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The impact of neurobehavioral features on medication adherence in HIV: Evidence from longitudinal models

Stella E. Panos^{a,b,*}, A.C. Del Re^{c,d}, April D. Thames^{a,b}, Timothy J. Arentsen^{a,b}, Sapna M. Patel^{a,b}, Steven A. Castellon^{a,b}, Elyse J. Singer^e, and Charles H. Hinkin^{a,b}

^aDepartment of Psychiatry and Biobehavioral Sciences, UCLA Geffen School of Medicine, Los Angeles, CA, USA

^bDepartment of Psychology, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

^cDepartment of Health Services, Stanford University Medical School, Stanford, CA, USA

^dDepartment of Psychology, VA Palo Alto Healthcare System, Palo Alto, CA, USA

^eDepartment of Neurology, UCLA Geffen School of Medicine, Los Angeles, CA, USA

Abstract

Effective antiretroviral therapy has led to substantial improvements in health-related outcomes among individuals with HIV. Despite advances in HIV pharmacotherapy, suboptimal medication adherence remains a significant barrier to successful treatment. Although several factors have been associated with medication adherence in the extant literature, study assessing the effects of some of the neurobehavioral features specific to HIV has been limited. Moreover, although there is a growing body of literature measuring medication adherence in HIV prospectively, few employ advanced statistical methodologies suited to handle advanced models with multiple predictors that would strengthen our understanding of medication adherence trajectories in HIV. This study sought to integrate traditionally assessed predictors of medication adherence with neurobehavioral features of HIV in a longitudinal study of medication adherence to combined antiretroviral therapy (cART). The current study used multilevel modeling to examine a wide arrangement of categories of factors - demographic, medication related, psychosocial, and neurobehavioral - on medication adherence. The sample consisted of 235 HIV + individuals whose medication adherence was monitored over the course of six months using electronic monitoring devices. After controlling for the effects of demographic, medication, and psychosocial factors, neurobehavioral features added predictive validity to the model. In the final model, simultaneously controlling for the effects of each of the predictors within all the categories, age, self-efficacy, executive functioning, apathy, and frequency of stimulant use emerged as unique individual predictors of average medication adherence across the 6-month study. Self-efficacy and irritability predicted changes in medication adherence over time. Adherence behavior is multidetermined. Adequate assessment of these

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*Corresponding author. spanos@mednet.ucla.edu; stellapanos@gmail.com.

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factors, combined with timely intervention, appears to be warranted in order to boost adherence rates.

Keywords

HIV; AIDS; antiretroviral therapy; adherence; neurobehavioral; psychosocial

Introduction

Despite considerable treatment potential of combined antiretroviral therapy (cART), approximately 50% of individuals studied (Hinkin et al., 2002) fail to adequately adhere to their medication regimens, and this can pose a significant threat to individual and public health. Since the introduction of cART, a number of factors have been associated with medication adherence. From a demographic perspective, younger age (Beer et al., 2012; Hinkin et al., 2004), female gender (Beer et al., 2012; Turner, Laine, Cosier, & Hauck, 2003), lower education and/or literacy (Bottonari et al., 2012; Kalichman, Ramachandran, & Catz, 1999), and ethnic minority status (Beer et al., 2012; Simoni et al., 2012; Thames et al., 2012) have all been associated with suboptimal medication adherence. Medication-related factors that are negatively associated with medication to cART include adverse side effects (Applebaum, Richardson, Brady, Brief, & Keane, 2009) and dosage/regimen complexity (Hinkin et al., 2002). Fortunately, with the development of second-generation medications that reduce dosage/regimen complexity to once daily (Deeks & Perry, 2010), this later factor may no longer be pertinent. Amongst various psychosocial variables, self-efficacy has been found to be positively associated with medication adherence and mediates the relationship between other psychosocial variables (i.e., social support and patient-provider interactions) and medication adherence (Cha, Erlen, Kim, Sereika, & Caruthers, 2008; Johnson et al., 2006). In regards to substance use factors, active illicit substance use/abuse has the most deleterious effect on medication adherence, especially when individuals use stimulants and are acutely intoxicated (Hinkin et al., 2007; Malta, Strathdee, Magnanini, & Bastos, 2008; Moore et al., 2012).

Over the last decade, researchers have also begun to focus on the adverse impact of neurobehavioral features specifically associated with HIV, including HIV-associated neurocognitive disorder and psychiatric factors. Higher-order neurocognitive processes (e.g., executive functions, learning/memory) appear to be specifically predictive of medication adherence (Ettenhofer, Foley, Castellon, & Hinkin, 2010). Among psychiatric comorbidities, depression has a well-known deleterious impact on adherence (Springer, Dushaj, & Azar, 2012). Neuropsychiatric symptoms, considered to be direct manifestations of underlying HIV-associated neuropathology, such as apathy and irritability, have also emerged as critical comorbidities (Castellon, Hinkin, & Myers, 2000; Cole et al., 2007). Though limited, research assessing the impact of these specific neuropsychiatric symptoms on tasks of everyday function is beginning to emerge (Barclay et al., 2007; Kamat, Woods, Marcotte, Ellis, & Grant, 2012). To our knowledge, Barclay et al. (2007) are the only group to assess their impact on medication adherence using objective measures, finding that apathy was

associated with suboptimal medication adherence (using a cutoff of <95%) among younger HIV+ individuals.

The aim of the current study was to assess whether neurobehavioral features of HIV are predictive of adherence to cART above and beyond factors that are traditionally assessed in medication adherence studies and to integrate previous literature by identifying the most salient factors predictive of cART medication adherence in a longitudinal design that provides information about which predictors affect average adherence and which predictors contribute to changes in adherence behavior over time.

Methods

A total of 276 participants living with HIV were enrolled in a longitudinal study of medication adherence from 2001 to 2005. Participants were recruited from community agencies specializing in HIV-related care and via fliers posted at infectious disease clinics at university-affiliated medical centers. Inclusion criteria were as follows: (1) at least 18 years of age, (2) individuals taking cART, and (3) must be responsible for administering their own medications. Participants received baseline testing consisting of measures of side effects, self-efficacy, illicit drug use, neuropsychiatric symptomatology, and neurocognition. Medication adherence and urine toxicology screens were measured monthly for the course of six months. All participants provided written informed consent, and the study was approved by both the UCLA and West Los Angeles Veterans Administration Healthcare Center institutional review boards.

Adherence

Medication adherence was measured repeatedly over the course of the study using the Medication Event Monitoring System (MEMS cap [Apex, Union City, CA]), an electronic monitoring device. MEMS cap is a pill bottle with a microchip-embedded cap programmed to record the date, time, and duration of bottle opening each time the bottle opens. Medications were given priority for selection in MEMS monitoring based on the following order: protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, and other classes of medications. Participants were given the MEMS cap at their initial visit. Data was downloaded monthly onto computers and, for each month, percentage adherence was calculated by dividing the actual dose events by the prescribed doses and multiplying by a hundred. There were a total of six average monthly medication adherence time points. Participants were instructed to take their medications as prescribed, to avoid opening the bottle when not taking their medications, and to avoid removing additional medication for use at a later time. The following corrections were made to account for inaccurate bottle openings: (1) for every two-hour period, only one MEMS cap opening was counted, (2) the number of bottle openings per day were shortened to the total number of prescribed doses, and (3) bottle openings made by the research team were removed from the data.

Medication side effects

Participants were asked about frequency of adverse side effects experienced over the course of the last month, using a single question. A five-point Likert scale was used, ranging from 0 (not at all/once every 6 months) to 4 (everyday) was used.

Stimulant use

Urine toxicology screens were conducted at baseline and monthly thereafter to determine the presence or absence of cocaine or methamphetamine metabolites. An overall measure of stimulant use was computed based upon the percentage of positive screens and total drug screens conducted.

Self-efficacy

Self-efficacy was measured using the self-efficacy question on the ACTG baseline adherence questionnaire, developed by a panel of experts as part of the Adult AIDS Clinical Trials Group (AACTG; Chesney et al., 2000). It asked, "How sure are you that you will be able to take all or most of the study medications." A 4-point Likert scale ranging from 0 (not sure at all) to 3 (extremely sure) was provided for responses.

Neurocognition

Executive functioning and learning/memory were measured using commonly employed neuropsychological tests. Individual test raw scores were transformed into *z* scores based on the larger sample mean and standard deviation. Domain scores (executive functioning and learning/memory) were calculated by averaging test scores within each domain. These *z* scores were used as the outcome measure. See Supplemental Table 1 for the list of tests used.

Neuropsychiatric factors

Depression was measured using the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). Apathy and irritability were measured using an adapted version of the 7-item apathy and 6-item irritability subscales of the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) modified for use with HIV+ individuals (Castellon, Hinkin, Wood, & Yarema, 1998). Responses are dichotomous (yes/no), with higher scores indicating greater apathy and irritability.

Statistical analyses

Longitudinal mixed-effect modeling was employed. This approach utilizes a multilevel structure, allowing for the simultaneous modeling of both intra-individual (level 1) and inter-individual differences (level 2) in change. An empty model was first fit to assess overall means and variance from the grand mean. Then, time (in months) was included in the model at level one to assess for the effects of time on adherence (unconditional longitudinal/growth model). Finally, two conditional longitudinal models were conducted, which involved (1) entering a cluster of a priori hypothesized predictors of adherence at level two (individual level) hierarchically, (2) comparing to the next hierarchical model, and (3) assessing for model fit. The first model assessed the combined effects of demographics,

adverse side effects of the medications, self-efficacy, and drug use. The second model assessed the independent contribution of neurobehavioral features. Given that the independent significance of each of these predictors has been well documented in the literature, single predictor modeling was not conducted.

Statistical software

The “lme4” multilevel modeling package (Bates & Maechler, 2010) in the R statistical software program (R Development Core Team, 2010) was used for all multilevel models. Additional R packages were used in the data analytic process for data manipulation (reshape; Wickham, 2007) and confidence intervals (compute.es; Del Re, 2010).

Results

Of the 276 individuals, 235 participants had at least one medication adherence data point, and data points for the first step of the model. Participants without complete adherence data did not differ from those with complete data on demographic (age, education, sex, and ethnicity) or clinical characteristics (AIDS diagnosis, CD4 +, and nadir CD4 +) (p 's >0.05). See Table 1 for descriptive statistics of these remaining participants and study variables. The average age of the participants was 41.92 (7.03). From an ethnic/racial standpoint, 63.4% were African-American, 16.6% were Caucasian, 13.6% were Latino, and 6.4% “other.” Eighty-two percent were male and 66% met criteria for AIDS. The mean adherence rate for the sample was 67.21 (SD =26.06). For sample descriptive purposes, we also used normative data to illustrate the current sample's cognitive functioning relative to a healthy population. See Table 2 for the total number of returning participants across the six months and average adherence rates for each visit. Participants with missing adherence data did not differ from those with complete data on demographic (age, education, sex, and ethnicity) or clinical characteristics (AIDS diagnosis, CD4+, and nadir CD4 +) (p 's >0.05). The data was verified to ensure that the fundamental statistical assumptions were met.

In the first set of analysis, medication adherence was examined over time using an unconditional growth model (time being the only predictor), and there was significant variability in both intercept and slope. In the first model, traditionally assessed factors of medication adherence to cART were appraised (demographics, medication side effects, self-efficacy, and frequency of positive stimulant urine toxicology). As expected, average age ($\gamma=0.47$, $SE=0.21$, $p = 0.02$), average adverse medication side effects ($\gamma = -3.36$, $SE = 1.58$, $p =0.03$), average self-efficacy ($\gamma = 8.71$, $SE= 1.94$, $p <0.001$), and average stimulant use ($\gamma = -0.28$, $SE =0.04$, $p <0.001$) predicted overall average adherence (grand mean centered intercept) over the course of six months. None of the modeled variables were predictive of changes in medication adherence over time.

In the second model, neurobehavioral features of HIV were added (apathy, irritability, depression, learning/memory, and executive functioning). It should be noted that some of the data was missing for the second set of predictors (see Table 1), and the second model was based on this smaller (yet still the majority; $N =207$) subsample. With the exception of a trend for higher education (less than a year), among those included in the second step ($M = 13.07$, $SD = 2.11$) compared to those only in the first step ($M = 12.21$, $SD=2.33$), $F(1,233) =$

4.01, $p = 0.05$, there were no other demographic (age, sex, and ethnicity) or clinical characteristic (AIDS diagnosis, CD4+, and nadir CD4+) differences between the groups. As expected, the addition of the neurobehavioral symptoms improved the model ($\chi^2(30) = 25.64$, $p < 0.01$). See Table 3 for fit statistics. In this final model, average age ($\gamma = 0.59$, $SE = 0.22$, $p < 0.01$), self-efficacy ($\gamma = 11.32$, $SE = 2.07$, $p < 0.001$), stimulant use ($\gamma = -0.27$, $SE = 0.04$, $p < 0.001$), apathy ($\gamma = -2.50$, $SE = 1.07$, $p = 0.02$), and executive functioning ($\gamma = 4.26$, $SE = 1.71$, $p = 0.01$) predicted overall average adherence (grand mean centered intercept). None of the other variables were predictive of average adherence (gender, education, ethnicity, side effects, depression, irritability, or learning/memory). Predictors of changes in medication adherence over time were self-efficacy ($\gamma = 1.16$, $SE = 0.54$, $p = 0.03$) and irritability ($\gamma = -0.83$, $SE = 0.35$, $p = 0.02$) (see Table 4). As a follow-up analysis, ethnicity was broken down between groups (Caucasian, African-American, Latino, and other). Again, there were no main effects of ethnicity (p 's > 0.05), and the results remained unchanged.

Discussion

To date, several key categories of factors have been associated with medication adherence in HIV, including demographics, factors related to the medications, psychosocial factors, and neurobehavioral symptoms of HIV. The aim of the current study was to assess the unique contribution of the neurobehavioral features of HIV to cART and to integrate previous literature by identifying the most salient factors predictive of cART medication adherence in a longitudinal design that provides information about which predictors affect average adherence and which predictors contribute to changes in adherence behavior over time. Overall, the addition of neurobehavioral factors proved to explain additional variance in the model. Within the neurobehavioral factors, both neuropsychiatric as well as cognitive factors influenced medication adherence. Among the demographic variables, age alone emerged as a significant predictor of medication adherence in HIV, with older age predictive of better adherence. The protective effect of older age on medication adherence is consistent with prior studies (Becker, Dezii, Burtcel, Kawabata, & Hodder, 2002). The lack of significant findings between any of the other key demographic variables in the final model is noteworthy and suggests that demographics may be proxies for other key factors related to medication adherence. Indeed, researchers have found that African-American men report lower self-efficacy to adhere (Siegel, Karus, & Schrimshaw, 2000) and that other factors (e.g., health literacy) mediate the relationship between race and medication adherence (Osborn, Paasche-Orlow, Davis, & Wolf, 2007). The positive relationship between self-efficacy and medication adherence has long been documented in HIV (Ammassari et al., 2002). The current study extends these findings by demonstrating that individuals with lower self-efficacy evidenced not only lower average medication adherence but also steeper declines in medication adherence across time.

Controlling for all other factors, stimulant use remained a significant predictor of medication adherence to cART. To our knowledge, this is the first study to assess the relationship between stimulant use and medication adherence as a function of frequency of positive urine toxicology in HIV. Gorman, Foley, Ettenhofer, Hinkin, and van Gorp (2009) suggested three potential mechanisms by which substance use might affect medication adherence: (1) the

effects of the drugs may modify daily routines that serve as prompts to remember to take medications, (2) cognitive dysfunction resulting from drug use, and (3) certain stable traits of individuals. They suggest that the literature favors the first two mechanisms. The current study supports and extends these findings by demonstrating that increased frequency of positive stimulant screenings was associated with lower average medication adherence. Additionally, we were able to control for cognition. As such, the current findings suggest that the acute effects of the drugs independently affect medication adherence.

After controlling for all the other factors, several of the neurobehavioral symptoms (i.e., apathy, irritability, and executive functioning) that have been associated with HIV medication adherence remained robust predictors. Previous work suggests that symptoms of apathy and irritability are associated with cognition and may reflect HIV-associated CNS involvement (Castellon et al., 2000; Paul et al., 2005). The current study demonstrates that apathy and irritability were significant predictors of medication adherence, and this relationship to medication adherence was independent of both depression and executive functioning. Furthermore, these findings suggest that specific neuropsychiatric symptoms considered to represent more direct manifestations of underlying HIV-associated neuropathology also require clinical attention when assessing mood and medication adherence in HIV. Whereas higher apathy at baseline predicted lower average medication adherence across the six-month study, higher irritability at baseline predicted steeper declines in medication adherence across the six months. The mechanisms by which these symptoms affect medication adherence in distinguishable ways are unclear. One possibility is that irritability may present as a harbinger of future neurocognitive decline. Although both neuropsychiatric symptoms have been associated with basal ganglia functioning and tasks of executive functioning, there is some evidence to suggest separate neuroanatomical associations within fronto-striatal circuitry (Litvan, Paulsen, Mega, & Cummings, 1998). Further research is necessary to validate this hypothesis. Consistent with other studies of medication adherence and HIV (Ettenhofer et al., 2010; Hinkin et al., 2002), executive functioning remained predictive of medication adherence.

In the final omnibus model, the combination of individual predictors from each of the larger categories demonstrated the best overall fit of the data. However, there was a significant amount of variance that remained. Indeed, medication adherence is a complex and dynamic construct to assess and is dependent not only upon the ability to accurately select predictors but also on the validity of measures used to measure medication adherence. Regarding predictor selection, the current study attempted to incorporate the most salient factors based upon previous literature to date. The factors assessed were far short of an exhaustive list. Given these findings, continued assessment of novel predictors of medication adherence in HIV is warranted. The current study measured participants at baseline in order to predict future adherence across the six months. One important area of research may be to assess intra-individual changes across time for each of these predictors, and the relationship between these changes and changes in medication adherence. This may explain additional variance. Additionally, the assessment of interactive effects of sets of symptoms that tend to occur concomitantly (i.e., neuropsychiatric, mood, cognition) may also be a useful area of research.

Validity of measures used to assess medication adherence is also an important factor to which to attend. The current study used an objective method of measuring medication adherence, MEMS caps. Although the validity of this measure has been repeatedly documented across studies, there is some evidence to suggest that this method may underestimate actual adherence rates to some extent (Liu et al., 2001). Similar to the findings of Liu and colleagues, the current study found that medication adherence decreased as a function of time (at a trend level of significance). It is unclear whether this is indicative of a “Hawthorne effect,” pocket dosing over time, or simply a decrease in use of the MEMS cap over time. The current study sought to control for the effects of pocket dosing by directly instructing participants against this. Additionally, although we were unable to directly assess the exact etiology of the decline, we controlled for the effects of “time” in our models.

Consistent with predictions made by Ickovics and Meisler (1997) over a decade ago, a variety of interrelated factors influence medication adherence. Some of these variables are patient specific, some are disease related, and yet others stem from treatment-related factors. This study attempted to disentangle the unique effects of these core predictors of adherence behavior. While adherence behavior is multidetermined, these data suggest that neurobehavioral factors comprise a unique threat to adequate adherence. Hence, adequate assessment of these factors, combined with timely intervention, appears to be warranted in order to boost adherence rates. Finally, it must be noted that these findings apply to this sample as a whole. But certainly, there are subgroups for which different combinations of adherence predictors of greater import. Having now begun to disaggregate overlapping predictors of adherence, the next challenge is to apply this methodology toward identification of specific typologies of poor adherence and extend this line of research to encompass other diseases where medication adherence is equally critical.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1Descriptives ($N = 235$).

	M (SD)	N
Demographics		
Age	41.92 (7.03)	235
Education	12.97 (2.15)	235
Sex (% male)	82.1%	235
Ethnicity		
Caucasian	16.6%	39
African American	63.4%	149
Latino	13.6%	32
Other	6.4%	15
AIDS diagnosis (% yes)	66.4%	230
Most recent absolute CD4+ count (cells/mm ³)	457.15 (301.46)	224
Nadir absolute CD4+ count (cells/mm ³)	206.09 (186.59)	223
Medication side effects	0.40 (0.93)	235
Self-efficacy	2.29 (0.77)	235
Depression	13.71 (9.49)	230
Apathy	1.69 (1.86)	212
Irritability	1.26 (1.48)	212
Learning/memory ^a	42.52 (9.58)	235
Executive functioning ^a	42.45 (6.94)	235
Stimulant frequency	37%	235
Stimulant/cocaine abuse/dependence (%yes) ^b	31%	231

Notes:

^a See Supplemental Table 1 for list of tests and norms;^b Diagnoses derived from the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer, Williams, Gibbon, & First, 1992).

Table 2

cART medication adherence rates across the six months.

Time point	N	Mean	SD	Median
1st month	230	74.71	25.02	83.22
2nd month	217	70.28	28.53	80.40
3rd month	215	67.98	28.50	76.67
4th month	199	66.97	30.54	75.40
5th month	196	64.76	31.19	75.45
6th month	197	62.59	32.20	70.50

Table 3

Model fit statistics.

	AIC	Log-likelihood statistics
Model 1	9542.6	
Model 2	9536.9	χ^2 (30) 25.64, $p = 0.004$

Table 4

Final omnibus model: predictors of longitudinal medication adherence to cART.

Fixed effects	Coefficient	SE	p-value
For intercept			
Intercept	75.30	4.00	<0.0001
Time	−1.80	1.06	0.08
<i>Demographics</i>			
Age	0.59	0.22	<0.01
Gender ^a	−2.62	3.98	0.50
Education	−1.32	0.73	0.06
Ethnicity ^b	2.05	4.32	0.62
<i>Medication factor</i>			
Side effects	−1.96	1.83	0.27
<i>Health beliefs/self-efficacy</i>			
Self-efficacy	11.32	2.07	<0.0001
<i>Drug use</i>			
Stimulant use	−0.27	0.04	<0.0001
<i>Neurobehavioral</i>			
Depression	0.30	0.19	0.11
Apathy	−2.50	1.07	0.02
Irritability	−0.17	1.34	0.89
Learning/memory	1.25	1.64	0.43
Executive functioning	4.26	1.71	0.01
For linear slope			
<i>Demographics</i>			
Age	0.03	0.06	0.61
Gender ^a	−1.56	1.07	0.13
Education	−0.05	0.19	0.79
Ethnicity ^b	−0.01	1.16	0.98
<i>Medication factor</i>			
Side effects	0.52	0.48	0.26
<i>Health beliefs/self-efficacy</i>			
Self-efficacy	1.16	0.54	0.03
<i>Neurobehavioral</i>			
Depression	0.06	0.05	0.21
Apathy	0.29	0.29	0.29
Irritability	−0.83	0.35	0.02
Learning/memory	0.24	0.44	0.58
Executive functioning	0.74	0.45	0.09
<i>Drug use</i>			
Stimulant use ^c	−0.01	0.01	0.25

Notes:

^a Comparison group is males.

^b Comparison group is ethnic minority.

^c Frequency of stimulant use centered at mean.

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