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Variations in Patterns of Highly Active Antiretroviral Therapy (HAART) Adherence

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Strict adherence to highly active antiretroviral therapy (HAART) is necessary for successful suppression of HIV replication. A large number of individuals are not adherent, however, and the reasons for non-adherence are varied and complex. We utilized cluster analyses to identify subgroups of adherers in a sample of 222 HIV positive individuals whose HAART use was electronically monitored. Five distinct subgroups were identified, with characteristic variations across the week and over the course of the 4-week study. Additional comparisons of demographic and behavioral variables found the worst adherers to have higher rates of substance use, and that a group with higher rates of cognitive impairment had a consistent drop in adherence during the weekends. In addition, the group with the best adherence had more individuals over the age of 50 years. The results of the current study indicate that distinct subgroups of adherers may exist, and suggest that interventions designed to improve adherence can be designed to accommodate this variability in behavior.

KEY WORDS: antiretroviral therapy; HAART; adherence; HIV; substance abuse.

INTRODUCTION

Advances in the treatment of HIV infection, particularly highly active antiretroviral therapy (HAART), have greatly reduced mortality and improved quality of life for many people living with HIV/AIDS. Considerable research in recent years has focused on describing factors associated with non-adherence to HAART. Recent reviews have found that medication side-effects, stressful life events, poor social support, and the complexity of the medication regimen are most commonly associated with poor adherence (Ammassari *et al.*, 2002; Fogarty *et al.*, 2002). Findings from our research have also implicated neuropsychological impairment and regimen complexity as significant obstacles to adherence (Hinkin *et al.*, 2002). Substance abusers and younger adults may be particularly at risk for non-adherence (Hinkin *et al.*, 2004).

While a number of studies have examined methods of predicting medication adherence, considerably less attention has been devoted to how adherence changes over time. Recently, Howard *et al.* (2002) described the longitudinal course of adherence over a 6-month period in 161 HIV positive women. Using electronic monitoring devices to track adherence, the authors found a gradual decrease in overall adherence throughout the 6-month study, from 64% during month 1 to 45% at month 6. The greatest drop in adherence occurred between

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months 1 and 2 (from 64 to 55%). While the mean adherence leveled off after the first few months, the researchers noted that individual adherence rates were more variable, with adherence rates actually increasing in some participants. Other studies have also examined adherence dynamics longitudinally using self-report, and found significant variability in adherence patterns both between and within participants (Carrieri *et al.*, 2001).

One point that has emerged from these studies is the considerable variability in adherence. For example, Carrieri *et al.* (2001) found a dissociation between level and consistency of adherence, with some individuals being consistently good adherers, some individuals with consistently poor adherence, and others with fluctuating adherence rates. These results suggest that distinct typologies of adherence behavior may exist, but it is important to note that their data came from patient self-report, which can be unreliable (Bangsberg *et al.*, 2000; Liu *et al.*, 2001). To our knowledge, only one study employing electronic measuring sought to identify typologies of adherence (Wijngaerden *et al.*, 2002). This longitudinal study identified two subgroups: good adherers and "subclinical" non-adherers, with the latter group's adherence pattern described as "not yet accompanied by, but potentially leading to, poor clinical outcome." Despite the relative lack of empirical data, it is safe to speculate that while some non-adherers may have a relatively consistent pattern of missing doses, others may miss doses sporadically. Further, some individuals may miss doses on certain days of the week due to alterations in their regular schedule or involvement in other activities. Interventions used to improve adherence could potentially be engineered differently for such subgroups. In the current study we examined longitudinal adherence data in order to uncover common patterns of adherence to HAART, and also to characterize the individuals that exhibit those patterns.

METHODS

Participants

Our cohort consisted of 222 HIV positive adults recruited from the Los Angeles area who were enrolled in one of two studies examining factors associated with medication adherence. Participants were recruited through advertisements posted at university-affiliated infectious disease clinics as well as through community-based HIV/AIDS organizations. Most participants were not working or in school (81%), and many were receiving disability, welfare, or other assistance (73.2%). At the time of study entry, all participants were prescribed a regimen of HAART, defined here as a combination of three or more antiretroviral drugs, including protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside analogue reverse transcriptase inhibitors (NRTI), nucleotide analogue reverse transcriptase inhibitor (NtRTI).

Measure of Adherence

The Medication Event Monitoring System (Aprex, Union City, CA), or MEMS cap, was used to estimate adherence. The MEMS cap consists of a pill bottle with a microchip-embedded cap that records the date, time, and duration of bottle opening. One of each participant's HAART medications was monitored with the MEMS. The medication chosen by the research team was based on the class of medication. Priority was given to protease inhibitors (PIs); 44% of participants used their PI. If a participant was not currently taking a PI, then a medication was chosen from a list of nucleoside reverse transcriptase inhibitors (NRTIs); 36%. If neither PIs nor NRTIs had been prescribed, then a non-nucleoside reverse transcriptase inhibitor (NNRTI) was chosen; 19%. Data were downloaded from the MEMS cap at the end of the 4-week study period. Overall adherence rates were the primary outcome of interest. This was calculated as number of uses (as indicated by number of openings of the MEMS cap) divided by number of prescribed doses, the sum of which was then multiplied by 100. To correct for unintentional openings, or a suspiciously high number of openings within a limited time, the data were visually analyzed and corrected based on the following criteria: if the number of openings of the MEMS cap in a day exceeded the number of prescribed doses then the MEMS data was adjusted to reflect the maximum number of prescribed doses per day, if the MEMS cap was opened more than once in a 2-hr period then data was adjusted to reflect only one opening, and if the MEMS cap was opened by the research team for purposes such as counting pills then the opening was stricken from the data. We used a cutoff of 90% of doses taken to distinguish good from poor adherers. This cutoff was chosen primarily in order to maintain consistency with other studies coming from this laboratory.

Behavioral Measures

All participants underwent a structured clinical interview using criteria for psychiatric diagnoses (SCID, Spitzer *et al.*, 1992). Using the SCID, we assessed for current and past mood, psychotic, and substance use disorders. Diagnosis of current psychiatric illness (depression, psychosis, or bipolar disorder within the last month) was used in later analyses. Participants were also identified as current alcohol and/or substance abusing/dependent if they met diagnostic criteria within the last month, and this information was also used for analyses. All participants were administered a battery of standard neuropsychological tests. The neurocognitive domains yielded were processing speed, attention, learning and memory, verbal fluency, executive functioning, and motor speed. In addition, a global measure of cognitive functioning was obtained that collapsed functioning across all of these domains. Scores were converted to demographically corrected *T* scores using published normative data. Then, using a technique developed by Heaton and colleagues (Heaton *et al.*, 1991), deficit scores ranging from 0 to 5 were assigned to each measure based on the following *T* scores: $T > 39 = 0$; $T \leq 39$ and $\geq 36 = 1$; $T \leq 35$ and $\geq 30 = 2$; $T \leq 29$ and $\geq 25 = 3$; $T \leq 24$ and $\geq 20 = 4$; $T < 20 = 5$. The deficit scores for all neuropsychological measures that comprised a particular domain were then averaged to produce a domain deficit score. Participants were classified as impaired in a domain if their average deficit score was greater than or equal to .5. In addition, participants with an average deficit score across all tests of greater than or equal to .5 were classified as having global neuropsychological impairment. Estimated IQ was obtained through the American New Adult Reading Test, or AMNART (Grober and Sliwinski, 1991).

Statistical Analyses

K-means cluster analysis was performed to classify the 222 HIV positive participants into subgroups of individuals based on patterns of adherence during the week. Cluster analysis is a multivariate statistical method that creates relatively discrete, homogeneous groups based on specified variables (Everitt, 1993). These groups, or clusters, are internally homogeneous and externally heterogeneous with regards to the clustering variables. Percent adherence to the target medication for each day of the week (i.e., Monday through Sunday), averaged over 4 weeks, was used as the clustering variable. Previous cluster analyses done in our lab, using only those considered to be poor adherers (average of <90%), identified three clusters. The addition of good adherers into the current analysis prompted a prediction of two additional clusters, as we believed that this group was not heterogeneous with regards to adherence. Therefore, in the current study we ran analyses for 2–5 clusters. After visual inspection of these initial cluster analyses, we ultimately chose a 5-cluster solution due to its consistency with previous analyses in our laboratory and sufficient dissimilarity between clusters.

Next, repeated measures ANOVA were performed to characterize adherence patterns over the course of the 4-week study period. Paired-samples *t*-tests were used to compare weekend (Friday, Saturday, and Sunday) versus weekday (Monday through Thursday) adherence for each group identified through cluster analysis.

Finally, a series of analyses were performed to identify behavioral, medical, medication, and demographic differences between the groups, using either univariate ANOVA or χ^2 frequency analyses.

RESULTS

The majority of participants were male (80%), African-American (68%) and Caucasian (17%). The mean age was 43.8 ($SD = 7.2$) and participants had an average education of 13.1 years ($SD = 2.2$) with an estimated intelligence of 104 ($SD = 11$, Grober and Sliwinski, 1991). Sixty-one percent of participants had an AIDS diagnosis, 16% had a psychiatric diagnosis, and 21% had a substance use disorder.

The groups represented by the five clusters were as follows (see Table I): Group 1 ($n = 23$) consisted of very poor adherers with a consistent pattern across the week. They had a mean adherence of 24% on both weekends and weekdays. Group 2 ($n = 98$) was comprised of good adherers (>90%), with similar adherence on weekdays (96%) and weekends (94%). Group 3 ($n = 42$) was characterized by sub-optimal adherers, as participants' overall adherence rate was around 80%. They also had similar adherence on weekdays (80%) and weekends (83%). Group 4 ($n = 32$) was comprised of moderately poor adherers, with 51% adherence on weekdays and 52% on weekends. Group 5 ($n = 27$) demonstrated an interesting pattern of adherence, with significantly better adherence during the week (75%) than on weekends (57%). Mean change in adherence between weekdays and weekends is illustrated in Fig. 1.

Table I. Sub-Groups of Poor Adherers

			Percent adherence	
Group number	*N*	Description	Weekday	Weekend
1	23	Consistent, very poor adherence	24	24
2	98	Good adherers (i.e. >90%)	96	94
3	42	Suboptimal adherers (i.e. 70–90%)	80	83
4	32	Consistent, moderately poor adherers	51	52
5	27	Poor weekend adherers	75	57

In order to examine adherence patterns over the course the month, repeated measures ANOVA was employed for each cluster group described above. Figure 2 illustrates average adherence rates for weekdays (Monday through Thursday) and weekends (Friday through Sunday) for the entire sample across the 4 weeks of the study. By way of clarification, the Weekend 1 variable represents the average adherence rate for the first Friday, Saturday, and Sunday of the study, while Weekday 3 represents the average adherence rate for the third Monday, Tuesday, Wednesday, and Thursday. Repeated measures ANOVA found that adherence for Group 1, the consistently bad adherers, decreased significantly from the beginning to the end of the month ($p < .001$). Adherence for Group 2, the good adherers, did not change over the course of the study. Adherence over the course of the study for Group 3, the sub-optimal adherers, was found to worsen significantly from the beginning to the end ($p < .001$). Group 4, the moderately poor adherers, were also found to have decreasing adherence over the 4 weeks ($p = .04$). Finally, Group 5, the poor weekend adherers, maintained overall stability of adherence over the 4 weeks. These patterns of adherence across the 4-week study are shown in Fig. 3.

Groups were also compared with regards to medication regimen complexity, defined here as the total number of medications and the total number of pills taken each day, including non-HIV related medications. In addition, the type and dose requirements of the HAART medication monitored by the MEMS were compared among the groups. Due to the low number of participants on NtRTI ($n = 2$), this was not included in the χ^2 analysis of MEMS medication type. No significant differences were found between groups on total number of medications ($p = .39$) or pills ($p = .18$), or the daily dose requirements of the MEMS medication ($p = 39$). However, the χ^2 analysis of MEMS medication type revealed significant differences between the groups ($\chi^2 = 18.88$, $p = .02$). Group 1 had the largest proportion of individuals whose MEMS involved PIs and smallest involving NRTIs,

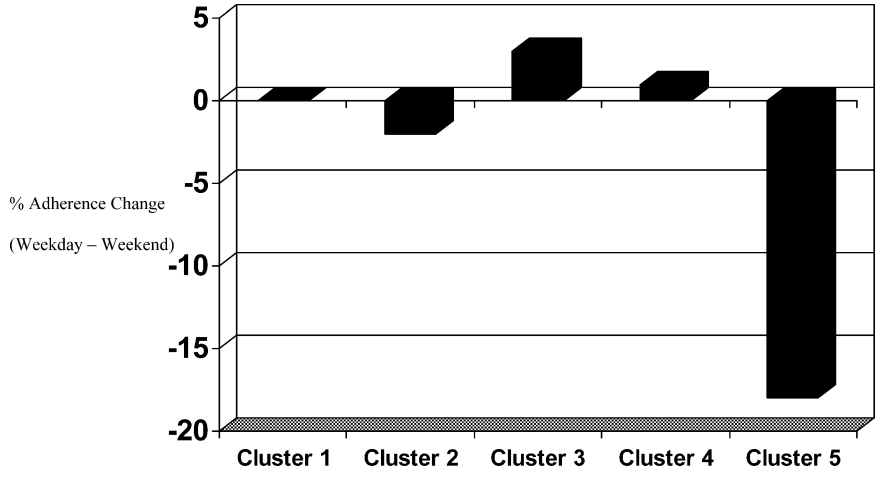

Fig. 1. Bars represent the overall difference in adherence between weekends and weekdays. Only Group 5 demonstrates a notable difference, with significantly greater adherence on weekdays as opposed to weekends.

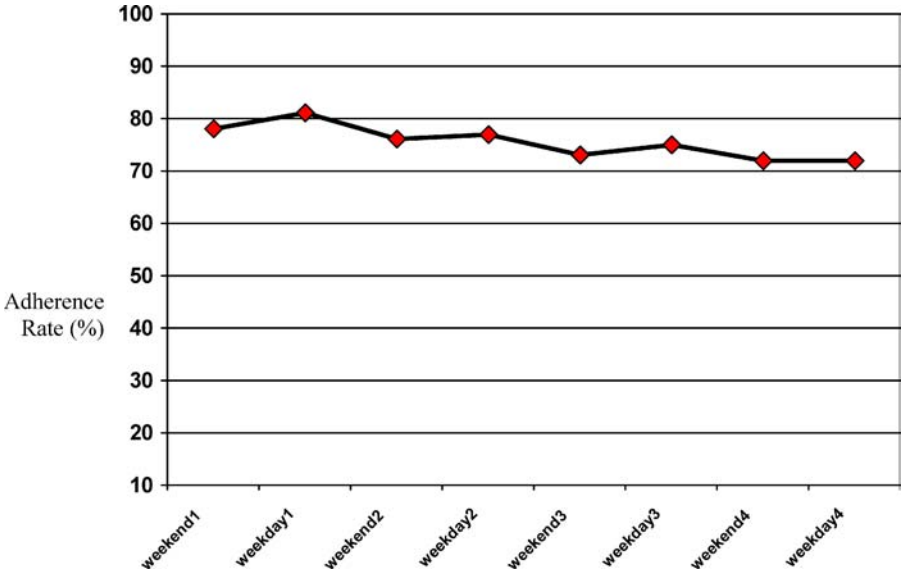

Fig. 2. Overall adherence pattern of all participants across the 4-week study. Adherence changed only slightly for the group as a whole.

while Group 2 had a greater proportion of members whose MEMS involved NNRTIs and a lower proportion involving PIs. The groups did not differ with regards to length of time on HAART prior to study onset ($p = .78$). These results are shown in Table II.

The final analyses involved comparison of the groups on demographic, cognitive, and behavioral measures. ANOVA and χ^2 analyses were employed with the following sub-sections.

Demographic Characteristics

Education did not differ significantly between the groups ($p = .68$). Age was found to differ significantly ($p = .001$). Post hoc analyses showed that

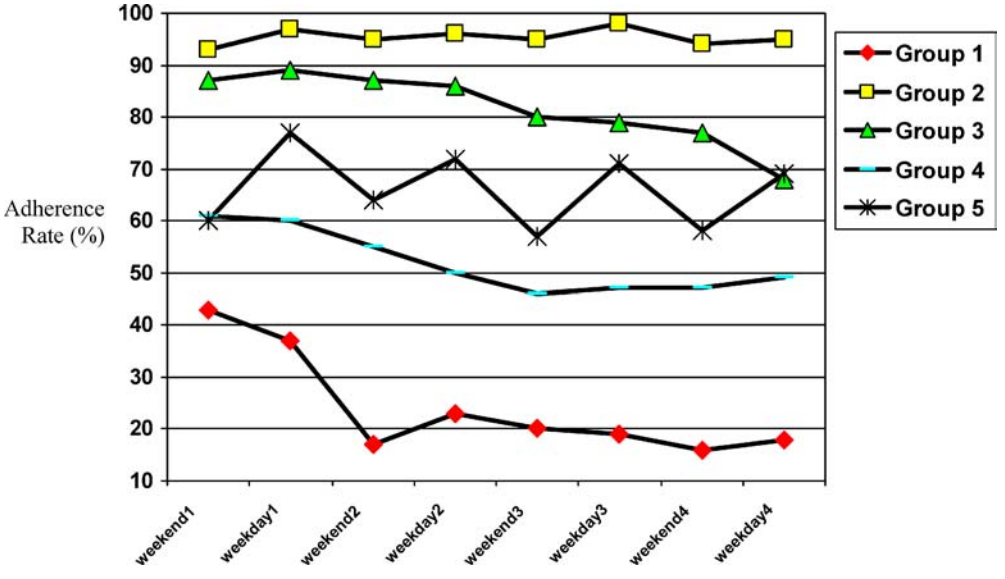

Fig. 3. Adherence patterns over the 4-week study by cluster group. Significant variations in adherence rate and patterns are illustrated.

Table II. Group Differences in Medication Complexity and Type

Measure	Mean (*SD*)					*p*-value
	Group 1	Group 2	Group 3	Group 4	Group 5	
Duration (in months) on HAART prior to study	127 (248)	94 (173)	106 (182)	100 (210)	150 (313)	.78
Total number of medications[a]	4 (2.3)	5.2 (2.6)	5.2 (2.8)	5.2 (3.4)	5.9 (5.9)	.39
Total number of pills taken daily[a]	10 (6.1)	14 (9)	14.5 (8.9)	15.2 (8.9)	16.8 (15.4)	.18
MEMS medication daily dose	1.9 (.4)	1.9 (.5)	2.0 (.4)	2.0 (.5)	2.0 (.4)	.39
Type of MEMS medication: % of participants						
PI	61.9	25	40.5	37.9	44.4	
NNRTI	14.3	29.2	9.5	13.8	11.1	.02
NRTI	23.8	45.8	50	48.3	44.5	

[a]This includes non-ART and non-HIV medications.

participants within Group 1 (mean age = 39.4) were significantly younger than those of Group 2 (mean age = 45.7). χ^2 analyses showed that gender and ethnicity did not differ in frequency between the five groups ($p = .23$, $p = .42$, respectively).

Cognitive Functioning

Groups differed with regards to estimated IQ ($p = .03$). Group 2 had the highest average IQ (106.4), while Group 1 had the lowest (100.5). Examination of performance on composite cognitive domains revealed that Group 5 performed significantly worse than any of the other groups on the global impairment index ($x^2 = 12.8$, $p = .01$) and the attention domain ($x^2 = 10.4$, $p = .03$). No significant differences were found in the other cognitive domains.

Psychiatric Symptoms

χ^2 analysis of current substance abuse/dependence was significant ($x^2 = 17.0$, $p = .002$), with Group 1 having the highest percentage of members with a current substance use disorder (60%), compared to rates between 17.6 and 23.1% in the other groups. Frequency of current psychiatric diagnosis (depressive disorder, bipolar disorder, mania, or psychosis) did not differ significantly between the groups ($p = .54$).

DISCUSSION

As hypothesized, distinct patterns of adherence behavior were identified based on variability in adherence over time. Five subgroups were identified based on daily adherence patterns over a 4-week period. These groups differed with regards to overall adherence rates, consistency in taking medications throughout the month, and pattern of adherence during the week. As Figs. 2 and 3 illustrate, had all poor adherers been examined together these patterns would not have been appreciated. Further, some groups were distinct with regards to certain demographic, behavioral, medication, and/or cognitive measures. For example, cognitive impairment was more common in those with relatively poor weekend versus weekday adherence. In fact, 91% of the members of this group (Group 5) had global cognitive impairment, with 65% impaired specifically in the domain of attention. Previous studies by our group found an association between cognitive dysfunction and poor adherence, as well as interactive effects between regimen complexity and cognitive compromise (Hinkin *et al.*, 2002). The data presented here confirm and extend those findings. Although not a focus of the present study, a possible reason for the distinctive pattern of adherence in Group 5 is that the loss of structure inherent in weekday activities (e.g., work and school) coupled with cognitive impairment resulted in decreased ability to adhere to the medication regimen on the weekends. However, the proportion of individuals in this group who were employed or in school was similar to that of the other groups, making this explanation less likely. Additional examination of these individuals, with more attention paid to daily routines/activities, will help disentangle the observed discrepancy.

Another notable finding is that those with very poor adherence (25%) across the week had a significantly higher frequency of current substance use disorders. Sixty percent of the members of this group were diagnosed with a current substance use disorder (alcohol or illicit drug), compared to rates of between 17 and 23% in the remaining groups. This finding is consistent with that of other researchers, who have found alcohol and drug use to be associated

with poor adherence (Cook *et al.*, 2001; Golin *et al.*, 2002). Age also appeared to be a significant factor. The group of good adherers (Group 2) was found to have significantly more members over the age of 50 years (34%), while very poor adherers (Group 1) had the fewest in this age group (4%). These two groups also differed from the others with regards to the class of medication being tracked by the MEMS cap (Table II). However, none of the groups differed with regards to MEMS dosage, suggesting that the regimen associated with the MEMS medication was not a factor in the differing adherence rates. Further, regimen complexity, or the total number of medications taken each day (including non-HIV medications) did not differ among the groups. This leads us to conclude that regimen complexity was not a factor in adherence for this cohort.

A potential direction for future research in this area will be to develop and assess a more comprehensive model of adherence in HIV that specifies barriers (and, ideally, facilitators) of adherence behavior. Such models of adherence might allow interventions to be systematically tailored based on the constellation of identified potential risk factors, such as substance abuse and cognitive impairment, and the degree to which each represents either trait- or state-like phenomenon. For example, those with cognitive impairment, who in our study were found to have significantly decreased adherence on weekends, might benefit from an external device that reminds them to take their dose. Further, treatment interventions for those with substance use disorders, who in this study were found to have very low adherence rates, might focus on decreasing drug use before beginning HAART, which would undoubtedly require both internally and externally directed interventions.

We acknowledge that the duration of our study was short, and therefore the adherence patterns identified during the 4-week trial may change considerably over extended periods of time. The decreasing adherence across the study noted in three of the groups suggests that true adherence patterns might not become apparent until overall adherence (i.e. average monthly rate) has stabilized. Howard *et al.* (2002) recently reported a similar decrease in adherence during their 6-month study. While they found the greatest decrease in adherence occurred during the first month, it may take several months before this decline plateaus. Therefore, it remains to be seen whether or not the typologies identified in the current study are stable over longer durations. We are currently following most of our cohort for a period of 6 months in order to answer this question. Limitations of the MEMS cap also pose potential confounds. For example, it is possible that some participants took "pocket doses," or removed extra doses of their medication while the MEMS cap recorded only a single opening. In addition, only one HAART medication per participant was monitored with the MEMS, leaving open the possibility that the other medications that comprised their HAART regimen were not taken with the same frequency. However, a recent study found that when patients missed one of their HAART medications they tended to miss them all (Wilson *et al.*, 2001). While it is not possible to completely control for these factors, the importance of using the MEMS properly was discussed with the participants at study onset.

In summary, it would be inaccurate to conceptualize medication adherence as a static phenomenon. Rather, for many patients adherence appears to decline over time. A related concern is for those HIV-infected adults who evidence inconsistent adherence over the course of the week since those individuals may be at greatest risk for the development of drug resistance. The presence of risk factors for poor adherence, such as neuropsychological impairment or substance abuse, may serve to identify subgroups of HIV-infected adults who are at greatest risk for adherence failure. Finally, given that multiple subgroups of poor adherers appear to exist, it follows that interventions designed to improve adherence could be tailored to accommodate this variability in behavior.

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