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Longitudinal Change in Cognitive Function and Medication Adherence in HIV-Infected Adults

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Abstract

Neuropsychological (NP) dysfunction has been linked to poor medication adherence among HIV-infected adults. However, there is a dearth of research examining longitudinal changes in the relationship between NP status and adherence rates. We hypothesized that declines in NP functioning would be associated with a corresponding decline in medication adherence while stable NP functioning would be associated with stable or improving adherence rates. Participants included 215 HIV-infected adults who underwent cognitive testing at study entry and six months later. Compared to the NP stable group, the NP decline group showed a greater drop in adherence rates. Further analysis revealed that, beyond global NP, learning and memory was significantly associated with changes in adherence rates. These findings further support the link between cognitive functioning and medication adherence and illustrates the importance of documenting changes in cognitive abilities for identifying individuals at risk for poor adherence.

Keywords

HIV; Medication adherence; HAART; Cognitive decline; Memory

Introduction

The introduction of highly active antiretroviral therapies (HAART) has led to improvements in clinical, virologic, and functional outcomes for individuals with HIV [1, 2]. However, successful treatment is highly contingent upon strict adherence to complex medication regimens. Studies examining HAART adherence have shown that a rate of 90% or greater

needs to be achieved before a patient can be classified as adherent [3–7]. This is significant in light of the documented high rates of suboptimal adherence among HIV infected individuals with as many as half of individuals on HAART failing to take their medications in accordance with dosage, time, and dietary instructions [8, 9]. Individuals using illicit substances, in particular, are over four times more likely to show suboptimal adherence compared to those with negative urine toxicology screenings [10].

Suboptimal adherence can lead to adverse personal and public health consequences. With treatment failure, virologic replication may increase, which in turn can trigger HIV disease progression. Infected individuals who are highly adherent (i.e., taking 90–95% of their prescribed doses) evidence considerably better disease outcomes, including lower rates of virologic failures [11], treatment resistant viral strains [12], and mortality [13]. Identifying salient risk factors for nonadherence can facilitate early detection and inform targeted cognitive and behavioral interventions to maximize adherence.

Deficits in neuropsychological functioning can adversely impact various aspects of adherence to health care regimens. It has been well-established that HIV infection can lead to significant cognitive compromise, ranging from mild deficits in processing speed and efficiency to frank dementia. Memory impairment (characterized by forgetfulness), motor and psychomotor slowing, attentional deficits, and executive dysfunction have all been repeatedly observed among individuals with HIV [14–17]. Previous cross-sectional work from our lab has shown that cognitively impaired participants were significantly more likely to have poor rates of adherence [18–20].

Methods to assess adherence that rely on self-report are prone to subjective biases and thus may overestimate actual adherence rates. To date, most studies examining neurocognition and medication adherence in the HIV population have been cross-sectional in nature. The temporal relationship between changing neurocognition and medication adherence is not clearly understood. To our knowledge, members of our group [21] were the first to address this issue by examining longitudinal change in patterns of adherence over a four-week period in HIV positive individuals classified as either cognitively normal or impaired based upon the deficit score approach to neuropsychological performance developed by Heaton and colleagues [22]. Levine et al. [21] found that cognitively impaired individuals evidenced a consistent drop in adherence on weekends, which was attributed to the loss of structure inherent to weekday activities that provides external assistance for completing daily functional tasks. However, this study did not examine how longitudinal changes in cognition covaried with changing adherence rates over time.

These studies highlight the importance of examining predictors of change in adherence rates among the HIV-infected population. Based upon findings from the aforementioned studies, we believe that fluctuations in adherence correspond with specific neuropsychological changes. The purpose of this study is to expand upon prior studies on neurocognition and medication adherence by tracking adherence rates and changes in neurocognition over a six month span. We hypothesized that declines in neurocognitive function would be associated with poor medication adherence rates, while stable or improving cognition would predict stability or increased medication adherence.

Method

Participants and Procedures

A total of 276 HIV-seropositive adults were enrolled in a study from 2001 to 2005 examining substance use and other factors associated with medication adherence. All procedures received IRB approval. Participants were recruited through advertisements

posted at university-affiliated infectious disease clinics, as well as through community-based HIV/AIDS organizations. At the time of study entry, all participants were prescribed a regimen of highly active antiretroviral therapy (HAART), defined here as a combination of three or more antiretroviral drugs, including protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside analogue reverse transcriptase inhibitors, and nucleotide analogue reverse transcriptase inhibitors. Exclusionary criteria included current diagnosis of psychotic spectrum disorder, seizure disorder, stroke, closed-head injury with loss of consciousness in excess of 30 min, or any other neurological disease, CNS opportunistic infection, or neoplasm. Participants were expected to be seen a total of seven times over a six month period (baseline and six monthly follow-up studies). Of the 276 participants, 215(78%) completed baseline and six-month follow-up neuropsychological evaluations and were not missing medication adherence data for two or more consecutive months throughout the study. Participants without complete data did not differ significantly from participants with complete data on demographics, disease related markers, and medication adherence rates. They differed significantly on cognition, $t(274) = 3.41$, $P = .001$. Participants without complete data had poorer cognition as indicated by higher baseline global deficit scores ($M = .98$, $SD = .54$) compared to participants with complete data ($M = .72$, $SD = .52$).

All participants were administered drug urinalysis screening at each visit. They were also administered a modified version of the structured clinical interview for DSM-III-R (SCID) at baseline and month six of the study [23]. Self-report was included in addition to urinalysis screening to assess for abuse/dependence and due to the inherent limitations of urinalysis screening (e.g. a positive cocaine result will only show up if use occurred within 3 days of testing). Within the entire sample, 69% tested positive for at least one substance during the six months. Cocaine was the most frequently used drug, with 45% of the sample testing urine-toxicology positive, followed by marijuana (37%), opiates (14%), amphetamines (13%), benzodiazepines (11%), barbiturates (3%), methadone (2%), and propoxyphene (2%). Within the entire sample, 56% met diagnostic criteria for substance abuse or dependence.

Measures

Medication Adherence—Medication adherence was assessed over the course of the study using medication event monitoring system (MEMS) caps, which employ a pressure-activated microprocessor in the medication bottle cap that automatically records the date, time, and duration of bottle opening. Data were retrieved from the cap using a specially designed communication module connected to a personal computer. Participants were instructed to take their MEMS-monitored medication as prescribed by their physician, not to open the bottles for any reason other than removing a dose, and to refill the bottle at a time when they ordinarily took a dose. They were also cautioned against pocket dosing (i.e., removing more than one dose at a time for later use). Data was downloaded from the MEMS cap and reviewed at each of the six monthly return visits. Adherence rates were calculated by dividing actual dose events by prescribed doses during the one-month period between visits. At each visit, participants were asked if they pocket dosed any of their medications. If MEMS cap openings exceeded the prescribed dosages, then the excess openings were subtracted from the total. Of the 215 participants, 37 (17%) had missing adherence data points. Participants with missing data were equally distributed among NP groups, and missing data was replaced with a mean score derived from the adherence data points immediately previous and subsequent from the missing data. The overall adherence rate was 66% across all participants for the six-month study.

Neuropsychological Tasks—Participants completed a comprehensive battery of neuropsychological (NP) tests (see Table 1) at baseline and visit seven of this study to assess

functioning in the areas of attention and working memory, speed of information processing, learning and memory, verbal fluency, executive functioning, and motor speed. Test scores were converted to demographically-corrected *T* scores (with a mean of 50 and a standard deviation of 10) using published normative data and grouped by neurocognitive domain [15]. Domain *T* scores were obtained by calculating the mean *T* score for all tests comprising a given domain. A global *T* score was calculated by summing individual test *T* scores and dividing by the number of tests administered.

Participants were classified as “stable” or having “declined” based upon their change in global deficit score (GDS) from baseline to visit seven. The GDS approach weights NP data in a manner that gives relatively less weight to performances within normal limits [15]. To obtain the GDS, first a global *T* score was calculated by summing individual test *t* scores and dividing by the number of tests administered. Deficit scores were then calculated using a method developed by Heaton and colleagues [22] that assigns an impairment rating to *T* scores as follow: $T > 39 = 0$; $39 \geq T \geq 34 = 1$; $34 > T \geq 29 = 2$; $29 \geq T \geq 24 = 3$; $24 > T \geq 20 = 4$; $T < 20 = 5$. The deficit score approach has been demonstrated to have good predictive validity for detecting cognitive impairments in HIV-infected individuals [24]. The NP stable group represented those whose global deficit score remained stable or improved across measurements ($\Delta M = -.27$, $SD = .24$) suggesting intact or improving neuropsychological functioning ($n = 140$). The NP decline group consisted of those whose global deficit scores worsened across measurements ($\Delta M = .29$, $SD = .27$) suggesting declining neuropsychological functioning ($n = 75$).

Statistical Analyses

All analyses were carried out with SPSS 13.0. Demographic and clinical characteristics were compared among cognitive groups using independent *t*-tests and χ^2 – statistics. A mixed-model repeated measures analysis of covariance (ANCOVA) was used to analyze between- and within-subjects effects of global cognitive change on medication adherence. To control for the impact of initial cognitive differences between groups, baseline global deficit score was included as a covariate. Medication adherence served as a repeated-measure with six time points each representing a one-month period. To adjust for violations of sphericity, a Greenhouse–Geisser correction was used. Significance was set at .05 for this analysis. Adherence was further assessed using mixed-design ANOVAs with NP domain change scores as predictors (NP domains are listed in Table 1). Change scores were calculated using the formula: $(D_1 - D_2) / D_1$, in which D_1 equals the domain deficit score for baseline visit and D_2 equals the domain deficit scores for the six-month follow up assessment. The change scores for all neurocognitive domains did not meet assumptions for normality and, therefore, each underwent a logarithmic transformation. To correct for multiple analyses with individual NP domains, a significance value of .01 was employed.

Results

Participant Characteristics

As seen in Table 2, the NP decline group was more likely to meet diagnostic criteria for current substance abuse/dependence than was the NP stable group. However, the NP decline group did not have a higher rate of positive drug urine screenings. No differences were found between the groups with respect to age, years of education, number of pills per day, length of antiretroviral therapy, or recent CD4 count. Also, gender, ethnicity, and AIDS diagnosis did not significantly differ across groups. The NP stable group performed significantly worse than the NP decline group on baseline global deficit score.

Medication Adherence

To examine longitudinal differences in adherence as a function of NP status, we conducted a Group (NP stable versus declining) $\times$ Time (six monthly adherence rates) repeated-measures ANCOVA (see Fig. 1). The means and standard deviations for monthly adherence rates are presented in Table 3. ANCOVA revealed a significant main effect for NP group, $F(1, 212) = 12.66$, $P < .001$, $\eta^2_p = .06$, with the NP stable group ($M = 72.25$, $SE = 2.1$) showing a higher overall adherence rate than the NP decline group ($M = 59.31$, $SE = 2.9$). A main effect was also found for time with both groups showing a decline in medication adherence across the six-month study, $F(3.45, 731.89) = 5.07$, $P = .001$, $\eta^2_p = .02$. Furthermore, a significant group $\times$ time interaction was found, $F(3.45, 731.89) = 3.35$, $P = .01$, $\eta^2_p = .02$, with the NP decline group showing a steeper drop in adherence rates compared to the NP stable group.

Having determined that a decline in global cognition was associated with worsening medication adherence, the next analysis explored whether active substance abuse/dependence moderated this relationship. NP decliners were significantly more likely than the NP stable group to endorse active substance abuse/dependence. Of the 75 NP decliners, 51(68%) endorsed active substance abuse/dependence, and 69(49%) of the 140 NP stable group endorsed active substance abuse/dependence. We conducted a 2 (NP stable vs. Declining) $\times$ 2 (current substance abuse/dependence vs. not-current) $\times$ 6 (monthly adherence rates) mixed-design ANCOVA. When controlling for baseline global deficit score, significant differences between NP groups remained, $F(1, 210) = 6.60$, $P = .01$, $\eta^2_p = .03$. Significant differences were also found between substance abuse/dependence groups, $F(1, 210) = 15.94$, $P < .001$, $\eta^2_p = .07$, with those endorsing substance abuse/dependence having lower overall adherence. A significant NP group $\times$ time interaction remained, $F(3.47, 728.51) = 2.53$, $P = .05$, $\eta^2_p = .01$. No significant NP group $\times$ substance abuse/dependence group interaction effect was found, $F(1, 210) = 1.12$, $P = .29$. No substance abuse/dependence group $\times$ time interaction effect was found, $F(3.47, 728.51) = 1.54$, $P = .20$, and there was no substance abuse/dependence group $\times$ NP group $\times$ time interaction effect, $F(3.47, 728.51) = .57$, $P = .66$.

Individual Cognitive Domains

The following set of analyses examined the relationship between individual NP domains and longitudinal medication adherence rates. As stated above, a significance value of .01 was employed to correct for multiple analyses with individual NP domains. Analyses were conducted using transformed difference scores for each cognitive domain as a predictor and medication adherence as the repeated measure. Significant main effects of NP domain change on overall adherence rates were found for information processing speed, $F(1, 213) = 11.41$, $P = .001$, $\eta^2_p = .05$, motor, $F(1, 212) = 11.66$, $P = .001$, $\eta^2_p = .05$, attention, $F(1, 213) = 8.00$, $P = .005$, $\eta^2_p = .04$, learning, $F(1, 213) = 7.54$, $P = .007$, $\eta^2_p = .03$. A trend was found for verbal fluency, $F(1, 211) = 5.21$, $P = .02$, $\eta^2_p = .02$, and executive functioning, $F(1, 213) = 4.32$, $P = .04$, $\eta^2_p = .02$. A NP change domain $\times$ time interaction effect was found for learning and memory, $F(3.45, 734.32) = 3.44$, $P = .01$, $\eta^2_p = .02$, with worsening learning and memory performance being associated with a decline in adherence. A trend was found for verbal fluency, $F(3.41, 720.52) = 2.90$, $P = .03$, $\eta^2_p = .01$. No significant interaction effects were found in executive functioning, $F(3.41, 725.37) = .64$, $P = .61$, information processing, $F(3.39, 722.60) = .93$, $P = .43$, motor, $F(3.41, 724.14) = 1.23$, $P = .30$, or attention, $F(3.96, 723.35) = .46$, $P = .73$.

Discussion

This longitudinal study expands upon cross-sectional investigations by examining individuals' changing adherence patterns as a function of changes in cognition. Consistent

with findings from previous research [5, 20], HAART adherence declined over time across the entire sample. Of greatest interest, we found that declining global cognition is associated with overall lower medication adherence as well as steeper declines in adherence rates over time. This finding remained significant even when accounting for active substance abuse/dependence. To our knowledge, the current study is the first to demonstrate a corresponding change in adherence in the context of documented cognitive decline. Upon examining individual NP domains, we found that overall lower adherence was associated with declines within most individual cognitive domains. However, only declines in learning and memory were associated with corresponding declines in adherence across the six-months study. Learning and memory is consistently associated with adherence rates [25], and this association is not surprising given the demanding complexity of the HAART regimen and the importance of prospective memory in completing this task. Prospective memory is the remembering to perform a future activity and is a predictor of medication adherence in HIV-infected adults [26, 27]. However, executive functioning is also highly involved in prospective memory. We did not see a similar association between executive functions and medication adherence in our study. This may be due to the nature of the executive measures used, the heterogeneous abilities included in this domain, or the susceptibility of practice effects for certain tasks that may have attenuated the measurement of true decline within this domain.

These findings underscore the need to address NP functioning when designing interventions to improve medication adherence. Utilizing compensatory strategies should be recommended to HIV-infected individuals exhibiting memory deficits (such as increased organizing and structure with the use of pill boxes, written times to take medications, digital reminders, etc.). Also, assessing cognitive functioning appears helpful in detecting individuals at risk for worsening adherence, and repeat testing may be useful to ascertain a potential change in functional status over time.

Limitations to our study include the method of measurement of adherence and our definition of cognitive change groups. Despite being instructed not to do so, participants may have confounded actual adherence rates by taking “pocket doses,” which is the removal of extra medication doses at a single event. MEMS cap would then under-estimate actual adherence rates. A second limitation is that NP groups were significantly different from each other on baseline GDS with the NP stable group exhibiting lower performance. Some members of the NP stable group may not have fallen into the NP decline group due to floor effects (i.e. baseline NP performance was so poor that retesting only allowed for a stable performance). Although the NP stable group continued to have significantly higher and relatively less declines in adherence rates, these findings may have been attenuated by the inclusion of neuropsychologically stable but impaired individuals. Finally, defining cognitive stability or change as a difference between global deficit scores over time has its limitations. Small declines in global cognition are not necessarily synonymous with a meaningful change in functioning.

We are uncertain whether declines in cognition precede or follow a concurrent drop in adherence. One possibility is that NP decliners, who entered the study with lower adherence rates, were more susceptible to the deleterious effects of suboptimal adherence which may have led to attenuation in cognition functioning. Alternatively, declining cognitive functioning could account for the drop in adherence rates. Despite documenting the corresponding changes between cognition and adherence, additional studies are needed to further elucidate this relationship, which is likely bidirectional in nature. In light of this study’s findings pertaining to learning and memory, future research should further explore this domain including different aspects of kinds of learning, in particular how changes in prospective memory may impact adherence rates over time. Also, different patterns of

suboptimal adherence may exist among different patterns of neurocognitive impairment. Further study is needed to refine our understanding of the complex interplay between cognition and medication adherence.

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Fig. 1. Medication adherence rates among neuropsychologically stable and declining HIV-infected participants. *Error bars* indicate the standard error of the mean. *Mo.#* indicates the month of the study

Table 1

Mean baseline t-scores of cognitive domains and associated neuropsychological tests

Cognitive domain	Neuropsychological test	Mean (SD)
Information processing speed	WAIS-III digit symbol	44.53 (7.1)
	WAIS-III symbol search	
	Trail making test A	
Learning and memory	CVLT-II total learning	42.98 (10.1)
	CVLT-II long delay free recall	
	BVMT-R total learning	
	BVMT-R delayed recall	
Attention	WAIS-III digit span	44.32 (8.1)
	WAIS-III letter-number sequencing	
	PASAT trial 1	
Executive	Trail making test B	42.34 (7.0)
	Stroop interference	
	WCST-64 perseverative errors	
Verbal fluency	COWAT (FAS)	44.84 (10.9)
Motor skills and motor speed	Grooved Pegboard, dominant hand	38.61 (9.4)
	Grooved Pegboard, non-dominant hand	

Note: *WAIS-III* Wechsler Adult intelligence scale-III, *CVLT-II* California verbal learning test-II, *BVMT-R* Brief visual memory test-revised, *COWAT* Controlled oral word association, *WCST-64* Wisconsin card sorting test-64

Table 2

Baseline demographics, clinical, and disease characteristics

Variable	Stable NP(N = 140)	NP Decliners (N = 75)	P
Age	42.3 (6.9)	40.9 (7.6)	.17
Years of education	13.2 (1.9)	12.7 (2.4)	.13
NAART VIQ score	104.8 (10.1)	105.0 (8.6)	.86
BDI-II total score	13.1 (9.0)	13.3 (9.3)	.86
# HIV medications	5.6 (3.6)	4.9 (3.1)	.20
# Pills taken per day	11.4 (7.5)	10.1 (5.9)	.21
Years on HAART	6.5 (4.1)	6.5 (4.8)	.91
CD4 count	458.0 (324.6)	454.9 (272.1)	.95
Baseline GDS	.8 (.5)	.6 (.5)	.004
	% of Sample	% of Sample	
Female	16.4	18.7	.68
CDCg-AIDS	68.4	62.2	.36
SCID drug abuse/dependence	55.2	72.9	.02
Overall positive urine screen	67.1	72.0	.46
Ethnicity			.75
African-American	62.9	70.1	
Caucasian	15.7	13.3	
Latin American	13.6	12.0	
Asian/Pacific Islander	2.9	2.7	
American Indians	1.4	.0	
Multiracial	3.6	1.3	

Note: NAART VIQ North American adult reading test verbal intelligence quotient, BDI-II Beck depression inventory-II, ART Antiretroviral therapy, GDS Global deficit score, CDC Center for disease control, SCID Structured clinical interview for DSM-III-R. Mean scores (*M*) and *SD* for age, years of education, NAART VIQ, BDI-II, # HIV medications, # pills/day, years on ART, CD4 count, and baseline GDS

Table 3

Medication adherence rates for NP decline and NP stable participants across the six-month study period

Month of study	NP decline (<i>N</i> = 75)		NP stable (<i>N</i> = 170)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Month 1	70.1	27.1	77.3	23.1
Month 2	64.9	29.1	73.3	27.9
Month 3	63.2	28.8	71.7	27.2
Month 4	57.5	30.9	71.9	28.6
Month 5	54.8	33.0	69.4	27.4
Month 6	51.8	32.6	66.4	31.7
All Six Months	60.4	26.9	71.7	24.2

Note: NP Neuropsychological. Mean scores (*M*) and standard deviations (*SD*) for adherence rates