specific medication at a future occasion (e.g., take medication X with food before going to bed), (2) retain the paired intention (i.e., take medication X) and cue (i.e., at bedtime) vis-à-vis the usual barrage of normal daily events (e.g., work, chores, and recreation), (3) accurately identify the retrieval cue and effectively disengage from an ongoing activity (e.g., preparing for bed), (4) recall the specific intention (i.e., take medication X with food), and (5) execute the intention (i.e., take the correct medication as instructed). In fact, the most commonly cited example of ProM in daily life is remembering to take a medication on schedule, for example after a meal (i.e., event-based ProM) or at a specific time during the day (i.e., time-based ProM). Despite these conceptual similarities, only three prior studies have directly examined the relationship between ProM and medication adherence (Hertzog et al., 2000; Vedhara et al., 2004; Woods et al., 2008b).

Beyond its conceptual appeal, ProM may be of particular relevance to cART adherence because HIV infection is associated with an increased risk of ProM impairment. Individuals living with HIV disease report an elevated level of ProM complaints (Woods et al., 2007a) and demonstrate mild-to-moderate deficits on performance-based laboratory (Carey et al., 2006; Martin et al., 2007) and semi-naturalistic (Carey et al., 2006) measures of ProM. The profile of HIV-associated ProM impairment is hypothesized to reflect deficits in the strategic aspects of intention encoding and retrieval (Carey et al., 2006), including increased errors of omission (i.e., not responding to a cue), commission (e.g., incorrectly responding to a cue), and loss of time (i.e., responding to a cue at the incorrect time) in the setting of normal recognition. HIV-associated ProM impairment correlates with deficits in executive functions, working memory, retrospective episodic memory, and information processing speed (Carey et al., 2006; Martin et al., 2007), as well as biological markers of neuroaxonal injury and macrophage activation (Woods et al., 2006b).

Only one prior study has examined the role of HIV-associated ProM impairment in medication management. Woods et al. (2008b) reported that higher frequency of ProM complaints and objective deficits on laboratory and semi-naturalistic ProM measures were associated with poorer self-reported medication management in HIV. Of particular note, HIV-associated ProM impairment demonstrated incremental validity as a predictor of medication management, above-and-beyond established risk factors for nonadherence, including psychiatric distress, psychosocial variables, environmental structure, and deficits in retrospective memory and executive functions. Although this study provided promising evidence that ProM may play a unique role in medication management, it nevertheless possessed several methodological limitations. For example, the study design was exclusively cross-sectional and therefore only provided evidence of concurrent, rather than predictive validity. Another significant limitation of this study was its use of a self-report measure of general medication management (i.e., Beliefs Related to Medications [BERMA] Survey; McDonald-Miszczak et al., 2004). Although there is no gold

standard for adherence (Osterberg & Blaschke, 2005), self-report measures tend to overestimate actual adherence (Levine et al., 2006). Moreover, this particular self-report measure was not specific to ARVs, but rather assessed all currently prescribed medications. Use of this measure also limited the prior study's ecological validity by not allowing for an objective cut-point to identify individuals who were nonadherent to cART, which is the classification of greatest clinical relevance.

Accordingly, the current study was undertaken to determine whether baseline indicators of ProM functioning accurately predict cART adherence as measured in a subsequent 1-month observation period using electronic medication monitors. It was hypothesized that HIV-associated ProM impairment would be associated with an increased risk of cART nonadherence independent of demographics, HIV disease severity, psychiatric comorbidity, and psychosocial factors.

METHOD

Participants

The study sample included 79 participants with HIV infection who were recruited from the San Diego community (e.g., *via* newspaper advertisements) and local HIV treatment clinics. All participants provided written, informed consent prior to enrolling in this study, which was approved by the institution's human research protections program. To be considered for inclusion, participants must have been prescribed at least one ARV medication. Study exclusions at enrollment included severe psychiatric illness (e.g., schizophrenia), neurological disease (e.g., seizure disorders, stroke, closed head injuries with loss of consciousness for more than 15 min, and central nervous system neoplasms or opportunistic infections), estimated verbal IQ scores <70 (based on the Wechsler Test of Adult Reading [WTAR]; Psychological Corporation, 2001), a recent diagnosis of substance dependence (i.e., within 6 months of baseline evaluation), and a urine toxicology screen positive for illicit drugs on the day of testing. A positive toxicology screen for marijuana (n = 17) was not a basis for exclusion since its metabolites remain detectable in urine for as long as 1 month and several drugs commonly used in the management of HIV (e.g., efavirenz, marinol) are known to produce positive toxicology results.

Participants were classified as either Adherent or Nonadherent based on the outcome of a 4-week continuous observation period using the (non-alarmed) Medication Event Monitoring System (MEMS; Aprex Corporation, Union City, CA). The MEMS observation period began on the day following participants' neuropsychological evaluation (described below). The MEMS cap system uses a medication bottle cap (Trackcap®) microchip device that recorded the time, date, and frequency with which the participants opened their medication bottle over the 4-week period. Participants were instructed to use only the MEMS bottle to dispense the target ARV and to remove only one dose at a time. Nonadherence was determined by a blind clinical review of the MEMS protocols and was defined as <90% adherence to their target ARV on any of the following variables: (1) percent days correct number of doses taken, (2) percent prescribed number of doses taken, and (3) percent prescribed doses taken on schedule. Table 1 displays the demographic, HIV disease, and MEMS ARV adherence characteristics of the Adherent (n = 48) and Nonadherent (n = 31) groups.

Materials and Procedure

The day prior to the beginning of their MEMS observation period, all participants underwent a comprehensive neuropsychological, psychiatric, and medical research evaluation.

Prospective memory assessment

The primary measure of interest was the Memory for Intentions Screening Test (MIST; Raskin, 2004), which is a 30-min, eight-trial test during which participants engage in a word search puzzle as the distractor task. Consistent with prior studies (e.g., Carey et al., 2006), we examined the following MIST variables: (1) summary score, (2) time-based scale, (3) event-based scale, (4) distractor total, (5) recognition total, (6) a retrieval index, and (7) a 24-hr delay trial for which examinees were instructed to leave a voicemail message for the examiner the day after the examination indicating the number of hours the participant slept the night after the evaluation (Carey et al., 2006). In addition, the following error types were coded: (1) no response (i.e., response omission errors), (2) task substitutions (e.g., replacement of a verbal response with an action or *vice versa*), (3) loss of content (e.g., acknowledgment that a response is required to a cue, but failure to recall the content), and (4) loss of time (i.e., performance of an intention greater than ±15% of the target time). Participants also completed the eight-item Prospective Memory Scale from the Prospective and Retrospective Memory Questionnaire (PRMQ; Smith et al., 2000), which was used to assess self-reported ProM complaints.

Basic neuropsychological assessment

A standardized battery of clinical tests of neuropsychological functioning was also administered to each participant. This battery was designed to be consistent with National Institutes of Health guidelines for assessing the cognitive domains that are most sensitive to HIV (Antinori et al., 2007; Butters et al., 1990), including retrospective learning and memory, executive functions, information processing speed, attention/working memory, verbal fluency, and motor coordination. Raw scores were converted to population-based z scores derived from the entire sample, then averaged across the tests in that domain to create a mean domain z score. The specific tests that comprised each of these domains (and their associated descriptive data) are displayed in Table 3 (Benton et al., 1994; Culbertson & Zillmer, 2001; Delis et al., 2000; Kløve, 1963; Morgan et al., in press; Psychological Corporation,

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Table 1. Participants' demographic, disease, and medication characteristics

Dependent variable	Adherent (n = 48)	Nonadherent (n = 31)	p
Demographic characteristics			
Age (years)	47.1 (9.4)	45.2 (9.7)	.392
Education (years)	13.5 (2.8)	12.6 (2.7)	.186
Estimated verbal IQ[a]	106.0 (11.0)	101.0 (12.5)	.075
Sex (% men)	79.2	93.6	.082
Ethnicity (% Caucasian)	66.7	58.1	.439
Disease characteristics			
Estimated duration of infection (years)	15.0 (7.1)	17.2 (6.6)	.178
Current CD4 count[b]	568.0 (449.5–770.5)	520.0 (267.8–693.3)	.153
Nadir CD4 count[b]	152.0 (57.0–269.0)	80.0 (25.0–180.0)	.022
HIV RNA $\log_{10}$[b]	1.7 (1.7–1.7)	1.7 (1.7–1.7)	.571
Acquired immunodeficiency syndrome status	64.6%	87.1%	.027
HIV-associated neurocognitive disorders	23.0%	29.0%	.113
Medication characteristics			
Total pill burden (no. pills per day)	9.0 (5.7)	9.8 (5.2)	.527
No. ARVs currently prescribed	3.8 (0.9)	3.7 (1.0)	.971
Duration of ARV regimen (months)	27.1 (29.4)	29.0 (43.3)	.834
Length of MEMS observation (days)	38.3 (10.3)	34.3 (13.4)	.168
% Prescribed no. doses taken	99.2 (2.8)	80.5 (16.0)	<.001
% Doses taken on schedule	94.0 (7.8)	52.7 (26.1)	<.001
% Days correct no. doses taken	95.4 (7.4)	70.8 (17.6)	<.001

[a]Verbal IQ (M = 100, SD = 15) was derived from the WTAR.
[b]Median (interquartile range).

1997; Reitan & Wolfson, 1985; Shimamura & Jurica, 1994; Stern et al., 1999; Woods et al., 2005).

Psychiatric assessment

Structured psychiatric interviews were conducted using the Composite International Diagnostic Interview (version 2.1; World Health Organization, 1998), from which lifetime and current (i.e., within 1 month of evaluation) diagnoses of major depressive disorder (MDD), generalized anxiety disorder, and substance-related disorders were generated per *Diagnostic and statistical manual of mental disorders* (4th ed., American Psychiatric Association, 1994) criteria. Participants also completed the profile of mood states (POMS; McNair et al., 1981) to assess current affective distress across four areas (i.e., depression/dejection, fatigue/inertia, vigor/activity, and tension/anxiety) and a Total Mood Disturbance score, for which higher scores indicate greater distress.

Psychosocial and environmental factors

Participants were administered the BERMA (McDonald-Miszczak et al., 2004) questionnaire, from which three scales were derived. The 23-item Dealing with Health Professionals Scale is intended to assess the strength of participants' relationship with their medical providers (e.g., "I have difficulty talking openly with my physician"). The 20-item Medication Management Efficacy Scale was designed to assess general medication management abilities (e.g., "I am less efficient at adhering to my medication regimen than I used to be"). Finally, the 10-item Attitudes About Medications Scale comprises items that measure participants' general health beliefs (e.g., "I am taking too much medication for my medical conditions"). All subscale items are rated on a 5-point Likert scale, ranging from 1 (*strongly disagree*) to 5 (*strongly agree*).

In addition, participants completed the Prospective Memory for Medications Questionnaire (PMMQ; Gould et al., 1997). The PMMQ is a 33-item questionnaire that assesses the frequency with which an individual uses different internal (e.g., "Do you regularly repeat to yourself the instructions for taking a prescription …?") and external (e.g., "Do you use a clock or watch alarm to remind you when it is time to take your medications?") medication-taking strategies. Participants are asked to rate how often they use each strategy on a 5-point Likert-type scale, ranging from 0 (*never*) to 4 (*always*), such that higher scores indicate more frequent strategy use.

Data Analyses

The MIST variables were nonnormally distributed (i.e., negatively skewed), and therefore, a series of Wilcoxon rank-sum tests were conducted and complemented by Cohen's d effect size estimates. Group differences on *a priori* selected measures of neuropsychological functioning, psychiatric variables, psychosocial and environmental factors, and disease and treatment status were conducted using either Wilcoxon rank-sum tests or a chi-square test. We then conducted a planned follow-up binary logistic regression analysis to evaluate the relative independence of ProM as a predictor of nonadherence

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as compared to the other cognitive (e.g., retrospective memory) factors. As noted above, there are numerous noncognitive factors that also increase the risk of nonadherence (e.g., demographics, psychiatric disease, substance-related disorders, and psychosocial variables). As such, we also conducted a follow-up binary logistic regression to examine the uniqueness of ProM as a predictor of nonadherence relative to salient noncognitive variables that differentiated the groups. A critical alpha level of .05 was used for all analyses.

RESULTS

Nonadherent participants performed significantly worse than the Adherent group on the MIST summary score ($p < .05$). As shown in Table 2, accounting for this overall effect were the Nonadherent group's lower scores on the time-based scale ($p < .05$), which were primarily driven by an elevation in loss of time (LoT) errors ($p < .01$). Although significantly correlated with all three indicators of adherence ($ps < .05$), LoT errors were most strongly associated with the proportion of ARV doses taken on schedule (Spearman's $\rho = -0.29$, $p = .011$). The Adherent and Nonadherent groups did not differ in their performance on the MIST event-based scale, other error types, the distractor test, the recognition posttest, or 24-hr delay trial (all $ps > .05$). Similarly, the Adherent and Nonadherent groups reported similar levels of ProM complaints on the PRMQ ($ps > .10$). As such, we conducted a series of focused, nonparametric (i.e., descriptive) classification accuracy statistics on the MIST LoT error score. As shown in Figure 1, a normative cutoff score of ≥1 LoT error (Woods et al., in press) afforded adequate overall predictive power, characterized by excellent specificity, but rather poor sensitivity. Of greater clinical value, positive and negative predictive powers for LoT were each approximately 70%. In fact, the nonparametric odds ratio (Bieliauskas et al., 1997) associated with elevated LoT errors was 5.8 (95% confidence interval = 1.9–17.5).

Post hoc analyses were undertaken to examine the possible correspondence between MIST LoT errors and a measure of time estimation (Mimura et al., 2000). Participants were asked to estimate how much time had elapsed during four brief intervals (i.e., 15, 30, 45, and 90 s in a randomized order), without the aid of a clock. The discrepancy between the actual time elapsed and the participants' response did not differ between the Adherent ($M = 49.3$, $SD = 37.2$) and Nonadherent ($M = 42.3$, $SD = 23.2$) groups ($p > .10$). LoT errors did not correlate with time estimation in either study group ($ps > .10$).

Table 3 displays the descriptive data for the two study samples on the basic battery of neuropsychological tests. The Adherent group performed significantly better than the Nonadherent sample on RetM Learning and RetM Memory domain z scores ($ps < .05$), which were primarily attributable to group differences on the Wechsler Memory Scale (3rd ed.) (WMS-III) Logical Memory I and II subtests ($ps < .05$). In a follow-up binary logistic regression that included the RetM Learning and Memory z scores and MIST LoT errors, ($\chi^2[3, N = 79] = 15.0$, $p = .002$), only LoT errors emerged as an independent predictor of Nonadherence ($p = .002$). Findings did not differ if only the significant RetM variables (i.e., WMS-III Logical Memory) or clinical ratings (Woods et al., 2004) were included in the regression instead of the domain z scores.

Descriptive data regarding the various noncognitive variables associated with nonadherence are displayed in Table 1 (i.e., demographics and HIV disease and treatment characteristics) and Table 4 (i.e., psychiatric, substance-related, psychosocial, and environmental factors). The Nonadherent sample had significantly lower nadir CD4 counts and a larger proportion of individuals with diagnoses of acquired immunodeficiency syndrome ($ps < .05$), but there was no association between ARV pill burden and adherence (Table 1). With regard to psychiatric predictors of adherence, Table 4 shows that the Nonadherent participants were significantly

Table 2. Prospective memory performance in the Adherent and Nonadherent groups

ProM variable	Adherent ($n = 48$)	Nonadherent ($n = 31$)	p	Cohen's d
MIST				
Summary score	39.9 (6.7)	35.9 (8.5)	.047	−.54
Time based	6.4 (1.3)	5.6 (1.4)	.022	−.60
Event based	6.9 (1.3)	6.5 (1.6)	.359	−.28
Error types				
LoT	0.1 (0.3)	0.6 (1.1)	.001	.69
No response	0.5 (0.7)	0.8 (1.0)	.229	.36
Task substitutions	0.9 (1.1)	1.0 (1.1)	.582	.09
Loss of content	0.7 (0.9)	0.7 (0.8)	.704	.00
Recognition posttest	7.7 (0.6)	7.5 (1.5)	.817	−.16
Retrieval index	1.9 (1.6)	2.8 (1.7)	.022	.55
Word search	16.5 (6.6)	16.9 (6.3)	.402	.06
24-hr delay	1.0 (0.9)	0.7 (0.8)	.106	−.35
PRMQ ProM total score	18.9 (5.3)	20.1 (6.1)	.286	.21

Note. ProM, prospective memory.

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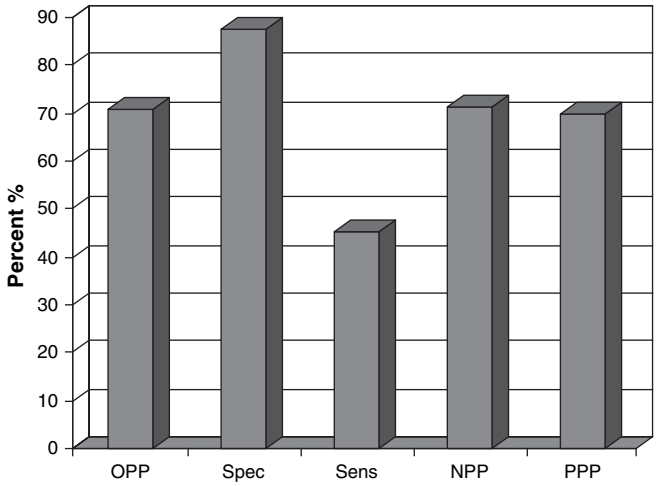

Fig. 1. Descriptive classification accuracy statistics for LoT errors on the MIST as an indicator of Nonadherence. A normative cut-point of ≥1 LoT error was used (see Woods et al., in press) to classify Nonadherent (n = 31) *versus* Adherent (n = 48) participants. OPP, overall predictive power; NPP, negative predictive power; PPP, positive predictive power; Sens, sensitivity; Spec, specificity.

more likely to have lifetime diagnoses of MDD, endorsed higher levels of acute distress on the POMS Tension/Anxiety Scale, and reported more difficulties in their general ability to manage their medications (BERMA Medication Management Scale; ps ≤ .05). A planned follow-up logistic regression analysis that included all these noncognitive factors ($\chi^2[6, N = 77] = 33.9, p < .0001$) showed that MIST LoT errors ($p < .0001$) and the POMS Tension/Anxiety scale ($p = .03$) were the sole independent predictors of Nonadherence. Additionally, the independence of the MIST LoT errors did not waiver if the various trend-level findings (e.g., sex, WTAR VIQ, BERMA dealing with health professionals) were included in the statistical model.

DISCUSSION

Nonadherence to cART is highly prevalent and significantly increases the risk of poor HIV disease outcomes, thus underscoring the value of identifying salient cognitive predictors of nonadherence that may inform the development of effective interventions. Results from the current study indicate that HIV-infected individuals with deficits in prospective memory (ProM) are at elevated risk of cART nonadherence as measured by electronic pill monitoring. At a group level, Nonadherent individuals demonstrated significantly poorer ProM functioning as compared to Adherent sample, particularly on an index of time-based ProM. These findings were associated with a medium-to-large effect size and were primarily driven by an elevated rate of LoT errors in the Nonadherent participants, meaning that although Nonadherent individuals remembered to perform the prescribed intention, they did so at an incorrect time (i.e., >15% away from the target execution time). Although slightly less than 50%

Table 3. Descriptive data on the standard neuropsychological tests in the Adherent and Nonadherent groups

	Adherent (n = 48)	Nonadherent (n = 31)	p	Cohen's d
Retrospective learning z score	0.15 (0.81)	–0.24 (0.65)	.039	–.52
CVLT-II total trials 1–5	50.42 (12.47)	45.27 (12.23)	.130	–.42
WMS-III Logical Memory I	43.15 (12.70)	35.90 (12.35)	.011	–.58
Rey BQSS immediate	11.98 (3.75)	11.29 (2.81)	.240	–.20
Retrospective memory z score	0.14 (0.85)	–0.23 (0.66)	.035	–.47
CVLT-II long delay	10.48 (4.40)	9.20 (4.33)	.172	–.29
WMS-III Logical Memory II	27.17 (9.90)	20.35 (9.11)	.002	–.71
Rey BQSS long delay	11.9 (3.67)	11.42 (2.88)	.458	–.14
Executive functions z score	0.00 (0.79)	0.01 (0.93)	.849	.01
Trail Making Test part B	66.35 (32.35)	71.35 (49.30)	.725	.13
ToL total moves	25.72 (20.37)	23.61 (18.42)	.732	–.11
Information processing speed z score	0.06 (0.92)	–0.08 (0.82)	.428	–.16
Trail Making Test part A	27.50 (9.16)	24.68 (7.31)	.181	–.33
ToL total execution time (s)	209.51 (93.78)	205.10 (94.19)	.803	–.05
Attention z score	–0.07 (0.49)	0.10 (0.63)	.361	.31
WMS-III Digit Span	17.83 (3.81)	17.13 (3.97)	.549	–.18
SOPT total errors	3.50 (1.69)	4.55 (2.45)	.056	.52
Verbal fluency z score	–0.21 (2.30)	0.29 (2.50)	.407	.21
Letter fluency (C)	15.06 (4.64)	15.03 (5.00)	.944	–.01
Animal fluency	20.19 (5.01)	23.07 (5.98)	.043	.53
Action fluency	17.23 (5.52)	16.71 (5.21)	.744	–.10
Motor coordination z score	0.04 (0.87)	–0.05 (1.00)	.610	–.10
Grooved pegboard dominant	72.65 (20.02)	68.58 (16.42)	.303	–.22
Grooved pegboard nondominant	77.87 (19.54)	79.39 (31.79)	.992	.06

Note. Values reflect raw scores unless indicated. CVLT-II, California Verbal Learning Test (2nd ed.); BQSS, Boston Qualitative Scoring System; ToL, Tower of London, Drexel version; SOPT, self-ordered pointing test.

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Table 4. Psychiatric and psychosocial characteristics of the study groups

	Adherent (n = 48)	Nonadherent (n = 31)	p	Cohen's d
MDD (%)				
Current	8.33	6.45	.758	—
Lifetime	39.58	64.52	.030	—
Current generalized anxiety disorder (%)				
Current	0.00	0.00	—	—
Lifetime	8.33	6.45	.758	—
Lifetime substance dependence[a] (%)	56.25	51.61	.686	—
POMS total	46.96 (32.08)	57.07 (33.51)	.192	.31
Tension/anxiety	6.90 (4.94)	10.39 (6.90)	.029	.60
Depression/dejection	8.04 (10.25)	8.35 (9.52)	.766	.03
Vigor/activity	17.50 (7.08)	15.68 (7.33)	.198	−.25
Fatigue/inertia	7.46 (6.89)	8.90 (7.44)	.318	.20
Beliefs related to medication adherence				
Medication management	82.90 (10.70)	75.67 (14.96)	.053	−.58
Dealing with health professionals	99.90 (12.83)	94.29 (15.94)	.080	−.40
Attitudes about medications	38.03 (6.03)	35.81 (6.76)	.131	−.35
PMMQ total strategy use	26.90 (13.77)	29.65 (17.10)	.456	.18

[a]Reflects any prior substance dependence diagnosis.

of Nonadherent persons made one or more LoT errors (sensitivity = 45.2%), the corresponding—and arguably more clinically relevant (Ivnik et al., 2000)—positive (70%) and negative (71%) predictive values of such errors were considerably better. In fact, individuals who committed one or more LoT errors were almost six times more likely to be classified as Nonadherent at 1-month follow-up (odds ratio = 5.8).

Notably, ProM LoT errors were a unique and independent predictor of nonadherence when considered alongside well-established predictors of adherence. Consistent with prior research, impairment in retrospective learning and memory (e.g., Hinkin et al., 2002), psychiatric comorbidity (e.g., DiIorio et al., in press), HIV disease severity (Nieuwkerk et al., 2001), and psychosocial factors (e.g., Wagner, 2002) were also associated with nonadherence. Nevertheless, ProM LoT errors remained a significant predictor of nonadherence, even when these other factors were included in the statistical model. The independence of ProM as a predictor of nonadherence suggests that this construct may play a unique role in successful medication management, as has also been demonstrated with general instrumental activities of daily living (Woods et al., 2008a) and in other clinical populations (e.g., schizophrenia; Twamley et al., in press). In this way, assessment of ProM may augment the ecological relevance of neuropsychological evaluations of persons infected with HIV.

Time-based ProM, and particularly LoT errors, demonstrated the strongest association with medication nonadherence in this cohort. LoT errors are rare in healthy adults (Carey et al., 2006; Woods et al., in press) but are mildly elevated in individuals with HIV infection (Carey et al., 2006), as well as in those with schizophrenia (Woods et al., 2007b). *Post hoc* analyses revealed that the occurrence of LoT errors was not a function of deficient basic time perception, as LoT errors did not correlate with time estimation (and moreover, the Adherent and Nonadherent groups did not differ in time estimation). An alternate hypothesis is that LoT errors reflect difficulties *monitoring* time concurrently with an ongoing task. Numerous studies, including those on healthy older adults and individuals with central nervous system disease (for a review, see Mäntylä & Carelli, 2006) show that better performance on time-based ProM measures is associated with more frequent time monitoring. For example, Shum et al. (2004) demonstrated that healthy adults engaged in clock monitoring more frequently during a time-based ProM task than individuals with schizophrenia, particularly as the time for execution neared. Moreover, time monitoring was positively correlated with performance on the time-based ProM task (Shum et al., 2004). In this way, the current findings converge with the profile of HIV-associated ProM impairment, which is thought to reflect difficulties in the strategic allocation of cognitive resources to properly manage the simultaneous burden of the cue monitoring (i.e., time) and ongoing foreground activities (e.g., Carey et al., 2006). In more applied terms, HIV-infected individuals with impaired ProM might not notice important time-based cues to take their medications during the course of day-to-day activities, thereby delaying (or missing) scheduled doses, which decreases the likelihood of maintaining adequate virologic control and favorable disease outcomes.

Results from this study extend a surprisingly small, but growing literature supporting the relationship between ProM impairment and medication nonadherence (Hertzog et al., 2000; Vedhara et al., 2004), which includes only one prior investigation in HIV (Woods et al., 2008b). Building on the limitations of the existing ProM and adherence literature, the present study employed a prospective, longitudinal design and used an electronic monitoring device to assess medication adherence. Although not without its limitations (Bova et al., 2005), this methodology provides an objective, behavioral indication of adherence patterns (Paterson et al., 2002) that

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is more sensitive to nonadherence than self-report (Levine et al., 2006). Indeed, in contrast to our prior study using a generic self-report measure of medication management (Woods et al., 2008b), the current data did not show an association between cART nonadherence and either ProM complaints or the 24-hr semi-naturalistic ProM task. Importantly, however, both studies demonstrated that a laboratory-based measure of time-based ProM functioning (i.e., the MIST) was independently predictive of medication management in HIV.

A few methodological limitations should be considered when interpreting findings from this study. Most importantly, little is known about the psychometric properties of LoT errors, which tend to be infrequent, raising concerns about their reliability and possible floor and ceiling effects. Another limitation of this study is the absence of a measure of time *production* (Barkley et al., 2001) or time monitoring during ProM (e.g., clock checking), both of which would allow for a better characterization of the relationship between time-based ProM and adherence. Considering the hypothesized relationship between time perception and frontal systems (see Meck, 2005, for a review), future studies may wish to examine brief and extended time estimation and production intervals in HIV more generally, as well as in the specific context of cART adherence. The external validity of the study is restricted because the sample was predominantly male (85%) and had generally mild HIV disease (median current CD4 count = 559). Although these sample characteristics are fairly representative of the HIV epidemic in the United States, whether they generalize to specific subpopulations (e.g., older women with advanced HIV disease) remains to be determined. In addition, we excluded individuals with active substance dependence, which, prior research shows, is a strong predictor of nonadherence (e.g., Hinkin et al., 2007). Finally, other important predictors of adherence were not available in this cohort, including such psychosocial factors such as access to healthcare, socioeconomic status, and health literacy.

In summary, findings from this study indicate that HIV-associated impairment in time-based ProM increases the risk of cART nonadherence independent of psychiatric comorbidity, HIV disease severity, general cognitive impairment, demographics, and select psychosocial factors. Together with prior literature on ProM and adherence (Hertzog et al., 2000; Vedhara et al., 2004; Woods et al., 2008b), such findings suggest that interventions that target ProM may be effective in improving adherence. For example, cognitive techniques such as goal management training (Levine et al., 2000), which uses structured exercises designed to teach individuals to engage in an "executive review" of their plans and intentions for the day (e.g., "What am I doing right now?", "What else do I have to do today and when?") may be effective in improving ProM, as was recently shown in patients with traumatic brain injury (Fish et al., 2007). Other intervention approaches might focus on reducing the need for strategic monitoring, perhaps by reducing cognitive load (i.e., reducing the number and complexity of intentions held "online"; Woods et al., 2006a) and/or minimizing ongoing distraction (e.g., McDaniel & Einstein, 2007). Relatedly, a noninvasive and relatively inexpensive (cf. caregivers) intervention option might involve a programmable electronic device (e.g., a watch) that prominently notifies the patient when it is time to take a medication with a detailed text message that includes the medication name, dosage, and particular conditions under which it should be taken (e.g., Andrade et al., 2005; Leirer et al., 1991; van den Broek et al., 2000). Prospective, theory-driven controlled trials of the effectiveness of these various strategies (perhaps as well as combined, individualized therapeutic approaches) as treatments for HIV-associated ProM impairment and nonadherence are needed.

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