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# Strategies for Promoting Adherence to Antiretroviral Therapy: A Review of the Literature

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## Abstract

The success of antiretroviral therapy (ART) for HIV infection, though widespread and resounding, has been limited by inadequate adherence to its unforgiving regimens, especially over the long term. This article summarizes the literature on behavioral interventions to promote ART adherence and highlights some of the most recent and innovative research on patient education and case management, modified directly observed therapy, contingency management, interventions emphasizing social support, and novel technologies to promote awareness. Research in the area of adherence in pediatric HIV infection and in resource-constrained international settings also is considered. Although adherence interventions have been successful in experimental trials, they may not be feasible or adaptable given the constraints of real-world clinics arid community-based settings. Implementation and dissemination of adherence interventions needs increased attention as ART adherence research moves beyond its first decade. We conclude with suggestions for incorporating research findings into clinical practice.

## Introduction

Antiretroviral therapy (ART), especially highly active antiretroviral therapy (HAART) combining at least three antiretroviral drugs, has markedly reduced morbidity and mortality among individuals living with HIV [1•]. Notably, AIDS death rates declined by 80% between 1990 and 2003 [2].

Seriously limiting ART is its lack of “forgiveness” in the face of imperfect adherence to its strict therapeutic regimens and dietary requirements [3]. Because interruptions of ART result in rapid return of viremia, ART adherence is a lifelong burden [4]. Resistant strains develop quickly in the absence of adequate therapeutic coverage, and individuals who inconsistently adhere can readily become resistant to multiple classes of ART coverage [5]. Resistant strains can be transmitted, thus imperiling the public health as well as that of the individual [6,7].



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Few patients in the West have been able to maintain the strict adherence levels required. Adequate adherence to medication regimens—pivotal for the 60% to 90% HIV-1 RNA viral suppression seen in clinical trials—has seldom been replicated in clinical practice, where about 50% achieve undetectable viral loads [8,9]. Early reports suggest that patients in China [10] and sub-Saharan Africa [11] show comparable or slightly better adherence than in the West, but long-term, maintenance of these levels may be difficult [12].

Perhaps never before has a medication regimen required such strict lifetime adherence with such devastating consequences for nonadherence. Reflecting the critical role of adequate adherence to individual and public health, a period of explosive growth in adherence research followed the introduction of HAART in 1996. Whereas the field of treatment adherence research before the HAART era consisted mainly of small pilot studies [13], ART adherence research comprises methodologically sophisticated investigations, randomized controlled trials (RCT), and comprehensive systematic reviews that have examined myriad issues, including the optimal levels of adherence [14], impact of nonadherence on viral load and development of resistant virus [15,16], relative merits of various adherence assessment methodologies [17–19], predictors and correlates of adherence [20], and conceptualizations of adherence [21•,22,23]. Research also has focused on pediatric ART adherence [24•,25] and on the health system demands of ART in resource-constrained settings, where treatment has become available recently [20].

Additionally, and perhaps more clinically relevant, considerable research has examined the efficacy of various strategies in enhancing ART adherence. In this article, we summarize the current research on behavioral interventions to promote ART adherence, highlighting the most recent and innovative findings including pediatric research and work within resource-constrained, high-seroprevalence settings internationally. We conclude with specific suggestions for incorporating research findings into clinical practice.

## Research Literature on ART Adherence Interventions

Behavioral interventions to promote adherence have been considered in several comprehensive reviews. Initial reviews focused on qualitative descriptions and reported concerns over atheoretical intervention approaches, lack of methodologic rigor, poor generalizability of results, and poor intervention outcomes [26,27]. The urgent need for improved methodology was emphasized.

Subsequent reviews incorporated more sophisticated meta-analytic methods. Amico et al. [28•] reviewed intervention outcome studies published from 1996 to 2004 for a total of 25 outcome effects and 13 follow-up effects. The vast majority of studies reviewed included some form of counseling support, but the actual active components of the interventions varied substantially, ranging from implementation of reminder devices or systems to directly observed therapy (DOT) programs [28•]. Although most studies continued to be relatively underpowered and relied largely on self-report measures of adherence, the mean effect size was “small” but significant ($d = 0.35$, OR = 1.88; $P < 0.05$), and better for studies that enrolled participants thought to have adherence difficulties. The second meta-analytic review included work published through September 2005, focused exclusively on findings

from RCTs, and examined effects on standardized versions of two dichotomous outcomes (ie, 95% adherence and undetectable viral load) [29•]. Findings based on the 19 studies meeting inclusion criteria (with 1839 participants) indicated that across studies, participants in the intervention arm were more likely than those in the control arm to achieve 95% adherence (OR 1.50; 1.16–1.94); the effect was nearly significant for undetectable viral load (OR 1.25; 0.99–1.59). The intervention effect for 95% adherence was significantly stronger in studies that used recall periods of 2 or 4 weeks (vs < 7 days). No other stratification variables (ie, study, sample, measurement, methodologic quality, and intervention characteristics) moderated the intervention effect. Taken together, these reviews suggest that various HAART adherence intervention strategies can be successful, but more research is needed to identify the most efficacious intervention components.

Interventions with quite different content often share commonalities in delivery systems. The most common systems are patient centered with specific strategies adopted from motivational interviewing/motivational enhancement therapy [30], cognitive behavioral therapy [31–33], or learner-based models [34]. Interveners vary and have included pharmacists, psychologists, nurses, physicians, physician assistants, and peer advocates, as well as computer-based virtual counselors. Across interventions, the need to carefully evaluate patients' adherence barriers within their specific life-circumstances and to adopt collaborative approaches that demonstrate both respect and compassion are well recognized. We have moved far beyond the prescriptive admonishments that characterized early efforts to encourage "compliance" to provider directives. In the following sections, we provide a brief overview of some of the most recent and innovative adherence promotion strategies within the area of antiretroviral adherence.

## Patient education and case management

Most adherence interventions include a patient support component that involves individualized or group education about ART and ART adherence, the development of basic medication management skills, and problem-solving with respect to adherence barriers. Consistent with current models of patient care and engagement (eg, the Chronic Care Disease Model [35]), these programs seek to foster a collaborative atmosphere where patients can independently adopt the intervention strategies or content delivered and take ownership of managing their behavioral and health care needs over time. A recent Cochrane review provided evidence of the effectiveness of patient support and education interventions, reporting that interventions targeting practical medication management skills, administered to individuals (vs groups), and delivered over at least 12 weeks were associated with improved adherence outcomes [36].

Although likely a necessary critical component in these programs, information alone may be insufficient. Indeed, the most recent patient-education and case-management approaches go well beyond merely providing information. In addition, they often provide social support, incorporate reminder devices or planning calendars, capitalize on therapeutic/counseling methods, emphasize patient-centered approaches, and integrate other adherence strategies [37,38].

### Modified DOT

Modified DOT (mDOT) or directly administered antiretroviral therapy (DAART) typically involves research or clinic staff or trained peers observing patients ingesting a portion of their full ART regimen. The distinguishing feature of mDOT is that patients continue self-administering the remaining portion of the ART regimen. The observations are typically tapered at some point under the assumption that patients will have generalized the behavior to all medications in their regimen and will maintain the behavior over time without support. Programs using mDOT have been prominent in much of the adherence work published in the past year.

Studies examining retention, attendance, and participant satisfaction have found mDOT programs to be acceptable and feasible across diverse settings and among various populations: substance users [39,40], persons with a history of poor adherence [41], ART-naive individuals or those changing regimens [42], children and adolescents [43], and others [44–46], In a review of 10 federally funded mDOT research projects, Goggin et al. [47•] concluded that mDOT for ART is feasible and easily adapted to many settings and target populations. Contrary to concerns that daily visits would be intrusive or burdensome, many patients reported that they appreciated the mDOT contacts. Evidence exists for similar acceptability of mDOT in international settings. For example, Pearson et al. [48] found that in Mozambique, the 175 participants assigned to receive mDOT kept an average of 93% of the 30 required daily mDOT visits, and 95% reported that the time with peers was very beneficial.

The efficacy of mDOT is promising. Although few mDOT programs have been examined in RCTs, available studies show mDOT is superior to self-administered therapy. A recent RCT in the United States on mDOT among drug users demonstrated significant improvement in viral load suppression and CD4 count [39]. Macalino et al. [49] found DAART to be effective at improving 6-month viro-logic and immunologic outcomes among illicit substance abusers. Similarly, in Africa, Pearson et al. [42] found mDOT participants, compared with those in standard care, showed significantly higher mean medication adherence at 6 months (92.7% vs 84.9%, 95% CI, 0.02–13.0) and 12 months (94.4% vs 87.7%, 95% CI, 0.9–12.9).

Although intensive interventions may be more expensive initially, greater sustained postintervention effects might make them more cost effective. In resource-limited clinics or in rural areas, providing and sustaining daily contact to observe dose-taking may prove difficult without additional staff or resources. Sensitivity to this issue is growing, and initial evidence for overall cost effectiveness of mDOT in resource-limited settings is being established [43].

### Contingency management strategies

Contingency management strategies based on operant conditioning behavior therapy principles have been examined as methods to support and improve adherence [50]. Contingency systems include voucher systems, rewards programs, or raffled prizes to reinforce behavior change [51–53]. An intervention that used prizes to reinforce adherence

based on data collected from electronic pill caps led to better adherence compared with standard of care, but improvements dissipated after the incentives were removed [52]. In other research where contingency management was paired with case management, beneficial viral load reductions were maintained after the intervention program was terminated [51], but the extent to which this may have been due primarily to the intensive case management component is unclear. Future research is needed to determine the efficacy of less costly nonmonetary reinforcers (eg, recognition by clinic staff, special privileges at the clinic such as prime parking spot or first choice of appointment time). Additionally, the field requires targeted inquiry into the mechanisms that promote internalization of reinforcement for adherence. The ultimate contribution of this research may lie in its success in helping patients to identify their personal sources of reinforcement for adherence behaviors over time.

## Social support adherence interventions

Although mDOT and contingency management are based largely on behavioral theory, other interventions focus extensively on social support aspects of adherence. Intervention programs using tenets of Social Action Theory (SAT) [54] and cognitive-affective models of social support [55] have been used to promote adherence. Guided by SAT, Remien et al. [54] demonstrated the effectiveness of a couple-based adherence-promoting intervention. Because the intervention was relatively brief (four 1-hour sessions delivered by a nurse-practitioner over a 5-week period), it may be feasible for implementation in resource-limited clinical settings. In such settings, however, securing personnel with the necessary training may not be feasible. Capitalizing on the association between adherence and various forms of social support, Simoni et al. [55] delivered an intervention over a 3-month period via six twice-monthly, 1-hour, peer-group sessions and weekly calls from a designated peer. Although the intervention failed to show an overall effect, self-reported adherence improvements were observed within the intervention arm in relation to dose-exposure. With other studies, this suggests that interventions fostering the development of social support may be worth pursuing, because adherence behavior is increasingly recognized as a dynamic process involving one’s social systems.

## Using technology to promote adherence

High-end technologies may help overcome scarce resources, including a limited supply of highly trained staff. Reflecting the recent nature of this area, most of these studies are yet to be published. An ongoing program, of research at the University of Washington’s School of Nursing (Seattle, WA) is examining the use of computer-based technology to educate and support HIV-positive individuals in adhering to specific ART regimens and safer sex practices [56]. The Center for Health, Intervention, and Prevention at the University of Connecticut (Storrs, CT) is currently evaluating a software-delivered information-motivation-behavioral skills–based adherence intervention with HIV-positive patients in clinical care [57]. In their project, HIV-positive patients use the software before meeting with their HIV care providers and are assigned intervention activities targeted to their specific adherence-related barriers. Initial results for both research programs are promising, and more extensive ongoing evaluation of software-based, media-rich strategies for

supporting HAART adherence should provide valuable insight into the feasibility and effectiveness of linking technology to intervention development and delivery.

In addition to these exceptionally comprehensive and highly tailored computer-based interventions, an increasing array of communication devices (eg, pagers, alarms, digital assistants, text messaging devices, and mobile phones) are serving as tools to assist with medication adherence (http://www.epill.com/diahetes1.html). Electronic reminders may be particularly useful for individuals with impaired memory, which is often associated with depression, dementia, substance abuse, and HIV progression. In an RCT among 58 HIV-positive patients, a Disease Management Assistance System (DMAS) device (combined with monthly adherence counseling) was programmed with ART regimen data to provide verbal reminders at dosing times [58]. Post hoc analysis of 31 memory-impaired individuals revealed significantly higher adherence rates among DMAS users (77%) than control subjects (57%). Another new device offers the advantages of electronic reminders with the convenience of a pillbox. Labelled MedSignals, it is a portable communicating pillbox that 1) provides access to as many as four prescribed medications; 2) prompts correct dosing times and warnings; and 3) records and uploads adherence data via the telephone (https://www.medsignals.com/default.aspx).

## ART Adherence Strategies for Pediatric Populations

Research in adherence-promotion strategies for pediatric HIV infection is limited. A review of the empirical literature through December 2005 located seven published studies, of which only one was an RCT. These studies provide limited support for the utility and efficacy of DOT, a 12-week educational program, gastrointestinal tube placement, and nursing home visits [59•]. However, most findings were based on pilot studies with very small samples, and adherence to the intervention itself often was problematic. The findings suggest that intensive interventions are required to produce efficacious outcomes; one-time interventions without ongoing education and support may be insufficient.

In the absence of empirical work to guide interventions with pediatric HIV populations, Dodds et al. [60] relied on clinical experience with pediatric populations in suggesting the benefits of initially determining psychologic and psychosocial treatment readiness. They stressed the need for intensive, continuous, coordinated, and nurturing case management services, with screening and treatment for mental health problems and substance abuse.

## ART Adherence Strategies in Resource-Constrained Settings

In resource-constrained settings, strategies that are practical yet cost-effective are critical. Barriers in these settings include inconsistent access to medications; geographically dispersed clinics; grossly understaffed clinics; costs associated with medications; acute HIV stigma; and instability of basic resources such as food and water [48,61,62]. One cost-effective strategy is the use of mass media to assist in widely disseminating accurate information [63]. Recently, the simple provision of pillboxes and training on how to use them has been highlighted as an efficacious strategy that can be deployed and maintained with minimal resources [64]. The use of pillboxes and pill organizers has a longstanding history as an adherence-promotion strategy across various illnesses; for some individuals,

providing structure and prompts for routine may be sufficient to promote adherence. However, some patients will have more complex needs, demanding more comprehensive and tailored interventions.

## Practical Guidelines: Adherence Promotion Strategies for the Clinic

In practice, empirically supported adherence programs may be too expensive or otherwise burdensome to implement. Discrete strategies adapted for clinical use are frequently the only realistic option for providers in resource-constricted settings. Because no research has been published on disaggregating active intervention program components, we can only tentatively suggest a compendium of potentially effective practices. We emphasize that, ideally, interventions should be evaluated in terms of their full package, including the underlying theory, the delivery system, the interventionist and training required, and the specifics of the approach. Table 1 provides a list of distinct strategies that may be effective and can be readily implemented in a clinic setting [65]. Providers should adopt, evaluate, and modify these as they see fit.

## Conclusions

More than a decade of experience with ART in the United States and Europe has shown that achieving optimal adherence is challenging and that adherence deteriorates over time as HIV illness improves, symptoms diminish, and side effects increase. Adherence is not static, but rather changes with time; long-term programmatic efforts may be necessary for the maintenance of effects [66]. Fortunately, research on behavioral interventions to promote adherence to ART is as dynamic as the targeted behavior, and is likely to continue expanding rapidly before any consensus is reached on the most efficacious intervention features in clinical practice. Once core elements are identified, further research will be needed to determine which interventions are relevant for which patients and when [67•]. In the meantime, published studies have set the stage for the synthesis and synergy of biomedical, psychosocial, and technologically innovative approaches. These are best implemented in a culturally sensitive manner that attends to structural barriers and individual deficits. In the area of ART adherence, adopting one perspective frequently leads to only partial understanding of this dynamic health behavior. Therefore, the best clinical practice will incorporate comprehensive, multidisciplinary approaches to promote antiretroviral adherence, bringing to bear on this seemingly intractable problem the focused attention and considerable effort likely required to address it.

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**Table 1**

Clinic-based strategies for promoting antiretroviral therapy (ART) adherence

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| Establish patient's readiness to take medication before prescribing—consider practice trials with sugar pills first |
| Evaluate the regimen—limit complexity as much as possible |
| Prepare the patient—fully educate about the need for strict adherence and potential for drug resistance, warn that the first regimen has the best chance for success |
| Assess and address any cultural beliefs or misinformation that might detract from adherence (eg, the misconceptions that ART cannot be taken with alcohol or nontraditional medicines and that brief self-imposed treatment interruptions are harmless) |
| Use multidisciplinary teams to create comprehensive treatment plans that include case management, social work services, dietary services, pharmacist consultation, and medical care |
| Solidify the patient-provider relationship—establish trust; serve as source of information and continuous support; remain available between visits |
| Manage side effects—prepare patient for possible adverse reactions, recognize their impact (particularly those that are disfiguring), and treat aggressively and prophylactically if possible |
| Be accepting and empathic (not judgmental or punitive) when discussing nonadherence to encourage accurate reporting |
| Regularly assess adherence—with normalizing introductions and specific, open-ended queries ("Most people find it hard to take ART exactly as prescribed. Which doses were hardest for you last week?"); remember it is often difficult to predict or identify nonadherers without careful assessment |
| Continue to examine and address barriers to adherence—including substance use; depression; and problems in everyday living such as limited income, housing instability, domestic violence, and child care needs |
| Problem solve—encourage patients to identify adherence barriers and brain storm strategies to address them |
| Encourage the use of reminder tools (eg, pill boxes, diaries, cell phone alarms), but realize they will likely not address all patients' adherence needs |
| Don't neglect patients reporting perfect adherence—they may need support and reinforcement as well |
| Endorse specific, practical strategies (eg, store medications by the coffee maker) over more global, likely less attainable slogans (eg, "every dose every day"). |
| Promote social support—including appropriate disclosure and the involvement of a designated treatment-adherence partner, peers, family members, partner, and friends |