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Antiretroviral Adherence Interventions: Translating Research Findings to the Real World Clinic

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Abstract

The success of potent combination antiretroviral therapy (ART) for HIV infection is compromised primarily by failure to maintain optimal levels of adherence over the long term. Recent reviews suggest behavioral interventions to promote ART adherence can have significant effects, but these tend to be small and to diminish over time; sustained improvements in biomarkers are particularly elusive. In this article, we update current reviews, focusing specifically on the 13 studies evaluating behavioral interventions to promote ART adherence published since September 2007. We describe the range of intervention strategies employed and qualitatively summarize findings of their efficacy. In conclusion, we consider implications and offer strategies for enhancing adherence in clinic-based HIV care prior to ART initiation, at initiation, and over the course of treatment.

Keywords

HIV/AIDS; ART; Adherence; Interventions; Review

Introduction

Soon after the introduction of combination antiretroviral therapy (ART) in the late 1990s, patient adherence emerged as the Achilles' heel in these otherwise potent regimens [1, 2]. Without strict attention to dosing schedules and dietary restrictions, the efficacy of ART was severely compromised [3, 4]. Indeed, perhaps never before in medical history has a therapeutic regimen required such strict lifetime adherence with such devastating consequences for nonadherence. New formulations have dramatically reduced pill burden to

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as little as one pill taken once daily, yet adherence remains challenging and is still a long-term predictor of viral suppression. Moreover, inconsistent adherence to simplified regimens continues to threaten treatment options for individuals who develop resistance to known agents.

Given the devastating consequences of suboptimal adherence to ART, including rapid onset of viremia and the development of resistant virus that is transmittable to others [5], an unprecedented amount of research has been undertaken to understand and promote ART adherence. A meta-analysis indicated that among the 24 behavioral interventions to promote antiretroviral adherence published through 2004 [6], there was a "small" but significant average effect ($d = 0.35$; odds ratio [OR] = 1.88; $P < 0.05$) on adherence, which was larger in studies that enrolled participants thought to have adherence difficulties. Focusing solely on RCTs, Simoni et al. [7] found that across 19 studies, participants in the intervention arm were about 50% more likely than those in the control arm to achieve 95% adherence (OR = 1.50; 95% CI, 1.16–1.94) and 25% more likely to have an undetectable HIV-1 RNA viral load (VL; OR = 1.25, 95% CI, 0.99–1.59). A recent update extended coverage of the literature through September 2007 to include 48 studies (6,810 participants total) and similarly found support for behavioral interventions targeting improvements in adherence ($d = 0.28$; OR = 1.66; 95% CI, 1.54–1.78), with somewhat larger effects in studies targeting poor adherers and smaller effects in studies with longer monitoring periods (over 45 weeks) or that targeted ART-naïve patients [8•].

In this article, we highlight recent advances in ART-adherence intervention strategies, focusing specifically on reports evaluating behavioral interventions to promote ART adherence published since September 2007. We describe the range of intervention strategies, with an emphasis on the most successful approaches. In concluding, we suggest how the findings might be incorporated into ongoing primary HIV clinic care.

Selection and Description of Studies

A search of PubMed (Medline) and PsychInfo with the terms "intervention and HIV" and "adherence/compliance and ART/HAART/ARV" yielded 70 peer-reviewed non-redundant articles published in English between September 1, 2007 and October 31, 2009. Among these, 13 were selected for review based on their evaluation of a behavioral intervention to promote ART adherence. Note that three studies in the initial search detailed aspects of adherence-promotion interventions but were excluded from the review because the evaluation of the intervention was initially reported prior to the inclusion date criterion [9•, 10, 11].

The 13 studies are described in Table 1. Nine were conducted in the United States, with the others conducted in Brazil, Canada, China, and Mozambique. Targeted samples included both men and women (11 studies, $n = 1849$, in addition to the 7018 beneficiary claims reviewed in Hirsh et al. [12•]) and women only (two studies, $n = 248$). Participants' ART history varied, with six studies targeting those who were switching regimens and/or were ART naïve, three studies of ART-experienced participants, and four studies of those with a full range of ART backgrounds, from naïve to highly experienced. Samples were largely drawn from a general HIV primary care clinic population, although some studies specifically targeted drug and alcohol users or other high-risk groups.

Intervention strategies and modalities were heterogeneous, including nurse-delivered individual counseling, peer group and individual peer support, facilitated group sessions, phone-based counseling, text/pager messaging, and data-driven approaches such as using electronic dose monitoring (EDM) as an intervention tool. The total duration of interventions varied from 1 months to 15 months. Most studies lacked any follow-up

assessments beyond immediate post-intervention; in others, follow-up was 6 months, 9–12 months, or 18–24 months. Exposure included as-needed patient or provider-initiated phone contacts, tapered daily pages, regularly scheduled individual sessions, and groups that met rarely (monthly) or frequently (5 days per week). Six of the interventions used theoretical approaches to guide the development of intervention content, mainly drawing from well-known theories of health behavior changes (eg, Information, Motivation, Behavioral Skills Model [13, 14], Transtheoretical Model [15], and Self-regulation Theory [16]). In five of the interventions, empirically supported approaches to facilitate health behavior change were specified (eg, motivational interviewing, cognitive-behavioral techniques, problem solving, and harm reduction approaches).

Study methodology to evaluate outcomes was generally rigorous, with ten randomized controlled trials. Most employed an intent-to-treat analysis followed by more specific or qualified outcome investigations. Nine studies included some self-reported measure of adherence, typically a recall of missed doses over the prior several days. Four studies used EDM, and three included a pharmacy refill or claims-based assessment of adherence; none used pill counts. Three studies evaluated their outcomes on multiple measures of adherence; the others used one. The majority of studies incorporated biomarkers as outcome indicators: CD4 only (one study), VL only (three studies), or both (five studies).

Overall, most studies demonstrated a clear or qualified impact on adherence. Only two failed to find support for any adherence metric, and both of these involved fairly intensive interventions in the control arm (Sampaio-Sa et al. [17] studied intervention contrasting an Information, Motivation, Behavioral Skills model-based educational workshop with a group video-based control of similar content, and Whol et al. [18] examined intensive weekly case management contrasted with standard case management). Six studies demonstrated efficacy in primary analyses and an additional five evaluations provided qualified support (eg, efficacy within a given group, for select adherence measures, or for some portion of the monitoring period). As indicated in Table 1, successful interventions included adherence approaches incorporated into pharmacy usual care [12•], one-on-one and group-based peer support [19, 20]; peer-delivered modified directly observed therapy [21]; patient-centered or motivational interviewing-based approaches delivered by a nurse in person or by telephone [22–24]; and one-on-one approaches covering specific aspects of adherence [25, 26]. Additionally, Koenig et al. [27] reported positive outcomes on adherence for their multicomponent intervention that involved both the patient-participant and an individual within the patient's support system identified as an adherence support person in individual and group sessions delivered by trained nurses. Sabin et al. [28] reported support for their approach of training participants in EDM use and using EDM data printouts with patients to review their adherence patterns, identify missed or outside of dose time doses, and explore barriers around those events. As noted in Table 1, the initial positive impact of an intervention on adherence outcomes often was attenuated at follow-up when interventions were discontinued.

Of the nine studies evaluating biomarker outcomes, three demonstrated clear support and three demonstrated qualified support for intervention efficacy. All of these studies reported generally positive findings in terms of ART adherence measures. Among the three studies failing to note effects on biological outcomes, two had demonstrated positive adherence outcomes [24, 28] and one [17] found no effects on biomarkers or adherence.

Implications for Clinic-Based HIV Primary Care

Building upon past literature, the more recent published work targeting adherence offers additional guidance in terms of specific strategies that might be considered for inclusion in

clinical practice. It is important to note that although we can select strategies that may be effective from the current literature, individual or discrete strategies are rarely evaluated outside of the context of larger comprehensive intervention approaches. What the most recent activity in adherence intervention design clearly signals is a movement towards compendium or multicomponent interventions that mobilize several support strategies and delivery modalities. Adopting a single approach from a multifaceted program (eg, making phone calls to check in with patients on their adherence, suggesting an adherence support person be identified within a patient's social network to help him or her with adherence, or creating an accessible 24-h adherence call-in line for use in clinic) may compromise its overall efficacy. Thus, independent strategies presented here are not clearly established or demonstrated as independent active ingredients, but they may nonetheless offer approaches that might be cautiously considered for incorporation in clinical care.

With this proviso in mind, we present in Table 2 some strategies to consider, based both on the studies reviewed here as well as the accumulated recommendations of previous reviews of this literature [29•]. These are grouped in terms of the pressing treatment and adherence tasks at hand when individuals are preparing to initiate ART, when they commence a regimen, and as they continue over time. These are somewhat artificial distinctions, as ART regimens are changed and individuals cycle among adherence phases. Overall, the strategies emphasize adopting a multidisciplinary team-based approach to anticipating challenges in adherence and directly assessing and addressing it with a diverse array of strategies, some brief and inexpensive (sensitively assessing adherence as part of routine clinical care) and other resource-intensive and long term (providing ongoing case management to address situational barriers such as mental health issues, housing instability, and substance abuse). Past studies suggest ongoing support is needed. Ideally, strategies should be considered for delivery over time and not delivered solely for intensive periods.

Clinics must weigh the intensity of contact required with respect to their financial and personnel resources. In the face of increasingly complex interventions (intensive one-on-one counseling, frequent professionally facilitated group sessions, automated text messaging), many clinics may find themselves ill equipped. Unfortunately, researchers only rarely provide cost-benefit data on adherence interventions; only one of the 13 studies reviewed here did so [21]. Issues germane to initial start-up costs, training required, person hours required, supplies to be purchased (eg, pill boxes, EDM devices), services maintained (eg, cell phone monthly fees, text messaging services, toll-free phone lines), and implementation support over time are all critical to consider. Cost considerations are even more influential in resource-constrained settings.

Conclusions

Published reports of behavioral interventions both recently and in the past decade suggest it is possible to intervene in ways that promote antiretroviral medication adherence, but effects are generally small and transitory and there are no clearly demonstrated simple strategies. Multifaceted, long-term, and flexible approaches are needed to support adherence behavior, which itself is complex and dynamic. As Sandelowski et al. [30] has recently noted, most of the interventions have an "individualistic and rationalistic" slant. Intervention strategies need to be refined and evaluated that target all the different domains of factors empirically demonstrated to impact antiretroviral adherence. These include societal factors as encompassing as stigma, situational factors such as clinic location and convenience, and even regimen characteristics such as less complicated, more easily tolerated regimens.

While awaiting further research, perhaps with outcomes on comparative effectiveness, clinicians should consider monitoring and evaluating their own strategies as part of quality

assurance procedures. These results of approaches based in actual clinical and not research settings will provide a perspective on feasibility and implementation currently lacking in the published literature on randomized controlled trials. Finally, focusing on medication adherence is necessary and appropriate but should not divert attention from efforts to retain patients in care once initiated. In fact, it is likely that interventions and strategies intended to enhance overall engagement in HIV care may prove particularly useful in both retaining individuals in care and encouraging frank discussions about ART adherence difficulties with providers. Finally, future research and practice should consider intervention approaches that address the "lived experience" of individuals in HIV care, which includes adherence challenges for those on ART but also other life priorities that influence treatment-related decisions. Only in full collaboration with patients, in recognition of their often trying life circumstances, can providers form partnerships with the best prospects for optimal health outcomes.

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Table 1

Recent studies of behavioral interventions to promote antiretroviral adherence

Study	Outcomes
Deering et al. [19], 2009	**Adherence:**
Location: Vancouver, BC, Canada	Self-report: yes
Sample: *n* = 20; W; ART-N + ART-E; community sample with current and/or past injection or other drug use, housing instability, sex work	Pharm refills: no
Facilitator/modality: Community facilitator/drop-in nurse consult; in person (group and individual)	**VL:** yes
Strategies: Peer-dyads (1 trained peer and 1 matched peer) attended facilitated group sessions (targeting health, wellness, and education in the areas of positive living, safe disclosure, side effects, depression, and nutrition); peer-dyads set medical/social support goals after group sessions; capacity building for peer health advocates; drop-in nurse consultation service	**CD4:** N/A
Intensity: Weekly hour-long small group and peer-dyad meetings (minimum of 6 months); nurse consults as initiated	
DiIorio et al. [22], 2008	**Adherence:**
Location: Southeastern Metropolitan Area, United States	EDM: yes[a]
Sample: *n* = 246; M and W; ART-N + ART-S; clinic population	**VL:** no
Facilitator/modality: Nurses in motivational interviewing/in person (phone if needed)	**CD4:** no
Strategies: Individual sessions exploring barriers/facilitators of adherence, strategies to improve adherence, and development of action plans	
Intensity: 11 one-on-one sessions (~ 20–90 min) with phone support over 4 months	
Hirsh et al. [12•], 2009	**Adherence:**
Location: California, United States	Claim records: yes
Sample: *n* = 10 pharmacies, 7018 Medi-Cal beneficiaries; M and W; ART-S + ART-E	**VL:** N/A
Facilitator/modality: Pharmacists/in person	**CD4:** N/A
Strategies: Individual face-to-face at time of refill with services for adverse reactions, assessment of adherence, linkage to clinical team and case manager, and recommendations for changes to regimen as needed	
Intensity: Average of 14 visits over 1 year	
Johnson et al. [25], 2007	**Adherence:**
Location: Los Angeles, CA; Milwaukee, WI; New York, NY; San Francisco, CA	Self-report: yes[a]
Sample: *n* = 204; M and W; ART-E; clinic and community sample with high-risk behavior	**VL:** N/A
Facilitator/modality: Trained facilitators/ in person	**CD4:** N/A
Strategies: Individual one-on-one with facilitator focusing on 1) coping, positive affect, and social support; 2) self-regulation issues, safer sex, safer drug use, and status disclosure; and 3) accessing health services, medication adherence, and medical decision making	
Intensity: 15 (90-min) sessions delivered over 15 months	
Koening et al. [27], 2008	**Adherence:**
Location: Atlanta, GA	EDM: yes[a]
Sample: *n* = 226; M and W; ART-N; clinic population with an identified adherence support person	**VL:** yes
Facilitator/modality: Nurse and peer/in person, telephone, group meetings	**CD4:** no
Strategies: Individual sessions (with and without peer support) aimed at identifying and solving adherence-related barriers via increased ART-related knowledge, improving recognition of mental health and support related issues, and improving prospective memory; support calls utilized an abbreviated procedure; multipatient educational groups provided ongoing adherence support outside of clinic visits	
Intensity: Six individual sessions were delivered pre-(2 sessions ~ 2–3 h each) and post-(4 sessions ~ 1.5 h each) ART initiation; post initiation 5 phone support calls were placed by nurse interventionist between individual sessions; group sessions; adherence support peers could attend all individual and group sessions but were required to attend one meeting prior to initiation and one of the first two meetings post initiation	
Lopez et al. [26], 2007	**Adherence:**

Study	Outcomes
Location: Miami, FL; New York, NY; Newark, NJ	Self-report: yes[a]
Sample: *n* = 228; W; ART-E; mixed in terms of substance use history (current use, former use, never having used)	**VL:** yes[a]
Facilitator/modality: Therapist trained in motivational interviewing and CBT, content-relevant professional (eg, pharmacist, nutritionist, etc.)/individual, group, in person, via video	**CD4:** N/A
Strategies: A multicomponent intervention focusing on substance use, nutrition, and positive living-related factors; adherence component used a problem-solving focus to address the importance of and challenges in attaining high levels of adherence, viral resistance	
Intensity: 10-session intervention (phase I) and six sessions of behavioral exercises (phase II); participants were assigned to receive all sessions either individually or in a group format; intervention content was then randomized to be delivered via high-intensity (dyadic presentations, in person attention) or low-intensity (video-based and educational print materials) condition across all intervention content areas [31]	
Simoni et al. [20], 2009	**Adherence:**
Location: Seattle, WA	Self-report: yes[a]
Sample: *n* = 224; W and M; ART-N + ART-S ; clinic population	EDM: no
Facilitator/modality: Peers, group facilitators with graduate training in psychology/group meetings, telephone calls, pager messages	**VL:** yes[a]
Strategies: Facilitated peer support group meetings twice monthly with weekly individual telephone contacts in which peers assessed barriers to adherence and provided social support, strategies, and referrals. Two-way pagers with automated text messages to cue doses and offer education and entertainment	**CD4:** yes[a]
Intensity: For 3 months, 1-h meetings twice a month and weekly telephone calls; pagers with messages sent daily for the first 2 months and then tapered last month	
Parsons et al. [23], 2007	**Adherence:**
Location: New York, NY	Self-report: yes[a]
Sample: *n* = 147; W and M; ART-E; clinic and community sample with current history of hazardous drinking	**VL:** yes[a]
Facilitator/modality: Masters-level counselor/one-on-one counseling	**CD4:** yes[a]
Strategies: Individual counseling sessions focused on factual information, increasing personal responsibility for adherence and hazardous drinking, developing a personalized plan and skills to address adherence-related and drinking-related challenges, identifying antecedents to adherence-related and drinking-related risk behaviors, relapse prevention, and linkage to related support services	
Intensity: A total of 8 (60 min) sessions were delivered approximately weekly (had up to 12 wk to complete)	
Pearson et al. [21], 2007	**Adherence:**
Location: Beira, Mozambique	Self-report: yes
Sample: *n* = 350; W and M; ART-N; clinic population	**VL:** N/A
Facilitator/modality: Peer-delivered; individual	**CD4:** No
Strategies: Peer-facilitated modified Directly Observed Therapy at the clinic Monday through Friday (ART self-delivered over the weekends) with the addition of structured discussions initiated by the peer concerning social support, information, stigma, adherence, general encouragement, and linkage to community resources	
Intensity: 6 weeks of modified Directly Observed Therapy (Monday through Friday), visits averaged 15 min	
Reynolds et al. [24], 2008	**Adherence:**
Location: Universities of Ohio State, North Carolina, Pennsylvania, Washington, and Nebraska	Self-report: yes
Sample: *n* = 109; W and M; ART-N + ART-S; clinic population	**VL:** N/A
Facilitator/modality: Nurse delivered; individual-based and telephone-based counseling	**CD4:** N/A
Strategies: Individually delivered intervention that started as in person then switched to a 24-h telephone-based support system providing education, enhanced motivation, and support; sessions including assessing knowledge, suggesting skills and strategies, proving reassurance, and working to improve coping with strong affect	
Intensity: 14 sessions over 16 weeks; calls placed 1/wk (~ 7.9 min) for weeks 1–12 and 14–16	
Sabin et al. [28], 2009	**Adherence:**
Location: Dali, Yunnan Province, China	EDM: yes

Study	Outcomes
Sample: *n* = 68; W and M; ART-E; clinic population	**VL:** no
Facilitator/modality: Nurse or provided/in person	**CD4:** no
Strategies: Patients with EDM-detected adherence<95% over the previous month received counseling that included a printout of the EDM data, review of adherence patterns, exploration of reasons for missed or off-time doses, identification of barriers, and discussion of strategies to improve adherence	
Intensity: 10–15 min sessions over 6 months	
Sampaio-Sa et al. [17], 2008	**Adherence:**
Location: Salvador, Brazil	Self-report: no
Sample: *n* = 107; W and M; ART-N; clinic population	Pharmacy refill: no
Facilitator/modality: Co-facilitators (psychologist and social worker)/group meetings	**VL:** no
Strategies: Small group-based educational workshops covered information, adherence barriers, health promotion, and behavioral skills including social support, addressing barriers, stress management, self-monitoring, and relapse prevention	**CD4:** no
Intensity: Weekly 2–3 h workshops for 4 wk	
Whol et al. [18], 2009	**Adherence:**
Location: Los Angeles County, CA	Self-report: no
Sample: *n* = 168; W and M; ART-N + ART-E; clinic population	**VL:** N/A
Facilitator/modality: Intensive adherence case management/in person	**CD4:** N/A
Strategies: Case management sessions including the identification of structural and personal barriers to adherence, the development of an individualized adherence plan, provision of strategies, goal setting, and appropriate referrals	
Intensity: Weekly sessions (~ 23 min) over 6 months	

Studies published in English language between September 1, 2007 and October 31, 2009.

ART antiretroviral therapy; *ART-E* ART experienced; *ART-N* ART naïve; *ART-S* switching ART regimens; *CBT* cognitive-behavioral therapy; *EDM* electronic dose monitoring; *M* men; *N/A* not available either because they were not assessed or were assessed but outcomes were not reported; *VL* viral load; *W* women

[a]Support found but qualified by a modification to the analysis (eg, specific group, one but not all measures, or one but not all time intervals)

Table 2

Strategies for promoting antiretroviral adherence

Prior to initiation
Establish patient's readiness to take medication before prescribing—assess experience with past regimens and consider practice trials with sugar pills
Evaluate the regimen—limit complexity as much as possible.
Tailor the regimen schedule—map out daily routines of the patient and superimpose potential dose times and impact of suspected side effects. If possible, link dose time(s) to regularly occurring events.
Involve patients in the decision-making process for dose timing and regimen
Facilitate conversations with peers currently on the regimens to allay fears and temper expectations
Explore common concerns (ie, stigma, privacy, disclosure, toxicity) and more ideographic ones (what will pose the greatest challenges for you?) in a strength-based approach (what resources and support do you have to help you when you start the regimen?)
Provide necessary information about ART agents, common side effects, management of side effects, regimen requirements, resistance, and what to do if doses are missed or problems are encountered
Provide a list of resources for community and clinic-based support
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)
Provide as comprehensive an approach as possible—use multidisciplinary treatment planning including case management, social work services, dietary services, pharmacist consultation, and medical care
Address situational concerns that may serve as major barriers to adherence (eg, mental health issues, homelessness, substance use)
At initiation
Provide information and support for the management of potential side effects—prepare patient for possible adverse reactions, recognize their impact (particularly those that are disfiguring), and treat aggressively and prophylactically if possible
Adopt a neutral stance when inquiring about adherence—avoid overly enthusiastic reinforcement of reported perfect adherence or negative responses to missed doses; creating an environment for patients to report nonadherence comfortably and to feel supported in their efforts is critical in long-term patient-provider relationships
Regularly collect adherence data and use this information to give targeted feedback about improving medication taking
Ask questions and listen to answers. Ask patients what gets in the way and what helps and allow for them to respond fully. Wait to move to problem-solving; listening can be therapeutic and can offer an opportunity to patients to identify their own strategies for addressing barriers.
Offer strategies and tools as needed—including memory prompts (alarms, cell phones, linking objects to medications, linking dose times to recurring events); storage and carrying tools (portable pill cases); organizational tools (journal, pill box, calendar); monitoring tools (tracking cards for lab values or identification of barriers); informational tools (websites, videos, written material, ART cards with summaries of medication requirements and interactions); and referral to support services (mental health, housing, case management)
Avoid close-ended questions about adherence that quickly terminate the discussion (you're taking your medications, right?).
Promote social support, including appropriate disclosure and the involvement of a designated treatment adherence partner, peers, family members, partner, and friends
Long-term and at periodic intervals
Continue exploration of potential facilitators and barriers of adherence with neutral inquiries about adherence (You've been on this regimen for a while now, what are your greatest challenges for taking the doses every day? What is the hardest part?). Barriers and facilitators of long-term adherence can be different than those initially encountered.
Build a toolbox of adherence strategies based on cumulative experiences of patients and colleagues
Inquire about reinforcement of continued adherence (Do you do something special for yourself when you've had a period of really consistent adherence? What keeps you going?) Incorporate recognition of success into clinic procedures (eg, staff standing ovations for achieving undetectable virus levels).
Facilitate sharing among patients of successful strategies. Partner with local community-based organizations in such endeavors.

ART antiretroviral therapy