Review

Antiretroviral Adherence Interventions: A Review of Current Literature and Ongoing Studies

Jane M. Simoni, PhD, Pamela A. Frick, PharmD, MPH, David W. Pantalone, AB, Barbara J. Turner, MD, MSEd

Adherence has proven to be the Achilles' heel of antiretroviral therapy. To achieve the nearly perfect adherence apparently necessary for optimal effects, individuals often require assistance. In this review, we examine antiretroviral therapy adherence intervention studies and reviews published through January 2003 as well as abstracts of ongoing National Institutes of Health-funded research projects aimed at enhancing antiretroviral therapy adherence. The 21 published studies we located utilized 4 intervention strategies: cognitive-behavioral, behavioral, directly observed therapy, and affective. Most of these were pilot or feasibility studies. However, the 4 randomized controlled trials conducted with adequate methodologic rigor suggest some promising yet preliminary effects of a pharmacist-led individualized intervention, a cognitive-behavioral educational intervention based on self-efficacy theory, and cue-dose training when combined with monetary reinforcement. The 39 ongoing federally funded studies offer superior methodologic sophistication and include some innovative strategies, such as the use of handheld devices, two-way pagers, and alarmed medication vials, along with enhancement of social and emotional support.

Numerous reports have documented that combinations of antiretroviral medications can inhibit HIV replication and result in precipitous declines in HIV-associated morbidity and mortality.[1-3] However, the high degree of success with antiretroviral therapy in achieving HIV-1 RNA levels below assay detection limits reported in clinical trials (ie, 60%–90%) has seldom been achieved in everyday practice.[4] Indeed, studies in primary care settings suggest that, on average, only 50% of patients achieve HIV-1 RNA levels below detection limits.[5,6] A primary reason for the lack of success in clinical practice appears to be either intentional or non-intentional poor adherence to medication regimens.[7-9] The level of antiretroviral therapy adherence needed to obtain optimal long-term benefits appears to be over 90%.[10-12] Compared with therapy for most other clinical conditions, antiretroviral therapy requires an unprecedentedly high level of adherence for an indefinite time period to achieve optimal viral suppression. Consequently, adherence has proven to be the Achilles' heel of antiretroviral therapy.

Adherence to demanding antiretroviral regimens requires substantial support and monitoring. Effective approaches to promote and improve patient adherence to antiretroviral therapy are the focus of intensive, time-consuming research. Most intervention studies are still incomplete. Nonetheless, results from available studies can offer instructive examples for clinicians and patients to consider while awaiting more definitive results.

In this review of the emerging research on interventions to improve antiretroviral adherence, we consider various conceptualizations of adherence and its correlates as well as interventions designed to enhance adherence. We review published reports as well as summaries of ongoing federally funded studies and conclude with recommendations for practice and directions for future research.

Conceptualizations of Adherence and Its Correlates

There is no universally accepted definition of medication adherence. With respect to HIV/AIDS care specifically, "medication adherence" has been defined as "the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing, and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function."[13]

In addition, few studies concur in their operationalization of adherence. Two common approaches to defining a categoric outcome are to consider whether the patient missed any pills over a specific interval or whether the patient has exceeded a set percentage of doses taken. The latter threshold approach may also consider the timing of taking the medications.[14] Less commonly, adherence is analyzed as a continuous variable, such as the proportion of prescribed doses taken as measured by an electronic monitoring device, self-report, or pill counts; the percentage of pills available for consumption by pharmacy refill records; or the number of missed doses over a specified time period, such as the last 3 days.

Many correlates of nonadherence have been identified from cross-sectional studies. Ickovics categorized these factors into 4 groups: patient characteristics; aspects of the provider and the patient-provider relationship; variables related to the treatment regimen or illness; and contextual or environmental factors.[15] With respect to correlates of nonadherence to antiretroviral

Author Affiliations: Department of Psychology, University of Washington, Seattle, WA (Dr Simoni and Mr Pantalone); Department of Pharmacy, University of Washington, Seattle, WA (Dr Frick); Division of General Medicine, University of Pennsylvania, Philadelphia, PA (Dr Turner). **Corresponding Author:** Jane M. Simoni, PhD, University of Washington, Department of Psychology, Box 351525, Seattle, WA 98195 (email: jsimoni@u.washington.edu).

therapy, 1 review found that several factors were often associated with nonadherence, including symptomatic disease and presence of adverse drug effects, psychologic distress, lack of social or family support, increased complexity of the antiretroviral therapy regimen, low patient self-efficacy, and inconvenience of treatment.[16]

Previous Reviews of Antiretroviral Adherence Interventions

The seriousness and urgency of problems related to nonadherence to antiretroviral medications have sparked increasing attention to this issue; however, scant empiric research on adherence interventions for HIV-infected persons has been published. Notwithstanding the embryonic stage of this research, there are 3 reviews summarizing current knowledge.

Haddad and colleagues reviewed controlled research studies published from January 1996 to April 1999 on interventions offering patient support and education to promote antiretroviral therapy.[17] They identified only one intervention (by Knobel and colleagues in a Spanish-language publication) that met the strict selection criteria.[18] Another review of the field through April 1999 identified 16 interventions designed to enhance HIV medication adherence, of which 12 were reported in conference abstracts and 4 in published articles.[14] The interventions incorporated strategies that were cognitive (ie, designed to teach, clarify, or instruct); behavioral (ie, designed to shape, reinforce, or influence behavior); or affective (ie, designed to optimize social and emotional support). Of the 16 reports, only 11 included data on intervention efficacy, and the effects of these interventions were generally weak. Among these, only 5 were RCTs, with a mean sample size of 58. Four of these reported no treatment effect between the intervention and control groups, and the fifth, a DOT study, reported temporary effects that disappeared after the intervention ended.[14,19]

A third review focused on reports of RCTs of interventions to enhance adherence to antiretroviral therapy that were published or presented at the International AIDS Conference in Barcelona in July, 2002.[20] The authors cited published reports of 2 promising interventions by Tuldra and colleagues and Rigsby and colleagues, as well as the Knobel and colleagues study cited above.[18,21,22] From the AIDS Conference presentations, the authors cited 2 successful RCTs, one involving an internet-based paging system and the other using continuous and personalized counseling. However, 2 other RCTs that were presented, 1 assessing a problem-solving and enhanced support intervention and the other based on motivational interviewing, showed no intervention effects.

Data Sources for the Current Review of Adherence Interventions

For the present review, we updated and expanded the existing literature reviews and included a description of ongoing federally funded research.

We searched PsychINFO and MEDLINE for articles published through January 2003 that contained various combinations of the terms *HIV/AIDS*, *adherence* (or *compliance*), and *intervention* (also keywords for specific types of interventions, such as *education*, *telephone*, *pager*, *peer*, and *alarm*). We selected from this list all research articles describing primary reports of interventions to enhance antiretroviral adherence. We also scanned bibliographies of relevant articles for additional studies. Given the early stage of research in this field, we included descriptions of all relevant studies in our review regardless of methodologic rigor. However, common methodologic weaknesses of the work (eg, no randomization, no control group, sole reliance on self-report, no follow up, insufficient power, no statistical significance testing, and no intent-to-treat analyses) are noted below.

Additionally, we searched CRISP (Computer Retrieval of Information on Scientific Projects), a searchable online database of ongoing federally funded biomedical research projects, using the terms *HIV*, *medication*, *adherence*, *nonadherence*, *compliance*, *noncompliance*, *antiretroviral*, and *HAART*.

Findings from Current Review of Adherence Interventions

Our review of the published literature identified 21 interventions focused on enhancing adherence to antiretroviral therapy (Table 1); we excluded the few that focused on antiretroviral monotherapy.

The interventions in Table 1 are divided into 4 categories of strategies, based loosely on the review by Fogarty and colleagues:[14] cognitive and behavioral, behavioral only, (modified) DOT, and affective. Although Ickovics and colleagues identified 4 distinct groups of factors that affect adherence,[23] most of the intervention strategies that we identified in these 4 categories targeted only patient characteristics.

Nine studies combined cognitive and behavioral strategies. The interventions were delivered in group settings, one-on-one, or via both modalities. A trained facilitator or adherence counselor was usually the intervener, but when a provider was involved, it was typically a nurse or pharmacist. Four intervention studies evaluated strictly behavioral strategies. The types of interventions spanned a drop-in store-front center, a pager system, frequent HIV-1 RNA monitoring, and monetary reinforcement.

The third category involved 6 interventions that provided some form of DOT where a provider, outreach worker, or peer delivered every dose (or, in the case of modified DOT, almost every dose) of prescribed medication and watched the patient ingest each dose. The expense and complicated logistics of having a professional home-deliver every dose makes this strategy unfeasible, but researchers have designed creative alternatives. Some interventions take advantage of having a captive population (eg, in prisons, hospitals, or methadone clinics) or deliver only the morning dose of a twice-daily scheduled medication or only the weekday doses, leaving other doses to be self-administered. The average duration of the interventions varied from 12 to 40 weeks, with some involving a gradual tapering of observed doses; however, there seems to be no consensus as to the optimal timeframe. In terms of affective strategies, 2 studies were identified. They utilized peer support and optimistic writing.

Table 1. Published Studies of Interventions to Enhance Antiretroviral Therapy Adherence, by Type of Intervention

Study Type (Citation)	Study Design	Participants	Intervention Strategy	Main Findings
Cognitive and Behavioral Strategies				
Nursing case management (32)	Uncontrolled pilot study with 10-day F/U	Home care patients in San Francisco, CA (N=10)	Nurse case manager assessment of client needs during initial home visit and implementation of tailored ARV therapy intervention strategies (eg, education, alarm, pill box, etc); F/U telephone calls on days 2, 4, and 10	Self-report of any missed doses the day before was 1 on day 2 and 0 on days 4 and 10
Individualized pharmacist advice (18)	RCT with 24 wks F/U	Patients in Barcelona, Spain (N=170)	Arm 1) 1 one-on-one pharmacist session providing individualized assessment and adherence advice with F/U telephone support available as needed (N=60) Arm 2) SOC (N=110)	At F/U, adherence levels over 90% (by self-report or pill counts) were identified for 77% of Arm 1 and 53% of Arm 2
Pharmacist counseling (33)	Uncontrolled pilot study with unspecified F/U period	Male veterans who did not refill their ARV Rx in Miami, FL (N=21)	Doctoral-level pharmacist provided 1 individual counseling session that included participants role-playing their medication dosing schedule and learning to fill their weekly pill container	At F/U, adherence as measured by monthly refill records increased from 48% to 75% 50% of participants had ≥0.5 log reduction in HIV-1 RNA levels
Group education and individual counseling (34)	2-arm randomized trial with undefined F/U	Mainly male IDUs on ARVs for >6 months and received care in an HIV unit for >1 year in Madrid, Spain (N=115)	Arm 1) Group education sessions conducted by family physicians to determine reasons for nonadherence and reinforce positive attitudes at baseline, 1 mo, and 3 mo, plus individualized counseling Arm 2) Individualized counseling alone conducted by nurses	Inclusion phase stopped because of 74% refusal rates, making it impossible to form groups with more than 4 patients (59% refused for "personal reasons")
Behavioral and educational strategies and social support (24)	RCT with 3 mo F/U	HIV clinic patients referred by PCP because of nonadherence who self-reported missing ≥1 dose per wk (N=79)	Arm 1) 5 alternating individual and group sessions consisting of behavioral strategies, patient information, social support, CBT, and psychiatric nursing over 7 wks Arm 2) SOC	At end of intervention and at 3-mo F/U (N=33), no significant treatment effect by self-report of dose adherence or of schedule adherence
Pharmacist education (35)	Non-randomized cohort study with concurrent matched controls	Men, primarily African American veterans in Miami, FL, with past or active drug use who did not refill their ARV Rx or who are on ≥4 ARVs and matched controls (N=42)	Arm 1) 5 monthly 20- to 25-min one-on-one meetings with doctoral-level pharmacist who provided education and positive reinforcement for self-management of regimen Arm 2) SOC	At 5 mo, significant adherence increase from baseline as measured by refill records for the intervention condition

Table **1.** Published Studies of Interventions to Enhance Antiretroviral Therapy Adherence, by Type of Intervention, Continued

Study Type (Citation)	Study Design	Participants	Intervention Strategy	Main Findings
Cognitive and Behavioral Strategies, Continued				
Multimedia education (36)	Uncontrolled pilot study	Treatment-naive youth at clinical sites (N=65)	8-wk program of one-on-one sessions with study coordinators at every clinical encounter, including audio, video, and reading materials based on stages of change model	At 8 wks (N=11) 50% maintained adherence "most of the time" during the year
Single-session counseling and medication monitoring (37,38)	Uncontrolled pilot study of 2 interventions with 12 wks F/U	Fenway Community Health Center clients in Boston, MA considered at risk for nonadherence, or self-reported <100% adherence in last 2 wks (N=56)	Arm 1) Single-session intervention presented by clinician or videotape utilizing CBT, problem-solving, and motivational interviewing techniques + F/U telephone call at 1 wk Arm 2) Self-monitoring: 2-wk minimal contact intervention utilizing pill diary	Self-reported % of pills taken in past 2 wks increased significantly from baseline to wk 2 for Arm 1 (from 74% to 95%) Adherence in Arm 2 increased, but not significantly (from 84% to 90%) At 12-wk F/U, levels were maintained
Psycho-educational Intervention (22)	RCT with 48 wks F/U	Consecutive patients starting 1st or 2nd ARV regimen in a university-affiliated HIV clinic (N=116)	Arm 1) Psychologist provided 1 one-on-one education session about the importance of adherence, how to manage adherence problems based on self-efficacy theory; at F/U visits (4, 24, and 48 wks), adherence was reinforced and any problems addressed Arm 2) SOC	At F/U in as-treated analysis (N=70), 94% of Arm 1 vs 69% of Arm 2 achieved ≥95% self-reported adherence in past mo 89% of Arm 1 vs 66% of Arm 2 had HIV-1 RNA levels ≤400 copies/mL
Behavioral Strategies Only				
Store-front, drop-in program (39)	Uncontrolled pilot study	Self-referred indigent patients in San Francisco, CA (N=68)	Store-front, drop-in program of up to 5 mo duration provided place to pick-up medications 6 days/wk, weekly $10 incentives, and pager that provided dose reminders	At 2 mo (N=25), 64% had HIV-1 RNA level <500 copies/mL 12% had at least a 2-log reduction in HIV-1 RNA levels
2-way pager (40)	Uncontrolled pilot study	Patients at HIV university-affiliated clinic for underserved population in Seattle, WA (N=25)	For a median duration of 7 mo, a 2-way pager sent messages to remind participants to take doses; the pager also educate, support, and encourage their adherence	Among 19 participants with ≥3 mo with pager, 58% of paged responses indicated perfect adherence over the past few days 79% felt pager improved adherence
Frequent HIV-1 RNA monitoring (41)	2-arm RCT	Predominantly low-income patients from 5 university-affiliated HIV clinics in CA (N=173)	12 mos of: Arm 1) Bimonthly feedback of HIV-1 RNA results Arm 2) Semi-annual feedback of HIV-1 RNA results	Compared with Arm 2, at 6 months (N=119), Arm 1 did not have improved self-reported adherence Arm 1 had a greater average reduction in HIV-1 RNA (0.85 vs 0.43 $\log_{10}$ copies/mL)

Table 1. Published Studies of Interventions to Enhance Antiretroviral Therapy Adherence, by Type of Intervention, Continued

Study Type (Citation)	Study Design	Participants	Intervention Strategy	Main Findings
Behavioral Strategies Only, Continued				
Cue-dose training with monetary reinforcement (21)	3-arm randomized trial with mean F/U of 8 wks	Mainly male, African American, formerly drug-using clinic patients in West Haven and Hartford, CT (N=55)	4 weekly sessions of: Arm 1) CD: Counselor-led personalized CD training (subjects identify daily cues for remembering dose times) + weekly feedback from MEMS® Arm 2) CD + CR: CD and weekly cash reinforcement for correctly timed MEMS® bottle openings Arm 3) Control group: Counselor-led inquiries and encouragement about adherence	During sessions (wks 0-4), CD + CR group (but not CD group) relative to controls had enhanced MEMS® adherence During F/U (wks 5-12), CD + CR group (but not CD group) had a significant loss of previous MEMS® adherence gains relative to controls
(Modified) DOT Strategies				
DOT (42)	Pilot study with comparison group	Predominantly male IDU prisoners in Italy (N=84)	For a mean duration of 8.6 mo, 37 prisoners at 9 prisons were given DOT by nurses; at 9 other prisons, 47 prisoners were given medications once daily for self-administration	At end of trial (range 3-19 mo), more in DOT group had plasma HIV-1 RNA levels below detection (62% vs 34%) Fewer in DOT group had CD4+ lymphocyte count <200/μL (5% vs 32%)
DOT (43)	Uncontrolled pilot study	Antiretroviral-naive inmates from 5 prison sites with HIV-1 RNA >400 copies/mL and no AIDS diagnosis (N=108)	24 wks of DOT with witnessed swallowing or patient visited dispensing site at specified times to receive doses twice daily	At 24 weeks, overall 68% with HIV-1 RNA ≤400 copies/mL Overall self-reported adherence to prescribed doses was 94%
DOT (44)	Pilot study with comparison group	Arm 1) 19 prisoners Arm 2) 30 outpatients in Northeastern Italy	24 wks of: Arm 1) DOT under strict nursing control Arm 2) Self-administered medication	At 12 weeks; mean HIV-1 RNA level lower for Arm 1 (65 vs 5541 copies/mL in Arm 2) Percentage achieved HIV-1 RNA below detection greater in Arm 1
Modified DOT (45)	Uncontrolled pilot study	Patients on complex ARV regimens adjusted to account for genotypic resistance referred by PCP or self in Jacksonville, FL (N=44)	For 12-16 wks, outreach worker observed weekday AM doses in home; PM and weekend doses were self-administered	At 12-16 wks (N=23), 26% achieved HIV-1 RNA <50 copies/mL

Table **1.** Published Studies of Interventions to Enhance Antiretroviral Therapy Adherence, by Type of Intervention, Continued

Study Type (Citation)	Study Design	Participants	Intervention Strategy	Main Findings
(Modified) DOT Strategies, Continued				
Modified DOT (46)	Uncontrolled pilot study	Methadone-maintained IDUs referred by PCP (N=5)	For 24 wks, received AM ARV therapy doses 6 days per wk at time of methadone dosing and telephone call as reminder to take Sunday doses; PM doses were self-administered	At 8 wks, 80% had HIV-1 RNA level <400 copies/mL Mean self-reported adherence was 97%-100%
Modified DOT (47)	Uncontrolled pilot study	Patients with a history of or anticipated poor adherence referred by PCP in Providence, RI (N=37)	For a mean duration of 10 mo, outreach worker observed weekday AM doses, usually in home; PM and weekend doses were self-administered Observation was tapered to weekly visits after several mo	82% of participants with complete 12-mo data (N=17) self-reported missing ≥1 dose in past 4 days at baseline, but only 35% reported the same at both 3 and 12 mo Participants enrolled 12 or more mo (N=18), the mean decrease in plasma HIV-1 RNA level from baseline was 1.53 $\log_{10}$ copies/mL (No *P* values reported)
Affective Strategies				
Peer support (48)	Uncontrolled pilot study	PCP-referred "poorly adherent" active IDUs in New Haven, CT (N=14)	Peer-driven intervention with mean duration of 9 wks in which each subject acts as (1) an advocate to provide weekly support and counseling to peers and (2) as a peer, advocates earned weekly nominal monetary rewards for eliciting positive responses from peers	At 9 wks, mean overall adherence as measured by advocate-conducted weekly pill counts was 90%
Optimistic future writing (49)	RCT	Women of low socioeconomic status (N=44)	For 4 wks: Arm 1) Wrote for at least 10 min 2 times per wk about a somewhat positive future in which they only had to take 1 pill each day for HIV Arm 2) Did not write All participants reminded of the importance of adherence	At 4 wks (N=40), among participants high in optimism, those who wrote self-reported significantly less adherence than those who did not

All participants were HIV-infected adults on combination antiretroviral therapy unless otherwise noted. All comparative results (not descriptives) included were statistically significant at $P \leq 0.05$. F/U indicates follow up; ARV, antiretroviral; SOC, standard of care; Rx, prescription; RCT, randomized controlled trial; mo, month(s); wk, week; CBT, cognitive-behavioral therapy; MEMS®, Medication Event Monitoring System; IDU, injection drug user; CD, cue-dose training; CR, cash reinforcement; PCP, primary care provider; DOT, directly observed therapy; min, minute.

Methodology

Most of these intervention studies lacked methodologic rigor. Specifically, half were feasibility or pilot studies without follow up after the intervention to evaluate sustainability of the effects. Only 36% reported descriptive information about adherence indicators at the end of the program. Few studies provided data for a within-subject pre or post comparison. Only the study by Tuldra and colleagues explicitly referred to a theoretic framework.[22] Most studies were small and likely underpowered: the average sample size was 66, with only 5 samples larger than 100. Less than one third of the studies incorporated a follow-up assessment period; among those that did, time of follow up ranged from 1.4 to 48 weeks, with 2 studies' time unspecified.

Two studies reporting improvements in adherence used only a self-reported adherence measure. Ten studies noted improvement in virologic or immunologic outcomes, but many offered descriptive information without testing for statistical significance. Most studies lacked controls or random assignment to conditions.

Randomized Controlled Trials (RCT)

Ten studies included control or comparison groups, but only 7 of these included the randomization to conditions and control groups that define RCTs. Of these, only 4 incorporated a follow-up period of assessment. The most comprehensive intervention employed behavioral and educational strategies as well as social support.[24] Unfortunately, it did not find any significant effects. The other 3 studies had encouraging findings but had numerous methodologic issues.[18,21,22]

The intervention described by Knobel and colleagues involved a pharmacist who offered a single one-on-one individualized educational session designed to provide detailed information about therapy and to help the participant fit the medication regimen into his or her lifestyle, followed by telephone support. At 24 weeks, participants in the intervention condition self-reported significantly improved adherence but the rate of achieving an HIV-1 RNA level below detection in this group was not statistically significantly better than the control group.[18]

The study by Tuldra and colleagues, based on Bandura's self-efficacy theory,[25] involved a psychologist who provided one-on-one education about the importance of adherence and managing adherence problems with the goal of increasing the patient's self-efficacy. In addition, a daily dosage schedule was developed. During follow-up visits at 4, 24, and 48 weeks, adherence was reinforced and any problems addressed. At 48 weeks, 32 patients (94%) in the intervention group, and 25 patients (69%) in the control group achieved a level of adherence of 95% or greater as measured by self-report ($P = 0.008$). In addition, 89% of the intervention group and 66% of the control group had a plasma HIV-1 RNA level of 400 copies/mL or below ($P = 0.026$). However, the significant intervention effects with respect to HIV-1 RNA levels of 400 copies/mL or below and the self-reported adherence at week 48 were from an "as-treated" and not an "intent-to-treat" analysis of only 70 of the original 116 participants.[22]

The intervention conducted by Rigsby and colleagues involved cue-dose training and monetary reinforcement. In 4 weekly sessions, counselors trained patients to time their doses based on personalized cues such as meal times or other regular daily activities. They also used feedback from the Medication Event Monitoring System (MEMS®), which uses electronic monitors that record the date and time of every opening of the medication vial. For example, if a particular dose was missed repeatedly, the counselor would suggest an alternative cue. In a second arm, cue-dose training was paired with weekly cash incentives for correctly timed MEMS® bottle openings. Incentives began at $2 per correct dose (within 2 hours of dosing time) and increased with each consecutive correct dose to a maximum of $10 per day. If doses were missed or not taken within 2 hours of the specified dosing time, the reinforcement was reset to $2. During the intervention (weeks 0 to 4), participants who received both strategies (but not those receiving only cue-dose training) demonstrated enhanced adherence according to electronic monitoring relative to controls. However, the change was not sustained at follow up (weeks 5-12).[21]

Ongoing Research Funded by the National Institutes of Health (NIH)

Our Computer Retrieval of Information on Scientific Projects (CRISP) search identified 39 abstracts for ongoing federally funded research involving interventions to enhance antiretroviral adherence (Appendix).

The studies in progress involve a variety of methods that further expand research within the 4 categories previously described for the published studies. Novel strategies utilize technology such as a handheld device to provide educational, affective, and behavioral components; a two-way pager; telephone-delivered habit training; and a medication storage device that incorporates a reminder alarm. Other innovative strategies include the optimization of social and emotional support through peer support groups, stress management, risk reduction, and the treatment of depression.

As expected given the highly competitive nature of NIH awards, these projects exhibit substantial methodologic sophistication. Most programs were theoretically based and were to be tested in RCTs with sufficient power, adequate follow up, and a variety of outcome measures. Consequently, these studies, compared with the current literature, will provide better evidence of intervention effects.

Guidelines for Best Practice

The empiric data necessary to make strong recommendations regarding the most efficacious way to improve antiretroviral therapy adherence are currently lacking. Indeed, the only encouraging evidence from methodologic RCTs with follow-up assessments suggested there might be some promise in pharmacist-led individualized interventions, cognitive-behavioral educational interventions based on self-efficacy theory, and a combination of cue-dose training and monetary reinforcement.

In response to this dearth of empirically sound data, a common response from experts has been to recommend strategies based on methodologically limited data, research from adherence in other fields, empirically demonstrated correlates of adherence, and clinical experience. For example, the Best

Practices Guide, published online by the American Public Health Association proposes a 4-step practical approach (Table 2). Unfortunately, an accurate and well-accepted measure of adherence and a clear approach to defining and addressing potential barriers are lacking.[13]

Chesney offered more specific advice, emphasizing the patient's role and conceptualizing adherence as a skill that can be learned when the patient masters specific tasks.[26] Turner, as well as the American Psychological Association, in its congressional testimony, offered similarly prescriptive guidelines (Table 2[13,26-28]). Finally, Stone and colleagues offered strategies for optimizing adherence based on research and clinical practice for each of the 4 main groups of factors found to correlate with adherence: those focused on the patient, regimen, clinical care setting, or provider.[29]

Suggestions for Future Research

The body of research on improving adherence to antiretroviral therapy, although in its infancy, is likely to grow rapidly in the near future. The gold standard for research is the RCT, but RCTs need to have: appropriate theoretic frameworks; adequate sample sizes; psychometrically sound and clinically useful outcome measures; clear and consistent operationalization of adherence and outcome; and better adherence assessment methods.[30] Moreover, RCTs will likely need to combine interventions, given the relatively small effects observed from studies of single interventions, as well as expand the breadth of adherence issues addressed by these interventions. As mentioned above, most of the intervention strategies have focused on patient characteristics; interventions are also needed that focus on the provider and the patient-provider relationship, variables related to the treatment regimen or illness, and contextual factors. Better communication and collaboration among investigators may enhance the development of knowledge and reduce duplication of efforts. Most important, researchers need to submit and editors need to publish reports of interventions with nonsignificant treatment effects if the field is to avoid past mistakes and the needless re-evaluation of unpromising strategies.

Multifactorial interventions leave a study vulnerable to the critique that it is impossible to distinguish which aspect of the intervention is the most effective. It is important to emphasize to reviewers and to researchers that adherence studies need to provide a combination of interventions to promote a long-term behavior such as adherence to medication. Since adherence behavior is dynamic, often decreasing initially in response to side effects or disease status, further research is needed about the timing of interventions.[20] Front-loaded, prophylactic strategies are probably best, but when should they begin and how long should they last? What type and quantity of booster sessions are required? Studies need to demonstrate, if possible, how much time is required for complex behaviors, such as antiretroviral therapy adherence, to become habitual and to provide information regarding how quickly such behaviors extinguish.

As successfully tested interventions emerge, we also need to address the issue of efficacy versus effectiveness: what works in RCTs might not work in clinics challenged by limited staff time, inadequate resources, and diverse patient populations.

Table **2.** Suggested Strategies for Providers to Improve Adherence

Proposed by APHA[13]	• Assess factors that may influence adherence and function as potential barriers • Develop and maintain a therapeutic alliance with the patient	• Monitor the level of medication adherence with numerous measures • Implement numerous targeted interventions to resolve barriers to adherence
Proposed by Chesney[26]	• Clarify the regimen • Tailor it to the patient's lifestyle • Teach the patient how to keep a medication diary • Establish a time to set out pills • Establish set places for pill taking • Plan ahead for changes in routine	• Make special plans for weekends and holidays • Have clinics lower barriers to care • Invite patients to become active partners in care • Refer patients to social services • Follow up, monitor, and track adherence over time
Proposed by Turner[27]	• Simplify and explain the regimen • Provide reminder devices • Discuss side effects	• Provide social support • Treat concomitant psychologic disorders and substance abuse
Proposed by APA[28]	• Clarify the regimen • Tailor it to individual lifestyles • Facilitate interaction with clinic staff • Identify and remove personal barriers to adherence • Refer patients with special needs, such as substance abuse, to appropriate treatment • Enhance self-efficacy	• Offer positive feedback for new skills • Demonstrate problem solving and ways for patients to integrate the regimen into their lives • Create a social environment conducive to adherence • Enlist support from patient's social network • Maintain support of clinical team

APHA indicates American Public Health Association; APA, American Psychological Association.

What types of ancillary medical and mental health providers can assist the physician, physician's assistant, or nurse practitioner in the job of promoting and reviewing adherence? Can pharmacists take on the additional work of adherence counseling, and how can they be compensated for their time in the current managed care climate? Is there a role for non-health care providers, such as peers or near-peers, in ongoing adherence work?

Given the complex array of factors associated with nonadherence, no single strategy is likely to be effective for every patient. Therefore, different sets of targeted interventions may be needed for special groups such as children, pregnant women, or active substance users. For example, all patients do not need DOT, but it may be that DOT and self-efficacy training in the context of a drug treatment program are necessary to help drug users successfully adhere to therapy. Unfortunately, because of the cost of such highly individualized interventions, it may be unfeasible to incorporate these interventions into most clinics. Cost-effectiveness data are needed in the long term to assess the practical value of various types of interventions to promote adherence.

Finally, the international AIDS pandemic requires us to consider antiretroviral therapy access and adherence in resource-poor settings such as developing countries.[31] Initial studies are disproving fears about inadequate adherence levels in resource-poor settings, but other issues remain unresolved. For example, will DOT or other strategies such as culturally relevant information, motivational, and skills-building strategies be most cost effective? Given the possibility of transmission of resistant virus to drug-naive individuals, it is important when initiating antiretroviral therapy in resource-poor countries to emphasize the importance of adherence and the risk of sharing medications.

Conclusions

Some of the initial optimism regarding the efficacy of antiretroviral therapy has dissipated in the face of the onerous challenges of maintaining nearly perfect adherence indefinitely. Current research on correlates of adherence to HIV medications offers preliminary support for the efficacy of such strategies as assessing and addressing individual patient needs and barriers; nurturing the therapeutic alliance as well as other sources of social support; employing comprehensive and individualized cognitive, behavioral, and affective strategies; and continuously monitoring adherence with a variety of assessment methods. Empiric research focusing specifically on interventions to bolster antiretroviral therapy adherence is in a nascent stage of development. Results of 4 RCTs conducted with adequate methodologic rigor lend some support to a pharmacist-led individualized intervention, a cognitive and behavioral educational intervention based on self-efficacy theory, and cue-dose training combined with monetary reinforcement. However, even these encouraging findings were marred by methodologic limitations. Finally, a review of ongoing federally funded research revealed 39 adherence intervention projects evaluating a diversity of adherence strategies. Fortunately, intensive work is underway to address the seemingly intractable problem of antiretroviral therapy nonadherence.

Appendix. Ongoing Research on Antiretroviral Therapy Adherence Interventions Funded by the National Institutes of Health

Cognitive and Behavioral Strategies

ATKINSON, JH. (DA012800-03). Better Antiretroviral Adherence: HIV+ Amphetamine Users. Research of HIV-infected methamphetamine-dependent individuals in early recovery. This RCT (N = 75 per arm) of an 8-week intervention compared (1) SOC, (2) informational-motivational-behavioral (IMB)-based adherence training alone, and (3) IMB-based adherence training with stimulant relapse prevention. At baseline, end of treatment, and 4 and 6 months after baseline, the investigators will measure adherence, HIV-1 RNA level, urine toxicology, substance use, quality of life, and neuropsychiatric status. ARV therapy will be measured by self-report, MEMS®, and serum medication concentrations.

BUNTING, SM. (NR007718-01). Modifying Facilitators and Barriers to HIV Adherence. Pilot test of RCT (N = 88) of 3-month intervention comparing (1) SOC with (2) individualized assessment, education, counseling, and referrals administered by a research nurse in-person with telephone-based follow-up sessions. Adherence to all prescribed medications will be measured at times 1, 2, and 3 by self-report and pill counts. Adherence to 1 antiretroviral medication will also be monitored by MEMS®.

CATZ, SL. (MH065858-02). Adherence Intervention—Late Middle–Aged/Older Adults. For HIV-infected late middle-aged and older persons, development and pilot testing of individual-level and group-level adherence interventions based on motivational interviewing techniques and behavioral skills training.

CROSBY, GM. (AA012009-04). HIV Treatment Adherence Among Alcohol Abusers. Among HIV-infected alcohol-dependent patients (globally), RCT (N = 617) of (1) SOC and (2) 6-session individualized intervention based on social action theory.

Investigators will measure plasma HIV-1 RNA levels, plasma CD4 + lymphocyte counts, and rates of self-reported adherence confirmed through MEMS® data.

DIIORIO, CK. (NR004857-04). An Adherence Intervention for Antiretroviral Regimens. RCT (N = 240) of 12-week intervention comparing (1) SOC with (2) 1 in-person introductory session and 4 telephone-based motivational interviewing sessions, written self-help materials, and a self-help videotape.

ERLEN, JA. (NR004749-05). Adherence to Protease Inhibitors. RCT (N = 200) of 24-week intervention comparing (1) SOC with (2) 12 weeks of telephone-delivered habit-training and problem-solving sessions, followed by 12 weeks of telephone-delivered maintenance sessions. Adherence will be measured with self-report diaries, pill counts, and MEMS®. Clinical response will be assessed using HIV-1 RNA levels and CD4 + lymphocyte count.

FARLEY, JJ. (HD036613-05). Peer Education and Adherence to HIV Therapy in Children. Multiple baseline (N = 80) of (1) 6-months of SOC adherence education followed by (2) 30 months of monthly peer health educator home visits. An intensive intervention will be added for families who continue to show poor adherence (which increases the frequency of home visits to a weekly basis and adds individualized mental health services). Adherence will be measured by MEMS® and clinical response measured through HIV-1 RNA levels.

GOLIN, CE. (MH001862-04). Adherence To Antiretroviral Therapy: a Controlled Trial. Develops an intervention for seropositive patients starting new ARV regimens, trains patients to participate in medical decision making, and provides feedback and follow up over a 12-week period. Study will assess the impact of the intervention on patient participation, patient and physician satisfaction with the medical visit, and the impact of patient participation on adherence.

HOLZEMER, WL. (NR004846-04). Outpatient Nurse-Managed HIV Adherence Trial. RCT (N = 222) testing (1) SOC and (2) Client Adherence Profiling-Intervention Tailoring (CAP-IT), implemented by nurse case managers during regularly scheduled home care visits. Investigators will measure adherence as well as CD4 + lymphocyte count, HIV-1 RNA level, and antiretroviral therapy resistance.

HOSEK, SG. (MH064348-02). A Pilot Adherence Intervention for HIV-Infected Youth. For HIV-infected adolescents and young adults, pilot RCT comparing (1) SOC and (2) cognitive-behavioral depression and coping skills intervention.

KALICHMAN, SC. (MH062287-04). HIV Treatment Adherence for Persons with Low Literacy. For HIV + persons who demonstrate poor literacy skills, develop and field test an RCT (N = 80) comparing (1) a wait-list control group with (2) an intervention using pictograph-based IMB skills training to improve adherence. Investigators will measure self-report adherence and variables relevant to testing the IMB skills adherence intervention model.

KANOUSE, DE. (MH061695-03). A Training Intervention to Enhance Adherence to Antiretroviral Therapy. RCT (N = 270) of (1) SOC, (2) an adherence training intervention with psycho-educational components alone, or (3) the psycho-educational intervention delivered in the context of a brief training trial of an inert medication that mimics antiretroviral therapy. Adherence will be assessed using self-report and MEMS®. Investigators will measure the clinical outcomes of HIV-1 RNA levels and resistance assays.

MALOW, RM. (DA013802-03). Cognitive Behavioral Treatment (CBT) of HIV + Drug Abusers. For recovering drug users, RCT (N = 320) of (1) SOC and (2) Cognitive Behavioral Stress Management intervention specifically for recovering drug users. Endpoints include distress and quality of life, drug relapse, unsafe sex, antiretroviral therapy adherence, and health status.

MCDONNELL, MK. (NR008094-01A1). Motivating HIV+ Women: Risk Reduction and ART Adherence. RCT of (1) SOC of an 8-session attention equivalent control condition consisting of a health promotion program led by a nurse health educator, and (2) a group intervention based on motivational interviewing consisting of 8 nurse-led 90-minute sessions over 4 months. Adherence will be measured by self-report via Audio Computer-Assisted Self-Interviewing (ACASI), MEMS®, and a Multi-Component Adherence Index. HIV-1 RNA levels and CD4 + lymphocyte counts will be obtained by chart review.

PARSONS, JT. (AA013556-02). Adherence Intervention for HIV+ Alcohol Users. RCT of 8-session intervention comparing (1) an attention control condition of standard education with (2) motivational interviewing and behavioral skills training based on the IMB skills model. Primary outcome measures will be the biological markers for HIV-1 RNA level, CD4 + lymphocyte count, and tests for alcohol use. Other outcome measures will include self-reported adherence, prescription refill data (via pharmacy records), adherence to medical appointments (via chart review), and self-reported alcohol use and alcohol-related problems.

REMIEN, RH. (5R01MH061173-04). Serodiscordant Couples, Medical Adherence, and HIV Risk. For serodiscordant couples, RCT of (1) SOC and (2) a brief, structured, theory-based intervention with the couples. Investigators will measure adherence to HIV medications, clinic appointment attendance, and prescription refills. Secondary aims of the study are to examine the relationship between attitudes and beliefs about effective medical treatments and sexual risk and participants' behaviors.

SAFREN, SA. (MH066660-01A1). CBT for HIV Medication Adherence and Depression. For patients with major depression and a detectable HIV-1 RNA level, RCT of 4-month inter-

vention comparing (1) a single-session adherence intervention with (2) CBT for both major depression and antiretroviral therapy adherence. Control group participants will be re-assigned to CBT after the initial phase of the study if they have not improved on key outcome variables.

SMITH-DAHL, CB. (MH068202-01). Video Tool for Low-Literacy Antiretroviral Therapy Adherence. Targeting African-American and Hispanic individuals with low functional literacy, an informational intervention in video format based on the Health Belief Model. Investigators are currently completing development of the video and will next evaluate its effectiveness.

WEISS, SM. (MH055463-07) and TOBIN, JN. (5R01MH061208-02). Behavioral Interventions for Women with HIV/AIDS. Two linked interactive research project grant applications for a multi-site clinical trial focused on poor women of color living with HIV/AIDS. Phase I: RCT (N = 450) of (1) individual psychoeducational comparison condition and (2) cognitive-behavioral stress management training combined with expressive-supportive therapy. Phase II: RCT comparing (1) individual health educational control with (2) a group skills training program. Outcome measures will include medication adherence, nutritional intake and physical activity, sexual risk taking, and substance use behaviors.

Behavioral Strategies Only

BRUE, V. (AI052634-01). A Novel Technology to Improve HIV Medication Compliance. The aim of this project is to design and develop a prototype device to allow convenient storage and transport of antiretroviral medications, incorporating reminder alarms at dosing times and usage reporting functions. Once developed, the device will be tested in clinical trials to determine its usability and functionality in increasing medication compliance in persons infected with HIV.

BUDMAN, SH. (AI043750-03). Compliance Enhancement in HIV/AIDS Patients. An uncontrolled feasibility study (N = 156) will follow patients for 9 months to test the effectiveness of the MedMate® system, a user-friendly handheld device that will contain educational, affective, and behavioral components designed to enhance antiretroviral therapy adherence, monitor side effects, and permit customized adherence feedback.

GREENE, PG. (AI045403-03). Promoting Adherence to Antiretroviral Regimens. RCT (N = 216) of 6-month intervention of (1) SOC Adherence Promotion Program and (2) a theory-based behavioral intervention addressing specific psychosocial issues associated with medication adherence. Adherence will be measured by self-report and pill counts. Secondary outcome measures will be HIV-1 RNA levels, CD4 + lymphocyte counts, and genotypic viral resistance.

GROSS, R. (MH001584-04). Adherence to Protease Inhibitors in HIV. Planned RCT will evaluate (1) SOC, (2) a MEMS®-based beeper as a "mnemonic aide," (3) a case management intervention based on the social problem-solving model, or (4) both a beeper and a program of case management.

HOFMANN, RH. (AI044558-03). A Computer-Based HIV Medication Adherence Intervention. A computer-assisted, self-administered adherence medication assessment program aimed at assessing medication adherence, reducing regimen misunderstandings, delivering an adherence intervention, and producing adherence reports for providers. The goals of this project are to simplify the assessment tool, to develop the intervention component, and to test the complete program's efficacy.

INGERSOLL, KS. (MH001688-04). HIV Adherence Mentored Research Scientist Development Award. RCT (N = 189) of 12-week intervention comparing (1) SOC, (2) prospective self-monitoring, and (3) prospective self-monitoring with a "trial run" of their selected antiretroviral therapy regimen using vitamins to practice. Adherence will be measured using a novel telephone reporting system to record patient-reported adherence, which has been studied in a prior research project by the same investigator.

PETRY, NM. (DA014618-01A1). Lower-Cost Contingency Management in a Group Setting. For HIV-infected individuals recovering from substance abuse, RCT (N = 172) of 6-month intervention comparing (1) standard 12-step group treatment and (2) voucher contingency management intervention. Participants can earn prizes for submitting clean urine specimens and taking steps toward treatment goals such as keeping medical appointments, maintaining a medication diary, and filling prescriptions. Investigators will measure group attendance, drug use, medical problems and services received, and risky drug use and sexual behaviors.

REYNOLDS, NR. (NR005108-03). Improving ARV Adherence: Effects of Telephone Follow Up. RCT (N = 200) of 9-month intervention comparing (1) SOC and (2) Registered Nurse (RN)-delivered telephone-based behavioral intervention rooted in the Self-Regulation Model. In addition to adherence, clinical outcomes will be measured (virologic, immunologic, and clinical events).

ROSEN, MI. (MH061169-03). Improving Compliance With Antiretroviral Medications. RCT (N = 90) of (1) SOC or (2) 24 weeks of the intervention condition, where patients' MEMS®-generated printouts are reviewed with them by a therapist trained in Motivational Enhancement Therapy. The primary outcome measure will be MEMS®-measured adherence to correct dose time. The clinical outcome measure will be HIV-1 RNA level.

SAMET, JH. (AA011785-05). Medication Adherence in Alcohol Abusing HIV Patients. For alcohol-using HIV-infected individuals, RCT (N = 240) of (1) SOC and (2) RN-delivered individualized behavioral intervention comprised of 3 clinic visits and 3 home visits. Outcome measurements will include adherence, clinical, laboratory, and health status outcomes. Adherence reports will be corroborated by MEMS®.

WILSON, IB. (DA015679-01). Understanding and Improving Adherence in HIV Disease. Multiple baseline RCT (N = 150) comparing (1) SOC to (2) MEMS® data being fed back to physicians in the form of a report, prior to outpatient medical visits. Detailed patient interviews will collect adherence data in addition to the MEMS®. Primary outcome measures for the intervention study will be changes in adherence as assessed by MEMS® and changes in HIV-1 RNA levels.

(Modified) DOT Strategies

FLANIGAN, TP. (DA013767-03). Directly Observed Antiretroviral Therapy for Active Substance Abusers. For active substance users on a 1-a-day antiretroviral therapy regimen, RCT (N = 120) of 18-month intervention comparing (1) SOC self-administration of medications with (2) 12 months of daily directly observed therapy (DOT) followed by a 6-month gradual tapering phase. Adherence will be assessed by patient self report in an ACASI questionnaire. HIV-1 RNA quantification, drug resistance testing by genotype, and CD4 + lymphocyte count determinations will be used to assess the effect of DOT on virologic suppression and development of resistance.

LUCAS, GM. (DA015616-01). Directly Observed Antiretroviral (ARV) Therapy in Drug Abusers. For HIV-infected patients in a methadone treatment center, prospective matched RCT comparing (1) SOC with (2) 1-year of antiretroviral therapy. Outcomes measured include virologic and immunologic responses to therapy, incidence of opportunistic diseases, and death.

TULSKY, JP. (DA013892-02). A clinical trial of DOT for antiretroviral therapy in jailed drug users. In jailed drug users, RCT testing (1) SOC DOT and (2) an intervention of structured self-administered therapy. Outcome measurements will be virologic and immunologic outcomes in jail and following release from jail, as well as physical and mental health status and lifetime and current antiretroviral therapy adherence.

Group 4—Affective Strategies

BANGSBERG, DR. (MH063011-02). Depression Treatment to Improve ARV Therapy Adherence. For HIV-infected homeless and marginally housed persons with depression, RCT testing the efficacy of (1) SOC and (2) antidepressant therapy. Investigators will examine 5 primary aims, including depression treatment, antiretroviral therapy adherence, duration of sustained antiretroviral therapy treatment, initiation of treatment, and viral suppression.

MANNHEIMER, SB. (DA012363-04). Harlem Adherence with Retroviral Therapy Study. RCT (N = 160) of 12-month intervention comparing (1) SOC and (2) individual and group intervention based on the Transtheoretical Model of Change, to provide social support and assistance in overcoming barriers to adherence. Adherence will be assessed via a self-report adherence questionnaire, confidential participant survey, and by provider and peer assessments. Biologic surrogates of adherence will include plasma HIV-1 RNA levels and HIV genotypic resistance patterns.

MURPHY, DA. (MH059419-05). Medication Adherence Intervention for HIV-infected Persons. RCT (N = 144) of (1) SOC and (2) a 5-session social support and patient education group intervention facilitated by a behavioral psychologist and a nurse practitioner, followed by 4 subsequent booster sessions.

NAAR-KING, S. (DA014710-02). Motivational Therapy/ Reduce Risk Behaviors/HIV/Youth. For HIV-infected youth, pilot of 3-month RCT (N = 60) with wait-list control comparing (1) SOC with (2) Motivational Enhancement Therapy, an empirically validated risk reduction intervention.

SIKKEMA, KJ. (MH062965-03). Intervention for Coping with HIV and Trauma. For individuals who are HIV-infected and experiencing trauma-related stress and psychiatric distress, RCT (N = 240) comparing (1) SOC support group and (2) an HIV and trauma coping group. Outcomes include measurements of psychiatric distress, quality of life, rates of adherence to medical treatment, levels of substance use and sexual risk behaviors, and health status as indicated by HIV symptomatology, CD4 + lymphocyte count, and HIV-1 RNA level.

SIMONI, JM. (MH058986-05). Peer versus Pager Support to Enhance Antiretroviral Adherence. RCT (N = 240) of 3-month intervention comparing (1) SOC, (2) carrying an alphanumeric programmable pager, (3) having an HIV-infected buddy to give peer support, and (4) having both a pager and a buddy. Adherence will be assessed using self-reports, pharmacy refills, 3-day recall telephone interviews, and MEMS®. HIV-1 RNA level and CD4 + lymphocyte count will be assessed as clinical outcomes.

Financial Disclosure: Drs Simoni, Frick, and Turner, and Mr Pantalone have no affiliations with commercial organizations that may have interests related to the content of this article.

Acknowledgements: The authors acknowledge Steven Safren for his comments on an earlier draft of this review article. A version of this article will be published as a chapter in the text "Best Practices in the Behavioral Management of Chronic Disease," edited by Jodie A. Trafton and William Gordon, and published by the Institute for Disease Management in Los Altos, CA.

Top HIV Med. 2003;11(6):185-198

References

1. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA.* 1998;279:450-454.

2. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med.* 1998;338: 853-860.

3. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet.* 2003;362:22-29.

4. Carpenter CCJ, 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: 1962-1969.

5. Nieuwkerk PT, Sprangers MA, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Arch Intern Med.* 2001;161:1962-1968.

6. Casado JL, Perez-Elias MJ, Antela A, et al. Predictors of long-term response to protease inhibitor therapy in a cohort of HIV-infected patients. *AIDS.* 1998;12:F131-F135.

7. Rabkin JG, Chesney MA. Treatment adherence to HIV medications. In: Kalichman SC, ed. Psychosocial and Public Health Impact of New HIV Therapies. New York: Kluwer Academic/ Plenum Publishers; 1999:61-82.

8. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med.* 2001; 134:968-977.

9. Knobel H, Guelar A, Carmona A, et al. Virologic outcome and predictors of virologic failure of highly active antiretroviral therapy containing protease inhibitors. *AIDS Patient Care STDS.* 2001;15:193-199.

10. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clin Infect Dis.* 1999;29:824-830.

11. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133:21-30.

12. Bartlett JA. Addressing the challenges of adherence. *J Acquir Immune Defic Syndr.* 2002; 29(Suppl 1):S2-S10.

13. Jani AA. Adherence to HIV treatment regimens: recommendations for best practices. Available at: http://www.alpha.org/ppp/hiv/ Best_Practices.pdf. Accessed December 12, 2002.

14. 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.

15. Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: a framework for clinical research and clinical care. *J Clin Epidemiol.* 1997;50:385-391.

16. Ammassari A, Trotta MP, Murri R, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *J Acquir Immune Defic Syndr.* 2002;31(Suppl 3):S123-S127.

17. Haddad M, Inch C, Glazier RH, et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS (Cochrane Review). *Cochrane Database System Review.* 2002;CD001442.

18. Knobel H, Carmona A, Lopez JL, et al. Adherence to very active antiretroviral treatment: impact of individualized assessment. *Enferm Infect Microbiol Clin.* 1999;17:78-81.

19. Wall TL, Sorensen JL, Batki SL, Delucchi KL, London JA, Chesney MA. Adherence to zidovudine (AZT) among HIV-infected methadone patients: a pilot study of supervised therapy and dispensing compared to usual care. *Drug Alcohol Depend.* 1995;37:261-269.

20. Ickovics JR, Meade CS. Adherence to antiretroviral therapy among patients with HIV: a critical link between behavioral and biomedical sciences. *J Acquir Immune Defic Syndr.* 2002;31(Suppl 3):S98-S102.

21. Rigsby MO, Rosen MI, Beauvais JE, et al. Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. *J Gen Intern Med.* 2000;15:841-847.

22. Tuldra A, Fumaz CR, Ferrer MJ, 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.* 2000;25:221-228.

23. Ickovics J. Measures of adherence. Adherence to New HIV Therapies: A Research Conference. 1997; Washington, DC.

24. Murphy DA, Lu MC, Martin D, Hoffman D, Marelich WD. Results of a pilot intervention trial to improve antiretroviral adherence among HIV-positive patients. *J Assoc Nurse AIDS Care.* 2002;13:57-69.

25. Bandura A. Self-efficacy mechanisms in human agency. *Am Psychol.* 1982;37:122-147.

26. Chesney MA. Compliance: how you can help. Available at: http://www.hivnewsline.com/ issues/Vol3Issue3/comply.html. Accessed December 12, 2002.

27. Turner BJ. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *J Infect Dis.* 2002;185(Suppl 2):S143-S151.

28. American Psychological Association. APA Testimony on the adherence to HIV/AIDS drug therapy. Available at: http://www.apa.org/ppo/ issues/paids.html. Accessed July 29, 1998.

29. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HERS study. *J Acquir Immune Defic Syndr.* 2001;28:124-131.

30. Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. *Ann Pharmacother.* 2001;35:1010-1015.

31. Farmer P, Leandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet.* 2001;358: 404-409.

32. Holzemer WL, Henry SB, Portillo CJ, Miramontes H. The Client Adherence Profiling-Intervention Tailoring (CAP-IT) intervention for enhancing adherence to HIV/AIDS medications: a pilot study. *J Assoc Nurses AIDS Care.* 2000;11:36-44.

33. Malow RW, Baker SM, Klimas N, et al. Adherence to complex combination antiretroviral therapies by HIV-positive drug abusers. *Psychiatr Serv.* 1998;49:1021-1024.

34. Martin J, Sabugal GM, Rubio R, et al. Outcomes of a health education intervention in a sample of patients infected by HIV, most of them injection drug users: possibilities and limitations. *AIDS Care.* 2001;13:467-473.

35. McPherson-Baker S, Malow RM, Penedo F, Jones DL, Schneiderman N, Klimas NG. Enhancing adherence to combination antiretroviral therapy in non-adherent HIV-positive men. *AIDS Care.* 2000;12:399-404.

36. Rogers AS, Miller S, Murphy DA, Tanney M, Fortune T. The TREAT (Therapeutic Regimens Enhancing Adherence in Teens) program: theory and preliminary results. *J Adolesc Health.* 2001;29(Suppl 3):30-38.

37. Safren SA, Otto MW, Worth JL, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behav Res Ther.* 2001;39:1051-1062.

38. Safren SA, Otto MW, Worth JL. Life-steps: applying cognitive behavioral therapy to HIV medication adherence. *Cognit Behav Pract.* 1999;6:332-341.

39. Bamberger JD, Unick J, Klein P, Fraser M, Chesney M, Katz MH. Helping the urban poor stay with antiretroviral HIV drug therapy. *Am J Public Health.* 2000;90:699-701.

40. Dunbar PJ, Madigan D, Grohskopf LA, et al. A two-way messaging system to enhance antiretroviral adherence. *J Am Med Inform Assoc.* 2003;10:11-15.

41. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. *AIDS.* 1999;13:1099-1107.

42. Babudiere S, Aceti A, D'Offizi GP, Carbonara S, Starnini G. Directly observed therapy to treat HIV infection in prisoners. *JAMA.* 2000;284: 179-180.

43. Kirkland LR, Fischl MA, Tashima KT, et al. Response to lamivudine-zidovudine plus abacavir twice daily in antiretroviral-naive, incarcerated patients with HIV infection taking directly observed treatment. *Clin Infect Dis.* 2002;34: 511-518.

44. Lanzafame M, Trevenzoli M, Cattelan AM, Rovere P, Parrinello A. Directly observed therapy in HIV therapy: a realistic perspective? *J Acquir Immune Defic Syndr.* 2000;25:200-201.

45. Mitty JA, Stone VE, Sands M, Macalino G, Flanigan T. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress. *Clin Infect Dis.* 2002;34:984-990.

46. McCance-Katz EF, Gourevitch MN, Arnsten J, Sarlo J, Rainey P, Jatlow P. Modified directly observed therapy (MDOT) for injection drug users with HIV disease. *Am J Addict.* 2002;11:271-278.

47. Stenzel MS, McKenzie M, Mitty JA, Flanigan TP. Enhancing adherence to HAART: a pilot program of modified directly observed therapy. *AIDS Read.* 2001;11:317-318.

48. Broadhead RS, Heckathorn DD, Altice FL, et al. Increasing drug users' adherence to HIV treatment: results of a peer-driven intervention feasibility study. *Soc Sci Med.* 2002;55:235-246.

49. Mann T. Effects of future writing and optimism on health behaviors in HIV-infected women. *Ann Behav Med.* 2001;23:26-33.