Journal of the International Association of Physicians in AIDS Care (JIAPAC)

Results of an Antiretroviral Adherence Intervention: STAR (Staying Healthy: Taking Antiretrovirals Regularly)

Debra A. Murphy, William D. Marelich, Neil B. Rappaport, Dannie Hoffman and Charles Farthing J Int Assoc Physicians AIDS Care (Chic III) 2007; 6; 113 DOI: 10.1177/1545109707301243

The online version of this article can be found at: http://jia.sagepub.com/cgi/content/abstract/6/2/113

Published by: SAGE Publications http://www.sagepublications.com

On behalf of: International Association of Physicians in AIDS Care

Additional services and information for Journal of the International Association of Physicians in AIDS Care (JIAPAC) can be found at:

Email Alerts: http://jia.sagepub.com/cgi/alerts

Subscriptions: http://jia.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Citations (this article cites 38 articles hosted on the SAGE Journals Online and HighWire Press platforms): http://jia.sagepub.com/cgi/content/abstract/6/2/113#BIBL

Results of an Antiretroviral Adherence Intervention: STAR (Staying Healthy: Taking Antiretrovirals Regularly)

Debra A. Murphy, PhD, William D. Marelich, PhD, Neil B. Rappaport, PhD, Dannie Hoffman, MA, and Charles Farthing, MD

A randomized 2-group medication adherence intervention is evaluated with HIV-infected adults (N = 141) assessed at baseline, 3-, and 9-month follow-ups. Cognitive (self-efficacy, behavioral intent), mental health (depression, well-being), and substance use indicators were the outcome measures. In addition, a posttest-only analysis from 3 to 9 months evaluates intervention impact on antiretroviral adherence, measured through Medication Event Monitoring System and pill counts. Compared to the standard care group, the intervention group showed significant increases in adherence self-efficacy and behavioral intent at 3 and 9 months and marginal improvements in mental health. Although the standard care group had higher adherence at 3 months (no baseline data were available prior to intervention), intervention group patients showed significant increases in adherence from 3 to 9 months. Although adherence levels achieved by intervention patients may not be sufficient for virological control, this is one of the first studies to provide promising results of longer term effectiveness of a behavioral adherence intervention.

Keywords: experimental design; sampling (experimental); human immunodeficiency virus; maintenance therapy; drug therapy

Adherence is defined as the extent to which a patient's health-related behaviors correspond with medical advice.¹ Over the past 3 decades, for many different diseases, noncompliance has been a significant problem for medical practice. So although adherence is not a new problem, the scope of the issues associated with adherence to highly active antiretroviral treatment (HAART) for HIV has not been seen before for other illnesses.

Nonadherence to antiretroviral therapy has been noted as one of the greatest public health challenges associated with the management of HIV/AIDS.² Even occasional nonadherence to antiretrovirals can have

DOI: 10.1177/1545109707301243 © 2007 Sage Publications Please visit the *Journal* at http://jiapac.sagepub.com. a major negative impact on the benefits of treatment. A decrease of 10% in adherence has been associated with a doubling of the HIV ribonucleic acid (RNA) level, suggesting that small differences in adherence can result in major differences in virological control.³ Consequently, even interventions that only increase adherence levels moderately could have important clinical significance for patients. Successful long-term treatment of HIV/AIDS requires at least 95% adherence to HAART to prevent emergence of drug-resistant HIV, which can lead to regimen failure and may also limit future therapy options.^{3,4} Therefore, HIV-infected patients are in the extremely difficult position of needing to strive for "perfect" (100%) adherence.

In addition to adherence being beneficial to patients, there are considerable public health benefits when HIV-infected patients meet adherence criteria. Poor adherence may engender public health concern given the potential for the rapid development of medication-resistant strains of HIV.³ This may have serious consequences for the public^{3,5} due to potential transmission of drug-resistant HIV by nonadherent patients, resulting in increased virulence of the mutated strains.

From Health Risk Reduction Projects, Integrated Substance Abuse Programs, Department of Psychiatry, University of California, Los Angeles (DAM, DH); Department of Psychology, California State University, Fullerton (WDM); Medical Psychology Associates, Atlanta GA (NBR); and AIDS Healthcare Foundation, Los Angeles CA (CF).

This study was supported by Grant # MH 59419 from the National Institute of Mental Health. We thank the participants in the research project. We also thank the intervention facilitators, Debra Norman, RN, and Chris LaBelle, PhD; the interviewers, Anita Guerrero, Claudia Perdomo, and Michael Magturo; the data manager, Jeremy Hunter; and the research assistant for this project, Tim Castro.

Correspondence: Debra A. Murphy, PhD, Health Risk Reduction Projects, Department of Psychiatry, UCLA, 11075 Santa Monica Blvd, Suite 200, Los Angeles, CA 90025-7539; e-mail: dmurphy@ mednet.ucla.edu. Studies of HAART adherence indicate that adherence is poor for adolescents, adult women, and adult men.^{3,6-9} For example, Roca, Gomez, and Arnedo¹⁰ found that after a median follow-up of 12 months, only 46% of patients showed adequate adherence. Adherence rates in HIV-positive adults have been found to range from approximately 20% to 70% or 80%, with rates likely to be lower with more complex combination therapies. The majority of studies have found adherence rates well below the necessary 95%, and a substantial proportion of HIV-infected patients do not achieve or sustain maximal reductions in viral load.¹¹

Interventions to assist patient adherence are urgently needed. In a 2002 review, Fogarty et al¹² reported on 16 HIV medication adherence interventions, only 5 of which were randomized clinical trials. Evidence of effectiveness was weak: 4 of the studies found no difference in adherence between treatment and control groups. The fifth study, a directly observed therapy intervention, found only temporary effects that ended when patients were no longer observed. In a later review article, Simoni, Frick, Pantalone, and Turner¹³ conducted an examination of 21 studies of antiretroviral adherence. The majority were feasibility or pilot studies without sufficient follow-up after the intervention to evaluate sustainability of effects, and many found no effects of the intervention. The encouraging evidence of the randomized control trials suggests that there might be some promise in cognitive-behavioral educational interventions based on self-efficacy theory, pharmacist-led individualized interventions, or a combination of cue-dose training and monetary reinforcement. However, even among studies that did find intervention effects, there were often only transient improvements.¹⁴

Findings from adherence interventions published since those reviews have also not been promising overall. For example, well-received reminder devices have not been found to affect adherence among HIVpositive women.¹⁵ In one of the larger studies (N = 174), which was a randomized trial of an intensive 10-session cognitive-behavioral stress management and expressive supportive therapy intervention, the intervention did not improve adherence.¹⁶ As Rigsby et al noted,¹⁷ no intervention has been shown to improve objectively verified adherence in a randomized controlled trial. The one exception is the recent study by Andrade et al, which showed a reminder device did lead to better adherence for HAART patients with memory impairment.¹⁸

The conceptual model for our intervention was based on social cognitive theory,¹⁹ which emphasizes the roles of outcome expectancies, self-efficacy beliefs, and

reinforcement for implementing behavioral change. The theory posits that behavior change requires: (1) accurate information to increase awareness and knowledge of health risks and benefits; (2) skills acquisition that allows for effective health behavior implementation; (3) development of self-efficacy, usually through observation of modeling, guided practice, and corrective feedback on skill performances; and (4) creation of supportive reinforcement for behavior change. The fields of behavioral medicine, health psychology, and health behavior change have given rise to social learning principles that have been used to assist in improving other health behaviors (eg, smoking cessation, cardiovascular risk reduction, management of chronic pain, reducing the conditioned negative effects of chemotherapy in the treatment of cancer, and risk reduction for obesity and substance use^{20,21}). Specific to medication adherence, behavior change strategies have been found to be successful in improving adherence.¹³ In addition, social support has been found to be related to adherence²² as has various psychosocial and mental health issues,6,11,12 and lower health literacy has been found to be associated with higher viral load.²³

In the current study, these 3-components behavior change strategies, social support, and simplified patient education information-were included in the intervention trial. Moreover, it is essential to place health psychology interventions in the general context of health care systems,²⁰ because psychological interventions complement and work in conjunction with biomedical interventions. Therefore, the intervention was interdisciplinary. Group facilitators consisted of a cognitive-behavioral psychologist and a nurse practitioner. It was hypothesized that patients assigned to the intervention condition would be more likely to be adherent to antiretroviral medications than those patients in the standard care condition (ie, control condition). It was also hypothesized that patients assigned to the intervention condition would report improved mental health and affective status, self-efficacy and behavioral intent for adherence, substance use, and levels of social support.

Method

Participants

A total of 141 individuals met the recruitment requirements and provided data for the current study. Participants were recruited from an HIV clinic through physician referral and flyers posted in clinic waiting rooms. Eligibility criteria were as follows: 18 years of age or over; HIV diagnosis; prescribed HAART; nonadherent to antiretroviral medication regimen; English-speaking; receiving care at AIDS Healthcare Foundation (AHF); CD4 count > 100; no opportunistic infections occurring 1 month prior to enrollment (CD4 count and opportunistic infection criteria recommended July 18, 2000, by Michael Samson, Los Angeles County Department of Health Services and faculty member at the 5P21/Rand Schrader Clinic; such criteria would include patients whose health was challenged by the chronic illness of HIV/AIDS but who could reasonably be expected to participate in an extended intervention and assessment study); no participation in any other medication adherence study; no current participation in a clinical trial; and no psychiatric condition (eg, schizophrenia, bipolar disorder especially if associated with delusions or hallucinations) that would make them unable to participate in a group experience, as assessed by the referring physician and/or their staffobserved interactions during enrollment and screening using the clinic's standard practice for such assessments.

In addition, participants had to miss medication doses at least once a week to be eligible. Nonadherence was established by (1) referral by a clinic physician as having adherence problems with HAART and (2) response to a screening instrument stating that each study participant skipped medications at least once a week.

Participants provided written informed consent for the study, including consent to medical record abstraction. Initial eligibility as to diagnosis, receipt of any medication currently listed in AMA guidelines as HAART, CD4 count, opportunistic infections, and participation in other studies were verified through chart abstraction. CD4 and HIV viral loads were performed, usually via Labcorp, on average, about every 3 months at the recruitment agency.

Assessment Procedures

Interviews were conducted at baseline; immediate postintervention; and 3, 9, and 15 months postintervention, using computer-assisted personal interviewing. For the current study, only the baseline and 3- and 9-month follow-up assessments were included; immediate postintervention was removed because it provided little information regarding long-term intervention effectiveness (preliminary findings generally showed increases postintervention), and 15-month follow-up was removed due to attrition. The interviews took about 75 minutes to complete. Participants were paid \$20 for each assessment interview and \$25 for each pill count/MEMS reading. Medical chart abstraction was conducted within 1 month of all assessment points to obtain viral load and CD4 counts.

Intervention Procedures

Computer-randomized numbers were used to assign participants to either the intervention or the standard care condition. Following randomization, baseline interviews were conducted. Ten groupings/waves of the cognitive-behavioral intervention to improve medication adherence were conducted. Waves consisted of 6 to 8 participants per condition and were mixed gender; when women were part of an intervention, at least 3 women were assigned to each condition for that wave. Standard care was the regular care provided by the clinic and consisted of addressing and monitoring adherence during all HIV primary care encounters, incorporation of adherence goals in all patient treatment plans, and increasing intensity of clinical monitoring and recruiting additional health team members for brief counseling when indicated.

The intervention sessions were led by a cognitivebehavioral psychologist and a nurse. Facilitators followed a detailed content and procedures manual for intervention delivery. Intervention participants attended a series of 5 weekly sessions and 4 later booster sessions. They were paid \$15 for each session attended.

Intervention Description

The five 90-minute intervention sessions were developed using a combination of behavioral and cognitive-behavioral techniques, as well as simplified patient information about HIV/AIDS and social support. Examples of cognitive-behavioral techniques were problem-solving strategies, communication skills development (eg, assertiveness skills to ask questions of a health care provider), and reframing/relabeling procedures; all cognitive-behavioral instruction included practice exercises (role-plays) with coaching provided by the facilitators. Behavioral strategies included simple reminder strategies, self-monitoring techniques, reinforcement strategies, and medication preparations systems. These techniques helped form the initial foundation of each participant's individualized adherence program (IAP). The main philosophical objective across sessions was to redefine each participant's IAP using their increased knowledge base, personal experiences (previous successes or failures), and adherence skills level. Full details of the intervention may be requested from the authors.

In addition to the 5 sessions, 4 one-hour booster sessions were scheduled for each group. Two weekly booster sessions, 1 week apart, were conducted at midpoint between the last intervention session and the 3-month follow-up assessment, and again at midpoint between the 3- and 9-month assessments. Boosters included review of the intervention and participant experiences since the last session, a *Jeopardy*-like adherence game, and continued review of barriers to adherence and problem solving.

Assessment: Adherence

Self-reported adherence to dose and schedule. Three measures of adherence to antiretroviral medications were obtained using the Adult AIDS Clinical Trials Group (AACTG) Adherence Baseline Questionnaire.²⁴ Respondents were asked to report the following for each of their antiretroviral medications: (1) name of drug, (2) prescribed doses per day, (3) prescribed number of pills per dose, and (4) any special instructions regarding food/liquid restrictions. Participants were then asked to state the number of pills and doses they took for each identified medication yesterday, the day before yesterday, and last Saturday.

Schedule for assessment of pill counts and MEMS. Adherence data were collected using the Medication Event Monitoring System (MEMS; Aardex USA, Union City, CA) and pill counts beginning 2 months postintervention. Subsequent measurement of these adherence measures corresponded with the 3- and 9-month follow-up assessment interviews.

Pill counts. Compliance measured by pill count is defined as the number of capsules dispensed per month minus the number of capsules remaining in the vial at month's end, divided by the number of capsules dispensed per month, $\times 100.^{25}$ Research and clinic staff developed a pill count schedule series (to be initiated after completion of the intervention sessions) that would measure adherence at monthly intervals to match the 3- and 9-month follow-up assessment interviews. Each "series" consisted of 3 counts: (1) a count 1 month before a follow-up assessment interview (to be used as a starting count), (2) a count at the assessment interview, and (3) a count 1 month after the assessment interview. For the current study, the counts used to derive adherence rates were the second and third pill counts at the 3-month assessment interview to ensure an adherence percentage for participants who missed the first count in this series, and the first and second counts at the 9-month assessment. Pill counts were completed at the clinic. In the rare circumstance when pill bottles were not brought in (the incentive paid to clients helped limit any missing counts), patients were rescheduled so counts could be performed.

Electronic monitoring of adherence. One month before the 3-month assessment interview, participants were given 1 or 2 types of electronic medication monitoring devices to monitor either their protease inhibitor or, in the absence of a protease inhibitor, a nucleoside reverse transcriptase inhibitor or nonnucleoside reverse transcriptase inhibitor. The first MEMS device was a medication bottle cap containing microelectronics that record each time the bottle is opened (child-resistant caps were provided to participants who requested them). The second device, called MINI-MEMS, was given to participants who reported using dosette boxes or multiple packaging of medication. The device was installed on mock vials, and participants agreed to open the mock vial every time they took a dose of the tracked medication. The MINI-MEMS was incorporated into the trial due to patient requests for continued use of pill boxes that assisted them with adherence, and the fact that previous studies have found that a large portion of patients report using pill boxes and removing more than one dose at a time.²⁶⁻²⁸

Participants were asked to bring their MEMS when they came in for pill counts, and readings were taken when pill counts were conducted. Internal circuitry permitted exclusion of multiple openings separated by 2 or fewer seconds and contains sufficient memory reserve to record up to 350 consecutive opening events, and data from the caps can be downloaded for analysis by microcomputer. Compliance was calculated as total openings (total openings per inter-visit interval/ total number of pills prescribed for the interval) × 100 and optimal intervals (number of inter-dose intervals corresponding to the near-optimal hours/total number of vial openings for the interval) × 100.²⁹

The MEMS provided a continuous, real-time measurement of adherence percentage by day and by dose. To match the 3- and 9-month assessment interview protocol of the study, adherence percentages were derived from cap readings taken at the 3- and 9-month assessment interview points (the 3-month MEMS reading was taken at the 3-month assessment interview, and the 9-month MEMS reading was taken 1 month after the 9-month assessment interview). To derive stable estimates, initial adherence percentages based on less than 20 days of monitoring were removed from the analysis (only 1 case was removed using this criterion, whose adherence percentage was based on only 1 day of monitoring).

Assessment: Mental Health Indicators and Affective Status

Mental health. The RAND Mental Health Inventory^{30,31} was administered as a measure of psychological distress

and well-being. The inventory has 5 factors (anxiety, depression, loss of behavioral/emotional control, general positive affect, and emotional ties) and 2 higher order factors (psychological well-being and psychological distress). For the current sample, internal consistency coefficients (Cronbach's α) for the 5 factors ranged from .75 to .92, and the correlation between the 2 higher order factors was –.68 (P<.01).

Depression. Depression was measured using the CES-D³²⁻³⁵; Internal consistency reliability (Cronbach's α) for this sample was .91.

Social support. Social support was measured using the Social Provisions Scale,³⁶ which assesses overall social support (Cronbach's $\alpha = .89$).

Health-related anxiety. A 4-item scale was administered to assess health-related anxiety over the past week.³⁷ This scale taps 4 domains that can be significantly affected by anxiety: sleep, appetite, social contact, and concentration at school or work (Cronbach's $\alpha = .84$).

Assessment: Cognitive Effects (Self-efficacy and Behavioral Intent)

Self-efficacy for adherence. A 25-item scale was created based on the AACTG adherence instruments²⁴ and was administered to assess patient self-efficacy to carry out important health-related behaviors. Items addressed issues on communication with clinical staff, sticking with the treatment schedule, and continuing with treatment and were scored on a 10-point scale (higher values indicate greater confidence; Cronbach's $\alpha = .94$).

Behavioral intent. A 5-item measure of behavioral intent was derived using guidelines for assessing behavioral determinants developed during the 1991 NIH Theorist's Workshop.³⁸ The measure explored intentions relative to adherence to dose, schedule, and special instructions for antiretroviral medications, and were rated on a 7-point scale (higher values indicate greater intent; Cronbach's $\alpha = .81$).

Assessment: Substance Use

The NIDA Risk Behavior Assessment Questionnaire³⁹ was used to determine frequency and level of alcohol and marijuana use in the past 3 months.

Study Design and Analyses

This study consists of 2 complementary designs. For the mental health, cognitive, and substance use assessments, a randomized pretest-posttest 2-group design with repeated assessments was used.⁴⁰ For the adherence measures (ie, pill count and MEMS cap), no pretest assessment was available, and self-report adherence was not validated by viral load.* Therefore, the design for the adherence measures reduced to a randomized 2-group design with repeated assessments,⁴⁰ also known as a randomized 2-group posttest-only design. All study patients were analyzed per their assigned randomized group—known as an "as randomized" or intent-to-treat analysis.

A description of the sample is presented first, followed by least square means and standard errors for all analysis variables (see Table 1). The model for the mental health, cognitive, and substance use variables was a 2 (group: intervention vs standard care) \times 3 (time: baseline, 3-month, 9-month) between-within design. Since pill count and MEMS cap data collection began 2 months into the study, only 2 points were used to assess change (at approximately 3 and 9 months). This model was a 2 (group: intervention vs standard care) \times 2 (time: 3-month vs 9-month) between-within design.

A mixed-model approach for repeated measures was employed to evaluate group differences using SAS Proc Mixed (Ver. 9.0), which uses an algorithm to retain cases where missing data are evident.⁴¹ Simple effects tests were performed on significant group-by-time interaction effects, focusing on within-group comparisons across time to evaluate growth or decline.⁴² Significant time effects were evaluated using paired *t* tests with a Bonferroni adjusted alpha level (P < .03) to protect against type I error.⁴³

One possible biasing factor in evaluating the group-by-time interaction effects is preexisting group differences, which, if evident, could explain significant findings. The t tests were performed examining preexisting group differences at the initial time points where any significant interactions were found. No significant findings at the .01 level were noted, which included baseline group comparisons for the randomized 2-group design and 3-month follow-up group comparisons for the 2-group posttest-only design used for adherence.

Results

Although 141 patients provided data for the current study, initially 184 were invited to participate. Of the initial 184, 15 refused to participate, and another 15 were ineligible: 52% had CD4 counts < 100; 20% did not meet nonadherence screening criteria; 7% were not prescribed HAART; 7% were participating

*Unlike the Medication Event Monitoring System and pillcount data, the self-report adherence measures were found to be unreliable at 3- and 9-month follow-up in conjunction with HIV biomedical markers and were subsequently dropped from analyses.

				up, I III 000				מה שווש	,			
		Bas	seline			3-Month	Follow-up			9-Month	Follow-up	
			626	é CI			95%	6 CI			95%	CI
	Ν	SE	Lower	Upper	Ν	SE	Lower	Upper	Ν	SE	Lower	Upper
MEMS cap measures Percentarie dose adherence												
Standard care	I	I	I	I	67.71	7.85	52.32	83.10	59.26	5.22	49.03	69.49
Intervention		I			55.17	8.24	39.02	71.32	70.35	5.35	59.86	80.84
Percentage days adherence												
Standard care		Ι			51.61	8.13	35.68	67.54	34.25	4.79	24.86	43.64
Intervention		I			42.53	8.53	25.81	59.25	46.14	4.91	36.52	55.76
Percentage pill-count adherence												
Standard care	I			I	87.94	3.96	80.18	95.70	69.25	5.35	58.76	79.74
Intervention		I			79.25	3.57	72.25	86.25	78.34	5.18	68.19	88.49
Mental health indicators												
Anxiety												
Standard care	25.29	1.05	23.23	27.35	24.08	1.32	21.49	26.67	22.70	1.38	20.00	25.40
Intervention	26.27	1.00	24.31	28.23	23.59	1.26	21.12	26.06	25.23	1.33	22.62	27.84
Depression												
Standard care	9.84	0.59	8.68	11.00	9.11	0.58	7.97	10.25	10.03	0.46	9.13	10.93
Intervention	9.65	0.56	8.55	10.75	10.05	0.56	8.95	11.15	10.97	0.44	10.11	11.83
Loss of behavioral/emotional control												
Standard care	21.13	0.99	19.19	23.07	19.44	0.98	17.52	21.36	18.39	1.05	16.33	20.45
Intervention	21.92	0.94	20.08	23.76	19.07	0.94	17.23	20.91	20.91	1.01	18.93	22.89
General positive affect												
Standard care	39.93	1.33	37.32	42.54	40.30	1.52	37.32	43.28	41.82	1.49	38.90	44.74
Intervention	37.76	1.26	35.29	40.23	41.66	1.45	38.82	44.50	39.71	1.44	36.89	42.53
Emotional ties												
Standard care	7.92	0.36	7.21	8.63	7.85	0.39	7.09	8.61	8.34	0.40	7.56	9.12
Intervention	7.75	0.34	7.08	8.42	8.23	0.38	7.49	8.97	7.66	0.39	6.90	8.42
Life satisfaction												
Standard care	4.03	0.17	3.70	4.36	4.26	0.21	3.85	4.67	4.46	0.17	4.13	4.79
Intervention	3.86	0.17	3.53	4.19	4.39	0.20	4.00	4.78	4.31	0.17	3.98	4.64
Psychological well-being												
Standard care	55.76	1.80	52.23	59.29	56.34	2.09	52.24	60.44	58.72	2.04	54.72	62.72
Intervention	52.88	1.71	49.53	56.23	58.13	2.00	54.21	62.05	55.21	1.97	51.35	59.07
Psychological distress												
Standard care	41.20	1.64	37.99	44.41	39.44	2.09	35.34	43.54	37.33	2.15	33.12	41.54
Intervention	43.42	1.55	40.38	46.46	38.86	1.99	34.96	42.76	41.12	2.07	37.06	45.18
Social Provisions Scale												
Standard care	72.92	1.34	70.29	75.55	75.52	1.56	72.46	78.58	79.05	1.47	76.17	81.93
Intervention	71.71	1.26	69.24	74.18	75.54	1.50	72.60	78.48	74.87	1.43	72.07	77.67

Table 1. Least Square Mean Estimates and Standard Errors for MEMS Cap. Pill Counts. Well-Being. and Intent by Group and Time

CES Depression total												
Standard care	37.56	1.52	34.58	40.54	35.74	1.62	32.56	38.92	35.16	1.69	31.85	38.47
Intervention	40.00	1.44	37.18	42.82	36.05	1.55	33.01	39.09	36.68	1.64	33.47	39.89
Health anxiety												
Standard care	7.62	0.48	6.68	8.56	7.35	0.52	6.33	8.37	7.60	0.55	6.52	8.68
Intervention	8.54	0.45	7.66	9.42	7.49	0.49	6.53	8.45	7.67	0.54	6.61	8.73
Alcohol/Drug use Alcohol												
Standard care	2.25	0.15	1.96	2.54	2.34	0.15	2.05	2.63	2.38	0.18	2.03	2.73
Intervention	2.36	0.14	2.09	2.63	2.18	0.15	1.89	2.47	2.07	0.18	1.72	2.42
Marijuana												
Standard care	0.99	0.18	0.64	1.34	1.00	0.21	0.59	1.41	0.99	0.21	0.58	1.40
Intervention	1.23	0.17	0.90	1.56	1.19	0.20	0.80	1.58	1.02	0.20	0.63	1.41
Cognitive effects (intent)												
Adherence efficacy												
Standard care	216.19	5.72	204.98	227.40	220.38	6.02	208.58	232.18	228.31	6.40	215.77	240.85
Intervention	203.26	5.42	192.64	213.88	226.87	5.77	215.56	238.18	224.46	6.18	212.35	236.57
Behavioral intent												
Standard care	32.27	0.54	31.21	33.32	31.81	0.58	30.67	32.95	32.61	0.47	31.69	33.53
Intervention	30.80	0.51	29.80	31.79	32.82	0.55	31.74	33.90	33.56	0.46	32.66	34.46
MEMS = Medication Event Monitoring {	System; CI = co	infidence ir	ıterval.									

Murphy et al

Variable	Time F (df), r	Group F (df), r	Time × Group Interaction, F(df), r
MEMS cap measures			
Percentage dose adherence	0.37 (1, 72), .07	0.01 (1, 72), .01	4.61 ⁺ (1, 72), .25
Percentage days adherence	1.57 (1, 72), .15	0.03 (1, 72), .02	3.64* (1, 72), .22
Percentage pill-count adherence	5.36 ^{tc} (1, 83), .25	0.00 (1, 83), .00	4.41 ⁺ (1, 83), .23
Mental health indicators			
RAND Mental Health Inventory			
Anxiety	4.14 ^{†a} (2, 139), .24	0.46 (1, 139), .06	1.76 (2, 139), .16
Depression	3.38 ^{†a} (2, 139), .22	0.85 (1, 139), .08	1.48 (2, 139), .14
Loss of behavioral/emotional control	7.75 ^{§a,b} (2, 139), .32	0.69 (1, 139), .07	2.46* (2, 139), .19
General positive affect	4.08 ^{†a} (2, 139), .24	0.33 (1, 139), .05	2.28* (2, 139), .18
Emotional ties	0.35 (2, 139), .07	0.13 (1, 139), .03	2.18 (2, 139), .17
Life satisfaction	5.83 ^{‡a,b} (2, 139), .28	0.09 (1, 139), .03	0.66 (2, 139), .10
Psychological well-being	4.04 ^{†a,b} (2, 139), .23	0.43 (1, 139), .06	2.39* (2, 139), .18
Psychological distress	4.62 ^{†a,b} (2, 139), .25	0.60 (1, 139), .07	1.69 (2, 139), .15
Social Provisions Scale total score	11.42 ^{§a,b} (2, 138), .38	1.28 (1, 138), .10	1.63 (2, 138), .15
CES Depression total score	5.18 ^{‡a,b} (2, 139), .26	0.59 (1, 139), .07	0.62 (2, 139), .09
Health anxiety	1.92 (2, 139), .16	0.46 (1, 139), .06	0.86 (2, 139), .11
Alcohol/Drug use			
Alcohol	0.80 (2, 139), .11	0.21 (1, 139), .04	1.50 (2, 139), .15
Marijuana	0.41 (2, 139), .08	0.40 (1, 139), .05	0.41 (2, 139), .08
Cognitive effects			
Adherence efficacy	8.38 ^{‡a,b} (2, 139), .33	0.26 (1, 139), .04	3.02 [†] (2, 139), .20
Behavioral intent	6.27 ^{‡b} (2, 139), .29	0.11 (1, 139), .03	4.72 [†] (2, 139), .25

Table 2. Main Effects, Interactions, and Effect Sizes of Group and Time (Baseline, 3- and 9-Month Follow-up) on Analysis Variables

MEMS = Medication Event Monitoring System; Effect sizes using Pearson's R.44

 $^{*}P < .10. ^{\dagger}P \le .05. ^{\ddagger}P < .01. ^{\$}P < .001.$

a. Baseline mean differs from 3-month follow-up mean (paired *t* test at P < .03).

b. Baseline mean differs from 9-month follow-up mean (paired *t* test at P < .03).

c. Three-month follow-up mean differs from 9-month follow-up mean (paired t test at P < .03).





in another adherence study; 7% were unable to comprehend enrollment process; and 7% were not receiving care at the research site. Of enrolled



Figure 2 Behavioral intent: Time × *Group interaction.* Note: Groups did not significantly differ at baseline at the .01 level.

patients, 13 did not provide data at either baseline or 3- or 9-month follow-up assessments. The final sample of 141 provided data at one or more of these time points for this study, with 74 patients allocated to the intervention and 67 receiving standard care.

The mean age of patients was 39.9 years (ranging from 26-59; SD = 7.05); 82.4% were male. Racial/ethnic composition was as follows: 47.9% Black/African American; 23.2% White/Caucasian; 19.0% Latino/ Hispanic; 4.2% mixed race/ethnicity; 1.4% Asian/ Pacific Islander; 2.1% American Indian/Alaskan Native; 2.2% were missing. Median monthly income was \$1000 (ranging from \$180-\$3000). The majority of the patients were not working (77.5%). Medical abstracts were used to obtain viral load and CD counts. Viral load (RNA copies per ml) at baseline was as follows: 39.4% had viral loads of 400 or less; 30.3% were in the 401 to 10 000 category; 13.4% were in the 10 001 to 50 000 category; 8.5% had viral loads of over 50000; viral load data were not available for 12 patients, or 8.5%. CD4 counts ranged from 94 to 1618 (M = 474.80, SD =295.9); CD4 count data were missing for 10 patients (7.0%). Regarding antiretroviral medication use, the most frequent medications used by patients were stavudine (52.3%), lamivudine (49.2%), nevirapine (37.5%), combivir (30.0%), and abacavir (28.1%). In addition, 5% of patients used the single pill 3-drug combination medication trizivir.

Medication Adherence

MEMS data and pill counts. Overall, by the 9-month follow-up assessment, dose adherence for the intervention group was 70% based on MEMS and 78% based on pill counts. The standard care group adherence level was 59% and 69%, respectively.

Repeated measures analyses show significant time main effects for percentage pill-count adherence, with a decline from 3-month to 9-month follow-up (see Table 2). Group-by-time interaction effects (the main interest of the analysis illustrating effects of the intervention) were noted for all adherence measures. Simple effects tests for the intervention group showed a significant increase in percentage dose adherence from 3-month to 9-month follow-up (simple effects F[1, 72] = 3.76, P =.05), but no change for the standard care group across time. A marginally significant (P = .06) group-by-time effect was noted for percentage days adherent, with a decline noted for the standard care group from 3month to 9-month follow-up (simple effects F[1, 72] =5.07, P = .02), and no change across time for the intervention group. Group-by-time effects were also noted for percentage pill-count adherence, with a decline noted for the standard care group from 3-month to 9-month follow-up (simple effects F[1, 83] = 9.22, P < .01), and no change for the intervention group. As noted earlier, no significant (P < .01) preexisting group

differences were evident at the 3-month follow-up assessment for any of the measures.

Mental Health, Cognitive, and Substance Use

Mental health indicators and affective status. Significant time main effects were noted for 7 of the 8 RAND Mental Health Inventory subscales, for Social Provision Scale total score, and for CES-Depression total score (see Table 2). No other significant effects (interaction or group effects) at the .05 level were noted. Post hoc comparisons revealed significant (P < .03) change from baseline to 3-month follow-up, and from baseline to 9-month follow-up for most measures. Measures associated with negative affect showed significant declines across time, whereas those related to positive affect showed increases. See Table 2 for specific time differences.

Self-efficacy for adherence and behavioral intent. Significant time main effects were noted for both measures (see Table 2). Post hoc comparisons on adherence selfefficacy showed significant increases from baseline to 3-month follow-up and from baseline to 9-month follow-up. For behavioral intent, a significant increase was noted only from baseline to 9-month follow-up.

Significant group-by-time interaction effects were also noted for both measures (see Figures 1 and 2). Simple effects tests on adherence self-efficacy for the intervention group showed significant differences (simple effects F[2, 139] = 10.16, P < .01) but no differences in the standard care group. Simple comparisons for the intervention group revealed increases in self-efficacy from baseline to 3-month follow-up (paired t[139] = 4.29, P < .01, and from baseline to 9-month follow-up (paired t[139] = 3.35, P < .01). For behavioral intent, simple effects tests revealed intervention group differences across time (simple effects F[2, 139] =10.77, P < .01) but no differences in the standard care group. Simple comparisons for the intervention group showed significant increases from baseline to 3-month follow-up (paired t[139] = 2.98, P < .01) and from baseline to 9-month follow-up (paired t[139] = 4.55, P < .01; see Figure 2). As noted earlier, no significant (P < .01)preexisting group differences were evident at the baseline on any of the measures.

Alcohol and marijuana use. No significant group, time, or interaction effects were noted.

Discussion

Many of the randomized adherence intervention studies conducted thus far have not even shown short-term significant effects,^{12,13} much less long-term intervention effects. For the current study, gains attributable to the intervention were shown on the cognitive attributes, with marginal improvements also noted on 3 of the RAND subscales addressing mental health. In addition, the intervention appears to have positively affected adherence levels, at least from the 3- to 9-month follow-up assessments (the time periods available for our adherence measures). Resulting effect sizes for the adherence findings approached a medium effect of .30 (see Table 2), indicative of moderate intervention influence.⁴⁴

Adherence self-efficacy and intent to adhere were both shown to be affected by the intervention. Compared to the standard care group, patients in the intervention condition at the 3-month follow-up assessment also had significant increases in self-efficacy for adherence and behavioral intentions to adhere, and these findings were sustained through the 9-month follow-up assessment. As noted in the introduction, the conceptual model for our intervention was based on social cognitive theory,¹⁹ which emphasizes the roles of self-efficacy beliefs. In this model, behavior change requires development of self-efficacy, which is acquired though observation of modeling, guided practice, and corrective feedback on skill performances-all of which were utilized throughout the intervention sessions. In turn, perceived self-efficacy is a major determinant of behavioral intention. Efficacy beliefs affect performance both directly and by influencing intentions.¹⁹

Beyond the impact of the intervention, the overall adherence levels reached or maintained by the patients in the intervention were still not sufficient for virologic control. Successful long-term treatment of HIV/AIDS requires at least 95% adherence to HAART to prevent emergence of drug-resistant HIV, although more recent and potent regimens are yielding better viral suppression at moderate adherence levels.45 At 9-month follow-up assessment, the intervention group had an average adherence rate of 70% based on MEMS data (29% were 95% adherent or higher, compared to only 7.5% of the standard care group) and 78% based on pill counts. It is clear from the studies conducted thus far, including this study, that adherence to HIV antiretrovirals is an extremely difficult target for behavior change.

One strength of this study is that this sample was fairly representative of the typical patients seen in all the AIDS health care facilities throughout greater Los Angeles in terms of age, sex, ethnicity, and socioeconomic status. However, there are a number of limitations that should be considered for this study. The first is that there currently is not an acknowledged "gold standard" measure of adherence—each adherence measure has both assets and liabilities, and each method measures a different aspect of adherence.⁴⁶ Therefore, multiple measures have been considered the most effective means for evaluating adherence.⁴⁷ In some studies, MEMS has been selected as the most informative of the methods,^{46,48} and that appears to be the case in this study. Yet patients participating in research using MEMS devices may actually experience declines in adherence since their typical delivery system (eg, pillboxes) has been replaced by such electronic monitoring devices⁴⁹ and may also suffer from high study dropout rates.⁴⁸ Whether such factors influenced the current study findings is unknown.

Second, the study design for the MEMS and pillcount adherence measures would have been stronger if measurements had been taken at baseline-unfortunately, various constrictions limited our ability to make such assessments. A third limitation is that some patients missed scheduled appointments for pill counts or forgot to bring their pills. This may not have been random, and the most noncompliant patients might have purposely missed appointments or forgotten to bring their pills. Another caveat is that the generalizability of the study results to "like" populations may be problematic given (a) patients were paid to participate in the study, thus calling into question whether the intervention could be successfully implemented with patients not monetarily rewarded; and (b) those with a psychiatric diagnosis were excluded from study participation-given the cognitive change features of the intervention, it is possible the intervention would not be successful with such diagnosed patients.

In conclusion, as best as we can ascertain, the behavioral and cognitive behavioral strategies appeared to be the strongest component of this intervention in terms of driving adherence maintenance among the intervention group. Therefore, future studies need to incorporate strong behavioral and cognitive-behavioral skills training at perhaps a higher intensity than delivered through this intervention (dosage intensity was not varied within the current study, nor could dose effects be evaluated in terms of sessions attended because the majority of patients [68%] attended 3 to 5 sessions). In addition, methods of delivery to reduce attrition may be investigated. For example, delivering the intervention requiring fewer but longer "workshop-style" sessions may mean more patients receive a higher dosage of the intervention because they have to attend fewer sessions. However, longer sessions would allow less time for patients to work through behavioral homework assignments in their natural settings.

In clinical settings, the implications from this study would suggest that providers may want to assess patients' self-efficacy for treatment adherence early in the process of prescribing antiretrovirals, as this will assist providers in determining how likely it is their patients will be successful. Patients with low self-efficacy may need to be referred for case management services that could focus on adherence intervention. In addition, providers who work to improve patients' self-efficacy for adherence may assist those patients in improving their ability to stick with their treatment regimen.

References

- Eldred L. Adherence in the era of protease inhibitors (The Hopkins HIV Report, July 1997). 1997. Available at: http:// hopkins-aids.edu/publications/report/jul97_4.html. Accessed August 18, 2004.
- Kennedy SB. Developing a self-administered tool to predict adherence to antiretroviral therapy: design, method, and objectives. *AIDS Patient Care STDS*. 2000;14:309-316.
- Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*. 2000; 14:357-366.
- 4. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA*. 1999;282:1135-1141.
- Friedland GH, Williams A. Attaining higher goals in HIV treatment: the central importance of adherence. *AIDS*. 1999; 13(suppl 1):S61-S72.
- Catz SL, Kelly JA, Bogart LM, Benotsch EG, McAuliffe TL. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychol.* 2000;19:124-133.
- Murphy DA, Greenwell L, Hoffman D. Factors associated with antiretroviral adherence among HIV-infected women with children. *Women Health.* 2002;36:97-111.
- Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort. *AIDS Care.* 2001;13:27-40.
- Nieuwkerk PT, Sprangers MA, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Arch Intern Med.* 2001;161:1962-1968.
- Roca B, Gomez CJ, Arnedo A. Adherence, side effects and efficacy of stavudine plus lamivudine plus nelfinavir in treatmentexperienced HIV-infected patients. *J Infect.* 2000;41:50-54.
- Chesney M. Adherence to HAART regimens. AIDS Patient Care STDs. 2003;17:169-177.
- Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Educ Counsel.* 2002;46:93-108.
- Simoni JM, Frick PA, Pantalone DW, Turner BJ. Antiretroviral adherence interventions: a review of current literature and ongoing studies. *Top HIV Med.* 2003;11:185-198.
- Sorensen JL, Mascovich A, Wall TL, DePhilippis D, Batki SL, Chesney M. Medication adherence strategies for drug abusers with HIV/AIDS. *AIDS Care*. 1998;10:297-312.
- Powell-Cope GM, White J, Henkelman EJ, Turner BJ. Qualitative and quantitative assessments of HAART adherence of substance-abusing women. *AIDS Care.* 2003;15:239-249.
- Jones DL, Ishii M, LaPerriere A, et al. Influencing medication adherence among women with AIDS. *AIDS Care.* 2003;15:463-474.
- 17. Rigsby MO, Rosen MI, Beauvais JE, et al. Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. *J Gen Intern Med.* 2000;15:841-847.

- Andrade AS, McGruder HF, Wu AW, et al. A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment. *Clin Infect Dis.* 2005;41:875-882.
- Bandura A. Self-Efficacy: The Exercise of Control. New York: W. H. Freeman; 1997.
- Compas BE, Haaga DAF, Keefe FJ, Leitenberg H, Williams DA. Sampling of empirically supported psychological treatments from health psychology: smoking, chronic pain, cancer, and bulimia nervosa. *J Consult Clin Psychol.* 1998;66:89-112.
- Kelly JA. Changing HIV Risk Behavior: Practical Strategies. New York: Guilford; 1995.
- Bloom JR. The relationship of social support and health. Soc Sci Med. 1990;30:635-637.
- Kalichman SC, Benotsch E, Suarez T, Catz S, Miller J, Rompa D. Health literacy and health-related knowledge among persons living with HIV/AIDS. *Am J Prev Med.* 2000;18:325-331.
- 24. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among patients in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care*. 2000;12:255-266.
- Geletko SM, Segarra M, Ravin DS, Babich MP. Zidovudine compliance as measured by different methods in an HIV ambulatory clinic. *J Pharmacol Technol.* 1996;12:105-108.
- Bova CA, Fennie KP, Knafl GJ, Dieckhaus KD, Watrous E, Williams AB. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. *AIDS Behav.* 2005;9:103-110.
- Samet JH, Sullivan LM, Traphagen ET, Ickovics JR. Measuring adherence among HIV-infected persons: is MEMS consummate technology? *AIDS Behav.* 2001;5:21-30.
- Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. *Ann Pharmacother.* 2001;35:1010-1015.
- Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Improved compliance measures: applications in an ambulatory hypertensive drug trial. *Clin Pharmacol Ther.* 1990;48:676-685.
- Stewart AL, Ware JE Jr, Sherbourne CD, Wells KB. Psychological distress/well-being and cognitive functioning measures. In: Stewart AL, Ware JE Jr, eds. *Measuring Functioning and Well Being: The Medical Outcomes Study Approach*. Durham, NC: Duke University Press; 1992:102-142.
- Ware JE Jr, Davies-Avery A, Brook RH. Conceptualization and Measurement of Health for Adults in the Health Insurance Study: Vol. VI. Analysis of Relationships Among Health Status Measures. Santa Monica, CA: RAND Corporation; 1980.
- Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977;1:385-401.
- Cockram A, Judd FK, Mijch A, Norman T. The evaluation of depression in inpatients with HIV disease. *Aust N ZJ Psychiatry*. 1999;33:344-352.
- Lyketsos CG, Hoover DR, Guccione M, et al. Changes in depressive symptoms as AIDS develops. *Am J Psychiatry*. 1996;153: 1430-1437.
- Revicki DA, Chan K, Gevirtz F. Discriminant validity of the medical outcomes study cognitive function scale in HIV disease patients. *Qual Life Res.* 1998;7:551-559.
- Cutrona CE, Russell DW. The provisions of social relationships and adaptation to stress. In: Jones WH, Perlman D, eds. *Advances in Personal Relationships*. Greenwich, CT: JAI; 1987:37-67.
- Murphy DA, Moscicki AB, Vermund SH, Muenz LR. Psychological distress among HIV+ adolescents in the REACH

study: effects of life stress, social support and coping. J Adolesc Health. 2000;27:391-398.

- Fishbein M, Bandura A, Triandis HC, Kanfer FH, Becker MH, Middlestadt SE. Factors Influencing Behavior and Behavior Change. Report From the Theorist's Workshop, Washington DC, October 3-5, 1991. Bethesda, MD: National Institute of Mental Health; 1991.
- National Institute on Drug Abuse Community Research Branch. Training Manual for Administering and Coding the Risk Behavior Assessment (RBA) Questionnaire. Bethesda, MD: Author; 1991.
- 40. Hoyle RH, Harris MJ, Judd CM. *Research Methods in Social Relations*. 7th ed. Pacific Grove, CA: Wadsworth; 2002.
- Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. SAS for Mixed Models. 2nd ed. Cary, NC: SAS Institute; 2006.
- 42. Winer BJ. Statistical Principles in Experimental Design. 2nd ed. New York: McGraw-Hill; 1971.
- Maxwell SE. Pairwise multiple comparisons in repeated measures designs. *J Educ Stat.* 1980;5:269-287.

- 44. Cohen J. A power primer. Psychol Bull. 1992;112:155-159.
- 45. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis.* 2006;43:939-941.
- 46. Wall TL, Sorensen JL, Batki SL, Delucchi KL, London JA, Chesney MA. Adherence to zidovudine (AZT) among HIVinfected methadone patients: a pilot study of supervised therapy and dispensing compared to usual care. *Drug Alcohol Depend.* 1995;37:261-269.
- Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med.* 2001;134:968-977.
- 48. Deschamps AE, Graeve VD, van Wijngaerden E, et al. Prevalence and correlates of nonadherence to antiretroviral therapy in a population of HIV patients using medication event monitoring system. *AIDS Patient Care STDS*. 2005;19:833-839.
- Kalichman SC, Demetria C, Cherry C, Kalichman M, Pope H. Pillboxes and antiretroviral adherence: prevalence of use, perceived benefits, and implications for electronic medication monitoring devices. *AIDS Patient Care STDS*. 2005;19:833-839.