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ORIGINAL PAPER

Computer-Based Intervention in HIV Clinical Care Setting Improves Antiretroviral Adherence: The LifeWindows Project

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Abstract We evaluated the efficacy of LifeWindows, a theory-based, computer-administered antiretroviral (ARV) therapy adherence support intervention, delivered to HIV + patients at routine clinical care visits. 594 HIV + adults receiving HIV care at five clinics were randomized to intervention or control arms. Intervention vs. control impact in the intent-to-treat sample (including participants whose ARVs had been entirely discontinued, who infrequently attended care, or infrequently used LifeWindows) did not reach significance. Intervention impact in the On Protocol sample (328 intervention and control arm participants whose ARVs were not discontinued, who attended care and were exposed to LifeWindows regularly) was significant. On Protocol intervention vs. control participants achieved significantly higher levels of perfect 3-day ACTG-assessed adherence over time, with sensitivity analyses maintaining this effect down to 70% adherence. This study supports the utility of LifeWindows and illustrates that patients on ARVs who persist in care at clinical care sites can benefit from adherence promotion software.

Keywords ARV · Adherence · Intervention · IMB-model · ART

Resumen Evaluamos la eficacia de LifeWindows, una intervención de apoyo para la adherencia a la terapia antirretroviral (TAR) basada en teoría y con administración informatizada para pacientes con VIH + en sus visitas clínicas rutinarias. 594 adultos de cinco clínicas con VIH + y bajo tratamiento fueron aleatoriamente asignados a un grupo de intervención o de control. No se alcanzó significación estadística al comparar ambos grupos bajo la estrategia de 'intención de tratar' (incluyendo los participantes cuyos TAR se habían interrumpido por completo, habían asistido a la clínica en pocas ocasiones, o usaron LifeWindows con poca frecuencia). Sin embargo, la intervención obtuvo un impacto significativo cuando se evaluó con la muestra bajo Protocolo (un total de 328 participantes cuyos TAR no fueron interrumpidos, asistieron a sus visitas clínicas y se expusieron a LifeWindows regularmente). Los

This article was written on behalf of the LifeWindows Team. The members of the team and their contributions appear in the Appendix.

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participantes bajo Protocolo de intervención obtuvieron niveles más altos de adherencia que el grupo control en tres días de Estudios de Grupos Clinicos con SIDA (EGCS) con repetidas evaluaciones y manteniendo como mínimo un 70% de la adherencia. Este estudio apoya la utilidad de LifeWindows e indica que los pacientes con TAR que asisten a las visitas clínicas, pueden beneficiarse de este software de promoción de la adherencia.

Keywords AR · Adherencia · Intervención · IMB-modelo · TAR

Introduction

Antiretroviral (ARV) medications are highly effective in reducing HIV-related morbidity and mortality [1]. ARV treatment failure often occurs, however, due to resistance, toxicity, drug potency, and notably, inadequate adherence [2]. Despite the fact that ARV regimens have become simpler and more tolerable, suboptimal adherence remains problematic and prevents many HIV + persons from benefiting fully from treatment [3–5]. While optimal rates of ARV adherence vary by regimen [6, 7], 90% or greater adherence, sustained over time, is thought to be necessary to achieve durable viral suppression [8–10]. Research suggests, however, that adherence rates in general clinical samples fall in the 75–80% range [11, 12] and that as length of time on ARVs increases, rates of adherence decrease [13, 14].

A number of models have been proposed to account for variations in ARV adherence [3, 15]. The Information-Motivation-Behavioral skills (IMB) model [16], for example, identifies fundamental determinants of adherence to medication regimens and provides guidance for designing, implementing, and evaluating adherence promotion interventions. The IMB model assumes that adherence-related information, motivation, and behavioral skills are critical factors in ARV adherence, and that individuals who possess appropriate adherence-related information and motivation will apply adherence-related behavioral skills and adhere to their ARV regimen. Adherence may be strengthened by identifying and addressing, through interventions, an individual's deficits in adherence-related information, motivation, and behavioral skills. The IMB model identifies additional factors that may affect adherence to regimen (e.g., mental health problems, substance abuse, homelessness), which may also be targeted in adherence promotion interventions [16]. The IMB model of ARV adherence has been supported in correlational research (e.g., [17–20]) and experimental ARV adherence promotion intervention studies [21–27].

A number of ARV adherence promotion interventions have been implemented and evaluated and in general appear to strengthen adherence to therapy. A meta-analysis of ARV adherence interventions published through 2004 [28] reported that the average intervention effect size was small to medium, and additional meta-analyses of intervention studies confirm these effects [29, 30]. Practical applicability of ARV adherence promotion interventions in clinical settings, however, remains a concern. ARV adherence interventions are often time-consuming and involve costly staff commitments (e.g., physician, pharmacist, nurse, and adherence counselor time and effort) [31]. In addition, effective adherence promotion interventions may require repeated administrations over time and must address myriad factors associated with adherence to regimen. For these practical reasons, many clinical care settings offer little more than minimal adherence assistance to patients on ARVs [32].

In recent years, computer technology has been exploited to provide effective and cost-effective health behavior change support in a number of domains (e.g., [33–35]). Meta-analytic research has demonstrated that computer-based interventions are effective at changing HIV risk behavior (though not yet ARV adherence), and the efficacy of computer-based interventions compares favorably to those involving human resources [36]. Given the importance of ARV adherence and the need to develop practical and inexpensive adherence support interventions [31], computer-based interventions to help HIV + individuals adhere to therapy hold promise. Preliminary work on developing approaches that use personal digital assistants (e.g., [37, 38]) and web-based platforms (e.g., [39]) has been reported, but to our knowledge, no comprehensive computer-administered adherence promotion intervention has been developed and found effective.

The current randomized controlled trial (RCT) evaluated the efficacy of LifeWindows, a theory-based, computer-delivered, ARV adherence promotion intervention delivered at regularly scheduled HIV clinical care visits over time, in enhancing adherence to ARV regimen.

Methods

Participants

HIV + patients were recruited via provider referral and notices about the study posted in five large HIV care clinics in Connecticut, USA. Individuals meeting study inclusion criteria (18 years of age or older, English language comprehension, free of marked cognitive impairment, prescribed ARV therapy at study inception), completed informed consent procedures and baseline measures. Participation was voluntary and research protocols were approved by Institutional Review Boards at participating

institutions. The enrolled sample approximated the targeted enrollment (600) determined a priori on the basis of 80% power to detect small to medium effects ($d = .32$).

Procedures

IRB-approved informational materials that were made available to potential participants requested that individuals on ARVs consider participating in a research study on ARV medication taking. Interested participants discussed details of the project with study personnel, and, if still interested, completed full consent procedures. Randomization at enrollment to control and intervention conditions involved use of randomly generated numbers, which were sequentially assigned. Participants interacted with the LifeWindows software via a desktop computer, mouse, and keyboard at each of their regularly scheduled HIV care visits over approximately 18 months, in a semi-private location within the clinic. Participants were able to complete a maximum of one control or intervention session per month and received US $20 each time.

LifeWindows Intervention Condition

LifeWindows is an interactive computer-based ARV adherence promotion intervention developed specifically for this research based on extensive formative work with HIV + patients and healthcare providers and on the basis of the IMB model of ARV adherence. The program consists of several sequential components: a tutorial, introduction to a virtual guide who accompanies participants through the software, general assessment module, targeted adherence promotion intervention activities (brief descriptions of the 20 interactive, audio and visually rich intervention elements built into LifeWindows appear in Table 1), goal selection activities, and a closing statement from the virtual guide. The general assessment portion of the program assessed participants' information, motivation, and behavioral skills barriers to adherence [40]. Participants were offered targeted adherence promotion strategies that addressed these barriers, selected an intervention activity from those suggested, engaged in it, and chose an adherence-related goal. Subsequent sessions included a "check-in" on goal progress from the virtual guide and additional intervention activities and goal selections. Average total time spent to complete a full intervention visit was 26 min with an average of 8 min devoted specifically to adherence intervention modules.

Control Condition

Standard-of-care control participants received identical exposure to introductory portions of LifeWindows and completed the general assessment module, but intervention components (strategy selection, intervention activity, goal selection) were not provided. Both experimental and control conditions received the standard of care with respect to adherence (typically quite minimal) at the clinic they attended. Average total time spent to complete a full control condition session was 14 min. Time differences between intervention and control condition use of LifeWindows are primarily due to time engaging in intervention activities.

Because LifeWindows was individually administered to participants by computer, both intervention and control conditions could be provided at the same clinic through computerized administration of different protocols, as described above.

Measures

The general assessment module completed at each LifeWindows session, by intervention and control participants, included measures of participants' demographic characteristics and mental and physical functioning [41], the LW-IMB-AAQ (a 33-item measure of information, motivation, and behavioral skills-related adherence barriers) [40], the AIDS Clinical Trials Group (ACTG) 3-day recall measure of doses taken [42], and a Visual Analogue Scale (VAS) 3–4 week ARV adherence assessment [43] adapted for computer delivery. Adherence to regimen was calculated as the total number of pills taken over 3 days divided by the total number of pills prescribed for all agents for that period (ACTG) and as the average percent adherence over 3–4 weeks for all agents (VAS). Both the ACTG 3-day recall measure and the 3–4 week VAS have well-supported associations with biological measures of HIV progression and other measures of adherence (cf. [44, 45]). Viral load data[1] were extracted from medical charts at the conclusion of the research period.

Analytic Strategy

Outcomes were evaluated with growth modeling via Hierarchical Linear Modeling (HLM) (v 6.0; [46]). HLM was selected a priori as the most powerful approach for analyzing the current data structure, which assessed adherence in conjunction with a LifeWindows visit that occurred solely in the context of one's regularly occurring medical care. HLM allows for variability in the total number of assessments and in the intervals between

[1] Assays varied between clinics and also within clinics over time. In order to equalize results from assays of varying sensitivity, we selected the highest minimum-detection threshold used (HIV-1 RNA $\leq$ 400 copies/ml) to define "undetectable" viral load.

Table 1 LifeWindows interventions

Intervention module	Description
Battle for health	A video game in which patients battle infections, take ARVs on-time to fight HIV, and use tools (e.g., pillboxes, alarms) to ensure that ARVs are taken, even in challenging situations.
Bill the pill	An animated character presents strategies for taking pills that are hard to swallow or taste bad, taking large numbers of pills, and taking medications that make one feel nauseous.
Celebrate success	Offered to patients with perfect adherence. Patients create a personalized reward certificate and then learn about maintaining adherence over time.
Doc talk	A video-based intervention in which patients can "ask" HIV doctors about a number of HIV-related issues, including HIV treatment, side effects, and resistance.
Felicia the pharmacist	A video-based intervention in which patients are able to "ask" a pharmacist questions about their ARV prescriptions.
Focus on the fight	Involves an activity that helps patients visualize the therapeutic effects of HIV medications.
Helping hand	By playing the role of an adherence counselor to help other people living with HIV (PLWH) overcome their barriers to adherence, patients learn strategies for dealing with their own adherence-related issues.
HIV, drugs, and alcohol	Discusses the effects of street drugs and alcohol on the body, interactions of street drugs and alcohol with ARVs, and tips for staying healthy when using street drugs and/or alcohol.
Journey through the bloodstream	An animated sequence that uses simple representations to explain T-Cells, CD-4 count, HIV, viral load, how ARVs help fight HIV in the body, and drug resistance.
Information station	Describes services locally available for PLWH, including counseling and support groups, mental health services, substance abuse treatment, and housing assistance.
Learning from a missed dose	Patients are taught to assess the circumstances surrounding a missed dose and learn to identify, understand, and overcome their barriers to adherence.
Lipodystrophy	Includes unscripted video accounts of four different personal experiences with lipodystrophy. The intervention also discusses possible causes and treatment options.
Match-up	Patients create and print a personalized calendar on which ARV dose times are matched up with recurring activities.
Med minders	Describes tools and devices that can help patients take their medications on time every day.
Misadventures of skip sisdose	Uses humorous animation to provide tips for fitting ARVs into one's daily life, taking ARVs when one's routine changes, and taking ARVs when others are around.
My meds	A comprehensive resource that provides information about ARV medications, including dosing, side effects, drug interactions, and dietary restrictions for each medication.
Patient-provider Communication	Training in how to communicate effectively with one's doctor is presented through a series of video-based doctor-patient interactions.
Positive voices	A video-based intervention in which participants can "ask" other PLWH about their experiences with HIV and ARV medications.
Side effects solutions	Presents detailed information regarding side effects associated with ARV medications, and provides participants with tips and strategies for managing their side effects.
Stress management	Patients learn about the nature of stress, particularly as it relates to living with HIV and ARV adherence. A variety of stress-reduction activities and strategies are provided.

assessments which is necessary for the accurate characterization of this study design. The distribution of adherence as a continuous variable was highly non-normal and given that the intervention sought to promote perfect and near-perfect adherence, our main outcome was level of *perfect adherence* (100%). This approach had been planned a priori and is not uncommon in the ARV adherence literature (cf. [28, 29]). Each adherence outcome was evaluated by the 3-day ACTG measure and by the 3–4 week VAS measure, both defined as 100% vs. imperfect adherence. Significant results were subsequently subjected to sensitivity analyses to determine the lowest adherence cut-off (e.g., 90, 80, or 70% adherence) for which effects were retained.

Adherence measured with the ACTG and VAS were used to estimate the primary outcomes—adherence over time. Analyses of each outcome using HLM employed all available pairs to estimate trajectories of adherence over time which required that participants included in the analyses have at least two valid adherence observations over the course of the study. All analyses were subsequently repeated using "missing-equals-failure" assumptions to determine consistency of outcomes when all baselined participants were eligible for inclusion in the primary analyses.

Outcomes over time were characterized by days from baseline assessment (where 0 represents baseline). We hypothesized that higher proportions of patients would

report perfect adherence over time in the intervention arm than in the control arm. For all analyses, the main arm effect on perfect adherence was estimated using a Bernoulli distribution and robust standard errors. For overall model characteristics in terms of reductions in error variance, models were rerun and compared using LaPlace estimation. Changes in proportion of individuals with undetectable viral load were also evaluated using available medical records data with Generalized Estimating Equations and Chi Square difference tests of proportion undetectable (set to at or below 400 copies/ml for all available test results) by study arm within time-interval, as well as survival analyses for time to virologic failure.

Two samples were employed in the evaluation of LifeWindows. These included (a) an Intent-to-treat (ITT) sample, and (b) an On Protocol (OP) sample. The ITT sample used data from all participants with two or more LifeWindows sessions in which adherence data were collected, regardless of whether participants continued to be prescribed ARVs throughout the study, attended the clinic with any regularity, or used LifeWindows regularly. The OP sample included participants who were relatively regular users of clinical care and thus users of LifeWindows and who remained on ARV treatment throughout the study. Specifically, the OP sample was identified on the basis of two criteria: (1) experimental or control group participation in 6 or more LifeWindows visits during the study, and (2) participants were prescribed at least one ARV throughout the course of the study (had no permanent or intermittent discontinuation of all ARVs on record during any clinical care visit). The first criterion represented the number of LifeWindows sessions a participant would take part in over the 18-month study period given current "every 3 months" guidelines for attendance at HIV clinical care [47]. The 6-session criterion also reflected the modal number of sessions completed by the current full sample. The second criterion, continuous prescription of ARVs, was identified so that ARV adherence was relevant and measurable in the OP sample throughout the study.

Intervention outcome analyses were conducted separately for the ITT and the OP samples. The analyses with the ITT sample speak to evaluating the impact of introducing the intervention into the clinical care system, and OP analyses assess intervention vs. control impact on "typical users" who are in relatively consistent contact with clinical care and remain on ARVs.

Because the OP sample was created from the ITT sample, pre-test equivalence between the study arms on baseline characteristics was examined in both the ITT and the OP samples. Additionally, differences between those excluded and those included in the OP sample were examined. Variables found to be significant in these analyses were included in the examination of intervention effects while controlling for each of these potential covariates.

Results

Participants

Baselined participants ($N = 594$) completed from one to 18 LifeWindows sessions (Mode = 6 sessions) during their clinical care visits over approximately 18 months, taking part in an overall total of 4,155 sessions of which 3,924 included assessments of ARV adherence.[2] Of 594 baselined participants, 328 (55%) met inclusion criteria for the OP sample (see Fig. 1). Participant characteristics for the ITT, OP-included, and OP-excluded samples are presented in Table 2. Those included in the OP sample are similar in most respects to those excluded with the exception that those included reflected larger numbers of women, unemployed, individuals on disability, and were slightly older. The OP sample also had a higher number of individuals with undetectable viral load at baseline. Note that these elements did not differ by study arm within the OP sample. No differences in baseline values by study arm assignment were noted in the ITT sample; study arm was not related to inclusion or exclusion in the OP sample, and the only differences between study arm in the OP sample were total income (lower income in the intervention arm) and self-reported sexual orientation (lower proportion of gay participants in the intervention arm).

The primary analytic approach was first to establish main effects for the intervention arm in each sample (ITT and OP). Variables that differed by study-arm in the OP sample or differed between those included vs. excluded from the OP sample were used to further evaluate the significance of any intervention effects observed, while controlling for these variables.

Analysis of Main Intervention Effects on Adherence

For the ITT sample, which includes participants who did not attend clinical care or use LifeWindows regularly or who were discontinued from all ARVs during the study, the observed pattern of an increasing proportion of participants in the intervention arm reporting perfect adherence on the ACTG 3-day adherence measure ($t_{(586)} = 1.55$, $p = .12$) and on the VAS 3–4 week adherence measure ($t_{(586)} = 1.55$, $p = .12$) as time progressed from baseline did not reach significance. Overall, patterns suggested that the intervention arm increased on perfect adherence over time

[2] Adherence assessments were not conducted at visits where patients' medical records indicated complete discontinuation of all ARVs.

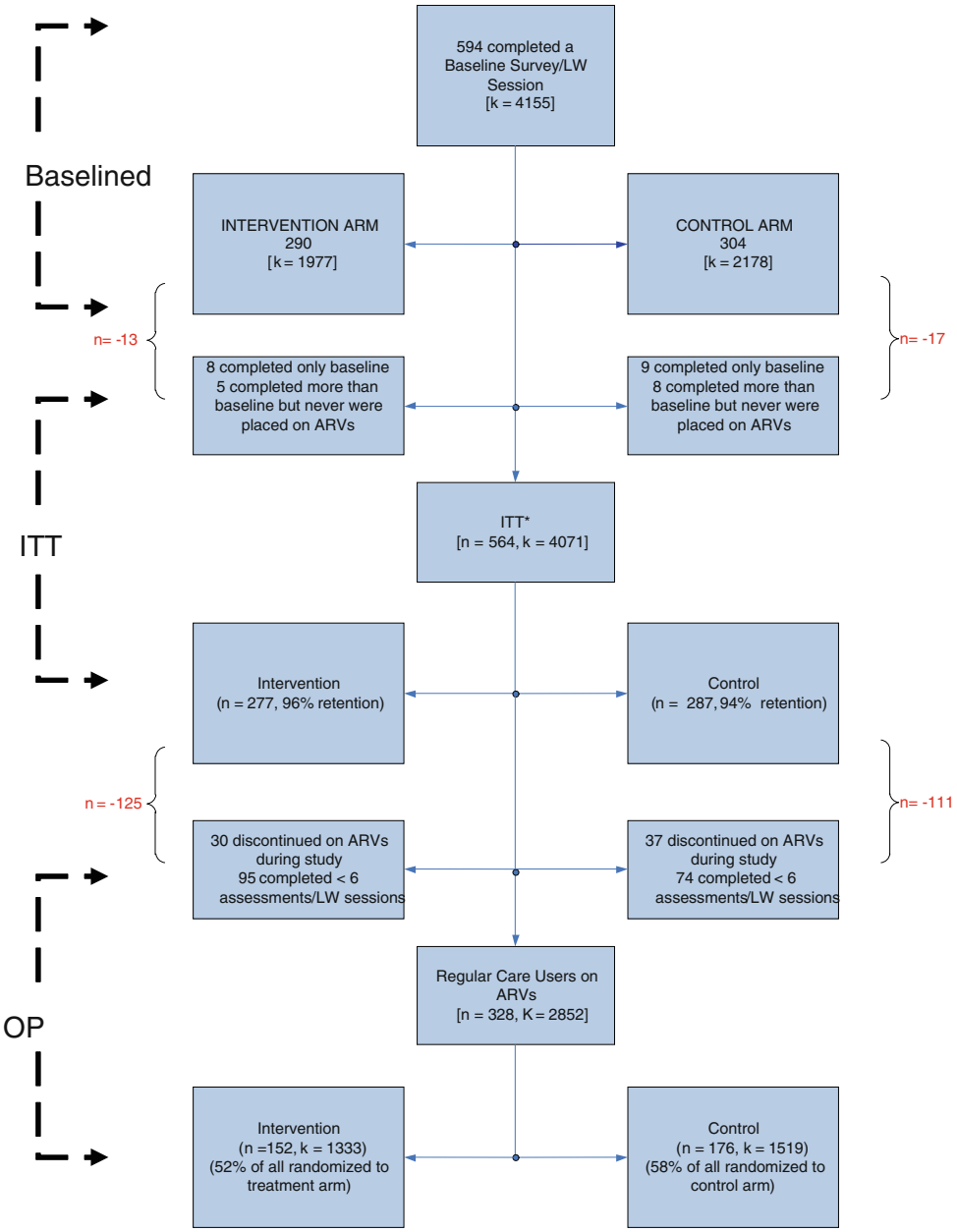

Fig. 1 Participant allocation. *ITT* intention-to-treat sample, *OP* on protocol sample (required six or more LifeWindows visits and no full ARV therapy interruption during the course of participation in the trial), *n* number of unique participants, *k* number of observations. *Primary analysis using HLM required at least two adherence observations (additional analyses using missing-equals-failure included all baselined participants)

as did the control arm, but control arm participants did so to a lesser and less consistent degree (see Fig. 2 for distributions of perfect adherence by LifeWindows visits over time).

Analyses of the OP sample were conducted on the 2,852 valid observations of adherence for the 328 individuals who completed 6 or more LifeWindows visits and were not interrupted or removed from ARVs during participation. In the OP sample, there was a significant main effect of study arm assignment on perfect ACTG-assessed 3-day ARV adherence ($t_{(326)} = 2.26$, $p = .024$), which was retained down to a 70% adherence cutoff (90% $p = .05$; 80% $p = .03$; 70% $p = .02$). An increase in the proportion of participants reporting perfect 3-day adherence was observed over time in the treatment arm, while this proportion decreased in the control arm. Analyses repeated using LifeWindows visit number instead of days from baseline as the time metric produced similar results (depicted in Fig. 3), and all models were supported by parallel analyses using LaPlace estimation. Results of the per day odds ratio extrapolated to a 90-day period suggest that over a three-month period, the odds of being perfectly adherent were 12% higher for those in the treatment than in the control arm. For the VAS measure, perfect past

Table 2 Characteristics of total ITT sample, on protocol sample, and participants not meeting criteria for on protocol sample

Study variable	ITT sample ($n = 594$)[a]	On protocol sample ($n = 328$)[b]	Excluded from on protocol sample ($n = 266$)	p (diff between op and excluded from op samples)
Gender				
Female, *n* (%)[c]	229 (39%)	138 (42%)	91 (34%)	<.05
Mean age in years, M (SD)[d]	47.0 (∼8)	48.0 (∼7)	45.8 (∼9)	<.001
Number of years since HIV diagnosis, M (SD)	13.21 (6.2)	13.46 (5.98)	12.90 (6.48)	.27
Self-reported sexual orientation				.71
Heterosexual, *n* (%)	431 (74)	236 (74)	195 (75)	
Homosexual, *n* (%)	112 (19)	61 (19)	51 (20)	
Bisexual, *n* (%)	39 (7)	24 (8)	15 (6)	
Living in stable housing, *n* (%)	538 (91)	303 (92)	235 (89)	.12
Race/ethnicity				.32
Black/African American, *n* (%)	262 (44)	154 (47)	108 (41)	
Latino/a, *n* (%)	151 (25)	77 (23)	74 (28)	
White, *n* (%)	141 (24)	73 (22)	68 (26)	
Other, *n* (%)	40 (7)	24 (7)	16 (6)	
Used injection drugs in past month, *n* (%)	38 (6)	17 (5)	21 (8)	.16
Employed, *n* (%)[e]	233 (39)	107 (33)	126 (48)	<.001
On disability, *n* (%)[f]	294 (49)	179 (55)	115 (43)	<.01
Mean yearly income, M (SD)	$17,225 (18k)	$16,172 (17k)	$18,523 (18k)	.11
HIV risk transmission				.73
Men who have sex with men (MSM), *n* (%)	85 (14)	43 (13)	42 (16)	
Heterosexual sex, *n* (%)	232 (39)	131 (40)	101 (38)	
Injection drug use, *n* (%)	126 (21)	73 (22)	53 (20)	
Blood transfusion, *n* (%)	15 (2)	10 (3)	5 (2)	
Other or refused, *n* (%)	136 (23)	71 (22)	65 (24)	
Mean physical health functioning score: PCS8, M (SD) (higher scores reflect better functioning)	45.84 (10.42)	45.85 (10.11)	45.83 (10.80)	.98
Mean mental health functioning score: MCS8, M (SD) (higher scores reflect better functioning)	43.07 (11.64)	43.89 (11.25)	42.06 (12.06)	.06
Uses a pillbox consistently, *n* (%)	270 (46)	157 (48)	113 (44)	.31
Has difficulty paying for medication, *n* (%)	42 (7)	20 (6)	22 (8)	.30
Characteristics of ARV regimen				
Mean number of ARVs in regimen, M (SD)	2.55 (.90)	∼3 (.90)	∼3(.90)	.81
Mean number of pills prescribed per day, M (SD)	∼5 (2.94)	∼5 (3.11)	∼5 (2.71)	.81
Has an NRTI in regimen, *n* (%)	540 (93)	308 (95)	232 (91)	.07
Has an NNRTI in regimen, *n* (%)	160 (28)	92 (28)	68 (27)	.66
Has a PI in regimen, *n* (%)	381 (66)	206 (63)	175 (69)	.19
Baseline measures of adherence				
Perfect adherence (3-day recall), *n* (%)	426 (73)	247 (76)	179 (70)	.12
≥90% adherence (3-day recall), *n* (%)	444 (76)	257 (79)	186 (73)	.08
≥80% adherence (3-day recall), *n* (%)	569 (98)	321 (99)	248 (97)	.18
Perfect adherence (visual analog scale past 3-4 weeks), *n* (%)	253 (44)	148 (46)	105 (41)	.29
≥90% adherence (visual analog scale past 3-4 weeks), *n* (%)	415 (72)	242 (74)	173 (68)	.08
≥80% adherence (visual analog scale past 3-4 weeks), *n* (%)	487 (84)	280 (86)	207 (81)	.11
Undetectable viral load (HIV-1 RNA ≤ 400 copies/ml), *n* (%)	304/421 (72)	203/256 (79)	101/165 (61)	<.001
Modal number of LifeWindows visits, mode (median, IQR 25th, 75th)	6 (7, 5–9)	6 (8, 7–10)	5 (4, 3–5)	<.001
Mean number of days of observation in the study, M (SD)	420 (138)	484 (53)	343 (168)	<.001
Mean numbers of days between lifewindows sessions, M (SD)	88 (53)	68 (20)	113 (69)	<.001

M mean, *n* number of participants, *SD* standard deviation, *ARV* antiretroviral, *NRTI* nucleoside reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *PI* protease inhibitors, *IQR* interquartile range

[a] Demographic variables varied in total number of valid responders at baseline from 513 to 594

[b] Demographic variables varied in total number of valid responders at baseline from 325 to 328

[c] OP sample had slightly higher numbers of females ($X^2_{(1,n\,=\,590)} = 4.06$, $p < .05$)

[d] Higher age in OP sample ($F_{(1,583)} = 12.14$, $p < .001$)

[e] OP sample had higher number of unemployed ($X^2_{(1,n\,=\,593)} = 13.69$, $p < .0001$)

[f] OP sample had higher number on disability ($X^2_{(1,n\,=\,593)} = 7.33$, $p = .007$)

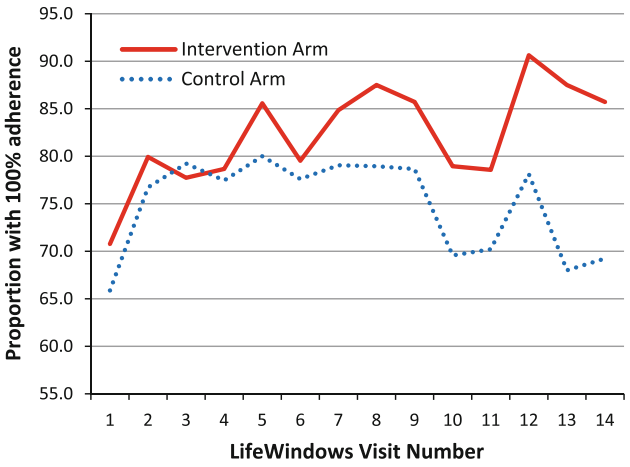

Fig. 2 Graphic representation of the proportion of participants in each study arm with perfect 3-day adherence in the ITT sample over 14 LifeWindows visits (baseline = 1). Proportions are from raw data for all available data at the designated LifeWindows visit. Note that HLM analyses used to evaluate intervention impact used all available data from participants with two or more adherence assessments to test for differences in growth rates using days (not visits) from baseline as the appropriate metric for time which varied across and within participants. (Arm effect in ITT sample on proportion with 100% adherence in HLM analyses was not significant: $t_{(586)} = 1.55$, $p = .12$)

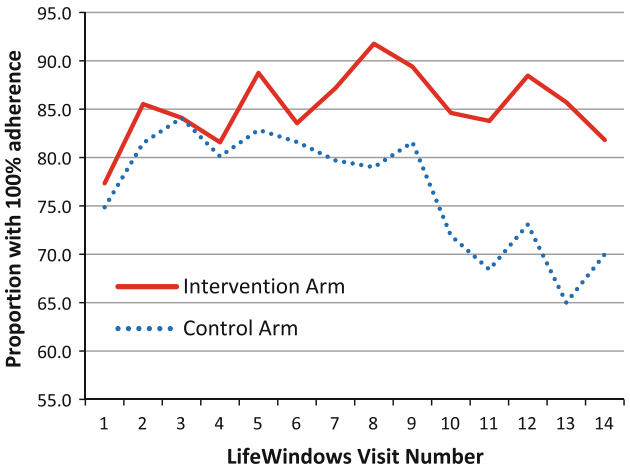

Fig. 3 Graphic representation of the proportion of participants in each study arm with perfect 3-day adherence in the OP sample over 14 LifeWindows visits (baseline = 1) Proportions are from raw data for all available data at the designated LifeWindows visit. Note that HLM analyses used to evaluate intervention impact used all available data from participants with two of more adherence assessments to test for differences in growth rates using days (not visits) from baseline as the appropriate metric for time which varied across and within participants. (Arm effect in OP sample on proportion with 100% percent adherence in HLM analyses was significant: $t_{(326)} = 2.26$, $p = .024$)

3–4 week adherence scores trended in the anticipated direction but did not reach significance ($t_{(326)} = 1.55$, $p = .12$).

Robustness of Intervention Effects in the OP Sample

Covariates of inclusion/exclusion in the OP sample (age, employment status, disability, gender, and baseline viral load) and of pre-test non-equivalence between study arms in that sample (annual income and sexual orientation) were added iteratively to the model that demonstrated intervention effects on perfect 3-day adherence in the OP sample. Across these analyses (including models where detectability of baseline viral load was added to slopes and intercepts), significance of results were retained. Additionally, significant intervention arm effects in the OP sample were retained when clinic membership was added to the model and when baseline rates of adherence were included. Thus, across participants with diverse backgrounds and varying rates of baseline adherence, the intervention retained its effect in the OP sample. All analyses were also repeated using missing-equals-failure assumptions, and produced no difference in overall outcomes.

Viral Load

The study was underpowered to detect differences in VL. We explored VL with data extracted from medical records beginning 30 days prior to baseline, producing 2,122 viral load data points for the ITT sample. Though the proportion of participants with a non-detectable viral load in the ITT sample at the final observed interval was higher in the intervention than the control condition (79 vs.74%), significant differences in viral suppression over time were not found (GLM p = NS; see Table 3). Missing data strategies (last observation carried forward and missing-equals-failure) did not change the GLM results. Sparcity of data in the later assessment intervals (see Table 3) limited additional exploration of potential effects on viral load. The OP sample was similarly examined and did not reach significance on viral load suppression.

Discussion

The current results establish that LifeWindows, an IMB model-based, computer-administered ARV adherence promotion intervention, resulted in significantly higher levels of perfect ACTG-measured 3-day ARV adherence over time for individuals on ARVs who attended routine clinical care and interacted with intervention software regularly. For similar control arm participants, adherence declined over time. These effects maintained significance while controlling for numerous potential covariates, including baseline rates of adherence, and remained significant when perfect adherence was replaced with lower adherence outcome thresholds, i.e., 90, 80, and 70%

Table 3 Proportion with undetectable viral load over time

	Baseline to 3 months (%)	3–6 months (%)	6–9 months (%)	9–12 months (%)	12–15 months (%)	15–18 months (%)
Intervention	70.3 (137/195)	77.0 (134/174)	75.0 (132/176)	76.8 (129/168)	76.5 (117/153)	79.3 (88/111)
Control	73.9 (167/226)	70.3 (147/209)	73.4 (146/199)	76.1 (143/188)	70.2 (125/178)	74.5 (108/145)

adherence. Parallel effects for VAS past-month adherence trended toward, but did not reach, significance.

Effects of LifeWindows were observed in the OP sample and not in the ITT sample, which comprised the more rigorous analysis. We note, however, that the OP sample is regarded as appropriate for examining intervention impact on HIV + individuals who are exposed to the intervention at reasonable levels and who remain on ARVs. The ITT sample included individuals who were not retained in care, received few LifeWindows sessions, or were discontinued from ARV treatment entirely at some point during the study and had LifeWindows sessions withheld during periods of ARV discontinuation. While the ITT sample produced patterns of results similar to the OP sample, they did not reach significance.

With no support for a linear dose–response relationship, we speculate that the significant intervention impact in the OP sample may have been a function of individuals having attended care consistently enough to use the LifeWindows software at least six times, over 18 months, which may be the threshold of attaining benefits of the intervention. This number is consistent with an expected exposure pattern for patients in clinical care [47]. Importantly, the OP results imply that LifeWindows holds promise as a practical, effective "real-world" approach to enhancing ARV adherence for the estimated 60% of patients in clinical care who remain consistently engaged in care [48, 49].

To date, a number of ARV adherence promotion interventions, including several based on the IMB model, have been demonstrated to be effective [28, 29, 51], but such interventions often involve high personnel and resource costs and have limited practical potential for widespread implementation. In an effort to create a broadly applicable adherence promotion approach, we applied the IMB model [16, 50] as the theoretical foundation for creation of a software-based intervention that HIV + individuals can access in the clinical care setting to address challenges to adherence which occur over the course of care. The present results constitute initial support for the potential of this software-based intervention to provide effective and ongoing adherence support for regular clinical care attendees without consuming considerable healthcare provider time or resources, and at a low per patient cost, once software development is complete. Other findings indicate that LifeWindows was highly acceptable to HIV patients, that its interactive and individually-targeted intervention modules were highly engaging [51, 52], and that LifeWindows can be integrated relatively easily into the clinical care setting.

Limitations of this research are several. First, this is the initial and therefore sole empirical demonstration of the outcomes of the LifeWindows intervention approach, and replication and extension are required. Second, while we view the OP sample of participants who interacted with LifeWindows regularly and remained on ARVs continuously as appropriate for demonstration of intervention efficacy, results for the ITT sample did not reach significance. Because LifeWindows was not developed to address issues associated with stopping and restarting ARVs, the current results cannot speak to the potential effect of computer-based interventions for those experiencing interruptions in ARV therapy. Future work is needed on interventions that specifically target the adherence needs of this sub-population. Since irregular attendance in clinical care was the primary factor that prevented participants in the ITT group from receiving sufficient doses of the LifeWindows intervention (or its control condition), future versions of LifeWindows might include elements to facilitate maintenance in care, which would have myriad benefits for patients. Further, it must be stated that while we have considerable confidence in the appropriateness of the criteria used for creating our OP sample, it was defined posteriori. Finally, while research staff at the sites could not be blinded to experimental condition, the fact that the intervention and outcome measures were fully computerized serves to mitigate any associated threats.

The current research was underpowered to detect changes in viral load, in part due to the large number of participants beginning the trial with undetectable viral loads, the minimal variability observed in viral load over time, and due to substantial reductions in number of viral load observations available over time. Given the complexities of the relation between adherence and viral load (cf. [53]), such results are not uncommon [29]. Despite lack of power and restricted variability, a pattern, which did not reach significance, was observed such that the LifeWindows intervention increased the proportions of individuals with undetectable viral load.

Conclusion

While the literature includes a growing number of ARV adherence promotion interventions, most are labor intensive and expensive to administer. The present research provided the first test of a comprehensive computer-delivered ARV adherence promotion intervention, and results suggest that this approach is feasible, easily integrated into the clinical care setting, and may be effective in enhancing ARV adherence among regular users of HIV clinical care.

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Appendix

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