ELSEVIER

Patient Education and Counseling 50 (2003) 187–199

Patient Education and Counseling

www.elsevier.com/locate/pateducou

A medication self-management program to improve adherence to HIV therapy regimens

Scott R. Smith[a,*], John C. Rublein[a,b], Cheryl Marcus[c], Tina Penick Brock[d], Margaret A. Chesney[e]

[a]*School of Pharmacy, Center for AIDS Research, University of North Carolina at Chapel Hill, Beard Hall, Campus Box #7360, Chapel Hill, NC 27599-7360, USA*

[b]*Department of Pharmacy, University of North Carolina Hospitals, 101 Manning Drive, Campus Box #7600, Chapel Hill, NC 27514, USA*

[c]*School of Medicine, University of North Carolina at Chapel Hill, AIDS Clinical Trials Unit, 211A West Cameron Avenue, Campus Box #7215, Chapel Hill, NC 27599-7215, USA*

[d]*School of Pharmacy, University of North Carolina at Chapel Hill, Beard Hall, Campus Box #7360, Chapel Hill, NC 27599-7360, USA*

[e]*School of Medicine, University of California at San Francisco, UCSF AIDS Research Institute, 74 New Montgomery Street, Suite 600, San Francisco, CA 94105-3444, USA*

Received 15 January 2002; received in revised form 12 June 2002; accepted 18 June 2002

Abstract

This study examined whether a self-management intervention based on feedback of adherence performance and principles of social cognitive theory improves adherence to antiretroviral dosing schedules. Forty-three individuals with HIV/AIDS who were starting or switching to a new protease inhibitor regimen were randomly assigned to be in a medication self-management program or usual care control group. The self-management program included skills development exercises, three monthly visits for medication consultations, and monthly feedback of adherence performance using electronic monitors on medication bottles. Participants also completed a 40-item questionnaire that measured self-efficacy to take medications, on schedule, in a variety of situations. Logistic regression analysis indicated that individuals in the self-management group were significantly more likely to take 80% or more of their doses each week than individuals in the control group ($n = 29$, OR $= 7.8$, 95% CI $= 2.2$–28.1). Self-management training with feedback of adherence performance is a potentially useful model for improving adherence to complex regimens in HIV/AIDS care.

Keywords: Adherence; HIV/AIDS; Self-management; Self-efficacy; Social cognitive theory

1. Introduction and review of the literature

1.1. Antiretroviral adherence and clinical outcomes

Poor adherence to treatment regimens is a long-standing problem in many chronic health conditions. In HIV disease, the problem is particularly important because suppression of viral replication and long-term health status are thought to be directly related to treatment and medication adherence. Intermittent non-adherence to therapy contributes to treatment failure and favors the development of viral mutations that often lead to drug resistance. Since cross-resistance of antiretroviral drugs is common, the development of mutant strains poses a potential threat to individuals and the public health. Consequently, the significant gains from the introduction of new pharmaceutical agents are of less clinical benefit unless patients are able to take antiretroviral medications as prescribed [1].

Previous studies have found antiretroviral adherence is associated with improved clinical outcomes. Unfortunately, measurement of adherence and definitions of non-adherence frequently differ between studies and consequently, cross-study comparisons are problematic. Patterson et al. [2] measured adherence in 81 patients with HIV/AIDS using electronic monitors on protease inhibitor bottles. When adherence was calculated as the number of doses taken divided by the number of doses prescribed, the authors found the overall average adherence rate was 75% for participants in the study. Only 22% of patients with adherence of 95% or greater failed therapy as compared with 80% of those with less than 80% adherence. In contrast, Gifford

* Corresponding author. Tel.: +1-919-966-1169; fax: +1-919-966-8486.
E-mail address: ssmith@unc.edu (S.R. Smith).

0738-3991/02/$ – see front matter
PII: S0738-3991(02)00127-1

et al. [3] used self-reported measures of adherence in 133 subjects and found 50% of the sample reported taking 100% of their medications each day in the last week. When subjects were categorized into three groups according to adherence levels, each category improvement in adherence had significantly lower plasma HIV concentrations. Similarly, Nieuwkerk et al. [4] used self-reported measures and also found that only half of patients reported taking all antiretroviral medications in accordance to time and dietary instructions. As in other studies, poor adherence was associated with a decreased likelihood of having suppressed viral loads.

1.2. Medication adherence interventions in HIV/AIDS

Although significant advances have been made in the pharmacologic treatment of HIV disease, similar accomplishments have not been attained in understanding and improving antiretroviral adherence. Few studies have tested the effectiveness of patient education programs and behaviorally based interventions for helping patients manage antiretroviral regimens. A recent literature review of articles and abstracts published before April 1999 yielded only 16 published interventions designed to improve antiretroviral adherence, 12 of which were presented in conference abstracts [5]. In most cases, the reviewed studies provided little or no evidence of effectiveness for the tested intervention. Similarly, a Cochrane review of interventions concluded that a pharmacist-led program of education and supportive counseling was the only intervention shown to improve adherence to antiretroviral therapy [6].

Nevertheless, the literature in HIV/AIDS adherence research is growing rapidly. Studies published after the search periods of the reviews discussed above have found that factors associated with medication adherence in HIV/AIDS include active substance use [7], depression [8–10], regimen complexity [11], social support [9,10] side effect severity [10,12] and HIV-related symptoms [4,12,13].

1.3. Self-efficacy to adhere to antiretroviral therapy

One factor consistently shown in past research to be positively associated with antiretroviral adherence is self-efficacy [3,10,14], a behavioral construct described in social cognitive theory [15]. Self-efficacy is defined as beliefs in one's capabilities to organize and execute the course of action required to perform a particular activity [16]. In short, self-efficacy theorizes that individuals perform behaviors they believe they are capable of performing well. Bandura has proposed that self-efficacy is the most important prerequisite for behavioral change, because it affects how much effort is invested in a given task and what level of performance is attained. The concept of self-efficacy is an integral component of self-regulation models [17] because efficacy beliefs are the perceived ability to regulate a behavior effectively and consistently, especially under difficult circumstances [18]. According to the theory, individuals who regard themselves as highly efficacious in their ability to adhere will set higher goals, be more firmly committed to them, and therefore, exercise higher control over behaviors that foster adherence.

Social cognitive theory has been applied frequently to examine adherence to treatment regimens in several chronic diseases. For instance, high-efficacy expectations have been associated with treatment adherence in diabetes [19,20], rheumatoid arthritis [21], and cardiovascular disease [22,23]. In HIV/AIDS, patients with higher self-efficacy beliefs about using antiretrovirals report significantly better adherence [3]. Likewise, a randomized intervention designed to improve self-efficacy in 116 patients starting highly active antiretroviral therapy (HAART) found that self-efficacy was independently related to higher levels of adherence [24].

1.4. Purpose of the study

This study aimed to expand the theoretic knowledge of antiretroviral adherence by assessing the role of self-efficacy in the self-management of antiretroviral medications. The objectives were (a) to pilot test a survey instrument for measuring self-efficacy to adhere to dosing schedules for antiretroviral medications, and (b) to determine whether a clinical intervention, based on feedback of adherence performance and principles of self-regulation, improves adherence to antiretroviral dosing schedules.

2. Methods

2.1. Sample

Participants were recruited through clinician referrals from a hospital-based Infectious Disease Clinic at the University of North Carolina Hospitals in Chapel Hill, NC for approximately 1 year beginning in July 1998. Inclusion criteria were HIV-1 infection, aged 18 years or older, and willingness to give informed consent. To qualify for the study, individuals were also required to be initiating therapy for a new regimen that included a protease inhibitor (PI) or switching to a new PI-containing regimen. The protocol for the study was reviewed and approved by the university's Committee on the Protection of the Rights of Human Subjects.

Participants in the study were recruited through referrals made at the discretion of staff clinicians. If an individual was interested in participating, a trained study nurse or pharmacist was contacted and met the patient in the Infectious Disease Clinic. After obtaining informed consent, the participant was escorted to the General Clinical Research Center for randomization, administration of questionnaires, and medication counseling. All patients were compensated monetarily for participating in the study.

At enrollment, participants were randomized to the self-management intervention or usual care. The self-management program was designed to provide both medication education and skills training while the usual care group was designed to only provide medication education. Patient interviews and data collection were conducted with the assistance of customized software that was developed for the study.

2.2. Baseline visit

At baseline, all participants were asked to complete identical questionnaires containing items on demographics and attitudes towards medications. After completing the questionnaires, all participants received oral medication counseling based on United States Pharmacopeial (USP) guidelines. The aim of the educational component was to increase participants' level of knowledge about the medication regimen including benefits of therapy, adverse effects, scheduling of dosing, drug interactions, storage recommendations, and what to do if a dose was missed. As an adjunct to the oral counseling, all participants received printed leaflets that included words and pictograms that further explained the key points about the proper use of the medications. In addition, both groups received assistance with scheduling of doses and were given a customized pocket grid that listed the names of the prescribed medications in the regimen, the agreed upon dosing times, and any special dosing instructions. Lastly, eight strategies to improve adherence were discussed with every participant and a written summary of each strategy was provided. The strategies included the following: (1) integrate your regimen into your daily routine; (2) keep a checklist of doses taken; (3) use a daily planner; (4) plan ahead for weekends and vacations; (5) keep your medications with you when traveling; (6) plan ahead for privacy; (7) keep a diary; and 8) use a support network of friends or family.

2.3. Usual care control group

After the medication counseling, individuals in the usual care group were given an electronic monitor (described below), a demonstration on its use, and printed instructions about the monitor. No study-related follow-up visits were scheduled but participants were asked to complete a questionnaire on self-efficacy monthly for 3 months and to electronically monitor the use of the prescribed protease inhibitor. Questionnaires were obtained by request from the affiliated hospital pharmacy during prescription refills or through prescheduled delivery by mail. For each questionnaire returned to the investigators, participants were mailed a check for US$ 5.00 (early enrollees) or US$ 10.00 (later enrollees). After 3 months, participants in the usual care group were asked to return the electronic monitor through mail. A cash bonus was given to all participants who returned the electronic monitors.

2.4. Self-management intervention group

Participants in the self-management program received individualized patient education and assistance with medication self-management and skills training by a registered pharmacist or nurse (i.e., an efficacy intervention). The self-management program consisted of three central components: (a) information exchange, (b) skills development, and (c) social support enlistment. In addition to the education and assistance, the self-management group scheduled three follow-up appointments with the study pharmacists or nurse and received private one-on-one counseling at approximately monthly intervals. Prior to each follow-up counseling session, participants were asked to complete the self-efficacy questionnaire.

2.4.1. Information exchange

Knowledge is the motivational precondition for adopting patterns of behavior [16]. Therefore, the aim of the baseline and follow-up information exchange components were to increase participants' level of knowledge about the medication regimen. In addition, attention was devoted to strategies for integrating dose schedules into lifestyle patterns. At follow-up visits, participants had one-on-one counseling and the opportunity to ask the study pharmacists or nurse questions about the prescribed medication regimen.

2.4.2. Skills development

According to social cognitive theory, information about the medication regimen is necessary, although not sufficient to develop and maintain adherence. Patients usually need guidance on how to cultivate self-regulatory and coping skills in order to translate information into action. Thus, the aim of the skills training component was to equip patients with successful strategies for self-regulation. The three components of the self-regulation skills training were (1) self-monitoring, (2) goal-setting, and (3) enlistment of self-incentives.

2.4.2.1. Self-monitoring. At baseline, patients were given a calendar diary and asked to keep track of non-adherence and the events that foster it. The purposes of self-monitoring were to self-diagnose the determinants of non-adherence, self-evaluate progress towards goals, and enhance self-regulatory efficacy. At follow-up visits, notes in the diary were discussed with the study pharmacist or nurse. In addition, supportive feedback was given to the participant about how closely he or she adhered to the prescribed dosing schedule since the last visit. The adherence feedback was provided by showing participants graphical dosing information gathered by the electronic monitoring caps.

2.4.2.2. Goal setting. At the baseline and follow-up visits, participants were asked by the study pharmacist or nurse to set proximal subgoals (e.g. achieving a 90% monthly

adherence rate) that were instrumental in achieving larger future goals (e.g., an undetectable viral load). It is theorized that proximal subgoals provided incentives and guides for action, and subgoal attainments bolster self-efficacy and produce self-satisfactions that sustain one's efforts at personal change along the way [25].

2.4.2.3. Enlistment of self-incentives. At the baseline and follow-up visits, participants were also asked to create self-incentives for attaining their subgoals. The rationale was that individuals achieve greater self-directed change if they reward their successful efforts than if they provide no incentives for themselves.

2.4.3. Enlisting social support

Past studies have demonstrated that treatment adherence is usually related to supportive social systems [9,10]. Therefore, at the initial counseling session, participants were asked to name a supportive partner or friend. During follow-up visits, the study pharmacist or nurse encouraged the participant to ask the named person to provide assistance, particularly if the participant was having adherence problems or expressed non-medical difficulties with adhering to the regimen.

2.5. Measuring self-efficacy

A 40-item survey instrument to measure self-efficacy was developed for use in the study. Items for the instrument were obtained by adapting (a) the ''Adherence Confidence Scale'' developed by the Center for AIDS Prevention at the University of California, San Francisco and modifying (b) the ''Long-term Medication Behavior Self-efficacy Scale'' developed by De Geest et al. [26]. Respondents were asked to rate their level of confidence for taking medications on schedule in a variety of situations by using a scale from 0 (i.e., cannot do at all) to 10 (certain can do).

2.6. Measuring adherence

Adherence in the study was measured electronically using the Medication Event Monitoring System (MEMS). These electronic monitors, also known as MEMS caps, use a computer chip in the cap of a medication vial that records the precise date and time the vial was opened and presumably when the medication was taken. Electronic monitoring provides information about drug intake behavior that cannot usually be obtained from medical histories or from clinical laboratory examination. In addition, when used correctly it supplies a more reliable measure of adherence than any other measure, including detailed information about the patterns of pill taking. In this study, the data from the electronic monitors were used to derive measures of medication adherence by the participants over time. In descriptive analyses, adherence represented the number of doses taken divided by the number of total prescribed doses during each observation period. In the longitudinal analysis, adherence was dichotomized and was defined as taking 80% or more doses per week as measured by electronic monitoring. This definition of adherence was chosen because the level of adherence needed to obtain maximum benefit from antiretroviral therapy is currently unknown and 80% is a commonly used threshold in other published studies.

2.7. Medical record review

Informed consent was obtained to review medical and laboratory records. The purpose of this review was to examine HIV viral load levels, CD4+ cell counts, and health status. This information was recorded and linked to other information collected during the course of the study.

2.8. Statistical analysis

Distributions of important variables were graphed and summary statistics calculated. A graphical display of weekly adherence was plotted. Data were analyzed using the SAS system for Windows, Version 8.01 (Cary, NC). For variables measured at the interval or ratio level, measures of central tendency (e.g. mean and median) and measures of dispersion (e.g. range and standard deviations) were computed. Frequencies of sociodemographic variables for the sample were totaled and percentages were calculated. In addition, responses obtained from the self-efficacy questionnaire were summarized.

To examine the between-subject effects of experimental group assignment on self-efficacy and the within-subject effects of time, a repeated measures analysis of variance (ANOVA) was conducted. In the analysis, the dependent variable was self-efficacy and the independent variable was treatment group assignment. An overall self-efficacy score was derived by summing each of the 40-items from the survey instrument that was administered at baseline and at monthly intervals. Likewise, to compare adherence over time between the two groups, a longitudinal analysis using logistic regression with generalized estimating equations was conducted. The primary response variable examined in the analysis was protease inhibitor adherence. Adherence was defined as taking 80% or more doses per week as measured by electronic monitoring. Due to the small sample size, treatment group was the only independent variable included in the ANOVA and logistic regression models. Missing data were assumed to be missing at random.

Since there were 12 weeks of observation, and therefore 12 possible responses from one individual, responses from the same individual were correlated. Analyses of longitudinal data using conventional regression methods could provide erroneous variance estimates and loss of statistical efficiency because of the conventional assumption that each response is statistically independent [27]. Therefore, parameters of the logistic regression model were estimated

using the generalized estimating equation (GEE) methods of Zeger and Liang [28]. This approach models both the regression of the response variable on the independent variables and accounts for the correlated nature of the responses.

3. Results

3.1. Sample characteristics

Table 1 presents the sample characteristics of the self-management and usual care groups. The study enrolled 43 individuals with HIV disease, 74% of whom were non-white, 91% were male, and 69% had less than 2 years of college education. On average, participants were 37 years of age. Of participants, 53% were not working, 73% had estimated annual incomes that were <US$ 10,000, and 37% had Medicaid insurance coverage for health care. Approximately half of the participants had not previously used a protease inhibitor. Sixty percent of the sample was starting or switching to a regimen that included the anti-retroviral drug nelfinavir and was taken twice daily; 24% were starting or switching to a combination of ritonavir and saquinavir, which was also taken twice daily; and 16% were starting or switching to indinavir, which was taken every 8 h. The self-management and usual care groups had similar baseline characteristics.

3.2. Self-efficacy

Table 2 presents the means, standard deviations, medians, and interquartile ranges for items that measured self-efficacy to take medications on schedule in a variety of situations. As shown in the table, the median self-efficacy scores at baseline ranged from 7 to 10 with 10 being the highest efficacy. Items with the most variability were related to taking HIV medications in social situations and related to side effects caused by the medications. Lower mean scores and higher standard deviations were observed for taking medications on schedule when visiting a bar; when feeling sick to the stomach; while at a party; when having difficulty with swallowing; when the medication is causing mild side effects; when the medicine gives a mild stomach ache; when feeling very ill; and when unknown people are watching. The mean scores for most of the remaining items were 8.0 or higher, most median scores were 9.0 or higher, and there was little variability in responses. All scores were highly correlated with each other, but almost none of the scores correlated with adherence by electronic monitoring during the first month of therapy (data not shown). In addition, the repeated measures analysis of variance showed there was neither a significant between-subject effect according to treatment group ($F = 0.91$, $P = 0.36$) nor a significant within-subject effect over time ($F = 1.49$, $P = 0.23$).

Table 1
Sample characteristics of study participants ($N = 43$[a])

Characteristic	Usual care *n* (%)	Self-management *n* (%)
Total	21 (49)	22 (51)
Gender		
Male	17 (40)	17 (40)
Female	3 (7)	5 (12)
Race		
White	4 (9)	7 (16)
Non-white	17 (40)	15 (35)
Age		
20–29	3 (7)	4 (10)
30–39	10 (24)	11 (26)
40–49	5 (12)	4 (10)
>50	2 (5)	3 (7)
Education		
≤11	4 (10)	5 (12)
HS/GED	11 (26)	9 (21)
≥2 years	5 (12)	8 (19)
HIV exposure		
Sex with man	9 (21)	14 (33)
Sex with woman	4 (10)	2 (5)
IV	2 (5)	1 (2)
Do not know	1 (2)	3 (7)
Multiple	4 (10)	2 (5)
Work		
Yes	9 (22)	10 (24)
No	10 (24)	12 (29)
Income		
<US$ 5000	4 (11)	8 (22)
US$ 5000–9999	9 (24)	6 (16)
>US$ 10,000	3 (8)	7 (19)
Children at home?		
Yes	3 (7)	4 (10)
No	17 (40)	18 (43)
Insurance		
Medicaid	7 (17)	8 (20)
Medicare/military/VA/other	10 (24)	4 (10)
Private	1 (2)	2 (5)
Self-pay	3 (7)	6 (15)
Previous use of protease inhibitor		
Yes	13 (30)	8 (19)
No	8 (19)	14 (33)
Protease inhibitor		
Indinavir	2 (5)	5 (12)
Nelfinavir	14 (33)	12 (28)
Ritonavir/saquinavir	5 (12)	5 (12)

[a] Numbers less than $N = 43$ are due to missing data.

3.3. Disease self-management

Table 3 presents the goals, self-incentives, adherence, and barriers to adherence for 12 participants in the self-management program. The 12 patients were chosen as illustrative examples of the study participants' responses and were also individuals with the longest participation in the follow-up

Table 2
Measures of central tendency and spread for self-efficacy items at baseline before medication counseling by study personnel ($N = 43$)

	Mean	S.D.	Lower quartile	Median	Upper quartile
How confident are you that you can take your medications on schedule ...[a]					
... when you are at home?	8.9	1.7	8.0	10.0	10.0
... even though the pills may be big and difficult to swallow?	8.4	2.1	7.0	9.0	10.0
... even though the medications are very expensive?	8.2	2.5	7.0	9.0	10.0
... in the absence of scheduling aids (e.g. pill box, calendars)?	8.4	1.9	7.5	9.0	10.0
... when nobody helps you get ready?	8.9	1.6	8.0	10.0	10.0
... while at work?	7.9	2.6	7.0	9.0	10.0
... during the weekend?	8.8	1.7	8.0	9.0	10.0
... when the medicine is causing mild side effects?	7.2	2.6	5.0	8.0	9.0
... even if it causes you to have a dry mouth?	8.0	2.4	7.0	9.0	10.0
... when feeling very healthy?	8.8	2.0	9.0	10.0	10.0
... when it is prescribed to be taken with lots of water ?	8.6	1.8	8.0	9.0	10.0
... when the time of intake does not coincide with your meal times?	8.3	2.1	7.0	9.0	10.0
... when you are in the middle of a project?	8.1	2.0	7.0	9.0	10.0
... when the medicine gives you a mild stomach ache?	7.4	2.7	6.0	8.0	10.0
... when nobody reminds you about the time at which you should take the medication?	8.5	2.0	8.0	10.0	10.0
... when you have visitors at home?	7.9	2.9	7.0	9.0	10.0
... after you have gotten very angry with a friend?	8.4	2.0	8.0	9.0	10.0
... when you are in pain?	7.9	2.3	7.0	9.0	10.0
... while watching an exciting program on television?	8.9	1.7	8.0	10.0	10.0
... when you feel very ill?	7.5	2.7	6.0	8.0	10.0
... when you feel very sad?	7.9	2.4	7.0	9.0	10.0
...while unknown people are watching you (e.g. in a restaurant)?	7.5	3.0	7.0	9.0	10.0
... when you feel sick to your stomach?	6.6	3.2	5.0	7.0	10.0
... when you are having an argument with your partner?	7.6	2.7	6.0	8.0	10.0
... when you are at a party?	7.0	3.4	5.0	8.0	10.0
... while taking a long walk?	7.5	3.0	6.0	9.0	10.0
... while visiting a bar?	6.2	3.9	2.0	8.0	10.0
... if it means taking it in front of people who do not know you are HIV-infected?	7.1	3.6	5.0	8.0	10.0
How confident are you that you can ...[b]					
... pick up your prescription refills at the pharmacy before running out of pills?	8.9	1.9	8.0	10.0	10.0
... arrange for someone to take you to a 2 h clinic appointment, and take you back home again, if you are not feeling well enough to get there by yourself?	8.5	2.1	8.0	10.0	10.0
... ask questions of the pharmacist, when everyone in the pharmacy seems busy?	8.5	2.3	8.0	10.0	10.0
How confident are you that you can stick to your medication schedule ...[b]					
... when you are in a fun-loving mood?	8.6	2.0	8.0	9.0	10.0
... even when your daily routine is disrupted?	8.0	2.2	7.0	9.0	10.0
... when you are traveling across time zones?	7.6	2.5	6.0	8.0	10.0
... when you are having difficulty swallowing?	7.1	2.8	5.0	8.0	9.0
... when it means changing your eating habits?	7.8	2.3	7.0	9.0	10.0
... for the next 7 days?	8.7	2.1	8.0	10.0	10.0
... for the next 14 days?	8.8	1.8	8.0	10.0	10.0
... for the next 30 days?	8.9	1.5	8.0	10.0	10.0
... for the next 2 months?	8.8	1.7	8.0	10.0	10.0

[a] Items adapted from [26].
[b] Items adapted from the Adherence Confidence Scale developed by the Center for AIDS Prevention at the University of California, San Francisco.

study visits. Overall, participants often articulated goals and incentives that were among those used as examples by study personnel. Goals focused on taking medications on time or improving clinical laboratory values, such as increasing CD4+ cell counts or reducing viral load. When a goal was met, a slightly higher threshold was generally set for the next scheduled meeting. If a stated goal was not met, the same goal was usually retained for the next follow-up meeting. By design, self-incentives for meeting goals were generally modest rewards, such as dining at a favorite restaurant or eating a favorite food, taking a short trip, talking or celebrating with friends and family, or rewarding oneself with a purchase.

In the calendar diaries and during discussion with the study personnel, participants in the self-management group noted a variety of barriers to adherence since the time of the previous visit. These barriers were generally related to bothersome side effects, being physically separated from the medications, social situations, and traveling. Reported side effects were stomach aches, peeling lips, nose bleeds,

Table 3
Goals, self-incentives, barriers[a], and adherence[b] of 12 selected participants in an HIV self-management program

ID	Baseline		First follow-up				Second follow-up				Third follow-up			
	Goal 1	Incentive 1	Adherence	Barriers 1	Goal 2	Incentive 2	Adherence	Barriers 2	Goal 3	Incentive 3	Adherence	Barriers 3	Goal 4	Incentive 4
1	Take 90% of prescribed doses	Go out to dinner with partner	87.5	Feeling sick to stomach, planning ahead—for instance was out and forgot to bring medicine	Take 90% of prescribed doses	Go out to dinner with partner	66.2	Early morning—feeling good and did not need to take the medicine	Take 90% of prescribed doses	Go out to dinner with partner and tell nurse practitioner in clinic	84.6	Busy month—entering contest in state fair, moving and buying new home	Take 90% of prescribed doses	Go out to dinner with partner and tell nurse practitioner in clinic
2	Decrease in viral load next visit	Share electronic monitoring (feedback) reports with mom	101.3[c]	Caught in traffic, argument with roommate, drinking, fixing meals	Decrease in viral load next visit	Share electronic monitoring (feedback) reports with mom	98.6	In jail temporarily since the last visit	Go to 400 or undetectable	May go back to work	104.3[c,d]	At a bar and forgot, also went partying with a friend and lost track of time, being away from home		Share electronic monitoring (feedback) reports with mom
3	Take medicine on time 75% for next month	Take self out to dinner	101.9[c]	Early morning dose sometimes a problem; weekends when activities away from home—remembering to take medicine with her	Continue to take medicine 80% for next month	Buy a new outfit	100	Bothered by peeling lips, nose bleed, tingling in hands, water tastes bad, food tastes bad, early morning dose	Continue to take medicine 85% for the next month	Going on a trip out of state	100	Bothered by weight gain, peeling lips, occasional nausea, scalp peeling, retaining fluid	Take medicine even though on vacation	Have a party
4	Undetectable viral load	Call friend	98.7	Getting focused on activity, feeling sick to stomach	Undetectable viral load	Eat some large shrimp	102.1[c]	Having people over and getting focused on activities	To get viral load below 100,000	Trip out of state	88.6	Traveling	Undetectable viral load	Eating shrimp
5	Tolerate the medication for the next month; if intolerance does occur he will stick it out and/or call for help	Take self to restaurant	92.7	Medication upset stomach	Open bottle in morning and again at night/take out multiple doses less often	Go for leisure ride	92.9	Electronic monitoring cap on pill bottle, social situations with family, prescribed sleeping pill causes him to occasionally oversleep	Get to 90% doses taken (as measured by therapeutic coverage)	Get new clothes (buy something shopping)	96.4	Sleeping, lots of body aches, some confusion about when to take non-HIV med, feeling low energy	Get to 95% doses taken (as measured by therapeutic coverage)	Go to the shopping mall
6	Take medication exactly on time for 7 days	Go to a movie	98.4	Oversleep, visitors at home	Take medication exactly on time for 30 days	Get healthier as time progresses—maybe a short trip	79.6	People, company in house, work getting in way of eating food	Undetectable for another 30 days	Call friend long-distance	Missing	People coming over to the house. Traveling on fishing trip	Stay undetectable	
7	1 day at a time with perfect intake	Go out to eat at a restaurant of choice	4.4	Traveling driving—worried about drowsiness effects of medicine	1 day at a time with perfect intake	Go out to eat at a restaurant of choice	10.7	Late doses because of hospitalization; no medications available at small community hospital	1 month with perfect intake	Go to beach	59	Two doses missed because throat hurting and unable to swallow nelfinavir; several missing MEMS points because took out two doses at once	Try again for perfect intake	Go to the beach

Table 3 (*Continued*)

ID	Baseline		First follow-up				Second follow-up				Third follow-up			
	Goal 1	Incentive 1	Adherence	Barriers 1	Goal 2	Incentive 2	Adherence	Barriers 2	Goal 3	Incentive 3	Adherence	Barriers 3	Goal 4	Incentive 4
8	Higher CD4+ count	Go out to a new movie	16.1	Missed dose because got caught up in TV	Perfect adherence for the next 30 days	A big milkshake	92.8	Ritonavir taste but now he is putting in capsules, flatulence, dry skin, change of complexion	To be undetectable	A big milkshake	98.4	None reported, ''smooth riding''	To be undetectable	
9	Take 80% of doses on time	Buy a milkshake	99.1	Parties and alcohol caused one missed dose and two late doses/also being mad at friend caused problems with medications.	Write more in daily reminder	Go to movies	99.2	Time change, traveled out of state for Christmas, meals different due to time change	Do more exercising	Buy a milkshake	97.3	Going to hospital, diarrhea, feeling low energy		
10	For skin to be better in 1 month	Going on a trip	19.6	Could not get here physically because of transportation problems	30 days of a perfect record	Going on a trip	31.3	Oversleeping, coming in late, Valentines day celebration	Thirty days of a perfect record	Going on a trip	Missing	None reported		
11	Not to miss any doses between now and next visit	Buy a new book	82.1	Traveling, Saturdays (waking up later, rushed to get on with day, kept thinking ''I will take it later'')	Take 90% of doses for next month	Buy a new book	75	Getting prescription filled—from the pharmacy being out of stock, Saturdays sometimes a problem	Take 90% of doses for next month	Buy a new book	No visit			
12	Take medicine exactly as prescribed for next month	Take self shopping	98.6	Morning doses sometimes a problem—possible due to other meds (sleeping pills, etc.)	Working on morning dose	Visit dad	No visit							

[a] All barriers may not have caused participants to miss medication doses. In some cases, participants may have encountered a barrier but overcame it and took the medication as prescribed.
[b] Adherence as measured by electronic monitoring represents the number of doses taken divided by the number of total prescribed doses during each observation period.
[c] An adherence score of >100% represents taking more doses than prescribed, a form of nonadherence.
[d] Adherence for participant 2 was calculated to be 104% despite reporting barriers and forgetting to take a dose. It is unknown whether the reported barriers caused the participant to completely miss a dose and subsequently take extra doses to compensate.

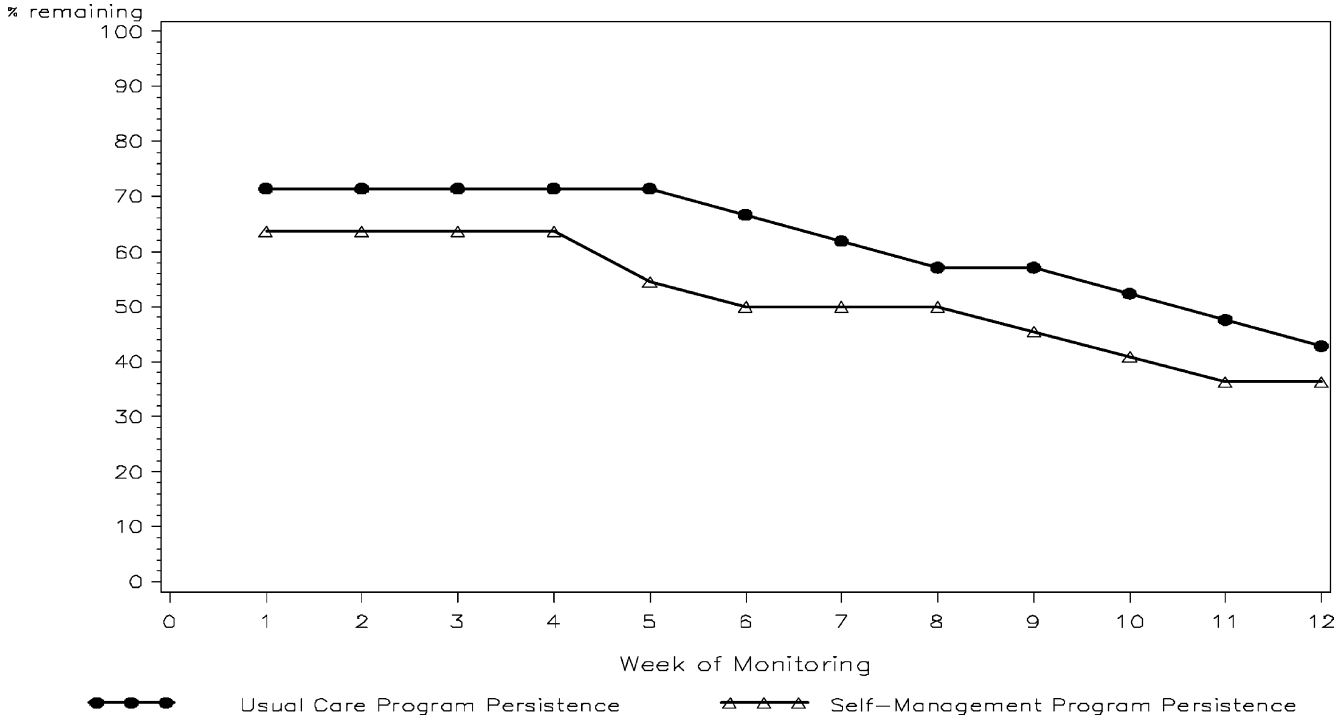

Fig. 1. Proportion remaining in study by week in self-management ($N = 22$) and usual care groups ($N = 21$).

"tingling in hands", taste disturbances, weight gain, fluid retention, "low energy", dermatologic problems, and drowsiness. Social situations identified as barriers were arguments, being arrested, "partying", having guests at home, work, holidays, and focusing on a project or activity. Traveling away from home and out of state were also barriers.

Special foods, movies, purchases, and travel were often used as self-incentives. In a few cases, incentives were also related to adherence barriers. For example, participant 4 reported taking a trip as an incentive during the second follow-up visit, but reported traveling as barrier in the fourth follow-up visit.

3.4. Program persistence

Fig. 1 displays the proportion of individuals remaining in the study at each week. Over time, a parallel decline in participation was observed in both groups. After 1 week, 71% (15/21) of the control group and 64% (14/22) of the self-management group remained in the study. By the twelfth week, 43% (9/21) participants remained in the control group and 36% (8/22) participants remained in the self-management program.

3.5. Adherence over time

Fig. 2 presents the average weekly adherence rates for the self-management and control groups. Adherence in the self-management group was higher than the control group at all time points. In addition, the average adherence of the group increased over time and by the end of 12 weeks, the average weekly adherence of individuals remaining in the study was 96%. On the other hand, the average adherence for the control group gradually declined and the average group adherence of those remaining was 37% by the end of the study. Logistic regression analysis indicated that individuals in the self-management group were significantly more likely to take 80% or more of their doses each week than individuals in the control group (Table 4, OR = 7.8, 95% CI = 2.2–28.1).

3.6. Clinical outcomes

Fig. 3 shows the proportion of individuals in each group and the lowest viral load obtained within 1 year of randomization. Only individuals who participated in the study for at least 1 month and had viral load data available in their medical record are included. As the figure shows, 64% (7/11) of individuals in the self-management group had at least one viral load of 400 copies or less as compared to 38% (5/13) of individuals in the control group. However, the differences between the two groups were not statistically

Table 4
Logistic regression analysis of weekly adherence[a] by treatment group for up to 12 weeks post-randomization $N = 29$

Group	Estimate	S.E.	95% CI		*P*
Usual care	Referent				
Self-management	2.0524	0.6556	0.7674	3.3375	0.0017

[a] Adherent is defined as taking 80% or more does per week as measured by electronic monitoring.

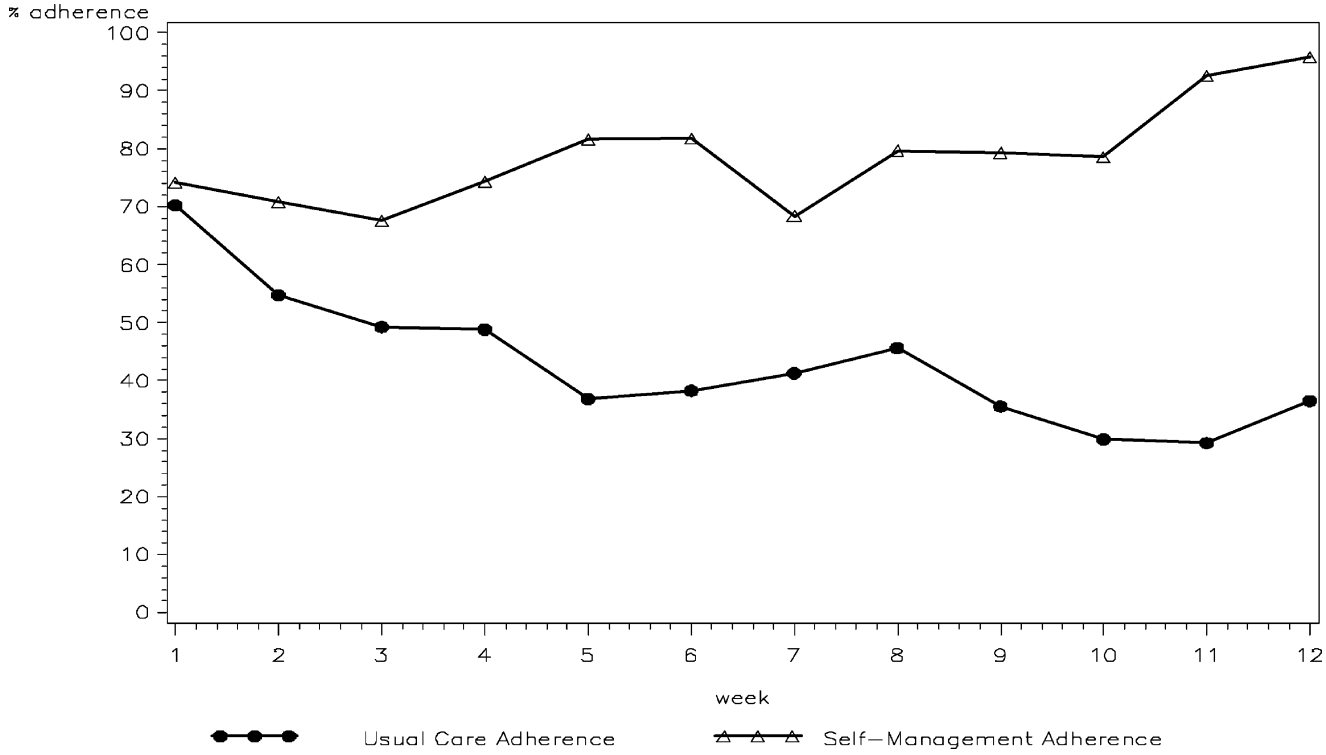

Fig. 2. Mean adherence by week in self-management and usual care groups.

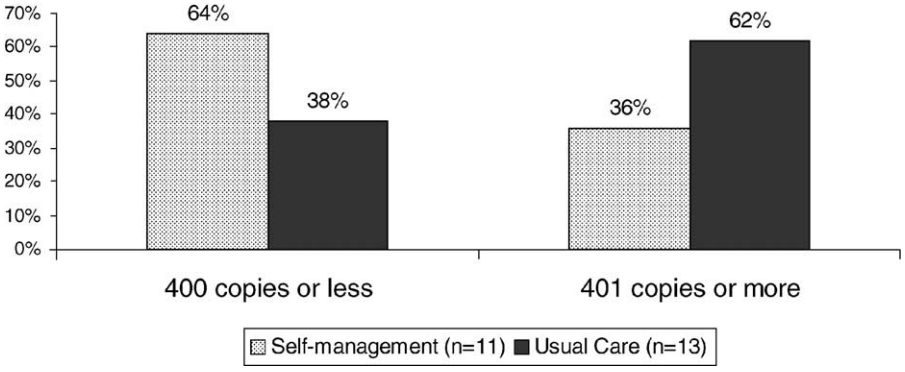

Fig. 3. Proportions of self-management and usual care groups by the lowest viral load measures recorded in medical records within 1 year of randomization.

different by χ^2 or Fisher's exact tests ($x^2 = 1.51$, $P = 0.22$). Notably, the sample size was small and the statistical tests exclude five individuals with missing viral load information. Consequently, the tests have poor statistical power to detect significant differences if they existed.

Similar results were observed when all individuals who enrolled into the study were examined. This group consisted of 34 individuals who had viral load information in their medical record. In this case, 41% (9/22) of individuals in the self-management group had at least one viral load of 400 copies or less as compared to 24% of individuals (5/21) in the control group. Again, the differences between the two groups were not statistically different by χ^2 or Fisher's exact tests ($x^2 = 1.23$, $P = 0.27$) and nine people were excluded due to missing data.

4. Discussion

This study found preliminary evidence that a clinic-based intervention based on feedback and discussion of adherence performance and principles of self-regulation improves adherence to dosing schedules for antiretrovirals. The behavioral intervention helped patients living with HIV/AIDS to develop the self-management skills needed for using a new drug therapy regimen. Key components of the medication self-management program were comprehensive medication counseling by a specially trained health professional, written medication information, skills development exercises, monthly visits for medication consultations, and monthly feedback of adherence performance using electronic monitors. Although a majority of people did not complete the

entire 3 months of the program, the mean adherence in the intervention group was higher at all time points than the control group.

The additional time spent with patients *at follow-up* likely resulted in higher adherence in the self-management group. Despite intensive medication counseling *at baseline*, participants frequently had an incomplete understanding of how to take their prescribed regimen at the follow-up visits. Patients often presented with very specific drug-related questions about their antiretroviral medications and how the medicines were to be taken. Participants in the self-management program commonly sought clarification of their dosing regimen and reinforcement to take antiretrovirals consistently on schedule. In collaboration with the pharmacist or nurse, individuals in the self-management program used feedback of adherence information to help self-diagnose and resolve individual adherence problems. In addition, self-management participants used the monthly consultation sessions to problem-solve with the pharmacist or nurse on issues related to medication side effects, insurance coverage, transportation, and concerns about privacy and disclosure of HIV status.

The feedback and discussion of adherence since the last visits were major components in this intervention. When reviewing adherence information with the patient, it was important for study personnel to be non-judgmental and supportive. Participants in the study who did not reach their monthly adherence goal sometimes expressed feeling discouraged or were concerned with how the results might be viewed by the counseling pharmacist or nurse. Since feedback of adherence could potentially discourage patients (and presumably reduce self-efficacy), clinicians who wish to use feedback should present the information in a supportive way, including planned strategies for providing patient assistance.

Additionally, adherence information was not shared by study personnel with patients' prescribers or dispensing pharmacists. Future research is needed to understand how levels of involvement by prescribers and dispensing pharmacists may influence and potentially improve the self-management program. In the current study, participants may have viewed study personnel as neutral third-parties with whom adherence behavior and barriers could be discussed openly and confidentially. In other cases, participants showed personal adherence reports to their prescriber or shared the information verbally. Although a better understanding of the effects of providing adherence information to providers is needed, integrating the intervention into usual clinical practice will likely optimize its effects on adherence.

At the initiation of new antiretroviral therapy, participants rated confidence in the ability to take medications on schedule as high for nearly all the situations posed. On the one hand, this finding may be due to self-selection into the study by patients and prescribers for individuals who demonstrate high confidence in ability to take therapy. On the other hand, the items used to measure self-efficacy in the study need further development and testing; additional measures of self-efficacy, such as those proposed by Lorig [29] may improve the responsiveness of the items. Nevertheless, routinely assessing self-efficacy may be valuable for distinguishing individuals who are ready to start antiretroviral regimens and those who need more extensive counseling and assistance. Current national guidelines on the use of antiretroviral agents recommend that clinicians assess patient readiness to begin therapy and the likelihood of adherence before initiating treatment [30]. However, no standardized assessment tool exists and the guidelines do not address remedial measures for assisting individuals with preparing for therapy. An instrument for measuring self-efficacy and a skills training program hold potential for helping individuals with preparing to take therapy. Furthermore, questionnaires assessing self-efficacy may be useful in busy clinical settings and community pharmacies to guide medication counseling. By reviewing a completed questionnaire prior to counseling, clinicians may be informed of situations that will potentially interfere with patients' ability to adhere. Using this information, clinicians can tailor communication about medications to fit situations patients identify as being potentially problematic.

4.1. Study limitations

The findings of this study are preliminary and have some important limitations. First, losses to follow-up in both the self-management and control groups were high and this may have potentially biased the results. Attrition may have been a function of the study location which was in a large state-supported medical center that provides specialized services for individuals living in surrounding rural communities. Since some participants lived several miles from the center, transportation may have been a barrier to completing the study. Second, a relationship between participation in the self-management program and clinical outcomes like viral load or CD4+ cell count was not found. Although adherence was higher in the self-management group it is unknown whether this led to improved health status. Third, the sample size of participants was small, partly due to inclusion criteria which specified that participants be new to therapy or starting a new regimen. The small size precluded some analyses of self-efficacy and consequently future studies are needed with larger numbers of participants to better understand the role of self-efficacy, adherence, and self-management in HIV disease. Fourth, recruitment in the study relied upon clinician referrals and these referrals may have influenced the size and composition of the sample. Fifth, the period of observation in this study was only three months. It is unknown whether the high rates of adherence in the self-management group were sustained.

It should also be noted that the baseline counseling and follow-up visits of the adherence program may increase the time patients initially spend with health providers. In some cases, there may be obstacles or disincentives for both patients and providers to spend extra time discussing

adherence during health care visits. Although the clinical and public health benefits of rigorous adherence are recognized in national HIV clinical guidelines [30], some health care settings may have limited capability to implement formal adherence programs due to limited resources, such as time, staffing, private space for counseling, and service reimbursement by third party payers. Even in the funded program presented here, resources limited the number of patients who could participate and resulted in a small sample.

Health care organizations who wish to implement a self-management program may need to reallocate or add resources in order to accommodate the time health professionals spend discussing adherence with patients. Likewise, the comprehensiveness of the program is likely to increase the time patients spend with health providers and some patients may be disinclined to do this. Although the clinical and public health benefits of increased antiretroviral adherence are significant, comprehensive adherence programs, such as the one described may be limited to a degree by the resources of the provider, reimbursement by third party payers, and patient interest.

4.2. Practice implications

Self-management training with feedback of adherence performance is a potentially useful model for improving adherence to complex regimens in HIV/AIDS care. This study applied principles of self-efficacy and self-regulation and designed a medication self-management program that can be used by pharmacists, nurses, or health educators to assist individuals with treatment adherence. As advances in technology improve the measurement of adherence through new electronic tools that are inexpensive and simpler to use, routine monitoring of adherence may become common in clinical practice. When used appropriately, electronic monitoring provides clinicians and patients with objective information that can serve as the basis for clinicians to provide encouragement, verbal reinforcement, and problem solving assistance with patients. In addition, on-going medication counseling and regular consultations help build confidence and understanding for patients to adhere to a treatment plan.

Acknowledgements

This research was funded by an unrestricted educational grant from Glaxo SmithKline Inc., by the Pharmacy Foundation of North Carolina, and by a grant (RR00046) from the General Clinical Research Centers program of the Division of Research Resources, National Institutes of Health.

References

[1] Deeks SG, Smith M, Holodniy M, Kahn JO. HIV-1 protease inhibitors. A review for clinicians. JAMA 1997;277:145–53.

[2] Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Int Med 2000;133:21–30.

[3] Gifford AL, Bormann JE, Shively MJ, Wright BC, Richman DD, Bozzette SA. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. J Acquir Immune Defic Syndr Hum Retrovirol 2000;23:386–95.

[4] Nieuwkerk P, Gisolf E, Sprangers M, Danner S. Adherence over 48 weeks in an antiretroviral clinical trial: variable within patients, affected by toxicities and independently predictive of virological response. Antivir Ther 2001;6:97–103.

[5] 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 Couns 2002;46:93–108.

[6] Haddad M, Inch C, Glazier RH, Wilkins AL, Urbshott G, Bayoumi A, Rourke S. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS (Cochrane Review). Issue 3, The Cochrane Library, Oxford: Update Software, 2000.

[7] Stein MD, Rich JD, Maksad J, Chen MH, Hu P, Sobota M, et al. Adherence to antiretroviral therapy among HIV-infected methadone patients: effect of ongoing illicit drug use. Am J Drug Alcohol Abuse 2000;26:195–205.

[8] Holzemer WL, Corless IB, Nokes KM, Turner JG, Brown MA, Powell-Cope GM, et al. Predictors of self-reported adherence in persons living with HIV disease. AIDS Patient Care STDS 1999;13:185–97.

[9] Gordillo V, del Amo J, Soriano V, Gonzalez-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. AIDS 1999;13:1763–9.

[10] 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;19:124–33.

[11] Stone VE, Hogan JW, Schuman P, Rompalo AM, Howard AA, Korkontzelou C, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HER study. J Acquir Immune Defic Syndr 2001;28:124–31.

[12] Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, De Longis P, et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr 2001; 28:445–9.

[13] Duran S, Spire B, Raffi F, Walter V, Bouhour D, Journot V, et al. Self-reported symptoms after initiation of a protease inhibitor in HIV-infected patients and their impact on adherence to HAART. HIV Clin Trials 2001;2:38–45.

[14] Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther 2001;39:1151–62.

[15] Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977;84:191–215.

[16] Bandura A. Self-efficacy: the exercise of control. New York: Freeman, 1997;79–115.

[17] Merluzzi TV, Sanchez MA. Assessment of self-efficacy and coping with cancer: development and validation of the cancer behavior inventory. Health Psychol 1997;16:163–70.

[18] Bandura A. Social cognitive theory and exercise of control over HIV infection. In: DiClemente RJ, Peterson JL, editors. Preventing AIDS: theories and methods of behavioral interventions. New York: Plenum Press, 1994;25–59.

[19] McCaul KD, Glasgow RE, Schafer LC. Diabetes regimen behaviors. Predicting adherence. Med Care 1987;25:868–81.

[20] Kavanagh DJ, Gooley S, Wilson PH. Prediction of adherence and control in diabetes. J Behav Med 1993;16:509–22.

[21] Taal E, Rasker JJ, Seydel ER, Wiegman O. Health status, adherence with health recommendations, self-efficacy and social support in patients with rheumatoid arthritis. Patient Educ Couns 1993;20: 63–76.
[22] Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary heart disease. The Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1994;89: 975–90.
[23] DeBusk RF, Miller NH, Superko HR, Dennis CA, Thomas RJ, Lew HT, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. Ann Int Med 1994; 120:721–9.
[24] Tuldra A, Fumaz CR, Ferrer MJ, Bayes R, Arno A, Balague M, et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. J Acquir Immune Defic Syndr Hum Retrovirol 2000;25:221–8.
[25] Bandura A. Self-efficacy: the exercise of control. New York: Freeman, 1997;1–35.
[26] De Geest S, Abraham I, Gemoets H, Evers G. Development of the long-term medication behaviour self-efficacy scale: qualitative study for item development. J Adv Nurs 1994;19:233–8.
[27] Liang KY, Zeger SL. Regression analysis for correlated data. Ann Rev Public Health 1993;14:43–68.
[28] Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–30.
[29] Lorig K. Outcome measures for health education and health care interventions. Thousand Oaks, California: Sage Publications, 1996.
[30] Centers for Disease Control and Prevention. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents: recommendations of the Panel on Clinical Practices for Treatment of HIV. MMWR 2002;51(RR-7):8–10.