

Test of a Web-Based Program to Improve Adherence to HIV Medications

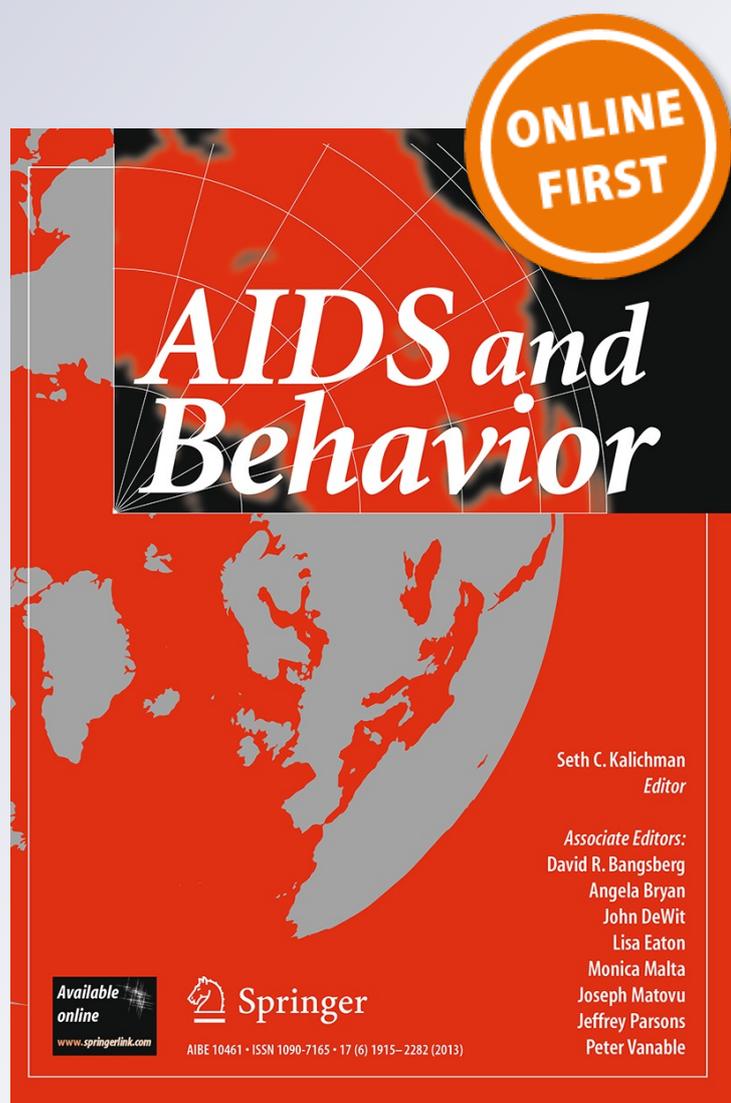
**Rebekah K. Hersch, Royer F. Cook,
Douglas W. Billings, Seth Kaplan, David
Murray, Steven Safren, Justin Goforth &
Joy Spencer**

AIDS and Behavior

ISSN 1090-7165

AIDS Behav

DOI 10.1007/s10461-013-0535-8



Your article is protected by copyright and all rights are held exclusively by Springer Science +Business Media New York. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at link.springer.com".

Test of a Web-Based Program to Improve Adherence to HIV Medications

Rebekah K. Hersch · Royer F. Cook · Douglas W. Billings ·
Seth Kaplan · David Murray · Steven Safren ·
Justin Goforth · Joy Spencer

© Springer Science+Business Media New York 2013

Abstract We evaluated the effectiveness of a web-based version of the Life-Steps intervention combined with modules for stress reduction and mood management, designed to improve medication adherence among HIV infected individuals. 168 HIV+ adults were randomized into either the Life-Steps program or a waitlist control condition. All participants completed a baseline assessment and provided a 2-week electronic pill (MEMS) cap baseline reading. Follow up data collection was conducted at 3, 6 and 9 months. Patients in the web-based Life-Steps condition had significantly higher antiretroviral medica-

tion adherence rates than patients in the control group over the nine-month period as measured by the MEMS cap. In addition, analysis of viral load data indicated that the program also resulted in a significant decrease in viral load. These findings indicate that a web-based Life-Steps program can be a useful and implementable tool for helping patients living with HIV maintain medication adherence.

Resumen Evaluamos la eficacia de una intervención de la versión de Life-Steps basada en el internet, combinada con módulos para la reducción del estrés y manejo de estados de comportamiento, diseñada para mejorar la adherencia a medicamentos entre personas viviendo con VIH. 168 personas viviendo con VIH fueron aleatorizadas al programa Life-Steps o a un grupo de control en lista de espera. Todos los participantes completaron una evaluación inicial y proporcionaron una referencia de los resultados de una prueba de dos semanas del sistema electrónico de monitoreo de medicamentos (MEMS) ubicado en la tapa del frasco de pastillas. Se recopilaron datos subsiguientes a los 3, 6 y 9 meses. Los pacientes asignados a la condición de Life-Steps tenían índices de adherencia al medicamento antirretroviral significativamente mayor que los pacientes en el grupo control durante el periodo de nueve meses de acuerdo al registro del sistema electrónico de monitoreo. Además, cuando se analizaron los datos de la carga viral se observó que el programa también resultó en una disminución significativa de la carga viral. Estos resultados indican que el programa Life-Steps puede ser una herramienta útil y aplicable para ayudar a las personas viviendo con VIH a mantener adherencia a sus medicamentos.

The research which served as the basis of this paper was conducted prior to Dr. David Murray's employment at NIH.

R. K. Hersch (✉) · R. F. Cook · D. W. Billings · J. Spencer
ISA Associates, Inc., 201 North Union Street, Suite 330,
Alexandria, VA 22304, USA
e-mail: rhersch@isagroup.com

S. Kaplan
Department of Psychology, George Mason University,
Fairfax, VA, USA

D. Murray
Division of Epidemiology, Statistics, and Prevention Research,
Eunice Kennedy Shriver National Institute of Child Health and
Human Development, National Institutes of Health, Rockville,
MD, USA

S. Safren
Massachusetts General Hospital, Harvard Medical School,
Boston, MA, USA

J. Goforth
Whitman Walker Health, Washington, DC, USA

Keywords Medication adherence · Web-based program ·
ART · Antiretroviral therapy

Introduction

With the advent of antiretroviral (ARV) medications, significant numbers of HIV+ individuals are living prolonged and healthier lives [1–3]. Treatment with ARV drugs, typically a combination of medications, leads to reductions in viral load, greater immune system function, and less likelihood of clinical immune deficiency in patients with HIV infection [4–6]. However, the effectiveness of ARV medications is wholly dependent on adherence to prescribed medication regimens. Poor adherence to ARV medications decreases the benefits of the medications as well as the chances of prolonged survival [7].

Unfortunately, the nature of HIV medication regimens can make adherence especially difficult. ARV medications may require different dosing schedules, different food intake patterns and different storage requirements. Many ARV medications cause side effects, which may necessitate further medication [2, 4–6, 8]. Because adherence can be threatened by stress, negative mood states, and drug use [1, 9], recent recommendations have underscored the importance of developing adherence interventions that also address stress, mood states and substance use [1, 3, 10, 11].

Despite the challenges of HIV medication adherence, considerable strides have been made toward solutions, and adherence strategies for HIV medications have demonstrated efficacy. More than a decade ago, Safren and his colleagues [2, 3, 12–14], developed Life-Steps, a single-session cognitive-behavioral HIV medication adherence program. Recently, Safren and his associates conducted a randomized controlled trial of an in-person cognitive behavioral therapy for adherence and depression for HIV infected individuals, an intervention that included many of the major elements of the Life-Steps program, and found that the intervention group showed greater improvements in both adherence and depression [10].

In-person medication adherence interventions, however, may present challenges with respect to efficiency and scalability. Such interventions require a significant allocation of resources to sufficiently train professional staff in the intervention procedures and further staff time for the delivery of the intervention across multiple sessions [15]. Computer technology offers a potential solution to the problems of efficiency and scalability, as several studies have demonstrated that computer-based interventions can produce positive changes in health behavior across a variety of domains [16–18]. Moreover, meta-analytic research has indicated that computer-based interventions promoting ARV medication adherence compare favorably to those involving substantial application of human resources [19]. Recently, a study of the efficacy of LifeWindows, a computer-based ARV adherence intervention, showed some support for the utility of the LifeWindows

program in promoting ARV adherence, although program effects were not especially strong [20].

The current study involved the construction of a web-based adaptation of the Life-Steps intervention, combining it with an evidence-based web-based stress and mood management program [21], and testing it in a randomized controlled trial with HIV+ individuals to evaluate its effects on medication adherence and related outcomes.

Methods

Participants

Study participants were HIV+ patients at a large urban health clinic. The clinic staff identified a pool of eligible patients based on the following inclusion criteria: HIV+, prescribed antiretroviral medication, not actively engaged in the clinic's medication adherence case management program for at least 6 months, having a detectable viral load (defined as >48), and not diagnosed with any mental disorder. We originally planned to use a viral load of >400 as the inclusion criterion as that was, until recent changes in the sensitivity of the HIV test, the threshold considered to be "undetectable" and the cut off used by Fisher et al. [20]. However, use of that criterion yielded a very small pool of potential applicants. After meeting with the clinic staff, we changed the inclusion criterion to a viral load of >48 as a proxy for non-adherence as that was the level that at the time was above the threshold for detectable levels of the HIV virus. That yielded a much larger pool of potential applicants. Participation was voluntary and all protocols and procedures were approved by the ISA Associates, Inc. Institutional Review Board.

Procedures

Letters were sent to all eligible participants from the clinic informing them about the study and asking them to call the on-site Research Assistant (RA) if they were interested in participating. Participant eligibility was verified when a patient called the on-site RA. Participants were informed that they would be asked to complete a confidential survey at four points in time and use the Medication Event Monitoring System (MEMS), an electronic pill cap. In addition, they were informed that half the participants would be randomly selected to use a new medication adherence program after the first survey and half would be able to use the program after the last survey. Finally, participants were informed that they would receive up to \$130 for completing all four surveys (\$20 each for the first survey and baseline MEMS reading, \$25, \$30, and \$35 for each subsequent survey).

Patients interested in participating were asked to come into the clinic to complete informed consent procedures and their first survey. For the first survey, the RA completed the first set of questions (regarding the ARV medications that participants were taking) with the participant on the computer. If the participant was able, he or she then completed the remainder of the survey. If needed (for example, if participants were not comfortable using a computer), the RA completed the survey with them. One hundred and seventy eight (178) participants completed the baseline survey.

Once the survey was completed, the RA explained how to use the MEMS caps for ARV medication. If participants were taking more than one ARV, they were asked to use the MEMS cap with the medication they found most difficult to take as prescribed. Participants were instructed to use the cap for 2 weeks and then return to the clinic to have the cap read. This 2-week period constituted the baseline period for the MEMS data.

After participants returned for their baseline MEMS reading, they were randomly assigned to either the program condition or the wait-list control condition. Of the 178 baseline survey participants (see Fig. 1), 168 returned after the 2 week baseline MEMS data collection and were

randomly assigned to the program condition (89) or the control condition (79). Four participants subsequently withdrew from the study after being randomly assigned (two from the program group and two from the control group).

Participants assigned to the program condition were given information about how to access the web-based program, *Life-Steps for Managing Medication and Stress*. Participants who did not have access to a computer were provided access to the program at the clinic. Twenty-eight participants used the program at the clinic and there were no differences between those who accessed the program at the clinic and those that accessed the program outside of the clinic with regard to adherence at baseline. For those that accessed the program outside of the clinic, there was no additional information regarding where the program was accessed. Program utilization was tracked for all participants. The RA contacted participants in the program condition to remind them to use the program if they were not completing program modules.

At 3, 6 and 9 months after baseline data collection, all participants were asked to again complete the survey and provide MEMS data. The RA was available at the clinic throughout the study to assist participants with the follow

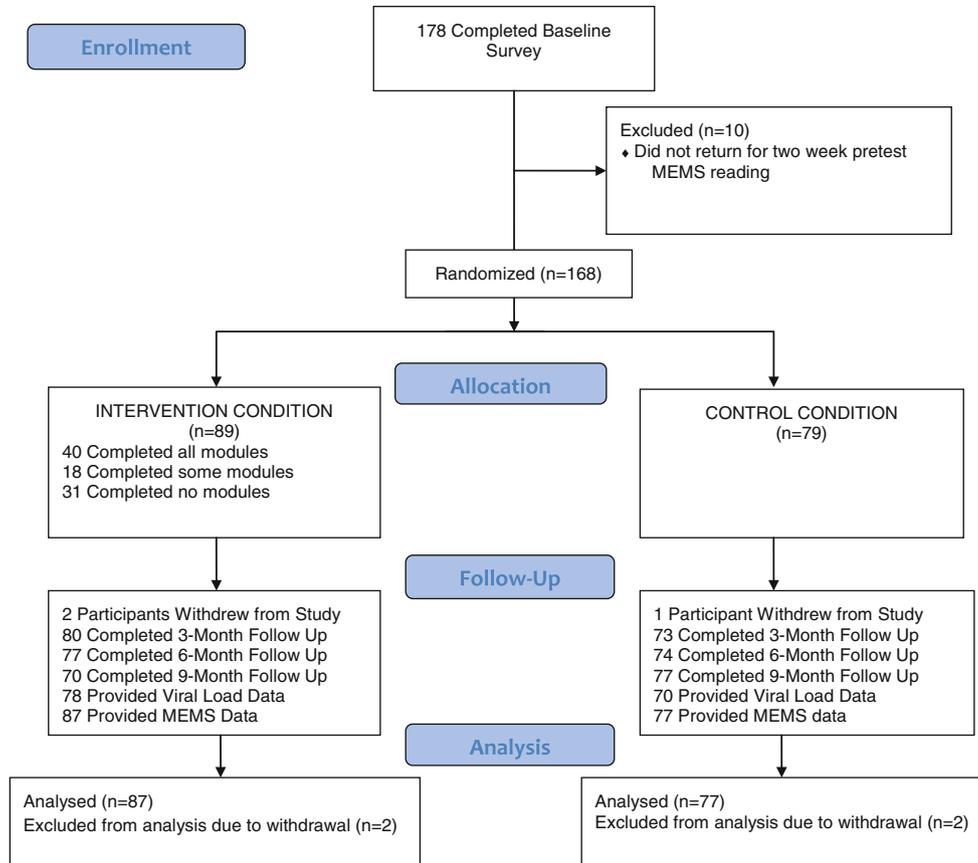


Fig. 1 CONSORT participant flow diagram

up surveys and provide in-person and telephonic technical assistance for participants using the program. Participants were allowed to complete later surveys even if the previous survey was not completed. The MEMS cap recorded continually throughout the study period so MEMS data could be obtained for the entire study period even if the participant only completed the baseline and fourth surveys.

Life-Steps Intervention

ISA staff created the web-based *Life-Steps for Managing Medications and Stress* (www.lifestepsforhealth.com) program, with assistance from Steven Safren, chief creator of the in-person CBT-AD program on which the web-based program was based, and from our software development partner, the Redmon Group. The web-based program is based on ISA's Stress and Mood Management program [21] and Safren's in-person CBT-AD program, which contained the Life-Steps medication adherence program [9]. The program is fully audio narrated and includes video vignettes and other interactive elements. The program includes six major sections: (1) Welcome and Introduction, (2) Life-Steps Medication Adherence, (3) Stress and HIV, (4) Assess Your Stress, (5) Stress Management Strategies, and (6) Resources. As part of the program, participants interact with an in-program "clinician." Photos of the clinician, along with text and audio are designed to simulate clinician-patient interactions as topics are covered. The medication adherence modules parallel Safren's Life-Steps program, presenting nine informational, problem-solving and cognitive-behavioral steps, as briefly described below. After reviewing Safren's CBT-AD manual, ISA staff developed storyboards for the web-based adaptation of the Life-Steps modules. Dr. Safren reviewed the storyboard material and a Beta version of the web-based program. An outline of the complete program is shown in Table 1. Detailed content of each segment may be found in the article on Life-Steps [12].

1. *Understanding Medication Adherence.* This section introduces the concept that medication adherence is a skill that requires some practice and includes an interactive exercise that asks users their thoughts about adherence and obstacles to adherence. Users complete the understanding adherence form to ensure that they understand the importance of medication adherence and come up with a personalized adherence plan. Participants are also introduced to the problem-solving approach that is used in other sections of the program. As is true throughout the program, testimonials from real people who are taking antiretroviral medications are included.
2. *Getting to Appointments.* The problem-solving approach is used to help patients identify and work through any

problems associated with getting to appointments with their health care providers. The Getting to Appointments interactive form helps users understand and overcome obstacles to getting to their appointments in order to ensure that they continue to take their medications as prescribed.

3. *Communicating with Your Treatment Team.* This segment focuses on the collaborative nature of the doctor-patient relationship, explaining that, although some people may feel uncomfortable asking questions of their doctor, it is important that all their questions be answered to ensure that they continue taking their medications as prescribed. This section includes video interactive practice exercises on assertive communication along with a Communication Plan form to be completed and used in subsequent doctor visits.
4. *Coping with Side Effects.* This segment begins by establishing that all antiretroviral medications have side effects and provides exercises to help the user identify and come up with a plan to cope with any negative side effects that might lead to the discontinuation of medication.
5. *Obtaining Medications.* This segment explains that just obtaining medications can be a deterrent to adherence. Users are encouraged to think about any personal obstacles to obtaining medications, (e.g. forgetting to refill prescription, stigma, transportation to pharmacy, etc.) and complete an exercise to come up with concrete plans for overcoming personal obstacles.
6. *Your Daily Medication Schedule.* An interactive, printable daily schedule form is presented and completed to help the user identify daily activities that can enhance treatment and ensure that taking medications is included in those activities.
7. *Storing Medications.* This segment presents examples of storage methods (e.g. pillboxes) that promote adherence.
8. *Cue Control Strategies.* The importance of using cues as reminders to take medications is emphasized in this segment. The main purposes of the cues are discussed: (1) as a memory aid and (2) as a cognitive reframe regarding taking medications.
9. *Handling Slips.* Users are presented with guidance on how to respond if they forget to take their medications, emphasizing the importance of getting back on track and not simply stopping medications if they feel better or decide they don't want to take them anymore.

Following the module on HIV medication adherence, there are three modules based on the Stress and Mood Management program ("Stress and HIV," "Assess Your Stress," and "Stress Management Strategies"). The program modules were modified to be specifically relevant to individuals who are HIV+. In addition, each of the sections

includes a review of the medication adherence information. Table 1 contains the structure and content of the full Life-Steps for Managing Medications and Stress program.

Measures

The primary outcome measure for the study was based on data collected through the use of an electronic pill cap, the MEMS® 6 Medication Event Monitoring System (AARDEX) or (MEMS). We also collected viral load data and self-reports on medication adherence and self-efficacy, stress and mood, and substance use as secondary measures.

Electronic Pill Cap (MEMS)

Each participant in the study was given a MEMS cap and a pill bottle designed to hold one antiretroviral medication. As noted in the procedures, participants were asked to use the MEMS cap and bottle with their antiretroviral medication or, if they were taking >1 antiretroviral medication, with the antiretroviral medication that they had the most difficulty taking as prescribed. Prior to giving the MEMS cap and bottle to the participant, the RA recorded the medication name and number of doses per day prescribed in the MEMS software system. The data were collected continuously throughout the study period, and the MEMS caps were read

Table 1 Life steps for managing medications and stress program outline

Welcome and introduction	Stress management strategies
Opening	Medication adherence review
About the program	Avoid negative coping
Life steps for medication adherence	The trap
Understanding medication adherence	The drug trap
Communicating with your treatment team	Alcohol—a legal drug
Getting to appointments	Self-assessment
Coping with side-effects	Positive alternatives
Obtaining medications	Tips for cutting down
Formulating a daily schedule	Managing occasional social drinking
Using cue control strategies	Build a healthy lifestyle
Handling slips	Make positive choices
Review	Introduction
Stress and HIV	Adopt mental strategies
Medication adherence review	The mental lens
HIV-stress relationship	Choosing optimism
The stress response	Optimism v pessimism
This thing called stress	Avoid negative thinking
Primitive versus modern	Changing negative thinking
Fight or flight	Embrace positive thinking
A vicious cycle	Finding humor
What next?	Stress hardiness
Assess your stress	Adopt behavioral strategies
Medication adherence review	Physical activity
Assess your stress	Stress emergencies
Introduction	Relaxation practices
Self-assessment	Breathwork
Identify stressors	Progressive relaxation
Introduction	Guided imagery
Stress symptoms	Meditation
Recognize symptoms of stress	Social support
Identify personal stressors	Time management
What's next?	Take charge!
	Take charge at work!
	Take charge at home!
	Go for it!

and the data downloaded to the software program each time the participant came into the clinic to complete the survey. Adherence scores were calculated by dividing the number of doses taken by the number of doses prescribed for a specified period corresponding to baseline, 3-, 6-, and 9-months. We did not adjust for “pocketed” doses or doses removed from the pill box, but not taken. Five participants reported a problem with their MEMS cap or that the cap was lost or stolen. In each of those cases, the cap was replaced and the missing time period recorded as missing data.

Viral Load

Although the primary focus was on the MEMS results, viral load data also were available for 148 participants, and therefore viral load was examined as a secondary outcome. Viral load data were obtained for all patients who took a viral load test as part of routine medical treatment (not specifically for the study) during the study period, July 2010 through October 2011. We obtained the results for every viral load test that participants took during the study period. Viral load is reported as the number of copies of the HIV virus in 1 ml of blood. Viral load can range from “undetectable,” typically defined as <48 or <20 depending on the test, to over one million.

Self-Report Measures

The self-reported survey included the following measures and content areas:

Self-Reported Adherence Self-reported adherence was measured using the AIDS Clinical Trials Group (ACTG) Adherence Measure [22]. The measure asks participants to list all the HIV medications they are prescribed along with the number of pills each dose and the number of doses per day. The measure then asks how many *doses* were missed “yesterday,” “2 days ago,” “3 days ago,” and “4 days ago.” Additional questions about the medication regimen are also asked (e.g. “In the past 4 days, how many days did you miss taking all of your medication?”). Finally, the measure includes a question about how often participants missed taking their medication for specific reasons (e.g. “forgot,” “had too many pills to take,” “wanted to avoid side effects,” etc.) on a four-point scale from never to often.

Medication Adherence Self-Efficacy Medication adherence self-efficacy was assessed with the Self-Efficacy for Appropriate Medication Use Scale (SEAMS), a 13-item scale developed and validated by Risser and associates [23]. The measure asks participants to indicate their confidence for taking medications correctly in a number of different situations (e.g. When you have a busy day planned) using a

3-point scale. The measure has shown good test–retest and internal consistency reliability ($\alpha = 0.89$) and performed similarly across literacy levels in previous studies.

Symptoms of Stress The behavioral and physical aspects of stress were assessed with the symptoms of distress scale. Four items assessing the behavioral signs of stress (e.g. overeating, criticizing others) are combined with four items assessing the physical signs of stress (e.g. muscle tension, headache; $\alpha = 0.69$). Participants respond on a 4-point scale how often they felt each stress symptom during the past 30 days. This measure has been used in several studies by our team, including the recent RCT of the web-based Stress and Mood Management program, which found significant effects of the program on the measure [21].

HIV-Specific Stress Stress related specifically to living with HIV was measured with the HIV/AIDS Stress Scale, a 23-item measure with subscales covering three major types of stress related to HIV—social stress, instrumental stress and emotional/existential stress [24]. The measure asks participants to indicate how often they have experienced specific symptoms of stress in the past 30 days using a 4-point scale. Alpha coefficients on the subscales ranged from 0.76 to 0.85, and test–retest correlations (at 8 weeks and 12 months) ranged from 0.55 to 0.84 in previous studies indicating good to excellent internal consistency and temporal stability. The developers of the scale also report evidence for criterion validity (significant correlations between scale scores and stage of illness, social support and patient adjustment) and convergent validity (significant correlations between scale scores and a measure of threat appraisal) [24].

Mood Positive and negative mood were assessed with the Positive and Negative Affect Schedule (PANAS) [25], which includes a 10-item positive affect scale ($\alpha = 0.86$) and a 10-item negative affect scale ($\alpha = 0.87$) as reported by Watson et al. [25]. Participants respond on a 4-point scale indicating how often they felt each mood during the past 30 days.

Alcohol Use Alcohol consumption was measured by a widely used set of 4 items: (1) whether the respondent had a drink in the past 30 days, (2) the number of days in the past 30 days the respondent had a drink, (3) the number of drinks usually drunk on those days, and (4) the number of days the respondent had five or more drinks at one time.

Drug Use The use of illicit drugs and the misuse of prescription drugs was assessed by the Drug Use Checklist, developed and validated (with bio-specimens) by our group, and used in numerous studies of adult drug use [26–28]. Respondents are asked to indicate the frequency (from “not

at all” to “daily”) with which they used nine different types of drugs: marijuana, cocaine or crack, heroin, inhalants, hallucinogens, stimulants, tranquilizers, sedatives, and analgesics. Several examples of each drug type are provided. At baseline, participants completed two forms of the Checklist, one for use in the past 12 months (to identify recent/past users), as well as one for use in the past 30 days (administered at all posttests). For prescription drugs, the respondents checked usage only for non-medical use, defined as use “without a doctor’s prescription, or in greater amounts and/or more than prescribed.”

Demographic Information Demographic information included age, gender, education, ethnicity, race, income, time since HIV+ diagnoses, and how long on antiretroviral medication.

Statistical Analysis

Baseline Data

Consistent with recommendations for randomized clinical trials [29], we did not compare study conditions for baseline measures using statistical methods.

Outcome Data

The data were derived from a randomized controlled trial (RCT) with random assignment of individual participants to one of two study conditions (program vs. control). The primary outcome was the MEMS adherence data, and secondary outcomes were viral load data and self-report measures of stress, mood, substance use, adherence self-efficacy, and medication adherence.

Two analytic methods were considered a priori for the primary analysis of study outcomes. The first was an analysis of covariance (ANCOVA) comparing study conditions at posttest with regression adjustment for baseline. The second was a random coefficients model (RCM) comparing the linear slopes over time in the two study conditions. The questions addressed with these two methods are slightly different (adjusted posttest difference vs. slope difference) but both provide a test of the effect of the intervention. Because it was difficult to compare power for these methods a priori, we decided to conduct a blind power analysis at the end of data collection and to select as the primary analytic approach the method that provided the smaller standard error (SE). That is exactly the exercise we would have performed a priori had we had good estimates of the necessary parameters. The RCM analysis was run on the primary dependent variable (MEMS—percent of prescribed doses taken), fitting a model with random slopes and intercepts which were predicted by condition. The standard error for the intervention effect was

0.01573. An ANCOVA was run on the 6-month MEMS measure, producing a standard error of 4.3196. Much of the difference between the standard errors is a function of the time difference of the two methods (1 day for RCM vs. 180 days for the 6-month ANCOVA); however, the SE for the 6-month ANCOVA was ~1.5 times greater than the SE for the RCM even after accounting for the time difference. Because power is better for a smaller SE, other factors held constant, the RCM was selected as the primary analytic method for both primary and secondary outcome measures.

The primary analysis followed intent-to-treat (ITT) principles, including all participants irrespective of protocol violations and events arising post randomization [29]. Multiple imputation for all primary and secondary outcome variables was conducted, using the NORM program to conduct the multiple imputation [30]. There were <10 % missing data on the MEMS variable, while the amount of missing data for the self-report variables differed considerably. The imputation model included several covariates based on conceptual considerations (i.e. variables that theoretically may relate to the outcome variable) and on the amount of missing data for the covariates. Using this model, five imputed datasets were generated, each based on 1,000 iterations.

The random coefficients analysis was then conducted on all the MEMS, viral load, and self-report data. However, for the viral load data this analysis did not converge. The viral load data scores were extremely skewed (skew = 7.432, $p < 0.001$, with the 90th percentile of scores around 600 and a maximum value score of 280,510). Consistent with this skew, the residuals from the model deviated substantially from normality. To reduce skew, a square root transformation was conducted on the data. Despite the transformation, the distribution of viral load (VL) scores was still extremely skewed; e.g. the 90th percentile was around 300, and the maximum value was 16,240, and the model still failed to converge.

Given these results, we then ran the RCM analysis with dichotomous (0/1) scores, using the VL score of 400 as the cut-off score and specifying a Bernoulli distribution. A VL score of 400 was chosen as the cut-off because, as noted earlier, it was, until recent changes in the sensitivity of the HIV test, the threshold considered to be “undetectable.” We also ran the RCM analysis with the more sensitive cut-off of 48, which matched the inclusion criterion. Poisson regression models were also applied to the viral load data.

Results

Baseline Characteristics

The characteristics of the study sample for those providing demographic data are shown in Table 2. A total of 168 patients were enrolled in the study, most of whom were male

Table 2 Participant characteristics at baseline

	Program	Control
Gender		
Male	65 (73 %)	56 (71 %)
Female	19 (21 %)	22 (28 %)
Transgender male to female	5 (6 %)	1 (1 %)
Race		
Black	75 (84 %)	60 (79 %)
White	14 (16 %)	16 (21 %)
Asian/Pacific Islander	0	0
American Indian/Alaskan Native	0	0
Native Hawaiian	0	0
Latino		
Yes	5 (6 %)	4 (5 %)
No	84 (94 %)	74 (95 %)
Age		
19–29	7 (8 %)	2 (3 %)
30–39	15 (17 %)	17 (22 %)
40–49	35 (40 %)	31 (39 %)
50–59	26 (30 %)	20 (25 %)
60–69	4 (5 %)	9 (11 %)
Income		
<9,999	27 (31 %)	33 (46 %)
10,000–19,999	23 (27 %)	13 (18 %)
20,000–29,999	14 (16 %)	10 (14 %)
30,000–39,999	8 (9 %)	8 (11 %)
40,000–49,999	4 (5 %)	4 (6 %)
50,000 or more	10 (12 %)	4 (6 %)
How long since HIV+ diagnosis?		
1–6 months	0	0
6–12 months	0	0
1–2 years	8 (9 %)	5 (6 %)
3–5 years	11 (13 %)	13 (16 %)
5–9 years	11 (13 %)	11 (14 %)
10 or more years	50 (58 %)	47 (59 %)
How long taking medication?		
1–6 months	0	1 (1 %)
6–12 months	3 (3 %)	0
1–2 years	16 (19 %)	16 (20 %)
3–5 years	15 (17 %)	13 (16 %)
5–9 years	16 (19 %)	10 (13 %)
10 or more years	30 (35 %)	36 (46 %)
Missing	6 (7 %)	3 (4 %)

(73 %) and African American (84 %). Nationally, African Americans account for 44 % of people living with HIV infections [31]—much less than in our sample. However, the racial composition of our sample mirrors that of HIV-infected African Americans in Washington, DC, where 75 % of people living with HIV infections are African Americans [32]. Participants ranged in age from 19 to

Table 3 Program utilization

Number of completed modules	Number of participants (%)
Life steps medication adherence modules	
0	31 (35)
1	2 (2)
2	7 (8)
3	1 (1)
4	3 (3)
5	1 (1)
6	1 (1)
7	1 (1)
8	0 (0)
9	2 (2)
10	40 (45)
Stress management modules	
0	50 (56)
1	6 (7)
2	0 (0)
3	2 (2)
4	1 (1)
5	1 (1)
6	0 (0)
7	1 (1)
8	1 (1)
9	27 (30)

69 years with a mean age of 46 years. The majority of participants had finished high school and had incomes of <\$30,000. In addition, the majority of participants had been HIV+ and taking antiretroviral medication for >10 years. No significant differences were found between the two study conditions on any of these demographic characteristics.

Program Utilization/Dosages

As seen in Table 3, participant utilization for both the Medication Adherence and Stress Management topics split into two primary groups—participants who did not complete any of the modules and those who completed all of the modules. There were no significant differences between participants who completed the program modules and those that did not on any demographic variables. However, participants who access the program at the clinic were more likely to complete all ten of the Life Steps Medication Adherence modules ($\chi^2 = 4.81, df = 1, p = 0.03$).

MEMS Outcomes

The results of the RCM comparing the two groups across the four data collection points on percentage of prescribed

Table 4 Treatment effect on percent of prescribed number of doses taken

Fixed effects	Unstandardized effect	SE	t value	p value
Initial adherence rate for control group	85.20	2.96	28.80	<0.001
Difference between conditions in initial adherence rate	-2.67	4.07	-0.66	0.509
Change in adherence rate for control group	-0.053	0.002	-3.22	0.001
Difference between conditions in change in adherence rate	0.053	0.026	2.03	0.042

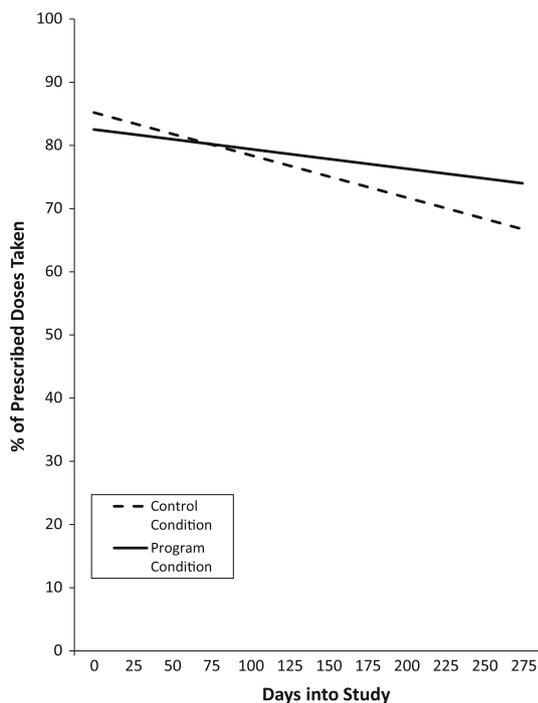


Fig. 2 Percentage of prescribed doses taken over time by condition

doses taken are shown in Table 4. These results show a significant treatment effect on medication adherence ($t = 2.03$, $p < 0.05$), as the control group adherence declined significantly more than the program group. Although within group analysis showed that the decline in adherence was significant for both groups (control group, unstandardized effect = -0.059 , $p < 0.001$; program group; unstandardized effect = -0.03 , $p < 0.01$), the more dramatic decline in the control group further indicates a significant effect of the Life-Steps program on medication adherence.

According to these results, the decline in adherence rate was significantly steeper ($p < 0.05$) in the control condition versus the program condition. The pattern is shown in Fig. 2; the control group declined in adherence from about 85 to 66 %, a decrease of ~21 %. The program group adherence also declined significantly, but only by about 12 %, from 83 to 73 %.

The two groups were also compared on the percentage of days on which the prescribed number of doses was

taken. As shown in Table 5, the effect of condition was in the expected direction, but was not statistically significant ($t = 1.244$, NS). In this case, the within group analyses indicated that the decline in the number of days on which the prescribed number of doses was taken was significant for the control group (unstandardized effect = -0.049 , $p < 0.001$) but not the treatment group (unstandardized effect = -0.016 , NS).

To test the effect of program usage on adherence, the percentage of prescribed doses taken was analyzed by total number of Life-Steps modules completed. As shown in Table 6, the effect was in the desired direction, and although not significant, it was indicative of a trend ($t = 1.667$, $p = 0.096$).

The potential effect of race and gender on the percentage of prescribed doses taken was also examined by RCM analysis, but neither was significant (gender: $t = -0.114$, NS; race: $t = 0.022$, NS). In addition, the effect of length of time on HIV medications on the percentage of prescribed doses taken was examined; it was also non-significant ($t = -1.233$, NS). Because these effects were non-significant, none of these variables was included as controls in the primary analysis.

Taken together, the results of the analysis of MEMS data indicate that the Life-Steps program had a significant positive effect on HIV medication adherence.

Viral Load

The RCM analysis with the more sensitive VL > 48 showed no significant treatment effect. As shown in Table 7, using the original cut off of VL > 400 there was a significant treatment effect, with the treatment condition VL scores decreasing significantly more than scores from the control condition over the course of the study ($t = -2.263$, $p = 0.024$). Interestingly, there was also a significant main effect of condition at baseline ($t = 2.22$, $p = 0.026$), indicating that randomization was not completely effective with respect to viral load. The RCM controlled for this by including the pre-intervention score in the analysis.

As seen in Fig. 3, VL scores dropped substantially for those in the program condition, but not for those in the control condition.

Table 5 Treatment effect on percentage of days the prescribe number of doses were taken

Fixed effects	Unstandardized effect	SE	t value	p value
Initial adherence rate for control group	74.41	3.85	19.34	<0.001
Difference between conditions	-1.90	4.81	-0.40	0.689
Change in adherence rate for control group	-0.044	0.019	-2.297	0.022
Effect of program on change in adherence rate	0.049	0.039	1.244	0.214

Table 6 Effect of program usage on percentage of prescribed doses taken

Fixed effects	Unstandardized effect	SE	t value	p value
Initial adherence rate (before completing any modules)	84.485	2.489	33.942	<0.001
Difference between conditions in initial adherence rate	-0.244	0.524	-0.466	0.641
Average change in adherence rate	-0.037	0.022	-1.700	0.089
Change in adherence rate for each module completed	0.004	0.002	1.667	0.096

Table 7 Treatment effect on viral load over time

Fixed effects	Unstandardized effect	SE	t value	p value
Initial viral load for control group	-2.212	0.336	-6.586	<0.001
Difference between conditions in initial viral load	0.954	0.430	2.221	0.026
Change in viral load for control group	0.001	0.001	0.511	0.609
Effect of program on change in viral load	-0.003	0.002	-2.263	0.024

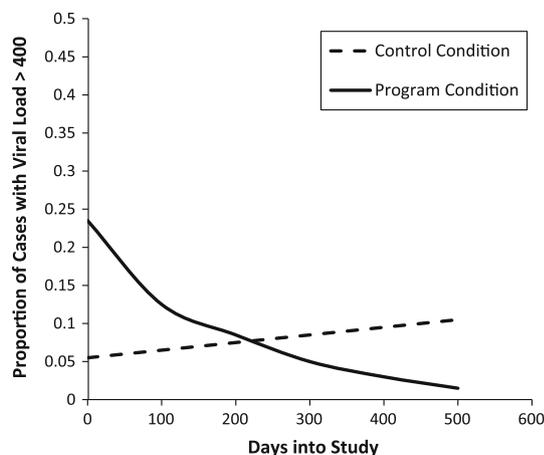


Fig. 3 Viral load by condition

Poisson regression models were also applied to the viral load data. The first analysis included 139 participants (76 from the treatment group and 63 from the control group) and produced an event ratio of 0.536, indicating that the viral load in the control group was 1.71 times that of the treatment group—an effect in the expected direction, but one which was clearly non-significant ($p = 0.7021$).

In post hoc analyses, the Poisson regression model was run two additional times. Limiting the sample to participants with viral load data within 45 days of randomization

(total $N = 74$) the event ratio was 0.257, indicating that the viral load in the control group was 3.89 times that of the treatment group—more strongly in the expected direction, but also non-significant ($p = 0.4896$). Finally, the models were run excluding participants above 900 (nine participants), resulting in an event ratio of 0.573—similar to the first analysis, but with a p value that is much more suggestive of a treatment effect ($p = 0.117$).

Self-Reported Outcomes

Self-reported medication adherence measures also were included as secondary outcomes. Three measures of self-reported adherence were used in the analysis: (1) How many days missed prescribed doses in the past 4 days (single item); (2) mean of four adherence items (How many doses missed—yesterday, day before yesterday, 3 days ago, 4 days ago); (3) mean of seven adherence items (the four above, plus: How closely did you follow your prescribed schedule over the last 4 days? How often did you follow specific instructions over the last 4 days? When was the last time you missed taking your medications?).

The RCM analysis found no significant treatment effect for any of the three self-reported adherence measures. Interestingly, though, the mean adherence rate actually slightly increased in the program group from Time 1 to Time 4 while declining in the control group. Partially

underlying the null findings for these data may have been the restricted variability on self-reported adherence, as the means for both groups across the four time points only varied from 89 to 96 %. In contrast to the MEMS data, there seemed to be little change in the average self-reported adherence. Indeed, the correlations between the two MEMS measures and the three self-report adherence measures were only moderate in size, ranging from 0.32 to 0.40.

RCM analysis of treatment effects on self-reported measures of mood, stress and adherence self-efficacy revealed no significant effects. The effect of treatment on drug use (any illicit drug use in the past 30 days) was also non-significant, although the effect was in the desired direction and approached significance ($t = -1.510$, $p = 0.13$). We included illicit drug use based on the relationship between drug use (particularly injection drug use) and HIV [33–35]. The number of participants who reported any past 30 day use of drugs at baseline was 27 for the program group and 23 for the control group. Consequently, the analysis of treatment effects on drug use was substantially underpowered as a function of the relatively small number of drug users in the sample.

Discussion

This randomized trial showed that patients given use of the web-based Life-Steps program had significantly higher antiretroviral medication adherence rates than patients in the control group over the 9-month test period, as indicated by the primary outcome measure, the MEMS measure. Although the adherence rate for the program group did not actually improve, but declined slightly, it remained above 72 % throughout the test period, while the adherence rate of the control group dropped from about 85 to 66 %. In addition, analysis of viral load data suggested that the Life-Steps program also resulted in a decrease in viral load—to be expected with the higher adherence rates in those exposed to the program. This pattern was observed both in the dichotomized RCM analyses and in the Poisson models, though it was significant only in the dichotomized RCM analyses. These findings indicate that a web-based medication adherence program based on the in-person Life-Steps intervention created by Safren and his associates [3, 10] can be a useful tool in helping HIV infected patients maintain medication adherence. The fact that the MEMS data showed no significant differences in treatment effects across gender, race or length of time taking the HIV medications indicates that the web-based program was a relatively robust intervention, effective regardless of these important patient characteristics. The significant intervention effect was found using intent-to-treat analyses, further underscoring the effectiveness of the intervention. Also,

although the evidence for a dose–response relationship (effects of number of modules accessed on adherence rates) fell short of significance, the findings were suggestive of such a potential relationship. Interestingly, the treatment effect found on the primary MEMS outcome measure (percentage of doses taken as prescribed) was not found on the somewhat less fine-grained MEMS-generated measure of percentage of *days* the prescribed doses were taken.

In contrast to the findings from the MEMS measures and viral load data, no significant effects were found on the secondary outcomes of self-reported adherence, stress, mood, and substance use, although the effect on drug use approached significance, doubtless affected by the relatively low numbers of self-reported drug users. The lack of significant effects on stress, mood, and substance use may be because less than half of the program group actually accessed the sections of program devoted to these topics. The fact that there was no significant effect of the intervention on self-reported adherence stands in some contrast to the findings from both the MEMS data and the viral load data. Past studies have found discrepancies between MEMS data and self-reports, with MEMS data typically generating lower adherence rates than self-reports [36–38]. A review of 11 studies by Shi and associates [37] found correlations between adherence rates measured by MEMS and self-reports ranged from 0.24 to 0.87, with a pooled correlation for the studies of 0.45. In this study, correlations between MEMS and self-report measures of adherence ranged from 0.32 to 0.40, toward the lower end of the correlations in the study by Shi and associates, but not dramatically different from the correlations in the 11 studies.

The relatively low correlation between the MEMS data and the self-reports and the lack of a significant treatment effect on the self-reports is most likely due to a combination of patients' memory failures and social desirability—patients wanting to appear more adherent than they actually were. Of course, the MEMS device is designed specifically to overcome these kinds of errors, and it is likely that the MEMS device, while not perfect, was a more accurate measure of medication adherence.

The suggestion of a treatment effect on viral load, although limited mainly to analysis of dichotomous data, further supports the efficacy of the web-based Life-Steps program, especially as the study was not initially designed or powered to find effects on viral load. Indeed, in an evaluation of another web-based HIV medication adherence program conducted by Fisher and his associates which found no significant effect on viral load, the authors stated that their study “was underpowered to detect changes in viral load”—a study with 594 participants in their ITT sample, more than three times the size of our sample [20]. Statistical power in our study (and in the Fisher et al. study)

was further eroded by the large number of participants with relatively low viral loads at baseline. Nonetheless, the combined analyses of viral load data suggest that a future study with a larger sample that is less adherent at baseline might show even stronger effects on viral load.

Although it seems clear that the web-based Life-Steps program had a positive effect on patients' adherence to HIV medication, one might question why the program did not completely stabilize—or increase—adherence at a high level. We suspect that there are a couple of reasons why adherence did not increase for the treatment group. First, the sample was already fairly adherent at the start of the study, averaging in the mid-to-upper eighties, according to both the MEMS data and self-reports, and it might be difficult to raise adherence much beyond this level. These adherence levels at baseline contrast markedly with baseline adherence levels of the samples in similar studies. For example, baseline adherence rates of samples in the studies by Safren and associates ranged from mid-fifties to mid-sixties [3, 10], and baseline rates of samples in the study by Fisher et al. ranged from mid-sixties to mid-seventies [20]. The relatively high level of adherence at baseline in our sample was probably a function of the inclusion of many patients with viral loads below 400, levels which are generally associated with good adherence practices. Second, it is also likely that the use of the electronic pill cap had some effect on adherence, especially at baseline. When patients were first given the device for 2 weeks to establish their baseline, it is entirely possible that patients whose adherence practices had been faulty in the past began attending more closely to their medication adherence because they knew their pill-taking was being electronically recorded. Indeed, there is evidence in the literature that the use of MEMS caps boosts adherence rates for usually 1–2 months [9, 39]. Therefore, the lack of an increase in MEMS-based adherence rates over the course of the study period was probably a function of decreasing MEMS effects together with a sample that was relatively adherent at baseline, placing a ceiling on the intervention effect. For these reasons, the Life-Steps intervention was unlikely to achieve any significant increase in adherence; the intervention could only minimize the decrease as the MEMS effect wore off—which it did.

The findings of this study compare interestingly to the results of another recent test of a computer-based intervention to improve HIV medication adherence [20]. That study did not use the MEMS device, relying instead on a 3-day self-report measure, supplemented by the collection of viral load data. Results indicated that there were no significant treatment effects in the intent-to-treat sample. However, analysis of data from participants who were relatively regular users of clinical care and LifeWindows

and who remained on HIV medications throughout the study found a significant treatment effect on one of the self-report measures.

Although questions remain about the “digital divide” and barriers to the use of computer-based interventions among low income, less educated African American HIV+ patients, access to computers and the Internet is increasing in this population. No data are available on Internet usage by HIV status; however, recent data from the Pew Research Center indicates that from 2000 to 2011, Internet usage increased from 35 to 71 % among African Americans, from 28 to 62 % among low income Americans (<\$30,000/year), and from 16 to 43 % among those without a high school diploma [40]. Moreover, although the digital divide—which is definitely decreasing—remains a barrier to use of an Internet-based program, it is less of an impediment when HIV+ patients can access a program through computers at community-based clinics—as our participants were able to do. This study indicates that such interventions can be promising approaches to promoting adherence among HIV+ patients. Moreover, we suspect that the utility and effectiveness of web-based medication adherence programs are likely to increase with further research and development efforts. The use of mobile technology to promote adherence is also showing promise [41]. With rapid advances occurring in the development and wider use of mobile technology, web-based medication adherence interventions built for mobile platforms will deserve increased attention in the future.

While computer/web-based interventions have begun to show that they can be effective tools to promote medication adherence among HIV+ patients [19, 20], more research and development are needed with regard to the particular structure, content and delivery modality of the interventions as well as target populations. Future research should test different types of computer/web-based interventions by types of target HIV+ populations (e.g. by ethnicity, income, etc.) with varying adherence levels.

Limitations of this research include sample size and the need to further refine and improve the web-based Life-Steps program. Although the study was sufficiently powered to detect treatment effects on the primary (MEMS-based) outcome measure, some outcomes that did not quite reach significance might do so with a larger sample. Finally, the content and structure of the web-based Life-Steps program deserves further refinement and improvement. In particular, it appeared that the stress management part of the program had no discernible effect on participants' stress or mood, and did not appear to contribute to their medication adherence. In future tests of the Life-Steps program, consideration should be given to revising these segments, as well as reducing or eliminating them.

Conclusion

Using multiple measures of HIV medication adherence, including MEMS (electronic pill cap) and viral load data, this study demonstrated that a web-based medication adherence program, adapted from the CBT-based Life-Steps program, can be an effective intervention for promoting adherence to ARV medications among HIV+ patients. Because a web-based program like Life-Steps can be accessed at any time or place an Internet connection is available, these findings suggest that such an intervention might serve as a cost effective alternative to more labor intensive in-person medication adherence programs, greatly expanding the reach and impact of HIV medication adherence programming.

Acknowledgments This study was funded by a National Institute on Drug Abuse grant (5R01DA028505), Royer F. Cook, Principal Investigator.

References

- O'Cleirigh C, Safren S. Optimizing the effects of stress management interventions in HIV. *Health Psychol.* 2008;27:4–14.
- Safren SA, Otto MW, Worth J, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behav Res Ther.* 2001;39:1151–62.
- Safren SA, O'Cleirigh CM, Tan JY, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. *Health Psychol.* 2009;28:1–10.
- Carpenter CJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1997: updated recommendations of the international AIDS society-USA panel. *JAMA.* 1997;277:1962–9.
- Flexner C. HIV-protease inhibitors. *N Engl J Med.* 1998;338(18):1281–92.
- Goebel FD. Combination therapy from a clinician's perspective. *J Acquir Immune Defic Syndr Hum Retroviro.* 1995;10:S62–8.
- Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA.* 2010;304:321–33.
- Catz SL, Kelly JA, Bogart LM, et al. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychol.* 2000;19:124–33.
- Hinkin CH, Barclay TR, Castellon SA, et al. Drug use and medication adherence among HIV-1 infected individuals. *AIDS Behav.* 2007;11(2):185–94.
- Safren SA, O'Cleirigh CM, Bullis JR, Otto MW, Stein MD, Pollack MH. Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial. *J Consult Clin Psychol.* 2012;80(3):404–15.
- Scott-Sheldon LAJ, Carey MP, Vanable PA, Senn TE, Coury-Doniger P, Urban MA. Alcohol consumption, drug use, and condom use among STD clinic patients. *J Stud Alcohol Drugs.* 2009;70:762–70.
- Safren SA, Otto MW, Worth J. Life-steps: applying cognitive-behavioral therapy to patient adherence to HIV medication treatment. *Cogn Behav Pract.* 1999;6:332–41.
- Safren SA, Hendriksen ES, DeSousa N, Boswell SL, Mayer KH. Use of an on-line pager system to increase adherence to antiretroviral medications. *AIDS Care.* 2003;15:787–93.
- Safren SA, Hendriksen ES, Mayer KH, Pickard R, Otto MW. Cognitive behavioral therapy for HIV medication adherence and depression. *Cogn Behav Pract.* 2004;11:415–23.
- Simoni JS, Amico KR, Pearson CR, Malow RM. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. *Cogn Behav Pract.* 2008;10:515–21.
- Cook RF, Billings DW, Hersch RK, Back A, Hendrickson A. A field test of a web-based workplace health promotion program to improve dietary practices, reduce stress, and increase physical activity: randomized controlled trial. *J Med Internet Res.* 2007;9:e17.
- Portnoy DB, Scott-Sheldon LAJ, Johnson BT, Carey MP. Computer-delivered interventions for health promotion and behavioral risk reduction: a meta-analysis of 75 randomized controlled trials, 1988–2007. *Prev Med.* 2008;47:3–16.
- Williams GC, Lynch MF, Glasgow RE. Computer-assisted intervention improves patient-centered diabetes care by increasing autonomy support. *Health Psychol.* 2007;26:728–34.
- Noar SM, Black HG, Pierce LB. Efficacy of computer technology-based HIV prevention interventions: a meta-analysis. *AIDS.* 2009;23:107–15.
- Fisher JD, Amico KR, Fisher WA, et al. Computer-based intervention in HIV clinical care setting improves antiretroviral adherence: the LifeWindows project. *AIDS Behav.* 2011;15(8):1635–46.
- Billings DW, Cook RF, Hendrickson A, Dove DC. A web-based approach to managing stress and mood disorders in the workforce. *J Occup Environ Med.* 2008;50:960–8.
- Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. *AIDS Care.* 2000;12:255–66.
- Risser J, Jacobson TA, Kripalani S. Development and psychometric evaluation of the self-efficacy for appropriate medication use scale (SEAMS) in low-literacy patients with chronic illness. *J Nurs Meas.* 2007;15:207–23.
- Pakenham KI, Rinaldis M. Development of the HIV/AIDS stress scale. *Psychol Health.* 2002;17:203–19.
- Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol.* 1988;54:1063–70.
- Cook RF, Bernstein A, Andrews C. Assessing drug use in the workplace: a comparison of self-report, urinalysis and hair analysis. NIDA research monograph 167. Rockville: National Institute on Drug Abuse; 1997.
- Cook RF, Back AS, Trudeau J, McPherson TL. Integrating substance abuse prevention into health promotion programs in the workplace: a social-cognitive intervention targeting the mainstream user. In: Bennett JB, Lehman WEK, editors. Preventing workplace substance abuse: beyond drug testing to wellness. Washington, D.C.: APA Books; 2003. p. 97–134.
- Cook RF, Hersch RK, Back AS, McPherson TL. The prevention of substance abuse among construction workers: a field test of a social cognitive program. *J Prim Prev.* 2004;25:337–58.
- Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. New York: Springer; 2010.
- Schafer JL. Analysis of incomplete multivariate data. London: Chapman and Hall; 1997.
- Centers for Disease Control. Estimated HIV incidence among adults and adolescents in the United States, 2007–2010. HIV Surveillance Supplemental Report. 2012;17:4. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/#supplemental>.
- Government of the District of Columbia, Department of Health. Annual report 2011: HIV/AIDS, hepatitis, STD, and TB epidemiology of the District of Columbia. Washington, DC: Department of

- Health: HIV/AIDS, Hepatitis, STD, and TB Administration (HAHSTA); 2012.
33. Centers for Disease Control. Methamphetamine use and HIV risk behaviors among heterosexual men -preliminary results from five northern California counties, December 2002–November 2003. *MMWR*. 2006;55:273–7.
 34. Molitor F, Truax SR, Ruiz JD, et al. Association of methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. *West J Med*. 1998;168:93–7.
 35. Royce RA, Sena A, Cates W Jr, et al. Sexual transmission of HIV. *N Engl J Med*. 1997;336:1072–8.
 36. 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;14:357–66.
 37. Shi L, Liu J, Fonseca V, Walker P, Kalsekar A, Pawaskar M. Correlations between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health Qual Life Outcomes*. 2010;8:99.
 38. Wagner GJ. Predictors of antiretroviral adherence as a measure by self-report, electronic monitoring, and medication diaries. *AIDS Patient Care STDS*. 2002;16(12):599–608.
 39. Deschamps AE, Van Wijngaerden E, Denhaerynck K, De Geest S, Vandamme AE. Use of electronic monitoring induces a 40-day intervention effect in HIV patients. *J Acquir Immune Defic Syndr*. 2006;43:247–8.
 40. Zickuhr K, Smith, A. Digital differences. Washington, DC: Pew Research Center's Internet and American Life Project. 2012. pewinternet.org/Reports/2012/Digital-differences.aspx.
 41. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS*. 2011;25(6):825–34.