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Does Economic Strengthening Improve Viral Suppression Among Adolescents Living with HIV? Results From a Cluster Randomized Trial in Uganda

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Abstract

To assess the effect of a savings-led economic empowerment intervention on viral suppression among adolescents living with HIV. Using data from Suubi + Adherence, a longitudinal, cluster randomized trial in southern Uganda (2012–2017), we examine the effect of the intervention on HIV RNA viral load, dichotomized between undetectable (< 40 copies/ml) and detectable (40 copies/ml). Cluster-adjusted comparisons of means and proportions were used to descriptively analyze changes in viral load between study arms while multi-level modelling was used to estimate treatment efficacy after adjusting for fixed and random effects. At 24-months post intervention initiation, the proportion of virally suppressed participants in the intervention cohort increased tenfold ($_{T2-T0}$ = + 10.0, p = 0.001) relative to the control group ($_{T2-T0}$ = + 1.1, p = 0.733). In adjusted mixed models, simple main effects tests identified significantly lower odds of intervention adolescents having a detectable viral load at both 12- and 24-months. Interventions addressing economic insecurity have the potential to bolster health outcomes, such as HIV viral suppression, by improving ART adherence among vulnerable adolescents living in low-resource

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environments. Further research and policy dialogue on the intersections of financial security and HIV treatment are warranted.

Keywords

ART; HIV; SUUBI; Adolescents; Assets; Economic empowerment; Savings-led intervention

Introduction

An estimated 2.1 million adolescents, aged 10–19 years, are living with HIV/AIDS (ALWHA) worldwide, with greater than 80% in sub-Saharan Africa [1]. Research has shown that early initiation of antiretroviral therapy (ART) and continued adherence to ART in persons living with HIV can lead to viral load suppression, extended life expectancy, and reduced risk of HIV transmission to uninfected sexual partners [2, 3]. ART adherence also delays disease progression to AIDS and decreases the incidence of serious non-AIDS events [4, 5]. With expanded coverage of ART globally to children; there is a growing number of perinatally-infected adolescents who are increasingly responsible for managing their ART regimens [6, 7]. However, studies have shown that adolescents have worse adherence compared to adults and younger children [8, 9]. Adolescents are the only group for which AIDS-related mortality has not decreased [10, 11] with AIDS being the leading cause of adolescent death in sub-Saharan Africa [12].

Financial instability remains a threat to adherence to ART and its potential effectiveness in persons living with HIV [13, 14]. The current evidence has primarily centered on HIV-infected adults, and suggests several mechanisms for why this may be the case. HIV-infected individuals may have inadequate economic access to ART, limiting resources to pay for real or perceived costs related to medications and treatment, including travel costs to remain engaged in care [15–17]. Many individuals living with HIV, including families affected by AIDS, may have lost employment or other sources of income over the course of their illness. They may subsequently avoid treatment or experience disruptions in ART due to lack of food or other financial support [18]. Food insecurities may hinder adherence to ART as a result of stress, anxiety, or physical ramifications of hunger [18, 19]. Once initiating ART, individuals and families affected by AIDS may also struggle to resume income-earning work if household assets were sold to sustain food or other living expenses during periods of illness and unemployment [18, 20]. For adolescents in particular, studies have also shown that caregiver inability to pay a fee for ART, inadequate meals to support medication consumption, and resource prioritization towards school expenses are all associated with low ART adherence in youth populations [21–23].

A limited number of economic interventions have been evaluated to address low ART adherence in resource-poor settings. The published literature has largely focused on poor adults who are living with HIV and includes strategies relating to financial and economic incentives [18, 24], food assistance [18, 25], medication vouchers and subsidies [26, 27], as well as microfinance [26] and entrepreneurial education [27]. By and large, these studies have found significant improvements in treatment adherence among HIV-infected adults.

Many of these studies were limited by non-experimental designs. The few studies targeting adolescent ART adherence have rarely addressed economic factors as key drivers of disengagement in care. In a recent systematic review of ARV adherence enhancing interventions for adolescents and young adults, aged 13–24 [28], only one of the ten intervention studies included an economic assistance component [29]. Since then, to our knowledge, only one other published intervention [21] has evaluated use of cash assistance to improve adolescent adherence to ART. In addition, while the literature on economic interventions and adolescent adherence is limited, the evidence examining cash assistance on HIV incidence among adolescents has been somewhat mixed [30], indicating that structural interventions may not always achieve similar results in all contexts and highlighting the need for further research in this area. To address this knowledge gap, our study assesses viral load suppression, a clinical marker of ART adherence, among PHIV adolescents randomized to receive an economic intervention that included a Child Savings Account (CSA) compared to adolescents randomized to receive a bolstered standard of care.

Methods

Study Design and Setting

This paper used the first three waves of data (baseline, 12-, and 24-months post-intervention initiation) from a longitudinal NICHD-funded cluster randomized trial in southern Uganda, entitled *Suubi + Adherence* (2012–2017). The *Suubi + Adherence* project is a family-based savings-led economic empowerment intervention focused on addressing ARV adherence for HIV-infected adolescents in four districts of southern Uganda (Rakai, Masaka, Kalungu & Lwengo), a region heavily affected by HIV/AIDS, with an HIV prevalence rate of 10.6%, three percentage points higher than the national average of 7.4% [31]. Despite rapid declines in poverty in the past decade, approximately 35% of Ugandans continue to live on $1.90 USD or less per day [32]. Such economic insecurity suggests that costs associated with HIV treatment, including transportation to clinics and access to food (to meet ART dietary requirements and avoid medication related gastrointestinal side effects), may negatively affect adherence, even where ART is provided without cost.

Sample

Nine hundred ninety adolescents from 40 HIV clinics were screened for eligibility. To be eligible for the study, adolescents must have met the following conditions: (i) tested positive for HIV (confirmed by medical report and aware of status); (ii) living within a family; (iii) aged 10–16 years; (iv) prescribed ART; and (v) enrolled in care at a medical clinic participating in the *Suubi + Adherence* project. Two-hundred and eighty-eight adolescents were excluded, predominantly for lack of awareness of HIV status and being under or over age. Participants were also excluded if they had a cognitive or severe psychiatric impairment that would prevent comprehension of study procedures as assessed during the Informed Consent process. Seven hundred and two adolescents were enrolled in the study and interviewed at baseline.

Clinics were eligible to participate if they (1) had existing procedures tailored to adolescent adherence (including adolescent clinic days and peer counseling); and (2) were accredited

by the Ugandan Ministry of Health as a provider of ART within the four study districts. Based on that criterion one clinic was excluded leaving a total of 39 clinics within the study sample, representing all clinics that met the inclusion criteria within the study districts. See Consort Diagram (Fig. 1).

Study Group Assignments

Following enrollment and baseline assessments, 39 participating clinics were randomly assigned to one of two study groups, resulting in 19 clinics (n = 344 participants) assigned to the control and 20 clinics (n = 358 participants) assigned to the intervention condition. A two-arm, cluster randomized trial design was employed where all participants attending the same clinic were assigned to the same study group. This was intended to reduce issues of contamination.

Randomization of clinics was carried out by an independent Columbia University Research Assistant. All participants received medical Standard of Care (SOC), as defined by the Uganda Ministry of Health Guidelines for pediatric and adolescent HIV care and treatment; and psychosocial SOC, consisting of information leaflets on adherence and support provided by lay counselors including persons living with HIV who have been trained in ART adherence counseling, known as "expert clients". Due to inconsistency in which SOC is often provided in the region, the Suubi-Adherence study provided adolescents in both the control and intervention conditions with a bolstered standard of care (BSOC), which included eight information sessions on adherence to ART adapting evidence-based, print cartoons to portray adherence topics in a relatable manner [33]. Adolescents in the intervention group received the BSOC as well as an economic empowerment intervention consisting of a Child Savings Account (CSA), matched at a rate of 1:1 and from which financial savings could be used for medical related expenses, family small business development or education related expenses (including school lunches and fees). As part of the CSA package, the intervention group also received four workshops blending financial management and life skills with topics including asset building, small business development, goal setting, and risk mitigation, components previously tested among adolescents in the region [34, 35].

Outcomes

The primary outcome of this analysis was viral suppression as reflected in HIV RNA viral load (VL). VL testing was done by the Rakai Health Sciences Program at each of the study's time points: baseline/pre-intervention initiation (time 0), 12-months post intervention initiation (time 1), and 24-months post intervention initiation (time 2). Plasma VL measurements were quantified in blood samples collected in EDTA tubes using Abbott RealTime HIV-1 RNA PCR, version 5.00. In accordance with the Abbott platform, VL was dichotomized between undetectable (< 40 copies/ml) and detectable (40 copies/ml) levels. Binary measures of VL have greater clinical relevance as health care practitioners aim to for all patients to achieve viral suppression. However, continuous measures of VL offer greater granularity for patient monitoring and data analysis. As such, in addition to our primary endpoint, we have included an exploratory analysis of the intervention's effect on the

continuous measure of VL, normalized using $\log_{10}$ transformation, reducing both skew and kurtosis (SK = 10.7 v. 1.1; KR = 159.4 v. 2.9).

Analysis

Cluster-adjusted comparisons of means and proportions using linear regressions with cluster-adjusted standard errors and Rao-Scott Chi square tests, respectively, were used to examine demographic and adherence characteristics at baseline and to descriptively analyze changes in adherence over time between study arms. Multi-level models were then used to estimate the effects of the intervention on adherence while accounting for clustering, specifically the nested nature of children within the same clinic and the repeated measures for each child. Mixed effects linear (Stata *mixed* command) and logistic (Stata *melogit* command) regression models were used for continuous and dichotomous outcomes, respectively. Linear mixed models were estimated using maximum likelihood estimation (ML); logistic mixed models were estimated via maximum likelihood using the adaptive Gaussian quadrature approach with 7 integration points. In initial unadjusted models, study group, time, and group-by-time interactions were incorporated to enable planned simple main effects comparisons of study arms within each time point and time points within each group. Subsequent covariate-adjusted mixed effects models were used to account for age, gender, and number of prescribed pills [36, 37], and to account for random effects as imposed by unmeasured characteristics at the clinic and individual level. An intention- to-treat (ITT) analysis inherent within the multi-level model allowed for the inclusion of every participant within the analysis, by the study group to which they were originally randomized, under the missing at random (MAR) assumption for cases with incomplete data via maximum likelihood estimation. All hypothesis tests were considered statistically significant at $p < 0.05$. Data were analyzed using STATA v14 (College Station, TX, USA).

Ethical Considerations

This study received ethics approval from Columbia University (Protocol #AAAK3852), the Makerere University School of Public Health (#IRB00011353) and the Uganda National Council for Science and Technology (Protocol #IRB00011353). Both adolescent assent and caregiver/guardian consent were obtained prior to the study. Adolescents were consented separately from their caregivers/guardians to avoid coercion to participate. The study's protocol is registered in the clinicaltrial.gov database (ID#NCT01790373).

Results

Sample Demographic Characteristics

Among the 702 enrolled participants, the mean age was 12 years and 56% were girls. On average, two ARV pills were taken per day by study participants. The mean VL was between 4.96 and 5.23 log units with approximately 62% of adolescents in the control arm and 56% in the treatment arm recording suppressed VL (< 40 copies/ml) at baseline. No statistically significant differences were observed between study groups at baseline (Table 1). Between baseline and follow-up at 24 months, attrition rates between study arms were relatively consistent with a 5.5% rate for adolescents in the control group and 6.5% rate for the treatment arm (Fig. 1). Seventy-eight percent of participants attended all eight BSOC

adherence sessions over the course of 8 months while 72% of intervention participants also attended the additional four workshops on financial management and life skills within a four-month time frame. Among intervention participants, mean self-reported savings increased from USD equivalent of $2.15 at baseline to $19.34 at 24-months while control group participant savings increased from $1.78 to $4.44 over the same time period. At 12- and 24-month follow-up, both control and treatment groups had approximately 1.0% of VL values missing for reasons other than loss to follow-up, withdrawal from the study, or death for which the attrition rate accounted.

Descriptive Analysis of Virologic Suppression by Study Arm

Analysis of pre-intervention VL data demonstrated no statistically significant difference between study arms in regard to the proportion of participants with suppressed VL. Likewise, exploratory analysis of the log of the VL showed no significant differences between the control and intervention arms (Table 1).

When measuring VL dichotomously to quantify viral suppression (< 40 vs. 40 copies/ml), adolescents in the control arm showed a small net increase in the proportion of participants with viral suppression between baseline and 24-months post-intervention initiation ($_{T2-T0}$ = + 1.1, p = 0.733), though the findings were not statistically significant. In contrast, during the same period, there was a statistically significant increase in the proportion of virally suppressed participants in the intervention cohort ($_{T2-T0}$ = + 10.0, p = 0.001) (Table 2, Fig. 2). Among intervention adolescents, a higher proportion of participants that achieved viral suppression did so within the 1st year of the intervention ($_{T1-T0}$ = + 7.4, p = 0.015) (Table 2, Fig. 2).

Comparisons of mean VL logs showed no statistically significant difference between the control and intervention arms from baseline to 12-months post intervention initiation or from 12- to 24-months. However, while the control group recorded a net increase in VL log units from baseline to 24-months ($_{T2-T0}$ = + 0.23, p = 0.124), the intervention group demonstrated a net decrease ($_{T2-T0}$ = − 0.28, p = 0.240); though these effects were not statistically significant (Table 2). For adolescents in the intervention group, a statistically significant reduction in VL log units did occur between baseline and 12-months post intervention initiation ($_{T1-T0}$ = − 0.33, p = 0.044) (Table 2).

Adjusted Effect of Suubi + Adherence Intervention

In mixed models, adjusting for pre-specified covariates of gender, age, and number of medications, no statistically significant group effect was identified for our primary outcome of analysis, the binary measure of VL. A significant time main effect was identified, indicating that the odds of viral suppression increased over time for both study groups (Table 3). However, the statistically significant group-by-time interaction qualified this time main effect such that the improvement in viral suppression was driven by adolescents in the intervention cohort (Table 3; Fig. 2). Simple main effects tests clarified this interaction by showing no significant differences for groups at each time point (all ps > 0.22), but a significant reduction in lower odds of having a detectable VL at 12 months (OR 0.424; 95% CI 0.248, 0.723; p = 0.002) and 24 months (OR 0.299; 95% CI 0.161, 0.554; p = <0.001) for

intervention adolescents. In contrast, no significant differences were found across time for the control group (Fig. 2).

In exploratory analysis of the intervention effect on the log of the VL, results supported our findings on the primary outcome of analysis. A group-by-time interaction was identified with intervention group participants, driven by the difference in the log VL between baseline and 24-months in the intervention group (Table 3). Simple main effects tests showed no significant differences for groups at each time point (all $ps > 0.28$), but did reveal a significant reduction in log10 VL from baseline to 12-months (mean difference = − 0.364; 95% CI – 0.667, – 0.060; p = 0.019) in the intervention group. Though not statistically significant at the conventional alpha level of 0.05, the simple main effect difference from baseline to 24 months exhibited a similar reduction (mean difference = − 0.350; 95% CI − 0.702, 0.001; p = 0.051).

Of note, while VL differences did exist at baseline (Fig. 2), they were not statistically significant in contrast with the differences found at 24-months, which were significant. Further, the significant group-by-time interactions suggest differential change over time across the two groups with intervention group participants improving.

Discussion

In a large sample of Ugandan adolescents between the ages of 10 and 16 years and living with HIV, a multi-component economic empowerment intervention, *Suubi + Adherence*, was found to significantly improve viral suppression, the primary marker of adherence to ART, as measured through the reduced mean log of VL and reduced odds of having a detectable VL (40 ml).

Our findings contribute to the scientific literature examining the efficacy of economic interventions in improving HIV treatment adherence [18, 24–27], and expand this evidence base to an adolescent population. To our knowledge, this is the first study to utilize a randomized experimental design to assess the longitudinal effects of an economic intervention on HIV viral suppression among adolescents.

There are several potential mechanisms by which the *Suubi + Adherence* economic empowerment intervention may have reduced detectable VL in adolescents, mechanisms that will be explored in future papers incorporating the final time point of the study. For adolescents who live in family care and remain dependent on their caregivers, financial hardship in the household may prevent consistency in care utilization. The promotion of financial stability may have addressed transport costs and food security, which are factors that have previously been identified as barriers to ART adherence [15–19]. Further, given that adolescents affected by HIV/AIDS and living in low resource communities are more likely to work in order to help improve the financial situation of their household [38], it is plausible that opportunities for income generation may interfere with clinic appointments to obtain ART refills. By improving economic security for the household, adolescents may feel less pressure to seek employment and thus have greater availability to travel to clinics to obtain their medication.

Beyond economic considerations, the asset-based economic intervention may have also improved psychosocial outcomes, such as hope, self-efficacy, and future orientation, which in turn facilitated health-seeking behavior. This pathway aligns with Asset Theory, which posits that tangible assets, including monetary savings, can fuel optimism, risk aversion, and greater future orientation [39]. Given that adolescence is characterized by a greater need for autonomy and control, markers of the forthcoming transition to adulthood, the accumulation of assets can improve an adolescent's self-concept and trajectory, with secondary education or a successful microenterprise endeavor a realizable goal. This enhanced sense of agency may motivate adolescents to take greater control over their HIV treatment. In other words, an asset-based economic intervention may provide a tangible foundation on which adolescents can construct a secure future, with hope and optimism mediating the positive relationship between savings and improved ART adherence. From the perspective of parents and caregivers of ALWHA, being able to imagine a positive future for adolescents under their care may also motivate stronger social and emotional support to ensure that their children adhere to therapy.

Relatedly, it is well documented that stigma is a key reason why adolescents do not want to disclose HIV status to their peers, as adolescence is a time when positive self-image and acceptance are some of the biggest considerations as adolescents build their network of peers and find their footing in the community [22]. As *Suubi + Adherence* is a combination intervention that integrates matched savings, financial education, and life skills for adolescents receiving the treatment, it is possible that participation in these program components provided ALWHA exposure to other adolescents with the same status and life circumstances, promoting confidence and alleviating perceived stigma on ART usage.

The ten percent increase in participants with viral suppression falls at the lower-middle range of outcome effects for adherence interventions in Sub-Saharan Africa [40]. However, the meta-analysis referred to above largely captures outcomes for adults who have been shown to be as much as 2–3 times more adherent than adolescents in the region [8], suggesting our findings to be clinically meaningful for an adolescent population. In addition, because viral suppression for intervention adolescents was most pronounced at 12 months as opposed to 24 months, it can be suggested that SUUBI + adherence can have rapid effects on treatment adherence. What is yet to be explored is whether the proposed pathways from economic and psychosocial benefit to ART adherence can be sustained over longer periods of time. Further, after the intervention has ended, is adherence maintained? Tracer studies would be useful to understand these effects longitudinally.

Taken together, our findings show that a combination intervention with an emphasis on economic strengthening may improve adherence to ART, but also highlight the need to further explore the intricacies linking economic vulnerability and ART adherence outcomes among adolescents in low-resource settings, such that future interventions can effectively target all causal pathways. This study reiterates the importance of a multidisciplinary, combination intervention approach to HIV treatment that includes an economic component. The findings also support efforts to promote a broader dialogue on the ability of social protection policies to improve public health outcomes.

Limitations

Several limitations are inherent within our treatment-effects analysis. First, given the nature of the *Suubi + Adherence* intervention as one with multiple components, it is difficult to disentangle the effects of savings alone; therefore, it is the entire package of services that has been evaluated. Nevertheless, public health scholars have widely called for greater research on combination interventions, recognizing that singular solutions to HIV prevention and treatment will likely be less effective given the interconnected vulnerabilities faced by persons at risk of or living with HIV [41–43].

Relatedly, the focus of our investigation was to test the efficacy of *Suubi + Adherence* to enhance viral suppression. While the study was efficacious in improving viral suppression for adolescents in the intervention arm, the relative comparability in viral load levels between study groups suggests that more research is needed to take into account and address ceiling effects when analyzing viral suppression among adolescents.

Future studies should explore mediators and moderators of the intervention effect in order to quantitatively examine various mechanisms of change. Scientific inquiry into the cost-effectiveness of this type of economic intervention for improving adherence is also warranted.

Further, our study was quantitative by design and thus we did not obtain qualitative data on adolescent perceptions of the program, which could have added nuance and context to better elucidate the causal pathways between program participation and ART adherence. Additional research is needed to qualitatively capture these themes.

Public Health Implications

Prior studies have indicated that elevated HIV RNA viral loads are associated with faster progression to AIDS and higher risk of HIV transmission, making adherence to ART to promote viral suppression a critical component in achieving an AIDS-free generation. Our findings suggest that interventions addressing economic insecurity have the potential to improve viral suppression, a clinical marker of ART adherence, among vulnerable adolescents living in low-resource environments. This supports previous research demonstrating the ability of economic initiatives to improve ART adherence and extends this evidence base to an adolescent population. Such results prompt important questions for both policy and practice when aiming to address the public health challenge of HIV/AIDS, necessitating further research and policy dialogue on the intersections of financial security and HIV prevention and treatment.

Acknowledgments

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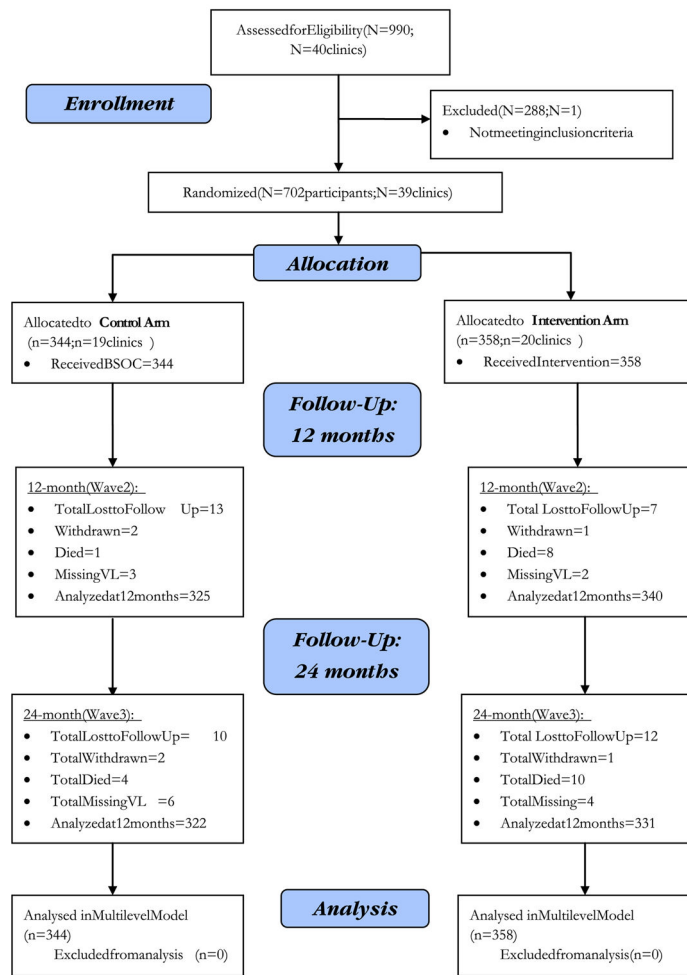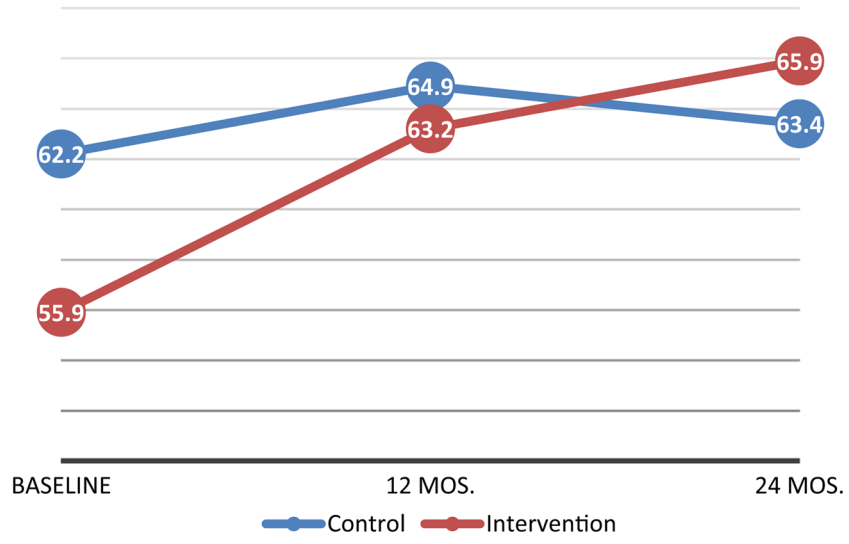
Fig. 1.
Consort diagram adherence study

Fig. 2.
Percentage of virally suppressed adolescents by study arm

Table 1

Characteristics of enrolled adolescents at baseline by randomly assigned group

	Control N = 344	Intervention N = 358	p-value[a]
Demographic characteristics N(%)			
Gender			
Female	193 (56.1)	203 (56.7)	0.88
Male	151 (43.9)	155 (43.3)	
Age			
Mean (SD)	12.4 (2.0)	12.5 (2.0)	0.77
Age 10–12	184 (53.5)	181 (50.6)	0.67
Age 13–16	160 (46.5)	177 (49.4)	
Number of pills in daily regimen			
Mean (SD)	1.95 (0.7)	2.05 (0.7)	0.33
Adherence measures N(%)			
Viral load			
Mean (SD)	12,344 (48,688)	23,710 (111,706)	0.08
Mean (SD) Log_{10} VL	4.96 (2.97)	5.23 (3.11)	0.25
Viral load (copies/ml)			
Below detectable (< 40 ml)	214 (62.2)	200 (55.9)	0.18
Detectable (40 ml)	130 (37.8)	158 (44.1)	

[a]Adjusted for clustering

Table 2

Descriptive analysis of viral suppression by study arm Adjusted for clustering of research participants within clinics

	Control						Intervention					
	T0	T1	T2	T1–T0	T2–T1	T2–T0	T0	T1	T2	T1–T0	T2–T1	T2–T0
Sample size	344	325	322	–	–	–	358	340	331	–	–	–
Viral load (copies/ml)												
% Undetectable (< 40 copies/ml)	62.2	64.9	63.4	+ 2.7	– 1.6	+ 1.1	55.9	63.2	65.9	+ 7.4*	+ 2.6	+ 10.0**
Viral load Log$_{10}$												
Mean (SD)	4.96 (± 2.96)	4.81 (± 2.82)	5.19 (± 3.18)	– 0.15	+ 0.38	+ 0.23	5.23 (± 3.11)	4.90 (± 2.91)	4.95 (± 3.09)	– 0.33*	+ 0.05	– 0.28

*
p < 0.05,

**
p < 0.01

Table 3

Multi-level regression analysis of viral suppression by study arm (N = 344)

	Adjusted estimate (± SE) and *p* value[a]	
	Detectable viral load (40 copies/ml) (adjusted odds ratio)	Viral load $\log_{10}$ (linear *B*)
Constant	0.099 (0.101)	5.081 (0.652)
	0.023 [*]	<30.001 [***]
Intervention (N = 358)	1.631 (0.662)	0.191 (0.278)
	0.228	0.492
12 month	0.656 (0.187)	− 0.222 (0.158)
	0.139	0.161
24 month	0.742 (0.236)	0.147 (0.184)
	0.348	0.425
Intervention × 12 month	0.646 (0.232)	− 0.142 (0.198)
	0.224	0.475
Intervention × 24 month	0.403 (0.147)	− 0.497 (0.199)
	0.013 [*]	0.013 [*]
Group × time χ^2 (2)	*6.22 (p = 0.045)* [*]	*6.57 (p = 0.037)* [*]

Results shown in italics are Chi square omnibus tests of the group-by-time interaction effect

Control N = 344; Intervention N = 358.

[*]
 p < 0.05,

[**]
 p < 0.01,

[***]
 p < 0.001

[a]Adjusted for clinic ID and child ID (random effects) and gender, age, and number of medications (fixed effects)