Two strategies to increase adherence to HIV antiretroviral medication: Life-Steps and medication monitoring

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Abstract

Advances in the medical treatment of HIV have made it clear that adherence to highly active antiretroviral treatment is a crucial feature for treatment success. The present paper had two goals: (1) to examine psychosocial predictors of adherence in persons receiving HIV antiretroviral therapy; (2) to compare two minimal-treatment interventions to increase HIV medication adherence in a subset of persons who self-reported less than perfect adherence. One of the interventions, Life-Steps, is a single-session intervention utilizing cognitive-behavioral, motivational interviewing, and problem-solving techniques. The other intervention, self-monitoring, utilizes a pill-diary and an adherence questionnaire alone. Significant correlates of adherence included depression, social support, adherence self-efficacy, and punishment beliefs about HIV. Depression was a significant unique predictor of adherence over and above the other variables. Both interventions yielded improvement in adherence from baseline, and the Life-Steps intervention showed faster improvements in adherence for persons with extant adherence problems. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Since the advent of highly active antiretroviral therapy (HAART) for HIV, significant numbers of HIV-positive individuals have had prolonged and healthier lives, such that HAART has been defined as the standard of care (Carpenter et al., 1997). HAART, which typically involves a
combination of one protease inhibitor and two nucleoside reverse transcriptase inhibitors, leads to reductions in viral load, greater immune system function, and less likelihood of clinical immune deficiency in patients with HIV infection (see Carpenter et al., 1997; Deeks, Smith, Holodniy & Kahn, 1997; Flexner, 1998; Goebel, 1995; Kelley, Otto-Salaj, Sikkema, Pinkerton & Bloom, 1998).

Despite these advances, HAART is not without problems. Almost perfect adherence to HIV medications is critical for successful treatment, particularly for prevention of viral replication (see Katzenstein, 1997; Carpenter et al., 1997; Deeks et al., 1997; Descamps et al., 2000). Partial adherence is not sufficient, with evidence of dramatic differences in viral suppression at levels of medication adherence that would be acceptable for a variety of other medical conditions. For example, Patterson et al. (1999) found that 81% of HIV positive individuals with greater than 95% adherence showed complete viral suppression, whereas only 64% of those with 90–95%, 50% of those with 80–90%, and 30% of those with less than 80% adherence showed viral suppression.

Typical predictors of poor adherence in chronic illnesses are longer illnesses, less severe or noticeable symptoms, complex treatment regimens, large numbers of medications or high frequency of dosing, a poor doctor–patient relationships, and substance use, depression, and patient beliefs (e.g. Becker, 1985; Chesney & Ickovics, 1997; Griffith, 1990; Haynes, 1979; Ickovics & Meisler, 1997). Many of these features are present in individuals being treated for HIV (e.g. Chesney & Ickovics, 1997; Kalichman, 1998; Safren, Otto & Worth, 1999).

HAART medications may require different dosing schedules (some at 12, 8, 6 or 4 h intervals), different food intake patterns (some should be taken on an empty stomach, others need to be taken with meals, some with fatty foods, some with non-fatty foods) and different storage requirements (some need to be refrigerated). Many of these medications cause side effects which necessitate further medication, and still other interventions may be required to treat secondary opportunistic infections (see Kelley et al., 1998). Patients on HAART are therefore required to adhere to a complex and frequently confusing combination of medications throughout an indefinite course of treatment.

HAART also requires patients to take pills for long periods of time, frequently in the absence of symptoms. Indeed, because of emergent side-effects, HAART medication may induce symptoms in HIV patients who may otherwise be relatively symptom free. Moreover, in the context of successful treatment, patients appear to face an especially difficult challenge remaining adherent. Clearly, strategies are needed to enhance adherence to HAART regimens for patients with HIV.

The present study had two major goals. First, we sought to examine psychosocial predictors of HIV medication adherence. Second we sought to evaluate two minimal-intervention approaches to increasing adherence to HIV-medication regimens in persons with less than perfect adherence. Specifically, we compared a single-session cognitive-behavioral intervention (Life-Steps; Safren et al., 1999) to a self-monitoring condition alone. The cognitive-behavioral intervention was based on a converging set of evidence that brief, cognitive-behavioral, problem-focused interventions were useful to improving medical adherence for problems ranging from diabetes (Kirkman et al., 1994; Mendez & Beledez, 1997) and asthma (Bailey et al., 1990) to psychiatric out-patient aftercare (Spooren, Van Heeringen & Jannes, 1998). Likewise, self-monitoring has received support as a minimal-intervention strategy for a variety of behavioral modification efforts (see Gambrill, 1977), and is typically used as an adherence intervention in clinical trials of medications. In the present study we conducted a randomized clinical trial to evaluate these minimal-intervention
strategies, and examined potential predictors of adherence in a sample of HIV-positive individuals with documented difficulties adhering to their HIV medications.

2. Method

2.1. Participants and setting

The study setting was a community health center which primarily serves a lesbian, gay, bisexual, and transgendered community, as well as persons infected with HIV. There were two parts to the present project: prediction of concurrent adherence, and a pilot efficacy study of two interventions in patients taking medications with less-than-perfect medication adherence. Participants in the predictors study were 76 men and 8 women with HIV who were considered at risk for adherence problems because they were starting medications, changing medications, and/or reported that they did not take all of their prescribed HIV antiretroviral medications for the past 2 weeks. Participants in the intervention study were the 49 men and 7 women from the original sample who reported that they had not taken all of their prescribed HIV antiretroviral for the past 2 weeks.

Potential participants were first recruited through advertisements in the health center and by health center primary care physicians and medical social workers. Adherence was assessed in phone interviews, and was evaluated with a self-report adherence questionnaire (see Section 2.2.2). To increase the representatives of the sample, and to attempt to match the demographics of persons with HIV/AIDS in Greater Boston, we extended recruitment efforts to persons with HIV in the community utilizing community centers and health clubs, and case managers at other community-based organizations in the Boston metropolitan area.

2.2. Measures

2.2.1. Demographics

At entry into the study, participants completed a self-report battery including demographic information such as age, ethnicity, sex, sexual orientation, living situation, and educational attainment (Table 1).

2.2.2. Assessment of adherence

The Adherence Questionnaire is a straightforward instrument that asks patients to record the number of pills prescribed and the number of pills taken each day over a specified time period (Chesney & Ickovicks, 1997). This measure has been utilized in AIDS Clinical Trials Group research (e.g. ACTG 384), and asks about “yesterday,” “the day before yesterday,” and “the past four days.” For the present study, we utilized the time period of “the past 2 weeks” instead of “the past four days,” and this was the major outcome variable for the analyses. The four questions together had a high level of internal consistency (α=0.90), and the question reflecting “the past 2 weeks”, had the highest loading (0.94) in a common factor analysis of the four items which yielded a single factor solution.

Accurate completion of the Adherence Questionnaire in this manner was aided by the use of
medication diaries. Each day, participants recorded the number of pills prescribed and the actual number of pills taken. The major outcome variable, the adherence questionnaire score for “the past 2 weeks” correlated highly with the medication diary score for the same time period \( r(78) = 0.92, \ p < 0.0001 \) ¹.

### 2.2.3. Psychosocial predictors of adherence

Depression was measured with the Beck Depression Inventory (BDI; Beck, Ward, Mendelsohn, Mock & Erbaugh, 1961). The BDI is the most widely used self-report measure for the assessment of depression, and has almost a 30 year history of psychometric reliability. It includes a statement of 21 symptoms of depression, on which individuals rate the intensity of the symptom for the past 2 weeks.

Perceived social support was be assessed using the short form (Sarason, Sarason, Shearin & Pierce, 1987) of the Social Support Questionnaire (SSQ; Sarason, Levine, Basham & Sarason, 1983). This measure yields scores for perceived satisfaction with social support and number of social supports. We used perceived social support rather than number of social supports because of its more consistent and stronger association with other variables related to adjustment (see Barrera, 1986; Robinson & Graber, 1995). The short form of the Social Support Questionnaire has comparable psychometric characteristics as the long form (Siegert, Patten & Walkey, 1987), and satisfaction with and number of social supports as assessed with the SSQ correlate strongly

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¹ This correlation was calculated at the two week assessment when we had 2 weeks of data for the medication diary with the adherence questionnaire reflecting the same interval.
with a variety of indicators of psychological adjustment (Sarason, Sarason & Pierce, 1990). Satisfaction with social support is assessed with six questions asking for a rating of 1 (very dissatisfied) to 6 (very satisfied) asking “How satisfied are you with help in this area?” (e.g. people to be dependable when you need help). Items are tallied and averaged.

Clinical experience suggested that adherence may be associated to punishment attributions and beliefs about having HIV. Therefore we introduced a novel, face-valid measure of punishment attributions about HIV and medications. Responses were summed from three statements on which participants rated their agreement on a scale from of 1 (strongly disagree) to 7 (strongly agree): “Medication is my punishment for getting HIV,” “It doesn’t matter what I am prescribed for HIV, because the disease is a punishment,” “I have HIV because I am being punished for things I have done.” Chronbach’s alpha was adequate for these three items (α=0.63).

Self-efficacy has shown to be a strong predictor of a number of health-related behaviors (Bandura, 1994), including HIV risk behavior among persons who are already HIV positive (Wulfert, Safren, Brown & Wan, 1999). Therefore we also developed a measure of self-efficacy specific to adherence based on questions used for self-efficacy about condom use (e.g. Wulfert & Wan, 1995). It therefore assessed perceived adherence self-efficacy in increasingly difficult situations: “I think I can remember my HIV medications even in a stressful week,” “I think I can remember to take my medications regularly even though I may have side effects,” “Even if I am in a bad mood, I can still remember to take my HIV medications”. Items were summed with a range of 1 (strongly disagree) to 7 (strongly agree) for each. Chronbach’s alpha was adequate for these 4 items (α=0.63).

Due to the association of substance use with various forms of unhealthy behavior such as unprotected sex (see Cooper, 1992; Donovan & McEwan, 1995; Leigh & Stall, 1993), we used a frequency index (see Czarnecki, Russell, Cooper & Salter, 1990; Webb, Redman, Sanson-Fisher & Gibbert, 1990) for alcohol and drug use. This included assessing the frequency of alcohol, marijuana, cocaine, and “poppers”, and other drugs during the past 6 months (from 1 never to 7 daily). This method of assessment has been shown to be a fast and effective way of assessing the association of substance use to other self-destructive behavior such as risky sexual behavior in a variety of samples, including persons who are HIV positive (e.g., Wulfert et al., 1999).

2.3. Interventions for adherence

2.3.1. Self-monitoring condition

The self-monitoring condition was a minimal-contact intervention that utilized a daily diary for recording the number of pills prescribed for the day, and number of pills actually taken. At the baseline enrollment meeting, participants were shown how to complete the medication diaries for the next 2 weeks. At the 2 week assessment meeting, participants returned their medication diary and completed the Week-2 adherence questionnaire. At this time, they were given their medication diary to complete for the 12th week after enrollment, and were scheduled for their Week 12 follow-up appointment.

For the Week-12 assessment, participants were telephoned approximately one week in advance. During this time they were reminded about their appointment, and were reminded to complete the Week-12 diary each day.
2.3.2. Life-Steps condition

The Life-Steps protocol is fully described elsewhere (Safren et al., 1999). Life-Steps is a single-session intervention utilizing cognitive-behavioral, problem-solving (D’Zurilla, 1986), and motivational interviewing (Miller & Rollnick, 1991) techniques to enhance motivation, rehearse adherence-related behaviors, and solve problems that interfere with adherence to HIV medications. It also consists of a follow-up telephone review (10 min) one week later. The first portion of Life-Steps involves informational and motivational interventions, aided by a videotape presentation. The videotape presents psychoeducational information about HIV medications in suppressing viral replication, and the consequences of missing a dose, and includes an animated cartoon segment that illustrates the inhibition of viral replication and the consequences of a missed dose. The session with the clinician includes eleven informational, problem-solving, and cognitive-behavioral steps for improving adherence:

1. psychoeducation;
2. transportation to appointments;
3. obtaining medications;
4. communication with providers;
5. coping with side-effects;
6. formulating a daily medication schedule;
7. storage of medications;
8. cues for pill-taking;
9. guided imagery review of successful adherence in response to daily cues
10. responses to slips in adherence; and
11. review of procedures (written on a note card for participants to take with them).

Participants in the Life-Steps program also followed the daily diary procedures from the Self-Monitoring condition.

2.4. Procedure

Potential participants spoke on the telephone with a research assistant who assessed eligibility criteria. This included verbal confirmation of the participant’s HIV-positive serostatus, and that the participant was having difficulties adhering to his or her current antiretroviral medication regimen. After briefly discussing the study, the research assistant scheduled the potential participant for the baseline meeting where written informed consent was obtained and patients were randomized into either the Life-Steps or Self-Monitoring Alone conditions.

At the first study visit, participants completed the self-report measures. All participants were asked to return for the two week acute outcome assessment and the 12 week follow-up assessment. Participants were reimbursed a nominal fee at each assessment period.
3. Results

3.1. Psychosocial correlates of baseline adherence

Associations, as assessed by Pearson correlation coefficients, between psychosocial predictor variables and baseline adherence are presented in Table 2. For these analyses, the adherence outcome measure was percent of pills taken for the past 2 weeks using the adherence questionnaire. Four of the six correlations were significant beyond the 0.01 level and these were in the moderate (0.30–0.40) range (see Table 2). As expected, depression and punishment beliefs about HIV infection were negatively associated with adherence and satisfaction with social support and adherence self-efficacy were positively associated with adherence. Contrary to our hypothesis, in this sample neither frequency of alcohol use nor other substance use (cocaine, marijuana, poppers or other drugs) was associated with baseline adherence.

To identify non-redundant prediction of baseline adherence, a forward entry step-wise regression analysis was performed utilizing significant correlates of baseline adherence as predictors. Depression scores on the BDI emerged as a unique predictor of baseline adherence \[ R^2 \text{(1,83)} = 0.13, p<0.001 \], and the other predictors did not significantly add to the prediction of adherence over and above depressed mood.

3.2. Two week and 12 week adherence outcome by intervention group

The main dependent variable for the outcome analyses was percentage of pills taken for the past 2 weeks. Mean adherence scores are presented in Table 3. Fifty-six participants were available for these analyses, with 30 receiving Life-Steps and 26 receiving Medication Monitoring.

A 2 (Time: Baseline versus Week 2) by 2 (Condition: Life-Steps versus Self-Monitoring) mixed analysis of variance of adherence scores was conducted, with time as a within-subjects variable and condition as a between-subjects variable. The interaction term is the variable of primary interest. This analysis yielded a significant main effect for time \[ F(1,54)=15.01, p<0.001, \eta^2=0.22 \] and a significant time by condition interaction \[ F(1,54)=4.41, p<0.05, \eta^2=0.08 \] such that those in the Life-Steps condition displayed greater changes in adherence scores from baseline to Week 2 than those in the Self-Monitoring condition. To follow up on these findings, individual

Table 2
Psychosocial predictor variables: means, standard deviations, and correlations of with baseline adherence

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Mean (standard deviation)</th>
<th>Correlation with baseline adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (BDI)(^a)</td>
<td>14.10 (8.77)</td>
<td>(r = -0.39, p&lt;0.01)</td>
</tr>
<tr>
<td>Satisfaction with social support (SSQ)(^a)</td>
<td>4.41 (1.46)</td>
<td>(r = 0.38, p&lt;0.01)</td>
</tr>
<tr>
<td>Punishment beliefs about HIV infection</td>
<td>5.92 (4.16)</td>
<td>(r = -0.34, p&lt;0.01)</td>
</tr>
<tr>
<td>Adherence self-efficacy</td>
<td>18.57 (6.62)</td>
<td>(r = 0.34, p&lt;0.01)</td>
</tr>
<tr>
<td>Frequency of alcohol use(^b)</td>
<td>3.01 (1.92)</td>
<td>(r = -0.06, \text{n.s.})</td>
</tr>
<tr>
<td>Frequency of other substances(^b)</td>
<td>2.65 (2.14)</td>
<td>(r = -0.18, \text{n.s.})</td>
</tr>
</tbody>
</table>

\(^a\) BDI, Beck Depression Inventory; SSQ, Social Support Questionnaire.

\(^b\) Seven point scale as describe above.
Table 3
Baseline, acute, and follow-up adherence scores for patients with existing adherence problems

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline adherence</th>
<th>Acute outcome (week 2)</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>84%</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>SD</td>
<td>17%</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>n</td>
<td>26</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Life-Steps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>74%</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>SD</td>
<td>28%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td>28</td>
</tr>
</tbody>
</table>

* M, Mean; SD, standard deviation; n, sample n.

Post-hoc within-group tests (Baseline versus Week 2) were conducted to examine improvement for the two conditions separately. For the Life-Steps condition, participants had significantly greater scores at Week 2 than they did at Baseline \([t(29)=3.97, p<0.001]\), but for the Medication Monitoring Group, Week 2 scores did not significantly differ from Baseline \([t(25)=1.41, \text{n.s.}]\).

For the Week 12 data, a similar 2 (Time: Baseline versus Week 12) by 2 (Condition: Life-Steps versus Self-Monitoring) mixed analysis of variance of adherence scores was conducted. This analysis yielded a significant main effect for time from Week 0 to Week 12 \([F(1,51)=10.64, p<0.01, \eta^2=0.17]\), but there was no significant main effect for condition \([F(1,51)=0.82, \text{n.s.}]\) and the interaction of time and condition across groups was not significant \([F(1,51)=1.18, \text{n.s.}]\).

3.3. Treatment by depression interaction for short-term improvement

Because depression was found to be a predictor of adherence in the baseline assessment, and because of the differential improvement at the 2 week outcome between Life-Steps and Medication Monitoring, we sought to determine if depression would differentially affect response to the intervention across conditions. Due to the combination of categorical and continuous variables, interaction effects between depression scores and intervention group (Life-Steps versus Self-Monitoring) were tested utilizing linear regression, dummy coding intervention group (see Pedhauzer, 1982). Change scores between Week 0 and Week 2 were utilized as the dependent variable. In this analysis, the overall regression equation yielded a significance \([R^2=0.26; F(3,55)=6.13; p<0.002]\). The interaction between depression and intervention group was a significant unique predictor of adherence change scores (semipartial \(r^2=0.067, p<0.05\)). Post hoc correlations between depression and adherence change scores indicated that baseline depression was positively associated with the degree of improvement in adherence for the Life-Steps group \((r=0.55, p<0.01)\), but not associated with improvement in adherence for the Self-Monitoring Group.

4. Discussion

Baseline adherence was significantly associated with depression, satisfaction with social support, punishment beliefs about HIV infection, and self adherence self-efficacy. Contrary to our
hypothesis, baseline adherence was not associated with self-reported frequency of alcohol or other substance use. Of these variables, baseline depression scores offered non-reduction prediction of adherence scores. Greater depressed mood was associated with poorer adherence, accounting for a total of 13% of the variance in adherence scores. These findings highlight the importance of provider or counsellor awareness of psychological and psychiatric difficulties among patients with HIV; these variables appear to affect adherence outcomes.

Patients with existing adherence problems who received the single session Life-Steps intervention exhibited faster improvements in adherence than patients who received the Self-Monitoring intervention, as evaluated by the change in adherence scores 2 weeks following the interventions. The improvements in adherence in both groups appeared to be maintained 3 months after receiving Life-Steps. These results suggest that more intensive, problem-solving and motivational interventions can be useful for persons with existing adherence problems.

Despite the baseline association between depression scores and poor adherence, for those in the Life-Steps intervention, depression scores were associated with greater improvement. This suggests that the Life-Steps was able to ameliorate some of the adherence problems linked to depressed mood. No such associations were evident for the Self-Monitoring condition (Fig. 1).

We would like to note to several limitations of our study. First, HIV medication adherence was assessed by self-report. Despite efforts by the study staff to reinforce the necessity of honesty in their estimates, it is possible that patients could forget which medications were taken, and/or could over- or under-estimate their adherence for reasons such as the demand characteristics of the study (see Halkitis, 1999; Kazdin, 1992). However, there is currently no known “gold stan-
dard” for assessing adherence, and any method is fraught with limitations. Electronic monitoring devices, for example, provide an accurate index of use of the pill bottle, but these devices do not account for participants who open the cap but do not swallow a pill, nor do they account for those who take all pills for the day out of the container at one time. Second, due to sample size this study had limited power to detect differences. Nonetheless, examination of effect size differences suggested a medium to large effect for Life-Steps and a small to medium effect (see Cohen, 1992) for Self-Monitoring at Week 2, with both groups having a medium to large effect between Week 0 and Week 12.

Future research addressing the effects of the two adherence interventions on biological outcome has the potential to test a wealth of hypotheses regarding the impact of psychosocial interventions on disease severity, longevity, and incidence of HIV associated opportunistic infections. The Life-Steps intervention showed faster improvements in adherence than medication monitoring. Although the two interventions did not show differences at the follow-up assessment points, the rate at which a patient recovers from poor adherence may be critical to suppressing viral replication before an adherence-based medication failure.

Acknowledgements

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