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BRIEF REPORT

Pilot Controlled Trial of the Adherence Readiness Program: An Intervention to Assess and Sustain HIV Antiretroviral Adherence Readiness

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Abstract To pilot the adherence readiness program, 60 patients planning to start HIV antiretrovirals were assigned to usual care ($n = 31$) or the intervention ($n = 29$), of whom 54 started antiretrovirals and were followed for up to 24 weeks. At week 24, the intervention had a large effect (50.0 % vs. 16.7 %, d = 0.75) on optimal dose-timing (85+ % doses taken on time) and small effect (54.2 % vs. 43.3 %, d = 0.22) on optimal dose-taking (85+ % doses taken) electronically monitored adherence, and medium effect on undetectable viral load (62 % 0.5 % vs. 43.4 %, d = 0.41), compared to usual care. These intervention benefits on adherence and viral suppression warrant further investigation.

Keywords HIV · Adherence · Readiness · Practice trials · Intervention

Introduction

The long-term success of HIV antiretroviral therapy (ART) is dependent on adherence to its dosing regimens, as poor adherence can result in the development of drug resistant virus and loss of treatment options [1]. Models of primary prevention and learning theory suggest that it is better to prevent problems of poor adherence than to try to correct or eliminate such patterns once they have developed. Original learning (e.g., pill taking patterns that form when first starting treatment) is more generalizable and context-free than the learning that attempts to replace it, and thus the first behavior learned is the most resistant to change [2], further emphasizing the need to establish good adherence behavior patterns at the outset of treatment. With the current emphasis on using treatment as prevention [3] and starting patients on treatment as soon as possible [4], ensuring that patients are ready to adhere well from the start of therapy may limit the development of adherence problems down the road and the need for increasingly limited resources to support adherence. Consistent with this approach, treatment guidelines emphasize the need for patients to be ready to adhere well prior to starting ART [4].

Evaluating patient adherence readiness and the need for additional adherence support before a patient is ready to start ART present challenges to both the patient and their provider. Unfortunately, there are no established methods for determining which patients need more or less adherence training, especially prior to the patient starting ART. Providers have been shown to be unable to accurately predict an individual patient's adherence [5], and self-report measures of readiness, commitment and motivation for adherence do not allow for accurate enough classification of readiness to inform decisions about whether to prescribe or defer treatment [6]. Practice trials with inert pills and dosing instructions that mimic ART provide a behavioral simulation for evaluating adherence readiness, but their utility as a tool for enhancing adherence readiness has not been systematically evaluated.

Without knowing who will need adherence support, the safest approach is to provide training to all patients starting ART. A plethora of HIV adherence interventions have been evaluated in recent years, and reviews of published findings suggest that interventions based on cognitive-behavior

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models that include educational, behavioral, and motivational components have been the most effective, but findings in general have been mixed [7]. Even the most effective interventions have resulted in modest, transient effects [7, 8]. A meta-analysis of HIV adherence interventions found that effect sizes were small on average, especially in studies that did not exclude patients without evidence of adherence problems, and that adherence declines over time [8], suggesting the need for some level of ongoing adherence support for many if not most patients. Yet countering the need for ongoing adherence training is the reality that most clinics have limited resources and are unable to provide adherence support to all patients, and in fact, not all patients need support.

To address these needs, an adherence intervention is needed that will not only help a patient achieve and maintain adherence readiness, but will also provide a method for determining when a patient is ready to adhere well and start treatment, and how much ongoing training a patient needs such that the training can be tailored to the needs of the individual patient (rather than "one size fits all"). Tailoring the amount of training to match individual patient needs is critical for an intervention to be effective, transportable and sustainable in routine clinic practice.

We report here the findings from a pilot randomized controlled trial of a comprehensive adherence readiness program (ARP) designed to provide clinicians with the tools needed to address these needs. Based on the information motivation and behavioral skills (IMB) model of health behavior [9], the ARP combines the use of pre-treatment practice trials to determine readiness, cognitive behavioral based adherence counseling and tailored intensity of maintenance adherence support. We examined the effects of the ART on dose-taking and dose-timing adherence, as well as virologic suppression.

Methods

Study Design

A randomized controlled trial was conducted to pilot test the ARP for identifying and sustaining adherence readiness. Sixty patients were randomly assigned to receive either usual care or the ARP on a 1:1 ratio. Primary assessments were administered at screening and weeks 8 and 24 following initiation of ART. Primary outcome measures included electronically measured dose-taking adherence, dose-timing adherence, and undetectable HIV viral load.

Study Participants

The study was conducted at the CARE Clinic, an HIV clinic within St. Mary's Medical Center in Long Beach, CA. Adult (age 18 years or older) English speaking patients were eligible to participate if they were about to begin or restart ART. We included both ART naïve patients and patients who had been on antiretrovirals in the past but had been off treatment for at least 2 months (to ensure a stable baseline assessment of viral load and CD4). The patient's physical health needed to be stable—i.e., no current acute opportunistic infection or medical condition that called for immediate antiretroviral treatment, as determined by the patient's provider. CD4 count was not part of the primary eligibility criteria; however, patients with CD4 counts <200 cells/mm^3 were required to be on prophylactic medication to reduce the risk of developing opportunistic infections in the event that they were assigned to the intervention group and ART was delayed a few weeks. Ultimately, the decision of whether the patient was an appropriate study candidate and could delay ART initiation to accommodate the study and intervention procedures was left to the patient and their primary care provider. Patients who met study criteria were informed of the study by their provider or the clinic's adherence counselor, and those who were interested were referred to the study coordinator for consent procedures. Patients who consented were administered the screening assessment battery, after which they were randomized to receive usual care or the intervention. Those assigned to the usual care control group were then issued their ART prescription, while those assigned to the intervention received their first intervention session that day or within the next week.

Usual Care Practices to Support Adherence

Usual care procedures at the clinic for supporting adherence were implemented, unaltered, to all participants. These procedures consist of having the clinic's adherence counselor educate the patient about the importance of adherence, evaluating the patient's commitment and motivation to adhere well, and working with the patient to address any significant barriers to adherence prior to initiating treatment. Once the patient starts ART, the primary care provider or nurse conducts routine inquiries about adherence and related problems at regular follow-up visits (often once or twice in the first month of treatment and then every 3 months). Structured, systematic protocols and the use of practice trials are not part of usual care at the study site.

Adherence Readiness Program (ARP)

The ARP consists of the following 3 stages of adherence training and includes the use of pre-treatment practice trials, adherence counseling, and a performance driven dose regulation mechanism to tailor the amount of training to the individual needs of the patients.

- Pre-treatment: A series of up to 4 one-week placebo practice trials accompanied by adherence counseling to help the patient achieve readiness, defined as 85+ % adherence in a single practice-trial, at which point the patient discontinues the practice trials and starts ART.
- Early treatment: Sessions at 2 and 4 weeks after starting ART to help patients successfully meet the adherence challenges (e.g., side effects) that emerge in the initial weeks of therapy.
- Maintenance: Two training modules, starting at weeks 8 and 16 after onset of ART, help patients maintain optimal adherence; each module ranges from one session (for those with 85+ % adherence in the prior month) to three biweekly sessions depending on the patient's adherence and how long it took them to achieve 85+ % adherence in between sessions.

The training sessions reflect each dimension of the IMB conceptual model as the content includes education about the importance of adherence, increasing motivation for adherence, enhancing social support and self-efficacy for adherence, side effect management, and using the practice trials and data from electronic monitoring of adherence to identify adherence barriers and facilitate the learning of problem solving and behavioral skills to overcome adherence barriers. Each session was manualized and included exercises that involved completion of worksheets and handouts that were given to the patient to take home for reference. An intervention manual is available upon request from the corresponding author, and a detailed outline of the sessions is included as an appendix in the electronic supplementary materials.

The clinic's adherence counselor was trained to administer the intervention. Each session lasted approximately 45–60 min and was audio-recorded for purposes of supervision and monitoring of intervention fidelity. To limit contamination, the training of the counselor stressed the need not to deviate from the clinic's normal procedures for enhancing adherence, while still providing counseling support as warranted to all participants.

Measures

All assessments were self-administered with the use of a computer-assisted self-interview. Participants were paid $30 for each completed assessment.

Demographic, Background and Medical Characteristics

These included age, gender, race/ethnicity, education level, housing arrangement, employment, sexual orientation, relationship status and medical insurance. Time since the patient started receiving care at the clinic and CD4 cell count were abstracted from the patient's clinic chart.

Adherence

Electronic monitoring caps [electronic drug exposure monitor (eDEM) caps, AARDEX Ltd., Zug, Switzerland] were used to continuously monitor adherence to the primary or "backbone" antiretroviral in each participant's ART regimen. The caps record the exact date and time that the cap is unscrewed from the bottle, which is intended to represent the time that a single dose was ingested. Computer software associated with the caps calculates percentage of prescribed doses taken (dose-taking adherence) and percentage of prescribed doses taken within specified time windows (i.e., ±2 h windows around optimal dosage times for twice-a-day regimens, ±3 h window for once-a-day regimens) (dose-timing adherence). Extra doses (i.e., doses taken above the maximum number of doses prescribed each day) taken during any given day were deleted from the calculation of adherence. For both dose-taking and dose-timing adherence, 85 % and above was considered the threshold for classifying optimal adherence because of recent research showing that this level of adherence is sufficient to sustain viral suppression with the newer, more potent ART regimens [1].

HIV Viral Load

HIV-1 RNA levels were collected from the patient's medical chart at ART baseline and the date closest to week 24 or end of study visit. HIV viral load represents a measure of response to ART and is influenced by adherence. Viral load at study endpoint was converted to a binary indicator of undetectable viral load (limit of detection was 50 copies/ml).

Psychosocial Functioning

The 9-item depression module of the patient health questionnaire (PHQ-9) was used to assess depression [10]; each item measures the frequency of a symptom over the last two weeks using a rating scale from 0 'not at all' to 3 'nearly every day', and scores are summed. A total score greater than 9 has been found to correspond highly to a diagnosis of major depression [10]. Substance use was assessed by asking each participant to indicate how often they had used each of a list of 8 substances over the past 6 months. Response options consisted of 'never', 'monthly or less', '2–4 times a month', '2–3 times a week' and '4 or more times a week'. If alcohol was used 2–3 times a week or more often, and if a drug was used 2–4 times a month or more often, the substance was considered to be used frequently. A binary indicator of frequent use of each substance was created, as was an overall indicator of frequent use of any illicit drug (not including alcohol), and frequent use of any substance (alcohol or illicit drug).

Statistical Analyses

Comparisons between the intervention and control groups were conducted with 2-tailed independent t-tests to assess differences with regards to continuous variables, while Fisher's exact tests were used for binary variables due to the low sample size and chi square tests for categorical variables. An intention-to-treat (ITT) approach, with dropouts considered to be non-adherent, was used when examining group differences on the primary outcomes, as well as analyses involving only participants with data available. Effect sizes were calculated with regard to intervention effects on primary outcomes in ITT analyses; effect sizes of d <0.35 were considered small, 0.35–0.65 as medium, and >0.65 as large.

Results

Sample Characteristics

Sixty patients enrolled in the study; 29 were randomized to receive the ARP intervention and 31 the usual care control. Six participants (5 intervention and 1 control) did not initiate ART, one of whom decided he was not ready to start ART and the others were lost-to-follow-up; of the 5 intervention participants, three completed the first practice trial and all had <70 % adherence, an indication of not being ready for treatment. Furthermore, 5 of the 6 reported frequent use of substances at baseline (mostly alcohol and crystal methamphetamine). We opted not to include these 6 patients in the ITT analysis of primary outcomes, rather than including these patients as "non-adherers" or non-responders, because the intervention could be viewed as successfully indicating that these patients were not yet ready to start ART—a specifically stated purpose of the pre-treatment phase of the intervention. The remainder of the analysis involved only the sample of 54 participants who initiated ART.

Table 1 lists the demographic, background and medical characteristics of the total sample of 54, as well as by study group. The only statistically significant difference between the groups was with regard to frequent use of alcohol or illicit drugs, with 66.7 % of the control group compared to just 33.3 % of the intervention group being frequent users (FET = 0.03). The most common antiretrovirals being

Table 1 Participant characteristics of total sample of participants initiating ART and by study arm

Characteristic	Total Sample ($N = 54$)	Intervention ($N = 24$)	Control ($N = 30$)	P value
Mean age (SD)	38.6 (10.0)	39.2 (9.7)	38.2 (10.3)	0.72[a]
Male	94.4 %	95.8 %	93.3 %	1.00
At least some college education	51.9 %	62.5 %	43.3 %	0.18
Race/ethnicity:	29.6 %	29.2 %	30.0 %	0.70[b]
White	25.9 %	33.3 %	20.0 %	
Black	33.3 %	29.2 %	36.7 %	
Latino (a)	11.1 %	8.3 %	13.3 %	
Other				
Single	68.5 %	62.5 %	73.3 %	0.56
Gay/bisexual orientation	81.5 %	79.2 %	83.3 %	0.74
Employed (full or part-time)	25.9 %	16.7 %	33.3 %	0.22
Rent or own apartment/home	46.3 %	50.0 %	43.3 %	0.78
Has private medical insurance	25.9 %	25.0 %	26.7 %	1.00
Frequent use of substance:	24.1 %	12.5 %	33.3 %	0.11
Alcohol	33.3 %	20.8 %	43.3 %	0.15
Illicit drugs	51.9 %	33.3 %	66.7 %	0.03
Any substance				
Depressed (PHQ-9 > 9)	24.1 %	29.2 %	20.0 %	0.53
New patient at clinic (within past 6 mos.)	83.3 %	83.3 %	83.3 %	1.00
Mean CD4 count (cells/mm^3; SD)	306 (220)	283 (200)	325 (238)	0.50[c]
Mean HIV viral load ($\log_{10}$ copies; SD)	4.70 (0.87)	4.65 (0.73)	4.74 (0.99)	0.73[d]
ART naive	70.4 %	66.7 %	73.3 %	0.77
ART regimen dosing:	82.4 %	81.8 %	82.8 %	1.00
Once-a-day	17.6 %	18.2 %	17.2 %	
Twice-a-day				

All statistics were based on Fisher's exact tests, with the exception of the following

[a] $t = -0.4$

[b] $\chi^2 = 1.4$

[c] $t = 0.7$

[d] $t = 0.4$

taken by the participants were one pill per day drugs truvada (18.2 %) and atripla (32.7 %); 82.4 % of the sample was on a once-a-day regimen. Of the 54 who started ART, 51 (92.7 %) completed at least 8 weeks of the study, and 43 (79.6 %) completed all 24 weeks. Of the 11 dropouts, 4 were in the intervention group and 7 were in the control group. No variables significantly differed between study completers and dropouts.

Intervention Effects on Adherence and Viral Load

Among the 24 patients who started ART and were assigned to the intervention, 19 demonstrated readiness to start ART (i.e., had at least 85 % dose-taking adherence) during the first practice trial, 4 during the second, and 1 during the third trial. Seventeen (70.8 %) attended all of the sessions according to the protocol.

Percentage of Prescribed Doses Taken (Dose-Taking Adherence)

At week 8, nearly a quarter more of the intervention group achieved optimal dose-taking adherence compared to the control group (81.8 % vs. 58.6 %) among participants with data at this time point, which was marginally significant (FET = 0.13); in ITT analysis, the group difference narrowed to 75.0 versus 56.7 % (FET = 0.27), but reflected a medium effect size (d = 0.39). At week 24, the proportion of intervention patients with optimal dose-taking adherence declined to 65.0 %, which did not differ significantly with the 56.5 % in the control group (FET = 0.76), among participants with data; ITT analysis also showed no group difference (54.2 % in the intervention group vs. 43.3 % in the control group; FET = 0.58) and a small effect size (d = 0.22). Mean dose-taking adherence did not differ significantly between the intervention and control groups at week 8 (89.4 vs. 83.4 %; t = −1.3, $p = 0.21$; d = 0.41) or week 24 (88.8 vs. 83.0 %; t = −1.3, $p = 0.20$; d = 0.40), but medium effect sizes were evident.

Percentage of Prescribed Doses Taken on Time (Dose-Timing Adherence)

Week 8 data showed that half of the intervention group had optimal dose-timing adherence compared to just under a quarter of the control group (50.0 vs. 24.1 %) among participants with data at this time point, which was marginally significant (FET = 0.08), and remained so in ITT analysis (45.8 % vs. 23.3 %; FET = 0.09) with a medium effect size (d = 0.50). At week 24, the group differences were greater and statistically significant (60.0 vs. 21.7 %; FET = 0.01) among study completers; this group difference remained significant in ITT analysis (50.0 vs. 16.7 %; FET = 0.02) and the effect size was large (d = 0.75). Mean dose-timing adherence in the intervention group did not differ significantly from that of the control group at week 8 (78.3 vs. 70.7 %; t = −1.3, $p = 0.20$; d = 0.39), but was significantly higher at week 24 (81.0 vs. 67.0 %; t = −2.2, $p = 0.04$) and the effect size was large (d = 0.67).

HIV Viral Load

All participants had detectable HIV viral load and there was no group difference in mean log viral load at baseline (see Table 1). At study end point, the mean change in log viral load did not differ between the intervention and control groups (2.85 vs. 2.97; t = 0.4; $p = 0.72$), but 75.0 % of intervention patients had undetectable viral load compared to 56.5 % of the control group; this difference was not significant among study completers (FET = 0.34) or in ITT analysis (62.5 vs. 43.3 %; FET = 0.18), but the latter represented a medium effect size (d = 0.41).

Relationship Between Adherence and HIV Viral Load

Patients with complete viral suppression at study end point did not differ from those with a detectable viral load in mean dose-taking adherence through 24 weeks (86.6 vs. 83.9 %; t = −0.6, $p = 0.56$) or the proportion with optimal dose-taking (60.7 vs. 60.0 %; FET = 1.00). However, those with an undetectable viral load had numerically higher dose-timing adherence through 24 weeks (76.6 vs. 67.8 %; t = −1.3, $p = 0.21$), and 50 % had optimal dose-timing compared to 20 % of the patients with detectable viral load, with the latter being marginally significant (FET = 0.10).

Discussion

The primary goal of this pilot of the ARP was to gauge its preliminary efficacy in improving medication adherence and suppressing HIV viral load, and to determine whether a larger, more rigorous evaluation is warranted. Given the small sample size and corresponding low statistical power, the emphasis of the evaluation was clinical significance more so than statistical significance, and the examination of effect size estimates. Our findings revealed mostly medium to large effect sizes (in the general range of 0.40–0.75) on electronically measured adherence, with a particularly strong effect on dose-timing adherence, which our data indicated was more closely related to complete viral suppression compared to dose-taking adherence. A clinically meaningful effect (and medium effect size) of the intervention was also observed on the presence of

undetectable viral load. The observed effect sizes are particularly encouraging given that a meta-analysis of HIV adherence interventions published by Amico et al. [8] demonstrated that published interventions like the ARP, which do not focus solely on patients with demonstrated adherence problems, have had an average effect size of only 0.19 compared to 0.62 for interventions that target only patients with adherence problems.

The most common adherence parameter used to evaluate effectiveness of adherence interventions is percentage of prescribed doses taken or dose-taking adherence. While there is no rule about what constitutes a clinically meaningful difference in adherence, we consider a 10-point difference in mean dose-taking adherence between groups, and a 15–20 % difference in proportion of the group with at least 85 % of doses taken, to be indicative of an effective intervention. Decrements of 10 % mean dose-taking adherence have been shown to have significant effects on clinical outcomes [11]. The ARP did not make this standard with regard to mean dose-taking adherence at either week 8 or 24; however, the difference (18–23 % depending on analytic approach) between the groups with regard to the proportion of patients with optimal dose-taking adherence at week 8 represented a medium sized effect. As seen in other interventions [7, 8], this effect reduced to a small effect size at week 24 as the intensity of the intervention decreased, suggesting the need for a stronger maintenance component.

The intervention effect on dose-timing adherence was noticeably stronger. Electronic monitoring allows for a precise measurement of when the patient takes each dose, and our data showed medium to large effect sizes in revealing advantages of the intervention group on mean dose-timing adherence (8–14 % percentage point difference) and optimal dose-timing adherence (33–38 % difference in group proportions) across weeks 8 and 24, in comparison to the control group. Some of the group differences were even statistically significant, despite our underpowered study, and medium to large effect sizes were observed for the intervention.

Given that the intervention had strong effects on dose-timing adherence, but more modest effects on dose-taking adherence, it is important to consider the relative importance of the two adherence parameters. Our electronic data revealed that it was dose-timing, not dose-taking adherence, that was more strongly associated with virologic suppression, even with most of the sample being on once-a-day regimens. The measures of dose-taking and dose-timing are not independent, as a missed dose also counts as a dose not taken within the intended time window; however, a dose that is taken outside of the intended time window is not reflected in the measure of dose-taking adherence. Therefore, dose-timing adherence is a more precise or specific measure of adherence, and hence may explain more of the variance of viral load. Theoretically, taking doses on time helps to sustain a therapeutic drug level and limits risk of toxicity (associated with too high a drug level when doses are taken too close in time) and drug resistance (when doses are taken too far apart in time). Similar to our study, Gill et al. [12] found that dose-timing not dose-taking adherence was more strongly associated with viral suppression. These results support the need for greater emphasis on dose-timing in adherence education with patients in order to fully maximize treatment benefits.

While adherence interventions more directly impact behavioral pill taking, the ultimate target of the intervention and reason for adherence is virologic suppression. Reviews of ART adherence interventions generally reveal that interventions either affect dose-taking adherence or virologic suppression, but often not both, and more often the effect is on the former and not the latter [7, 8]. The medium sized effect that we observed for the ARP suggests a possible intervention effect on complete viral suppression, with three-quarters of the intervention group achieving virologic suppression compared to just over half of the control group.

The most obvious limitation of this pilot study is its small sample size and corresponding low statistical power, which impeded our ability to detect statistically significant relationships. As a result our findings should be considered preliminary rather than conclusive, and we have placed more of an emphasis on effect size estimation and clinical relevance, rather than statistical significance. The small sample size also prevented us from being able to adequately examine whether variables found to differentiate the two arms at baseline may confound the observed intervention effects. Limitations related to risk of contamination and generalizability are present due to the intervention being administered by the clinic's adherence counselor, who provided usual care services to all clinic patients including those in the control group. The contamination risk is lessened somewhat by the fact that the pre-treatment practice trials and review of electronic adherence data were only available to intervention patients, and the structure of the intervention manual helped to promote better quality and systematic implementation of content. Also, any contamination would mean that the observed intervention effects actually underestimate the actual effects of the intervention and that the findings represent a conservative evaluation of the intervention. The adherence counselor who administered the intervention has several years of experience in the field and with him being the sole interventionist, the generalizability of the results to other counselors, especially those less experienced, is uncertain.

In conclusion, while preliminary and based on a small sample, this pilot study provides support for the potential

benefits of the ARP for both pill taking adherence and virologic suppression. The intervention had its strongest effects on dose-timing adherence, and it was dose-timing adherence that was most strongly correlated with virologic outcomes in our study. While the intervention displayed benefits for both behavioral adherence and virologic outcomes, there was also evidence for the need to strengthen the intervention in order to achieve even more robust effects, particularly with regard to dose-taking adherence and sustaining optimal dose-taking adherence over time. Nonetheless, the observed benefits of the intervention provide evidence to support the further development and evaluation of the intervention as a tool to help patients and providers achieve and sustain adherence readiness and optimal treatment outcomes.

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