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Medication adherence among HIV+ adults:

Effects of cognitive dysfunction and regimen complexity

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Abstract

Background—Although the use of highly active antiretroviral therapy in the treatment of HIV infection has led to considerable improvement in morbidity and mortality, unless patients are adherent to their drug regimen (i.e., at least 90 to 95% of doses taken), viral replication may ensue and drug-resistant strains of the virus may emerge.

Methods—The authors studied the extent to which neuropsychological compromise and medication regimen complexity are predictive of poor adherence in a convenience sample of 137 HIV-infected adults. Medication adherence was tracked through the use of electronic monitoring technology (MEMS caps).

Results—Two-way analysis of variance revealed that neurocognitive compromise as well as complex medication regimens were associated with significantly lower adherence rates. Cognitively compromised participants on more complex regimens had the greatest difficulty with adherence. Deficits in executive function, memory, and attention were associated with poor adherence. Logistic regression analysis demonstrated that neuropsychological compromise was associated with a 2.3 times greater risk of adherence failure. Older age (>50 years) was also found to be associated with significantly better adherence.

Conclusions—HIV-infected adults with significant neurocognitive compromise are at risk for poor medication adherence, particularly if they have been prescribed a complex dosing regimen. As such, simpler dosing schedules for more cognitively impaired patients might improve adherence.

The introduction of highly active antiretroviral therapy (HAART) regimens has improved the virologic, immunologic, and clinical outcomes of HIV infection.^{1–4} Protease inhibitors have been shown to improve neuropsychological functioning as well.^{5–8} These treatment advances have led to optimism among HIV-infected patients as well as among clinicians and researchers specializing in HIV/AIDS. Tempering such optimism are recent findings that suboptimal HAART adherence can have dire personal and public health consequences, including incomplete plasma HIV suppression and development of drug-resistant HIV strains.^{9–11} With treatment failure, virologic replication may increase, which in turn can trigger HIV disease progression.¹² Although treatment adherence does not guarantee successful clinical outcome, and suboptimal adherence does not inexorably lead to virologic

failure, it is generally accepted that patients who do not adequately adhere to their antiretroviral regimen (e.g., at least 90 to 95% of prescribed doses taken) are at higher risk for adverse virologic and clinical outcomes.^{9,13,14} For example, it was recently shown that adherence rates of 95% or greater optimized virologic and clinical outcomes (no opportunistic infections, increased CD4 count) among a sample of 99 HIV-infected patients.¹⁴ Similar findings have been reported by other groups.^{9,10}

Given the relationship between adherence and clinical outcome, efforts to better understand what factors predict poor (or successful) adherence are clearly needed. Studies have examined the degree to which various constructs, such as health beliefs, psychiatric status, substance abuse, demographic characteristics (e.g., age, ethnicity, socioeconomic status), social support, and cognitive functioning, might be associated with medication adherence among HIV-infected patients.^{9,13,15–21} One possible cause of poor adherence is HIV-associated cognitive impairment. HIV infection can lead to significant cognitive compromise ranging from subtle deficits in information processing speed and efficiency to a pronounced dementia syndrome. Memory impairment (characterized by forgetfulness), motor and psychomotor slowing, attentional deficit, and executive systems dysfunction have all been repeatedly observed among HIV+ individuals.^{22–25}

Cognitive compromise has previously been found to adversely impact various aspects of adherence to health care regimens, including, but not limited to, pill-taking.^{26–28} This relationship has been reported in HIV/AIDS as well as other chronic medical conditions such as diabetes and hypertension. A recent study of self-reported factors influencing adherence among participants in HIV clinical trials found that 66% of the 75 trial participants surveyed endorsed “simply forgot” as a reason for missing antiretroviral doses.¹⁵ Although HIV-infected patients frequently report that cognitive problems such as forgetfulness lead to poor adherence, only two studies to date have employed sensitive, objective measures of neuropsychological function to precisely quantify cognitive dysfunction. Of those studies, one relied on patient self-report to index adherence²⁹ and one employed pill counts.³⁰

Methods for measuring medication adherence vary in important ways that might influence the validity of the conclusions yielded using differing assessment methods. The fallibility of self-report may be particularly salient when dealing with a group of individuals with memory impairment. For this reason, the utilization of more objective electronic monitoring devices (e.g., Medication Event Monitoring System [MEMS], Aprex, Union City, CA) may better estimate actual adherence. MEMS caps, the technique used in the current study to measure adherence, employ a computer chip that is embedded in the top of the pill bottle that automatically records the date, time, and duration of pill bottle opening. Although electronic monitoring devices are not a perfect measure of medication adherence,³¹ studies have shown that they are more accurate than pill counts or self-report, both of which appear to significantly overestimate adherence rates.^{10,32–34}

The effective pharmacologic management of HIV/AIDS involves strict adherence to a demanding, often complex, medication regimen (often upwards of 20 to 30 pills/day, many having specific, compound instructions [e.g., “Take three times per day on an empty stomach”]). The relationship between neurocognitive integrity and medication adherence may be mediated by regimen complexity; adherence may be particularly problematic for the cognitively compromised patient on a more complex medication regimen. The current study examined the independent and interactive effects of HIV-associated cognitive compromise and regimen complexity on adherence to HAART regimen. It was hypothesized that the presence of HIV-associated neuropsychological impairment would be associated with poorer

medication adherence and that this relationship would be magnified among participants on more complex HAART regimens.

Method

Research participants

A total of 137 HIV-seropositive adults were enrolled in the current study. HIV status was confirmed with ELISA and Western blot. Demographic data for the sample are displayed in table 1. Participants were recruited using fliers posted in infectious disease clinics at two university-affiliated medical centers and from community agencies in the Los Angeles area that specialize in providing services to HIV-infected individuals. Sixty-three percent of the participants met the Centers for Disease Control diagnostic criteria for AIDS.³⁵ Sixty-nine percent of the participants were African American, 18% were white, 9% were Hispanic, and 1% were Asian or American Indian. The remaining 3% were multiracial. Women comprised 18% of the sample. Participants ranged in age from 25 to 69 years (mean 44.06, SD 7.53). Twenty-five percent were at least 50 years of age. The majority of participants had completed high school (mean years of education 13.42, SD 2.34). The overall estimated premorbid verbal IQ of participants, as determined using the North American Adult Reading Test, was in the average range (mean 103.62, SD 11.03). All participants were on self-administered HAART at the time of testing.

Neuropsychological measures

All participants completed a battery of conventional neuropsychological tests (Appendix). Test scores were converted to demographically corrected *t*-scores with a mean of 50 and a SD of 10 using published normative data^{36–42} and grouped by neurocognitive domain. Domain *t*-scores were obtained by calculating the mean *t*-score for all the tests that comprised the domain. A global *t*-score was calculated by summing the domain *t*-scores and dividing by the number of domains assessed. Subjects were classified as “impaired” on a particular cognitive domain if the domain *t*-score was less than 40 (i.e., at least 1 SD in the impaired direction). Individuals with global *t*-scores less than 40 (34% of participants) were classified as neuropsychologically impaired. Eighty-three percent of impaired participants were mildly to moderately impaired (1 to 2 standard deviations in the impaired direction) whereas 17% were severely impaired (i.e., greater than 2 standard deviations in the impaired direction). A structured clinical interview comprised of the mood, psychotic spectrum, and substance use modules of the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (SCID)⁴³ was also administered.

Measurement of adherence

Medication adherence was determined using MEMS caps to measure HAART adherence over a 4-week period. MEMS caps employ a pressure-activated microprocessor in the medication bottle cap that automatically records the date, time, and duration of bottle opening. MEMS cap data were later retrieved from the cap using a specially designed communication module connected to a personal computer serial port. For the majority of subjects (64%), MEMS caps were employed to track adherence to protease inhibitors. For those participants on a protease-sparing regimen, MEMS caps were used to track adherence to another antiretroviral medication (e.g., nucleoside reverse transcriptase inhibitor or non-nucleoside reverse transcriptase inhibitor). Participants who took at least 95% of their prescribed doses were classified as good adherers. Medication regimens prescribed on a three times daily basis were considered to be complex whereas one a day or twice daily schedules were classified as less complex.

Procedure

After providing written informed consent, participants completed a detailed demographics questionnaire and structured psychiatric interview and were administered a battery of neurocognitive tests. Trained psychometrists who were supervised by a board-certified neuropsychologist (C.H.H.) conducted all neuropsychological testing. Psychiatric interviewing was conducted by psychology fellows under the supervision of a licensed clinical psychologist with expertise in diagnostic interviewing (S.A.C.). Participants received instruction in how to use the MEMS caps and were scheduled to return 1 month later. At the follow-up visit, MEMS caps were collected and data downloaded. Participants received \$80.00 for participating in the study, which was approved by the institutional review boards of both UCLA and the West Los Angeles VA Medical Center.

Data analysis

The Statistical Package for Social Sciences, version 8.0⁴⁴ was used to analyze data. Two-way analysis of variance (ANOVA) was used to examine the effects of cognitive impairment (impaired vs normal) and medication regimen complexity (medication taken one or two doses/day vs three times daily) on antiretroviral adherence. Because of the skewed nature of the adherence data, the logarithm of percent adherence was used in all analyses. Stepwise logistic regression analyses were also performed to examine the extent to which cognitive dysfunction predicted medication adherence after first controlling for history of neurologic disease, psychiatric disorder, regimen complexity, and age. For the purposes of statistical analysis, participants with a history of HIV-associated opportunistic infections/neoplasm of the brain (e.g., cerebral toxoplasmosis, progressive multifocal leukoencephalopathy), head injury with loss of consciousness in excess of 30 minutes, or seizure disorder were classified as having a positive history of neurologic disorder. Participants with a history of psychotic spectrum disorder or bipolar disorder were considered to have a positive psychiatric history.

Results

The mean adherence rate across all 137 participants was 80.2% (SD 21.0). Only 46 of the 137 participants (34%) took 95% of their prescribed doses whereas 47% of participants were able to attain a 90% adherence rate. Adherence rates were not significantly associated with CD4 count or presence of AIDS diagnosis. To determine the effect of cognitive impairment and regimen complexity on adherence, the first series of analyses employed two-way ANOVA with impairment group (cognitively normal vs impaired) as one between-subjects factor and regimen complexity as the other factor. As hypothesized, results of ANOVA revealed a main effect for impairment group such that the cognitively impaired participants had lower adherence rates (73%) than the cognitively intact group (84%) [$F(1,136) = 20.39$, $p < 0.001$]. A main effect for regimen complexity was also obtained [$F(1,136) = 11.12$, $p = 0.001$]. Moreover, an interaction effect was obtained [$F(1,136) = 11.63$, $p = 0.001$], with the cognitively impaired subjects on more complex dosing schedules evidencing the lowest adherence rates (figure). Adherence rates for the cognitively intact subjects did not significantly vary as a function of dosing regimen, suggesting that complex medication regimens do not pose the same degree of challenge for cognitively normal patients as they do for the cognitively impaired.

An additional series of two-way ANOVA were repeated, substituting specific cognitive domains (e.g., memory, executive dysfunction) for global cognition. Participants with executive, or frontal systems, dysfunction were found to have lower adherence rates [$F(1,136) = 17.4$, $p < 0.001$]. There was also an interaction between presence of executive dysfunction and regimen complexity [$F(1,136) = 11.6$, $p = 0.001$]. Participants with

executive dysfunction who were on a three times daily schedule demonstrated disproportionate difficulty adhering to their medication regimen. The presence of higher-order attentional compromise was also associated with poorer medication adherence [$F(1,136) = 8.03, p = 0.005$]. Again, there was an interaction between compromised attention and regimen complexity [$F(1,136) = 9.83, p = 0.002$]. Participants with attentional impairment who were on more complex medication regimens demonstrated significantly lower adherence rates. No other cognitive domain was found to significantly interact with regimen complexity in the prediction of medication adherence rates, although there was a main effect for memory impairment leading to poorer adherence [$F(1,136) = 6.87, p = 0.01$].

A series of stepwise logistic regression analyses were then performed to further determine the predictive relationship between cognitive dysfunction and medication adherence. The first analysis examined whether global neuropsychological impairment predicted medication adherence, with good medication adherence conservatively defined as at least 95% of doses taken. After first controlling for history of neurologic disorder, current psychiatric disorder, regimen complexity, and age, logistic regression analyses revealed an association between neuropsychological compromise and poor medication adherence [$\chi^2(5, 136) = 12.3, p = 0.03$]. Younger age ($\beta = 1.08, p = 0.009$) and the presence of global neuropsychological impairment ($\beta = 0.85, p = 0.05$) also were associated with poor adherence (table 2). History of neurologic disorder, major psychopathology, and regimen complexity did not enter the prediction equation. Subjects over the age of 50 were almost three times more likely to be good adherers than were younger subjects (OR 2.96; 95% CI 1.31 to 6.70). After controlling for age, neuropsychologically compromised subjects were more than twice as likely to be poor adherers (OR 2.36; 95% CI 1.01 to 5.51).

Similar results were obtained using a more liberal cut-point to define adequate adherence (i.e., at least 90% of doses taken). After controlling for history of neurologic impairment, current psychiatric disorder, regimen complexity, and age, logistic regression analyses revealed an association between neuropsychological compromise and poor medication adherence [$\chi^2(5, 136) = 19.1, p = 0.002$]. Younger age ($\beta = 1.53, p = 0.0006$) was also associated with poor medication adherence. Neuropsychological compromise was associated with a twofold greater risk of adherence failure (OR 2.0, 95% CI 0.92 to 4.35), whereas younger age was associated with 4.6 times greater risk of adherence failure (OR 4.6, 95% CI 1.92 to 11.18).

Follow-up logistic regression analyses were then performed to determine the relationship between specific neuropsychological domains and medication adherence. Age, history of neurologic disorder, and history of psychiatric disorder were entered initially and then the six neuropsychological domains were entered in the second block. Although the overall model was significant [$\chi^2(10, 135) = 24.09, p = 0.007$], the only neuropsychological domain that was associated with poor medication adherence was memory dysfunction ($\beta = 0.81, p = 0.05$), with the presence of memory dysfunction conferring a more than twofold greater risk of adherence failure (OR 2.25; 95% CI 1.01 to 4.99).

Discussion

These data suggest that cognitive compromise is associated with deficient medication adherence among HIV-infected adults. The presence of cognitive dysfunction was found to confer a twofold greater risk of poor adherence, even after controlling for other HIV-associated risk factors such as neurologic disease and major psychopathology. Depending on the exact analytic strategy employed, memory impairment and executive dysfunction appear to be the driving factors behind this relationship. Others have reported that memory problems adversely impact adherence to antiretroviral regimens. Several studies have found

patient self-report of forgetfulness is associated with adherence difficulties.^{15,45} A strength of the current study is that cognitive performance was objectively measured using a comprehensive neuropsychological test battery. This is particularly important given the frequent dissociation between self-report of cognitive deficit and actual performance on neurocognitive tests in HIV-infected samples.^{46,47} The current results are also consistent with earlier work that found that executive dysfunction was associated with poorer HAART adherence as indexed using pill counts.³⁰

The current study found that cognitive compromise interacts with medication regimen complexity to increase the likelihood of suboptimal adherence. Cognitively impaired participants on three times daily dosing regimens were much more likely to be poor adherers. These results converge with and extend findings from a recent large survey study of 359 HIV+ patients and their treating physicians that found that the complexity of the medication regimen was an important factor in (self-reported) nonadherence.⁴⁸ Whereas complex drug regimens may adversely affect adherence, cognitively compromised patients are more likely to have difficulty adhering even to simpler dosing regimens than are cognitively intact adults.

To our knowledge, this study is the first to combine objective state-of-the-art measures of neuropsychological integrity with an objective measure of medication adherence (MEMS caps). These methodologic advances obviate the two major criticisms of past work in this research arena; namely, lack of precision and objectivity in the assessment of both cognition and adherence. Self-report methodologies, always subject to concerns about accuracy,⁴⁹ may be particularly problematic in populations with high rates of cognitive compromise. This calls into question the validity of self-reported adherence data among individuals who show memory deficits or executive dysfunction on psychometric testing. As the time frame over which an individual is being asked to recall adherence increases, perhaps so too should our skepticism about the accuracy of that recall. Our group is currently in the process of examining data that compare adherence measurement methodologies (e.g., MEMS vs pill counts vs self-report) among cognitively intact and cognitively compromised HIV+ persons.

Unexpectedly, there was a strong relationship between older age and better adherence. We had hypothesized that age-related cognitive decline would adversely interact with HIV-associated cognitive dysfunction and result in particularly poor adherence rates. In contrast, when good medication adherence was defined as at least 95% of doses taken, patients age 50 and older were 2.9 times more likely to adhere than were younger subjects. Several explanatory factors for this finding can be offered. Foremost, although the use of age 50 as a cutpoint to classify “older” adults is based on recommendations emerging from several NIH task forces on aging and AIDS, it is typically rare that clinically significant age-related cognitive decline have onset before the seventh decade. Because the majority of older subjects in the current study were younger than 60 years it may simply be that an attenuation in age range underlies these findings. Another potential explanation might be that taking medication requires less alteration in lifestyle for elders. Older individuals are more likely to have prior experience taking daily medications for other age-related illnesses. Also, the lifestyle alterations necessary for successful adherence may be less burdensome for older individuals, who may more easily be able to accommodate pill-taking into their daily activities.

Given the cross-sectional nature of this study, it would be premature to conclude that neuropsychological dysfunction caused poorer medication adherence. In fact, one could plausibly posit the reverse—poor medication adherence may have multiple untoward clinical consequences, including cognitive decline. Given the demonstrated neuroprotective effects of HAART,^{5,7,50–52} there is likely a bidirectional relationship between antiretroviral

adherence and neurocognitive functioning such that those who fail to take their medications are more likely to develop cognitive deficits that in turn further compromise adherence. Our group is currently in the midst of a longitudinal study that should help disentangle this issue. These data do not imply an obligatory relationship between cognitive compromise and difficulty adhering to complex medication regimens. Included in the current sample of HIV+ individuals is a subset of participants with neuropsychological deficits and excellent adherence and a group of neuropsychologically intact poor adherers. It is unclear how constructs such as social support and health beliefs might mediate the relationship between adherence and neurocognitive performance. Our group is currently completing data collection that should allow us to better address the undoubtedly complex and multidetermined route to adherence success and failure.

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Appendix

Neuropsychological tests by domain and normative data utilized

Speed of information processing

Symbol Digit Modalities Test³⁶

Trail Making Test Part A³⁷

Learning and memory

California Verbal Learning Test Trials 1–5³⁸

California Verbal Learning Test Short Delay Free Recall³⁸

California Verbal Learning Test Long Delay Free Recall³⁸

Verbal fluency

Controlled Oral Word Association Test^{39,40}

Attention and working memory

Paced Serial Addition Test⁴¹

Executive functioning

Short Category Test⁴²

Trail Making Test Part B³⁷

Stroop Color Word Test–Interference^{39,40}

Motor functioning

Grooved Pegboard Dominant Hand³⁷

Grooved Pegboard Nondominant Hand³⁷

Figure.

Relationship between cognitive status, regimen complexity, and medication adherence among HIV-infected adults. ● = One or two doses per day; ▲ three doses per day.

Table 1

Demographic characteristics of participants (n = 137)

Characteristics	Mean (SD) or %
Age, y	44.1 (7.5)
Education, y	13.4 (2.3)
Estimated premorbid intelligence	103.5 (11.1)
BDI II	14.3 (10.4)
BAI	11.9 (9.8)
CD4 count *	386.4 (244.2)
Female	18
Ethnicity	
African American	69
White	18
Hispanic	9
Other	4
AIDS diagnosis	63
History of neurologic disorder	10
History of severe psychiatric disorder	15

* CD4 counts were obtained on 125 participants.

BDI II = Beck Depression Inventory, 2nd ed.; BAI = Beck Anxiety Inventory.

Table 2
Logistic regression analysis predicting medication adherence in adults with HIV

Predictor	β	SE	Odds ratio	95% Confidence interval	
				Lower	Upper
Neurologic history	0.30	0.47	1.35	0.53	3.42
Psychiatric history	0.03	0.51	1.03	0.38	2.80
Regimen complexity	0.25	0.52	1.29	0.46	3.58
Age group	1.09	0.42	2.96	1.31	6.70 [†]
Global NP impairment	0.85	0.43	2.36	1.01	5.51 [*]

Good medication adherence defined as >95% of doses taken.

^{*} $p \leq 0.05$.

[†] $p \leq 0.01$.

NP = neuropsychological.