A small cluster randomised clinical trial to improve health outcomes among Argentine patients disengaged from HIV care

Omar Sued[a], Diego Cecchini[b,c], María José Rolón[d], Liliana Calanni[e], Daniel David[f], Sergio Lupo[g], Pedro Cahn[a], Isabel Cassetti[c], Stephen M. Weiss[h], Maria Luisa Alcaide[i], Violeta J. Rodriguez[h,j], Alejandro Mantero[k], Deborah L. Jones[h,*] COPA Study Group[1]

[a]Fundación Huésped, Buenos Aires, Argentina

[b]Hospital General de Agudos Dr. Cosme Argerich, Buenos Aires, Argentina

[c]Helios Salud, Buenos Aires, Argentina

[d]Hospital General de Agudos Dr. Juan A. Fernández, Buenos Aires, Argentina

[e]CEIN Unidad Infectológica, Neuquén, Argentina

[f]Hospital Guillermo Rawson, Córdoba, Argentina

[g]Instituto Centralizado de Asistencia e Investigación Clínica Integral (CAICI), Rosario, Argentina

[h]Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, USA

[i]Division of Infectious Diseases, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

[j]Department of Psychology, University of Georgia, Athens, GA, USA

[k]Department of Public Health Sciences, Division of Biostatistics, University of Miami Miller School of Medicine, Miami, FL, USA

*Corresponding author at: Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, 1440 Soeffer Clinical Research Building, 1120 NW 14th Street, Miami, Florida 33136. d.jones3@med.miami.edu (D.L. Jones).
[1]The COPA Study Group members are listed at the end.

Summary

Background—Patients disengaged from HIV care, e.g., missed medication pick-ups, not attending physician visits, account for 70% of new HIV infections. Re-engaging and sustaining engagement is essential to controlling the HIV pandemic. This study tested a physician-delivered evidence-based intervention, Motivational Interviewing (MI), to improve health outcomes, adherence to antiretroviral therapy (ART), HIV virologic suppression, CD_4+ count, retention in HIV care, and self-efficacy among patients disengaged from care in Argentina.

Methods—Regional clinics ($n = 6$) were randomised to condition, MI Intervention or Enhanced Standard of Care (ESOC), and recruited $N = 360$ patients disengaged from HIV care. ART adherence, HIV RNA viral load, CD_4+ count retention, and self-efficacy were assessed at baseline, 6, 12, 18, and 24-months. Indirect effects from condition to main outcomes were examined using patient–provider relationship as a mediator. The study was a cluster-randomised clinical trial entitled Conexiones y Opciones Positivas en la Argentina 2 ($COPA_2$) and was registered at clinicaltrials.gov, NCT02846350.

Findings—Participants were an average age of 39·15 ($SD = 10·96$), 51% were women; intervention participants were older ($p = ·019$), and more ESOC participants were women (60% vs. 42%, $p = 0·001$). Using mixed models, the intervention had no effect on ART adherence over time by condition on HIV RNA viral load, CD_4+ count retention, or self-efficacy. However, analysing mediated paths, there was an indirect effect of condition on ART adherence ($B = 0·188$, $p = 0·009$), HIV viral load ($B = –0·095$, $P = 0·027$), and self-efficacy ($B = 0·063$, $P = 0·001$), suggesting the intervention was associated with improved patient–provider relationships, which was in turn associated with increased ART adherence, lower HIV viral load, and higher self-efficacy.

Interpretation—These findings suggest that physician-delivered MI may enhance the patient-provider relationship, self-efficacy, and ART adherence, and reduced HIV viral load in patients disengaged from HIV care. However, these findings are preliminary due to the small number of clusters randomised, and replication is warranted.

Funding—National Institutes of Health.

Keywords

HIV; Clinical trial; Global health

Introduction

The impact of antiretroviral therapy (ART) on the reduction of HIV morbidity and mortality has been well-established,[1] yet late presentation for care, poor adherence to ART, and uneven retention[2] remain major impediments to achieving the UNAIDS 95-95-95 goals by 2030 (95% of PWH will know their serostatus, 95% of those diagnosed will be on ART, and 95% of those on ART will be virally suppressed).[3] Gaps persist at every stage of the HIV care continuum,[2] and patients disengaged from care, i.e., not receiving regular care and/or not virologically suppressed, account for the majority of new HIV infections.[4]

Innovative public health strategies to re-engage patients in HIV care are needed to halt the HIV pandemic.

An estimated 2.1 million people in Latin America were living with HIV in 2019. Regional numbers indicate no reduction in new HIV infections in the last 15 years, despite prevention strategies providing a pathway to no-cost HIV care and ART availability that have resulted in reduced AIDS-related mortality.[2] Argentina and Brazil were the first countries in Latin America to provide universal no-cost ART access and health care for people with HIV (PWH), removing access-related barriers to care for 70% of PWH.[5,6] Yet, in Argentina, in 2020, 67% of those diagnosed were on ART and only 45% had achieved viral suppression.[2] Though access to care is essential for promoting and sustaining health, without strategies to address individual patient factors that enhance engagement in these patients, HIV prevention programs across Latin American regions and populations cannot effectively control the pandemic.

Motivational Interviewing (MI) is an effective, evidence-based, patient-centred communication strategy that enhances readiness for behavioural change and can help patients explore and resolve their motivation for treatment adherence.[7] MI incorporates patient-provider collaboration and patient-centred care into clinical practice, treating each patient as an autonomous, unique individual. The use of MI has been associated with sustained engagement in care, fewer missed appointments, increased retention in care, and improved medication adherence.[8] MI has been effectively used in the management of chronic disease,[9] smoking cessation,[10] and antihypertensive medication adherence.[11] MI has been shown to enhance motivation among PWH to engage in health behaviours that are often resistant to change.[12] An MI-based provider intervention could capitalize on the patient-physician relationship to reinstate ART adherence and re-engage an especially challenging patient group, PWH disengaged from care.[13]

This study team conducted a pilot MI intervention study in clinics in urban Buenos Aires, Argentina and compared HIV viral load and ART adherence following physician-delivered MI or a patient-focused intervention. Overall, training providers to use MI was more effective in increasing ART adherence and reducing HIV viral load than working with patients alone,[14] highlighting the value of MI in enhancing the patient-physician relationship. Patients with MI-trained physicians also reported greater satisfaction with their patient-physician relationship, expressed greater motivation to optimize treatment behaviours and treatment engagement, and greater willingness to embrace other sources of support.[15] Both patients and physicians preferred a collaborative approach to HIV treatment and care utilizing both the physician's expertise and the patient's own experiences. This study team then launched a randomised clinical trial of MI and successfully trained physicians across Argentina to use MI in ongoing clinical practice.[16] Given the nature of the context and clinic settings, to prevent intervention contamination and to keep the ecological validity, the use of a cluster-randomised controlled trial design was selected, with clinics being defined as clusters. The trial examined the impact of physician-delivered MI compared to an enhanced standard of care on satisfaction with the patient-provider relationship, ART adherence, HIV viral load, CD_4+ count, retention in care, and self-efficacy. The study

team hypothesized that an intervention that focused on patients' strengths would be more successful in mobilizing prevention behaviours than standard clinical care.

Methods

Objectives and design

The primary objective of the study was to evaluate the impact of a physician-delivered, MI patient-oriented treatment program on ART adherence, HIV viral load, retention in care, and self-efficacy among PWH disengaged from HIV care. Additional details describing the methods utilized in this study have been described in the published protocol and related publications.[17] The study was a cluster-randomised clinical trial entitled Conexiones y Opciones Positivas en la Argentina 2 (COPA$_2$) and was registered at clinicaltrials.gov, NCT02846350. Each patient participant was assessed five times over two years (baseline, 6-months, 12-months, 18-months, and 24-months) from November 2016 through May 2020. Baseline assessment dates ranged from November 2016 to March 2018, 6-months assessment from May 2017 to October 2018, 12-months from November 2017 to April 2019, 18-months from April 2018 to October 2019, and 24-months from October 2018 to May 2020.

Ethical approval

Before engaging in any study-related procedures, approval was obtained from the affiliated US Institutional Review Board (IRB) and Ethics Committees at all participating Argentine sites in Buenos Aires city, Rosario, Cordoba, and Neuquén. All participants provided written informed consent before enrolment in the study. The consent included a release for medical record abstraction of treatment history and laboratory results.

Setting and clinic eligibility

The study was conducted in Argentina in which the HIV epidemic is mostly urban; 83% of PWH reside in metropolitan Buenos Aires, Córdoba, Santa Fe and Mendoza.[18] Clinic selection was based on a 2015 survey of 16 clinic sites across the four main urban areas in which the HIV epidemic is concentrated, Buenos Aires, Rosario (Santa Fe province), Córdoba and Neuquén, assessing willingness and capacity to participate. Ten sites met eligibility criteria: 1) willing to participate, 2) 5% HIV patients disengaged from care, 3) adequate numbers of patients lost to follow-up each year (> 80 patients meeting eligibility criteria outlined below), and 4) at least six infectious disease physicians interested in participating in the study. Clinics enrolled serve a diverse population representative of the broader HIV epidemic in Argentina. The number of patients disengaged from HIV care, here defined as not attending two or more appropriately spaced visits with a medical provider within one year, ranged from 5% to 35% lost to care.

Six clinics (three private clinics and three public clinics) were identified to participate in the study. Clinics were matched on public/private status to represent the healthcare system more broadly in Argentina, and on HIV census. The list of clinics was arranged in a column. A randomization sequence was then generated by a non-study affiliated statistician, creating a list of odd and even numbers; the odd and even numbers were each lined by the statistician

next to the list of clinics. Clinics were randomised by a blinded investigator not affiliated with the study who assigned the list of generated random numbers to either intervention (physician MI training, $n = 3$) or enhanced standard of care (physician Enhanced Standard of Care (ESOC) training, $n = 3$) condition. Clinics were then enrolled in the study by trial staff. At each of the clinic sites, six infectious disease physicians were enrolled by study staff as study providers ($n = 36$). Allocation was concealed at both the cluster and individual levels.

Blinding

Trained study staff across all clusters were not informed of the study outcomes, given that they regularly entered the patient data on the electronic data system. To further prevent information bias, patients were not informed about which condition they were enrolled in. Furthermore, to reduce the risk of performance and information bias, all investigators and study staff, including providers were blinded to the study outcomes.

Participants

Eligible patient study participants ($n = 360$) met the following inclusion criteria: 1) at least 18 years of age, 2) had received a diagnosis of HIV and initiated ART at least 6 months before recruitment, 3) had at least one HIV viral load of >500 copies/mL in the prior 3 months, and 4) were disengaged from HIV care, defined as either missing three medication pick-ups from the pharmacy in the prior 6 months and/or had not attended a physician visit in more than 12 months. All assessments were in Argentine Spanish by audio computer-assisted self-interview (ACASI) to avoid limitations arising from low literacy; the study staff guided participants in the use of ACASI and remained nearby to assist with any questions regarding ACASI items.

Recruitment and retention

Recruitment was led by study staff at each site who identified patients disengaged from HIV care in the prior year through a review of the clinic visits and/or pharmacy pickups. Clinic patients were contacted by study staff by phone, informed of the details of the study, and invited to an orientation session on the study procedures and time commitment. Patients who contacted study staff on their own were also invited to an orientation session if they met preliminary inclusion criteria. Following the orientation session, candidates provided informed consent, completed an ACASI assessment, and provided a blood sample for viral load assessment if a record of the participant's viral load for the past 3 months was unavailable. Participants were compensated with US $10 per study visit for travel. At each time point, patients also met with their HIV study provider for a routine medical visit. Study retention was coordinated by study staff trained by their sites based on site-specific retention programs. Study visits were combined with regularly occurring HIV clinical care visits. Participants were contacted following missed appointments and detailed, regularly updated patient locator forms containing an address, two contacts, home landmarks, workplaces, email, WhatsApp, etc. were utilized for tracking.

Intervention condition

Motivational interviewing (MI) overview.—MI is a client-centred counselling style that uses specific techniques, e.g., empathic listening, shared decision-making, and change focused talk, to elicit personal motivation for behavioural change. MI users establish a non-confrontational and supportive climate to target and resolve ambivalence towards realizing personal goals.[19] By creating an empathic, supportive, patient-directed approach, patient self-efficacy and motivation for change are enhanced, increasing the potential to improve adherence to treatment and overall health outcomes.[20] Physician-delivered MI in the clinical setting applies a non-judgmental and empathetic approach toward patient care, encouraging the patient to break down barriers to change, and supporting the patient to make positive changes.[16]

Training in MI.—The process of provider training, acquisition of MI skills, and supervision has previously been described and was comprised of workshops, readings, and coaching.[16] Briefly, the structured training protocol was comprised of a manualized MI program of three 8-hour workshops over 12 months – introductory training at baseline, and advanced training providing additional opportunities for skill-building at 6-months and 12-months. Sessions were structured using The Provider Training Intervention Manual and slide presentations developed by the team, which consisted of both didactic and interactive training on basic MI skills and MI "spirit" including collaboration, patient autonomy, evoking patient motivation, recognizing change focused talk, and MI consistency.[20] Training readings were drawn from Motivational Interviewing, 3rd Ed. (Spanish).[19] MI workshops and subsequent supervision were led by experienced MI trainers, and training and supervision of local co-trainers were undertaken to increase the sustainability of MI training for HIV healthcare providers. Additionally, front line staff were sensitized on the study and the collaborative spirit of MI.

MI Supervision.—Three one-hour MI supervision sessions ("coaching") were provided via video conferencing following each training workshop. Coaching was provided in 30 min sessions starting three months after baseline MI training, followed by another three months after 6-month advanced MI training, and a final session three months after the 12-month advanced training. MI coaching was based on collaborative review and discussion of physician generated video recordings provided to trainers of patient-physician clinical consultations. Discussion focused on the application of MI communication strategies.

Enhanced standard of care condition

An enhanced standard of care was utilized rather than the traditional control condition due to ethical concerns regarding the vulnerable nature of the study population. The ESOC provided to study physicians matched the intervention condition training in duration and was conducted in the same time frame as the intervention condition. The ESOC consisted of online training on HIV treatment updates, adherence, and retention. Attendance was commensurate with the intervention condition. The main difference between the experimental care model and the ESOC was therefore the training, delivery, and supervision of MI strategies. Specific details on other differences have been previously described in the published protocol.[17]

Measures of main study outcomes

Per the original protocol, ART adherence, HIV viral suppression, retention in care, and medication persistence were the primary outcomes of the study. At the end of the data collection period, changes to how HIV viral load was evaluated as a primary outcome had to be made given that viral suppression at baseline was a constant (see description below). Self-efficacy and patient-provider communication were the MI physician targets in the original protocol, as well as the theorised mechanisms by which the intervention was intended to work. Contrary to the study protocol, in the current study, we do not present medication persistence given issues related to pharmacy pickup data medical abstraction.

Patient-provider relationship.—Patient-provider relationship satisfaction and communication were assessed using a 10-item subsection of the Prerana Interview with a Likert-like scale describing the patient-provider relationship.[21]

Self-reported antiretroviral adherence.—Self-reported adherence was assessed every six months at all time points using a 10-point Visual Analogue Scale (VAS), with 0 representing none and 10 representing 100% (perfect adherence).[22] If a participant reported more than one pill per day, they then completed the VAS for each pill they were prescribed (up to three medications), and then the average VAS adherence for that time point was calculated by dividing the sum of the VAS scores by the number of medications reported.

HIV RNA Viral Load.—HIV RNA viral load was obtained from patients every six months; data was retrieved from medical records or blood sampling if a recent assessment was unavailable. HIV viral load units were the number of HIV-1 RNA copies per ml. Baseline HIV viral loads were obtained via medical record abstraction if these were from 3 months before the initial visit. If a participant missed a follow-up visit, HIV viral loads were obtained through medical record abstraction if they were within 90 days of the visit. For analyses, condition differences were analysed as a clinically significant reduction in HIV viral load from one-time point to the next, 0·50log. Though we originally intended to analyse HIV RNA viral load as the proportion of participants who were virally suppressed in each condition, the complete absence of participants who were virally suppressed at baseline precluded such analyses; that is, viral suppression at baseline was a constant at baseline.

CD4± T cells (CD4± count).—CD_4+ T cells/ml (CD_4+ count) was collected through medical record extraction. The medical record of the visit closest to the study visit was selected. At baseline, CD_4+ count was either the most recent assessment before enrolment, collected at the time of the baseline visit, or 90 days following the baseline visit. The 12- and 24-month assessments were collected 45 days before or after the 12- or 24-month visit.

Retention in HIV Care.—Retention in HIV care was calculated as to whether a participant completed a study clinical visit at any given time point.

Self-efficacy.—Patients' self-efficacy was assessed using the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES).[23] This 12-item scale assessed a participant's perceived self-efficacy in maintaining adherence and integrating their treatment into their daily routine

despite potential obstacles. Each item was scored on a scale of 0 ("Cannot do at all") to 10 ("Completely certain can do"). For analyses, the mean self-efficacy score (sum of each item divided by 12) was used for each time point.

Power analysis

Power analysis for the current study was conducted based on a pilot study conducted in Buenos Aires, Argentina, previously described in the published protocol.[17] The power analysis relies on obtained differences in viral suppression at 9 months for the pilot trial.[24] Specifically, 68% of patients in the experimental group achieved viral suppression by 9 months follow-up as opposed to 44% of those in the control condition. Assuming that a similar effect size would be observed in this larger trial and that the plausible range of viral suppression is 20% to 60% in the control group, a power analysis indicated that 6 clinics allocated in a 3:3 ratio with 6 providers and 60 patients per clinic would provide >80% power to detect a difference between groups using a two-tailed test at $a = 0.05$. This power analysis assumed 60% of the variance would be between providers within clinics and 40% would be between clinics. However, this power analysis was based on viral suppression in the pilot trial. In this larger trial, viral suppression was a constant at baseline; as such, viral suppression data was not analysed. Power in the current study is therefore limited by the small number of clusters analysed and included.

Data analyses

Frequencies and bivariate analyses were used to examine associations between condition groups and demographic variables. An attrition analysis was also used to examine bivariate (i.e., t-tests, chi-square tests) associations between demographic variables and participants with missing data at any time point.

To test the effect of the intervention on ART adherence, HIV viral load, CD_4+ count, retention, and self-efficacy, mixed modelling was used, with repeated measurements nested within individuals, and individuals nested within clinics. Longitudinal mixed models included main effects of condition and time as well as interactions. In these models, time was treated as a continuous variable.

Conceptually, the intervention condition was expected to improve satisfaction with the patient-provider relationship, which in turn was anticipated to impact the primary study variables. As such, indirect effects were examined as exploratory analyses using bivariate parallel latent growth curve (LGC) models in a structural equation modelling framework to estimate individual trajectories for patient-provider relationship and outcomes of interest (ART adherence, HIV viral load, CD_4+ count, retention, and self-efficacy). Mplus' indirect effect command, with bootstrapping ($n = 1000$), was used to formally test indirect effects. Specifically, indirect effects of condition on outcomes (ART adherence, HIV viral load, CD_4+ count, retention, and self-efficacy) were evaluated through patient-provider relationship satisfaction. The TYPE = COMPLEX command in Mplus (a sandwich estimator), which controls for nonindependence in nested data, was used to adjust for potential bias in standard errors associated with nested data. The TYPE = COMPLEX command in Mplus accounts for the lack of individual independence between observations

within clinics in the COPA$_2$ trial without modelling random effects, and yields coefficients identical to single-level modelling while correcting for standard errors, the primary concern of clustered data.[25] This sandwich estimator can also be used when different levels or cross-level interactions are not the primary goals of the analysis, which was the case for the current study.[25] In estimating indirect effects on Mplus, direct effects of condition on the outcomes were also requested. By default on Mplus, missing data were accounted for within the models using the full information maximum likelihood procedures.[26] Mplus applies a model-based approach to missing data to acquire appropriate estimates and standard errors. We used the comparative fit index (CFI 0·90) and root mean square error of approximation (RMSEA 0·06) to evaluate the model fit. LGCs were performed in Mplus version 8·4.[27]

Role of the funding source

Funders did not have any role in the study design, data collection, data analysis, interpretation, or writing of this report.

Results

The screening took place between November 2016 and March 2018, a total of 392 participants were screened and $n = 360$ were enrolled. From baseline to 6 months, 17·8% of participants did not complete an assessment (1·9% deceased, 15% missing or lost, and 0·8% withdrawn), 25·6% at 12 months (2·8% deceased, 20·8% missing or lost, and 1·9% withdrawn), 33·1% at 18 months (4·4% deceased, 26·7% missing or lost, and 1·9% withdrawn), and 26·7% at 24 months (4·7% deceased, 20% missing or lost, and 1·9% withdrawn). A summary of screening, enrolment, and retention data is summarized in Figure 1 (CONSORT Flow Diagram).

Demographic variables

Participants were an average of 39·15 years old (*Standard Deviation* (*SD*) = 10·96) and those in the intervention condition were older, 40·38 (10·44), versus enhanced standard of care, ESOC: *Mean (M)* = 37·92 (11·36) ($p = 0.019$). Half (51%) of participants were female; there was a greater proportion of female participants in the ESOC condition compared with the intervention condition (60% vs. 42%, $p = 0.001$). Slightly more than half (56%) of participants were employed and 65% had completed high school or higher. Further details are presented in Table 1.

Descriptive analyses of main study outcomes by condition and time

Figures 2–4 present the main study variables by condition and time, which included baseline, 6-months, 12-months, 18-months, and 24-months and are referred to as such below.

Antiretroviral adherence

Mean antiretroviral adherence was evaluated every six months at all time points. Longitudinal mixed models showed that the main effect of condition ($F(1,858) = 3·18$, $p = 0.075$), and the interaction between time and condition ($F(1,867) = 0·19$, $p = 0.666$) on ART adherence were not statistically significant. However, the effect of time ($F(1,867) =$

36·49, $p < 0.001$) on ART adherence was significant. Specifically, average self-reported ART adherence increased over time B (*standardized coefficient*) = 0·39, $p < 0.001$ averaging over conditions.

Indirect effects of condition on outcomes were evaluated through patient-provider relationship satisfaction using LGC models in a structural equation modelling framework. The conceptual diagram for indirect effects is presented in Figure 5. Indirect effects of the condition through patient-provided relationship on main outcomes are, similarly, summarized in Figure 5, and described in detail below.

Using LGC models, the intercept's variance was significantly different from 0 (*Variance* (V) = 4·66, $p < 0.001$), suggesting that individuals' baseline levels of ART adherence differed. However, the variance of the slope was not statistically significant, suggesting that individuals did not differ in their rates of change in mean ART adherence (V = 0·315, $p = 0.070$). The indirect effect of the condition on mean ART adherence through the patient-provider relationship was significant ($B = 0.188$, $p = 0.009$), suggesting that the intervention enhanced satisfaction with the patient-provider relationship, which was in turn associated with an increase in mean ART adherence. However, examining the direct effect of condition on ART adherence, the direct effect of condition on antiretroviral adherence was not significant ($B = -0.20$, $p = 0.388$). The model fit indices for these models were acceptable (i.e., CFI = 0·94; TLI = 0·94; RMSEA = 0·041).

HIV Viral load

HIV RNA viral load was evaluated at 6 months, 12 months, 18, and 24 months using continuous values. Longitudinal mixed models showed that the main effects of time ($F_{(1,610)} = 0.04$, $p = 0.834$) and condition ($F_{(1,572)} = 0.10$, $p = 0.757$), and the interaction between time and condition ($F_{(1,610)} = 0.19$, $p = 0.660$) on HIV RNA viral load were not statistically significant.

Using LGC models, examining HIV viral load, the intercept's variance was significantly different from 0 ($V = 0.302$, $p < 0.001$), suggesting that individuals' baseline HIV viral load values differed by condition. Similarly, the variance of the slope was statistically significant, suggesting that individuals' rates of change in HIV viral load differed by condition (V = 0·302, $p < 0.001$). The indirect effect of the condition on HIV RNA viral load was significant ($B = -0.095$, $P = 0.027$), suggesting the intervention was associated with increased satisfaction with the patient-provider relationship, which was in turn associated with a reduction in total HIV RNA viral load. However, examining the direct effect of condition on HIV RNA viral load, the direct effect of condition on HIV RNA viral load was not significant ($B = 0.13$, $p = 0.322$). The model fit indices for these models were acceptable (i.e., CFI = 0·92; TLI = ·92; RMSEA = 0·051).

CD4+ Count

CD_4+ count was evaluated as total CD_4+ count at baseline, 12 months, and 24 months. Longitudinal mixed models showed that the main effect of condition ($F_{(1,441)} = 0.30$, $p = 0.584$), and the interaction between time and condition ($F_{(1,515)} = 1.45$, $p = 0.229$) on CD+ count were not statistically significant. However, the effect of time ($F_{(1,515)} = 32.02$, $p <$

0·001) on CD_4+ count was significant. Specifically, average CD_4+ count increased over time $B = 25.41$, $p = 0·001$ for averaging over conditions.

Using LGC models, the intercept's variance was significantly different from 0 ($V = 0·699$, $p < 0·001$), suggesting that individuals' baseline CD_4+ count differed. However, the variance of the slope was not statistically significant, suggesting that individuals did not differ in their rates of change of CD_4+ count ($V = 0.001$, $p = 0·745$). The indirect effect of condition on CD_4+ count was not significant ($B = -0·04$, $p = 0·235$), and neither was the direct effect of condition on CD_4+ count ($B = -8·75$, $p = 0·469$). The model fit indices for these models were acceptable (i.e., CFI = 0·98; TLI = 0·96; RMSEA = 0·038).

Retention

Retention was evaluated at 6 months, 12 months, 18, and 24 months as to whether the participant completed a follow-up visit. Longitudinal mixed models showed that the main effects of time (*Wald X^2* = 0·36, $p = 0·074$) and condition (*Wald X^2* = 15·36 = 0·01, $p = 0·999$) were not significant. In addition, the interaction between time and condition (*Wald X^2* = 1·92, $p = 0·750$) on retention was not statistically significant.

The intercept's variance was significantly different from 0 ($V = 1·91$, $p < 0·643$), suggesting that individuals' retention differed. However, the variance of the slope was not statistically significant, suggesting that individuals did not differ in their rates of change for retention ($V = 0·338$, $p = 0·167$). The indirect effect of condition on retention was not significant ($B = -0·07$, $p = 0·382$), and neither was the direct effect ($B = 0·48$, $p = 0·131$). The model fit indices for these models were acceptable (i.e., CFI = 0·99; TLI = 0·98; RMSEA = 0·026).

Self-efficacy

Self-efficacy was evaluated every six months at all time-points. Longitudinal mixed models showed that the main effects of time ($F(1,857) = 2·70$, $p = 0·101$) and condition ($F(1,755) = 2·78$, $p = 0·096$), and the interaction between time and condition ($F(1,857) = 0·52$, $p = 0·4171$) on self-efficacy were not statistically significant.

The intercept's variance was significantly different from 0 ($V = 0·875$, $P = 0·006$), suggesting that individuals' baseline levels of self-efficacy differed. However, the variance of the slope was not statistically significant, suggesting that individuals did not differ in their rates of change in mean self-efficacy ($V = 0·021$, $p = 0·535$). The indirect effect of the condition on self-efficacy was significant ($B = 0·063$, $P = 0·001$), suggesting that increased satisfaction with the patient-provider relationship in the intervention condition, which was in turn associated with increased self-efficacy. The direct effect of the condition on self-efficacy, however, was not significant ($B = -0·238$, $p = 0·215$). The model fit indices for these models were acceptable (i.e., CFI = 0·93; TLI = 0·92; RMSEA = 0·06).

Discussion

This study compared the impact of physician-delivered MI to an ESOC on ART adherence, HIV viral load, CD_4+ count, retention, and self-efficacy among patients disengaged from HIV clinical care in Argentina. Interactions tested between time and condition suggested

that the intervention had no direct effect on the main outcomes (ART adherence, HIV viral load, CD_4+ count, retention, and self-efficacy).

Though the intervention did not have an effect on HIV viral load, MI had an indirect effect on HIV viral load as well as ART adherence – that is, the intervention was associated with increased satisfaction with the patient-provider relationship, which was in turn associated with a clinically significant increase in ART adherence and reduction in HIV viral load. Despite these significant indirect effects, the hypothesized direct effects of conditions on these outcomes were not significant. These results are contrary to previous outcomes observed in our pilot study, in which physician training in MI and increased satisfaction with the patient-provider relationship was associated with reductions in viral load and increased ART adherence among non-adherent patients disengaged from HIV care.[24] In addition, no association between CD_4+ count and condition was observed, but this outcome may have been due to different timing of CD_4+ count assessments, as well as the fewer numbers of CD_4+ count assessments. Study results also illustrated an indirect effect of condition on participant self-efficacy, indicating that increased satisfaction with the patient-provider relationship, an expected consequence of the use of MI techniques, was associated with increased self-efficacy. Given that the original power analysis was based on the large effects found in the pilot trial, this larger trial may have been underpowered to detect small effects. Therefore, these findings suggest a need for a fully powered trial to assess the effect of physician MI training on ART adherence and HIV RNA viral load. After all, the indirect effects through the patient-physician relationship were enhanced by MI, which in turn were associated with enhanced HIV outcomes.[15]

The use of MI, a collaborative, person-centred style of communication focused on change and self-efficacy that supports autonomy while encouraging motivation toward health behaviours, is not a communication style common to physician providers. Physicians in Argentina initially expressed hesitancy about the time needed to train in and provide MI in busy health care settings.[14] Study results illustrate physicians' successful delivery of MI to HIV patients lost to care, but the delivery of MI did not result in directly improved health outcomes.[8] Similarly, this study supports previous studies of the effective implementation and uptake of MI in the medical setting.[28] Therefore, a major strength of this study was the use of MI training, delivery, and clinical supervision of providers with differing levels of training in Spanish language. In our previous work on this intervention, we have reported providers' acceptability and feasibility ratings of MI training and implementation.[16] Providers generally found the intervention to be acceptable and feasible and believed that they had sufficient time to use MI with their patients. An additional benefit of the intervention was that it was not perceived as an added burden for an already challenging population. Given that large scale implementation of MI training, delivery, and supervision has not been examined in this context, these findings have potential implications for other Spanish-speaking countries as they support the findings from our pilot study.[24] Further, the initial pilot study from which this RCT was derived implemented the MI intervention in Buenos Aires, Argentina; the current RCT successfully implemented the intervention and reproduced its effectiveness on a broader, national scale in Buenos Aires, Rosario (Santa Fe province), Córdoba and Neuquén, providing support for the potential applicability of the intervention on a national and regional level.

Limitations to this study are individual, clinical, structural, and regional. The process of study recruitment and enrolment had the potential to stimulate some degree of re-engagement in all participants, regardless of study condition. The Argentina standard of care recommends that those re-engaged in care are regularly evaluated for viral suppression following relinkage, but added strategies targeting individual factors that reduce retention, such as depression and substance use, may be merited and instituted.[29] Standard of care and retention strategies may differ between regional clinics, e.g., tracking missed appointments, scheduling patients, providing information, and proximity to lab facilities. Another limitation was that as the study targeted challenging patients, only patients with detectable viral load were recruited. As such, at baseline viral suppression was a constant as no patients were virally suppressed, which precluded the analysis of viral suppression as an outcome, as originally proposed in the protocol. Additionally, given the small number of clusters (clinics) in the implementation of this study, the findings of the current study warrant further investigation and replication. Finally, although sites were accounted for as clusters, the sample size did not allow for the accounting of multiple multilevel systems (i.e., regions), which resulted in increased heterogeneity.

This study tested a strategy to re-engage patients accounting for the majority of new HIV infections,[4] those disengaged from care, i.e., not receiving regular care and/or not virally suppressed. In this patient group, training physicians to deliver MI may have provided regular doses of collaborative patient-centred medical care in the clinical setting, stimulating comparatively better ART adherence and virologic outcomes through an enhanced patient-provider relationship. Despite the absence of direct effects, MI was shown to impact satisfaction with the patient-provider relationship, and with it, health outcomes among PWH improved such that MI was associated with improved ART adherence, enhanced self-efficacy, and a reduction in HIV viral load. It must also be noted that the lack of condition differences in retention may have been related to the fact that participants were recruited and incentivized by study staff, given that study and clinical visits were often scheduled on the same day for the patients' convenience. Therefore, considering that these scheduling arrangements were made for patients in both arms, this recruitment strategy may account for the null findings which contradict previous findings.[24] Rapid re-engagement and retention remain essential to achieving optimal health outcomes. Medication adherence is reduced by poor retention and may decline over time and be discontinued entirely if the patient fails to persist in attending appointments.[30] Similarly, achieving viral suppression requires twice as long with suboptimal retention.[31] Continued research on re-engagement and retention of PWH disengaged from HIV care is essential; despite the advantages associated with MI, reengaging patients disengaged from HIV care and retaining them in real-world settings clearly may require sustained, intensive clinical strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

1: The COPA Study Group

Argentina: Agustina Arguello, Laura Cabrera, Florencia Cahn, Ana Crinejo, Norma Luna, Mariano De Stefano, Fabiana Enjamio, María Inés Figueroa, Marcela Gunning, Carolina Pérez, Rufina Pérez, Claudia Rodriguez, Alicia Sisto, Natalia Tokumoto, Liliana Trape, Gonzalo Vigo, Emanuel dell Isola, María Inés Figueroa.

USA: Lissa N. Mandell, Nicolle L. Rodriguez Yanes, Jennifer Knight, Fayeza Malik.

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Research in context

Evidence before this study

We searched PubMed for articles using the terms "HIV", "motivational interviewing", "Argentina", "disengaged", "adherence", "retention", "physicians", and "viral load" since 2015. Patients disengaged from care, i.e., not receiving regular care and/or not virologically suppressed, account for most new HIV infections. Regional numbers in Latin America indicate no reduction in new HIV infections in the last 15 years. Motivational Interviewing (MI) has been effectively used in the management of chronic disease including HIV (355 studies), smoking cessation, and antihypertensive medication adherence, and has been shown to enhance motivation to engage in health behaviors (235 studies) that are often resistant to change. Only 9 studies trained physicians to provide MI to enhance HIV treatment adherence, including a pilot MI intervention conducted in Buenos Aires, Argentina that compared HIV viral load and ART adherence following physician-delivered MI or a patient-focused intervention. The Argentina study found training providers to use MI was more effective in increasing ART adherence and reducing HIV viral load than working with patients alone, highlighting the value of MI in enhancing the patient-physician relationship. We found no randomised clinical trials of physician provided MI for patients disengaged from HIV care targeting HIV viral load, adherence, and retention.

Added value of this study

This study is the only randomised clinical trial to examine the impact of physician-delivered MI compared to an enhanced standard of care on satisfaction with the patient–provider relationship, ART adherence, HIV viral load, CD4+ count, retention in care, and self-efficacy. There was no direct effect of condition on the outcome variables, but an indirect effect of condition on ART adherence and self-efficacy was identified, suggesting the intervention was associated with improved patient–provider relationships, which was in turn associated with increased ART adherence, lower HIV viral load, and higher self-efficacy. Intervention participants reported greater satisfaction with patient-provider relationships, higher ART adherence, CD4+ counts (NS), and lower HIV viral load. Retention in HIV care was higher at 12 months but not sustained.

Implications of all the available evidence

Physician-delivered MI appears to provide regular doses of collaborative patient-centred medical care in the clinical setting, sustaining improved ART adherence and virologic outcomes. However, re-engagement of patients disengaged from care, i.e., not receiving regular care and/or not virally suppressed, is essential to achieving control of the HIV pandemic, and retaining these challenging patients in real-world settings may require sustained, intensive clinical strategies.
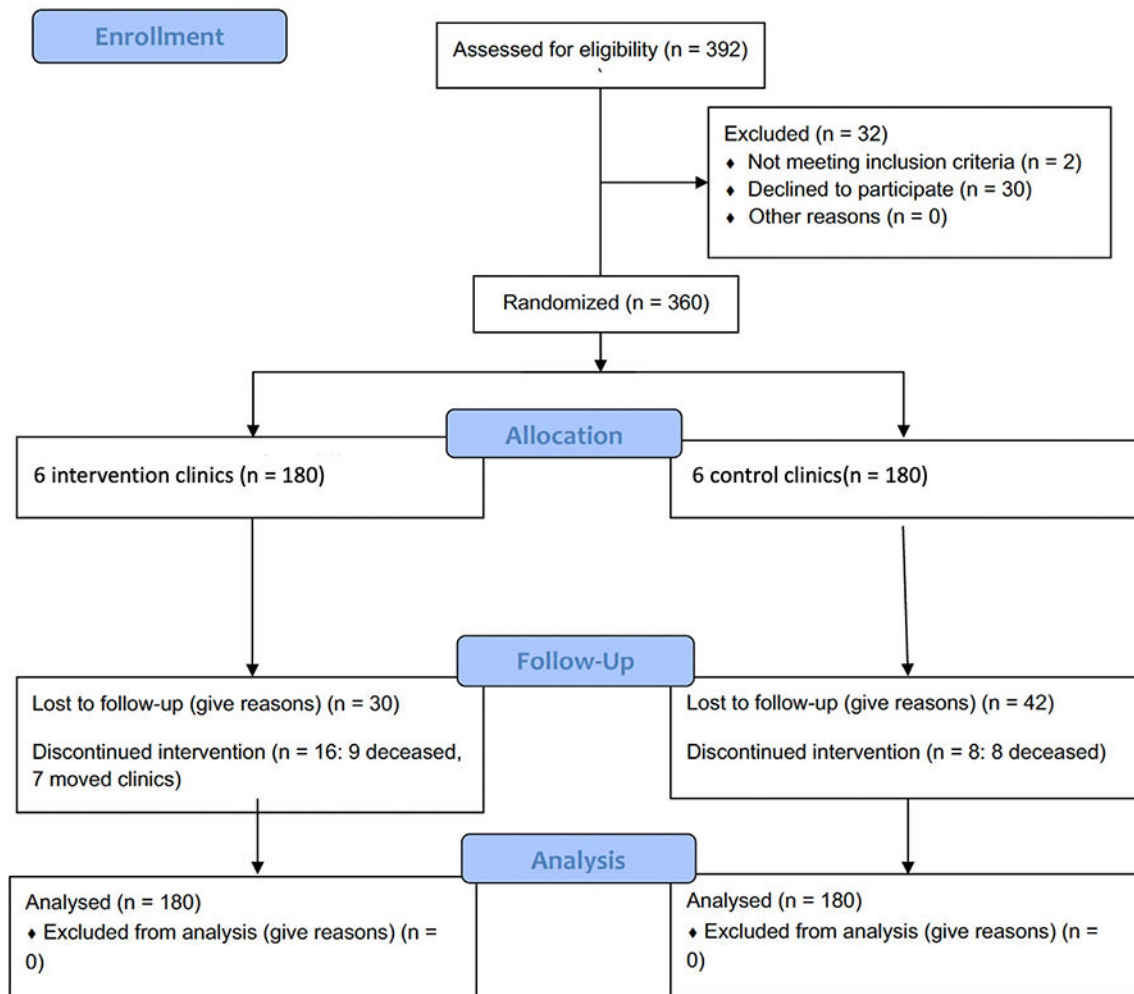
Figure 1.
CONSORT flow diagram.
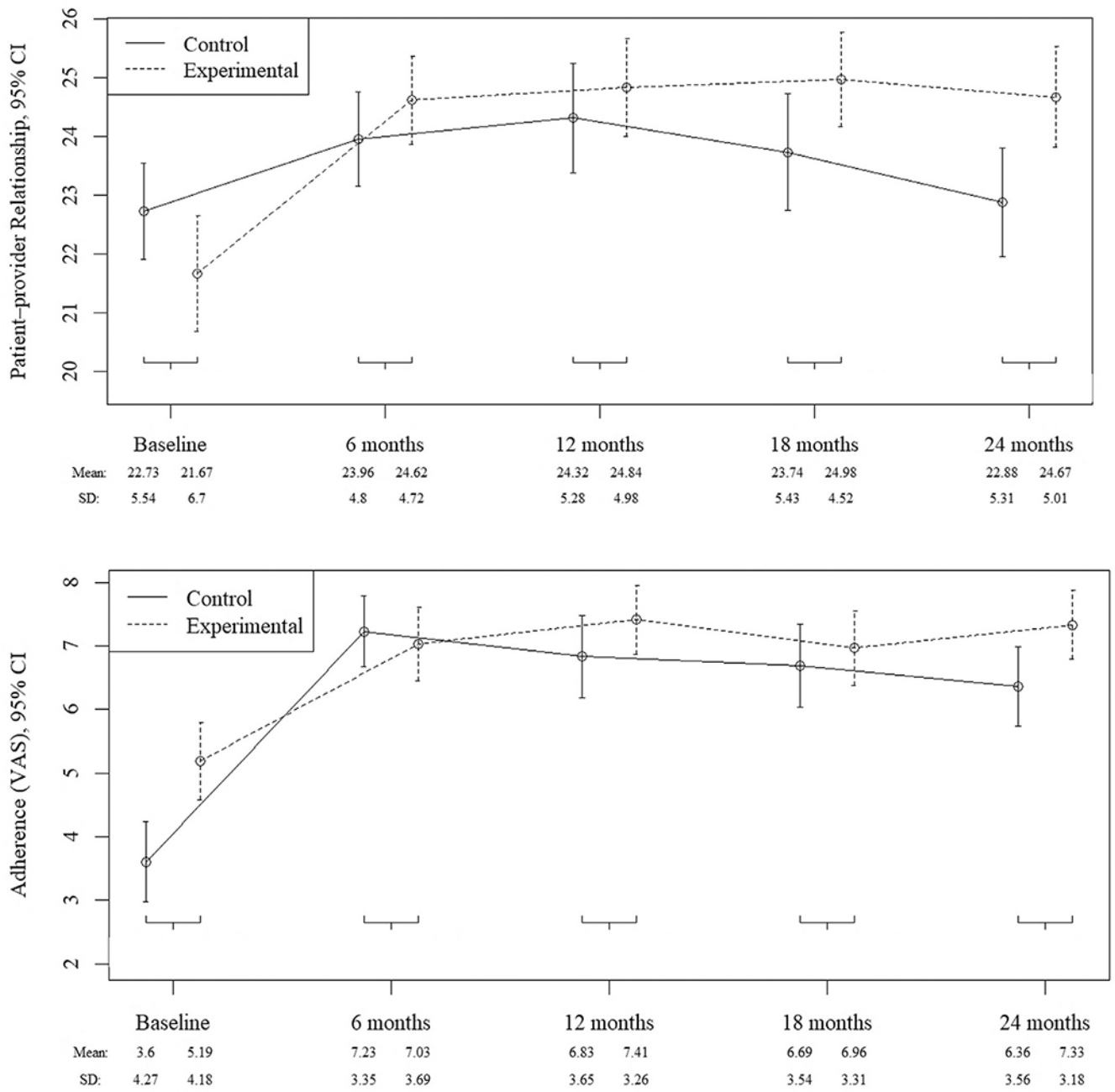Study recruitment and follow-up are depicted.

Figure 2.
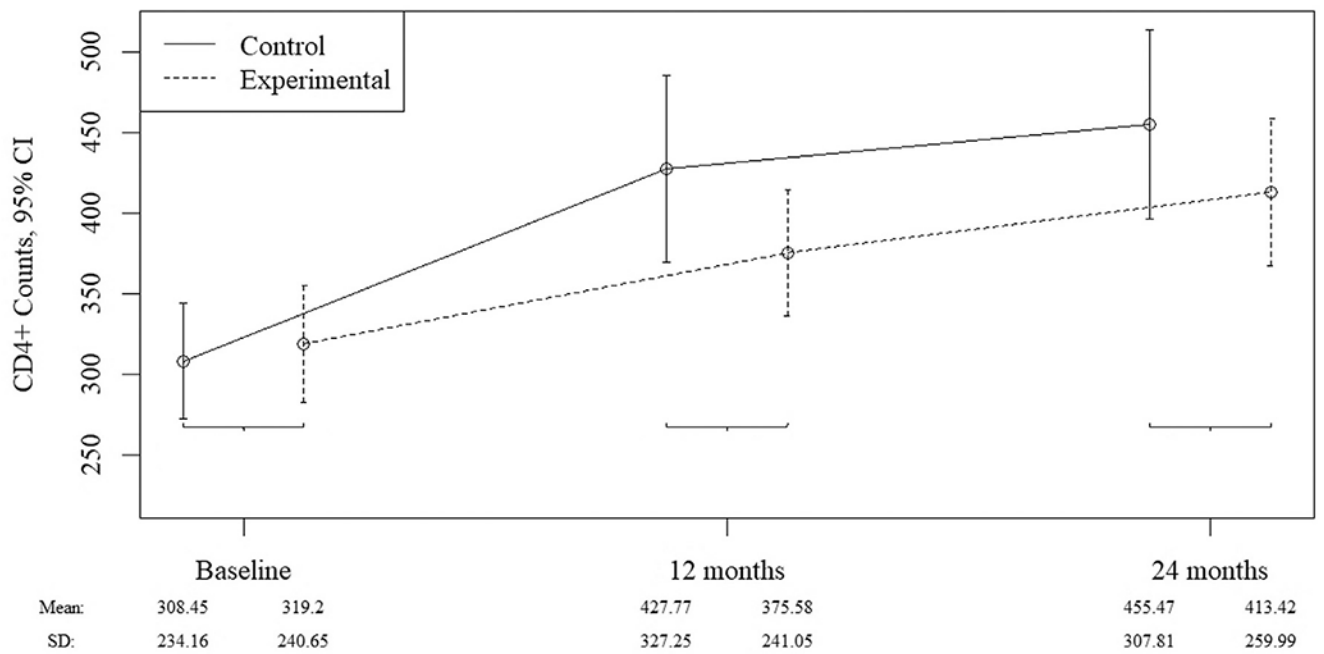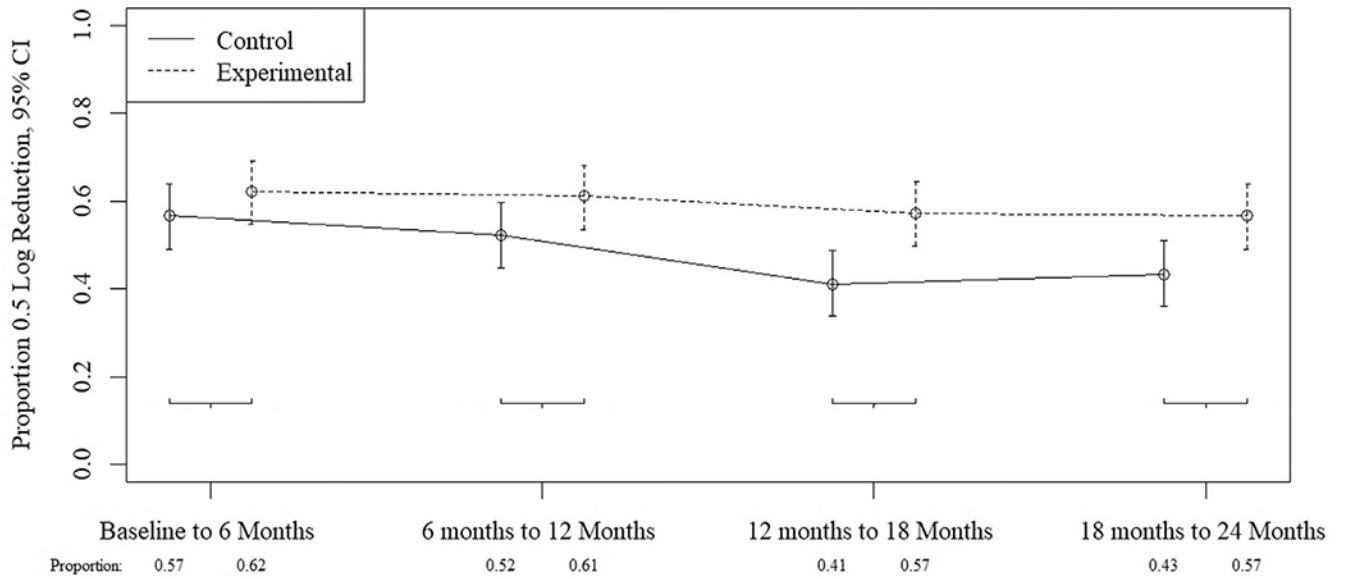Patient provider relationship and adherence over time by condition.

Figure 3.
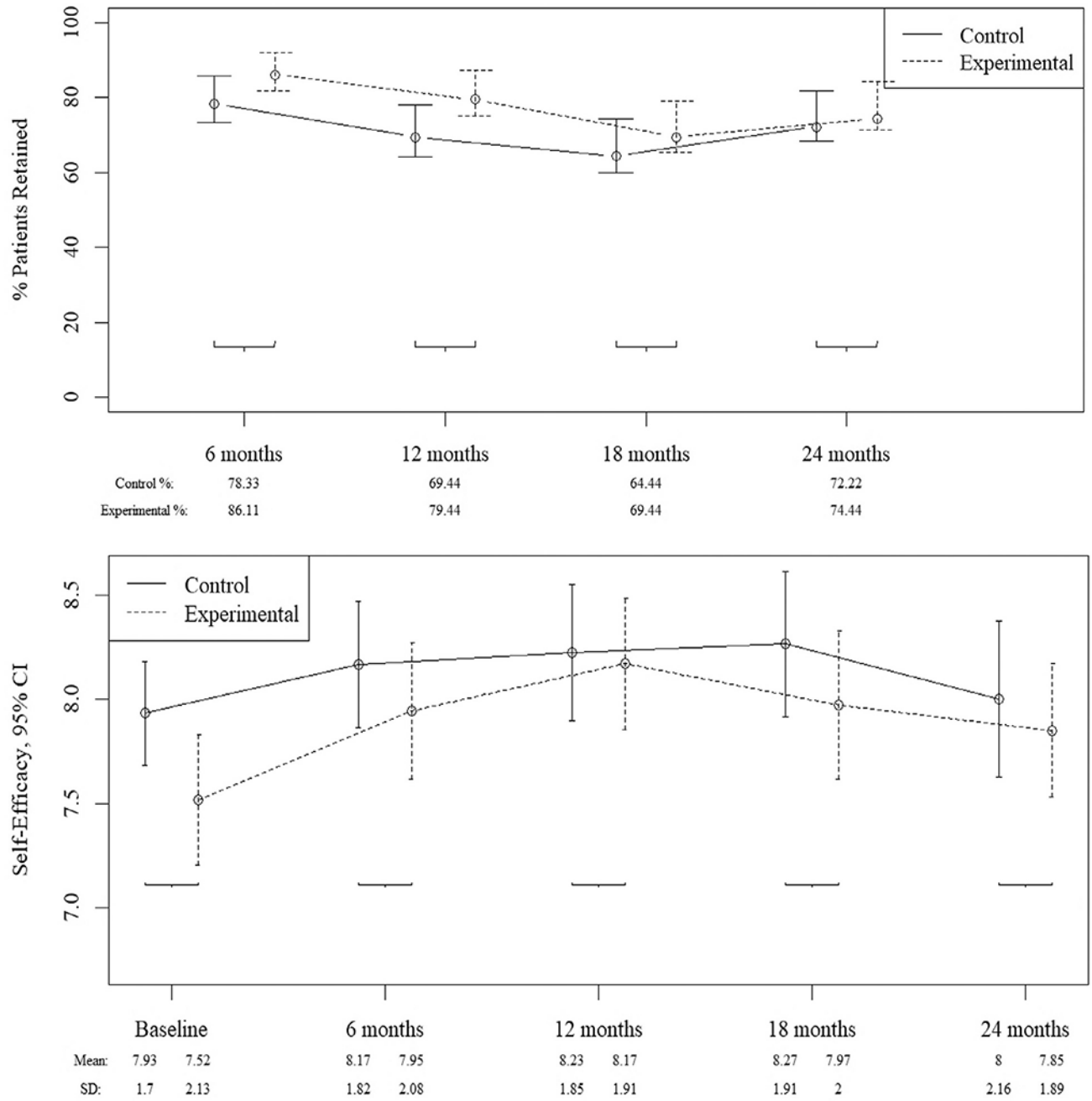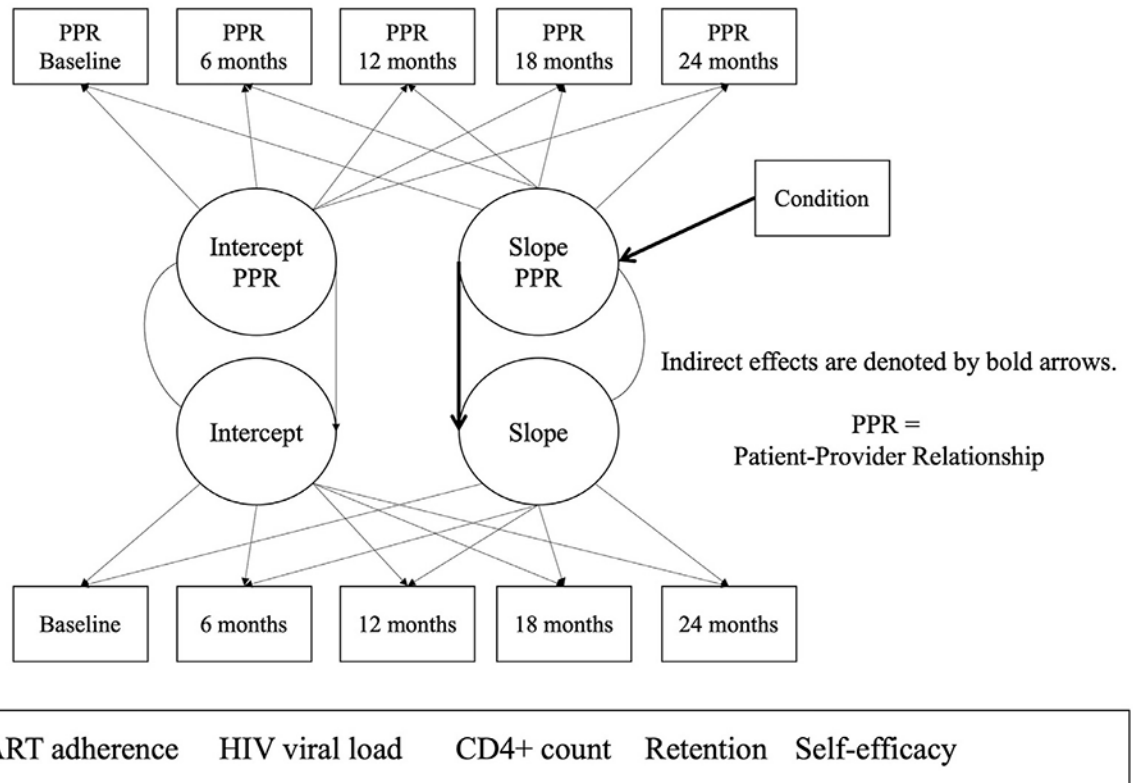HIV Viral load and CD4+ counts over time by condition.

Figure 4.
Retention and self-efficacy over time by condition.

Indirect Effects:
Condition → PPR → HIV Viral Load
$B = -0.10 (.05), p = .027$
Condition → PPR → ART Adherence
$B = 0.19 (.07), p = .009$
Condition → PPR → CD4+ count
$B = -0.57 (5.96), p = .924$
Condition → PPR → Self-Efficacy
$B = 0.06 (0.02), p = .001$

Figure 5.
Conceptual diagram of indirect effects of condition on study outcomes.
Conceptual diagram denotes indirect effects examined using bivariate parallel latent growth curve (LGC) models in a structural equation modeling framework to estimate individual associations between patient–provider relationship and outcomes of interest (HIV Viral Load, ART Adherence, CD4 Count, and Self-Efficacy).

Table 1:

Demographic variables ($N = 360$).

Variable	All Mean (SD)/n (%)	ESOC Mean (SD)/n (%)	Intervention Mean (SD)/n (%)	$t/Z/X^2$, p
Age	39·15 (10·96)	37·92 (11·36)	40·38 (10·44)	2·35, 0·019
Sex				
Male	177 (49·2%)	72 (40·0%)	105 (58·3%)	12·10, 0·001
Female	183 (50·8%)	108 (60·0%)	75 (41·7%)	
Currently Employed				
No	159 (44·2%)	93 (51·7%)	66 (36·7%)	8·21, 0·004
Yes	201 (55·8%)	87 (48·3%)	114 (63·3%)	
Highest Education Attained				
Less than high school	127 (35·3%)	79 (43·9%)	48 (26·7%)	11·69, 0·001
Completed high school or more	233 (64·7%)	101 (56·1%)	132 (73·3%)	
Clinic Type				
Public	248 (68·9%)	133 (73·9%)	115 (63·9%)	4·20, 0·040
Private	112 (31·1%)	47 (26·1%)	65 (36·1%)	

*
Note. Continuous variables reported as *Mean (SD)* and categorical variables reported as *n* (%).