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Research paper

Suubi+Adherence study protocol: A family economic empowerment intervention addressing HIV treatment adherence for perinatally infected adolescents

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ABSTRACT

Background: Globally, 1.8 million children<15 years are living with HIV. Sub-Saharan Africa (SSA), as a region, is heavily burdened by HIV, with 90% of new infections among children happening there. Within SSA, Uganda has an HIV prevalence of 7.2% among 15-49-year-olds, with high prevalence in Masaka region (12%). Uganda also reports unprecedented numbers of perinatally HIV-infected children, with close to 150,000 children (ages 0–14) living with HIV (CLHA). However adherence to antiretroviral therapy (ART) among children and youth is poor, and has been attributed to economic insecurity, including lack of finances for transportation to clinic appointments, inadequate meals to support medication consumption, and resource prioritization towards school expenses. Yet, few programs aimed at addressing ART adherence have applied combination interventions to address economic stability and ART Adherence within the traditional framework of health education and HIV care. This paper describes a study protocol for a 5-year, *Eunice Kennedy Shriver National Institute of Child Health and Human Development* (NICHD) funded, cluster randomized-controlled trial to evaluate a combination intervention, titled Suubi + Adherence, aimed at improving ART adherence among HIV perinatally infected adolescents (ages 10–16 at study enrollment) in Uganda.

Methods: Suubi + Adherence was evaluated via a two-arm cluster randomized-controlled trial design in 39 health clinics, with a total enrollment of 702 HIV + adolescents (ages 10–16 at enrollment). The study addresses two primary outcomes: 1) adherence to HIV treatment regimen and 2) HIV knowledge and attitudes. Secondary outcomes include family functioning, sexual risk-taking behavior, and financial savings behavior. For potential scale-up, cost effectiveness analysis was employed to compare the relative costs and outcomes associated with each study arm: family economic strengthening comprising matched savings accounts, financial management training and small business development, all intended for family economic security versus bolstered usual care (SOC) comprising enhanced adherence sessions to ensure more standardized and sufficient adherence counseling.

Discussion: This study aims to advance knowledge and inform the development of the next generation of programs aimed at increasing adherence to HIV treatment for HIV + adolescents in low-resource regions such as SSA. To our knowledge, the proposed study is the first to integrate and test family economic empowerment and stability-focused interventions for HIV + adolescents in Uganda (and much of SSA)—so families would have the necessary finances to manage HIV/AIDS as a chronic illness. The study would provide crucial evidence about the effects of an economic empowerment program on short and long-term impact, which is essential if such interventions are to be taken to scale.

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1. Background

Globally, 1.8 million children<15 years are living with HIV [1]. Sub-Saharan Africa (SSA), as a region, is heavily burdened by HIV, with 90% of new infections among children happening there [2]. Within SSA, Uganda has an HIV prevalence of 7.2% among 15-49-year-olds, with higher prevalence in Masaka region (12%) [3,4]. Uganda also reports unprecedented numbers of perinatally HIV-infected children, with close to 150,000 children (ages 0–14) living with HIV (CLHA) [5]. Despite progress made in the prevention of mother to child transmission [PMTCT] of HIV in Uganda [6], the uptake of PMTCT services and retention in care pose significant barriers [6–11]. Pregnant women may avoid participating in PMTCT programs due to HIV-related stigma resulting from unwanted disclosure and its consequences [6–11]. Since PMTCT services are largely clinic-based [7], children born to mothers without access to early antenatal care to facilitate HIV testing and enrollment into PMTCT services, possess a higher risk of exposure to HIV [9–12].

Thus, perinatally infected children, as a group, continue to grow although not at as high a rate as in the past. [9], Moreover, with increasing access to ART, a generation of children in SSA hitherto expected not to reach their 5th birthday will be entering adolescence, with a growing number of them surviving and coping with HIV as a chronic and transmittable illness [13–15]. Indeed, similar to findings from pediatric HIV cohort studies in countries with longstanding access to ART, many of these adolescents will experience compromised health, inconsistent ART adherence, elevated mental health difficulties, and risk behaviors with individual and public health consequences, including HIV transmission to others [6–11].

1.1. Risks associated with non-adherence to ART

Studies have documented the strong relationship between high ART adherence and better virologic, immunologic, and clinical outcomes [16–22]. Poor adherence leads to inadequate viral suppression, leading to clinical and immunological decline and development of drug resistant viral strains [18,20,23], posing a threat to public health [24–26]. The success of ART depends greatly on a patient's ability to access treatment and strict adherence to the required drug regimen. Patients must take the correct dosage of medication, at the same time every day in order for treatment to be effective [27]. Irregular medication (non-adherence) increases a patient's risk of developing drug resistant strains of the virus as well as spreading the virus to others [28]. Yet recent data from SSA indicates that adherence may be one of the biggest challenges and greatest barriers to realizing the full benefits of ART [16,18,22].

Adolescents are at great risk for non-adherence to treatment across health conditions and countries, with at least one study in SSA showing that compared to adults, adolescents are less adherent to ART and have lower rates of virologic suppression and immunologic recovery [29]. Key barriers that may interfere with strict adherence among adolescents include economic insecurity—detailed below. Other barriers to adherence include unpleasant side effects of medication, fear of disclosure and anticipated stigma [30], forgetfulness [31], mental distress [32,33], and lack of information about the disease [34]. In addition, lower levels of education and literacy generally result in lesser access to information about HIV [34], increasing the risk that the disease will spread and creating an environment prone to stigma and social exclusion for those affected. Thus, failure to address ART adherence needs of HIV + adolescents may lead to costly long-term consequences [13,35].

1.2. Economic insecurity and ART adherence

Economic insecurity, including poverty, is considered a significant factor in contracting HIV as well as a barrier to ART adherence once infected [36]. Individuals living with HIV in poverty-stricken communities face challenges accessing treatment due to economic insecurity, including lack of finances for transportation to clinic appointments and care facilities [37], inadequate meals to support medication consumption [38,39], resource prioritization towards school expenses [40], poor medical resources in their communities [36], and in places where there is no free ART or where there is stock out in government clinics, lack of finances to purchase antiretroviral (ARV) medicines [41,42]. Moreover, household earnings often decline because HIV positive family members in poverty-impacted communities are normally too ill to work consistently. For families with some form of income and savings, greater portions of the family's earnings are often reserved for medication and medical visits [43].

Studies from Uganda, and much of SSA, indicate that one group disproportionately affected by HIV are poor or economically vulnerable children [44–46]. Yet, for this population, adherence to treatment regimens – defined as the extent to which a person's behavior (including taking ART, attending healthcare follow-up appointments, undergoing blood tests for viral load assessments, and following a prescribed diet conforms with healthcare provider recommendation)s – may require a level of economic stability that many youths do not experience [38,39]. In short, poor children encounter greater challenges to ART adherence compared to children who are more economically stable [37,47]. Yet, to date, no adherence interventions have focused on the underlying economic drivers, which might help explain why results of adherence interventions with HIV + adolescents and adults living in poverty have had small to moderate effects at best [48,49].

Indeed, a recent study by Tuller and colleagues in western Uganda found that provision of free ART without addressing the financial barriers (including the cost of transportation to clinics to pick-up monthly refills) does not sufficiently address the problem of treatment interruptions [37]. The cost of transportation relative to income can be substantial, and often competes with other essential expenses. Individuals who missed medication doses cited problems finding transportation money as a key reason for not being able to maintain their regimen, explaining that they were unable to afford to travel to the clinic before their supply of medication ran out. Even for those not yet on ART, anxiety over the cost of transportation caused them to question whether they would be able to adhere to their medication regimens once they initiated treatment [37]. As a result, HIV-positive patients tend to sacrifice healthcare, including adherence to treatment, and other basic needs, including food and school fees for children due to financial constraints [38–42].

2. The *Suubi* + *Adherence* study

The Suubi + Adherence study examined a family-based economic empowerment intervention that aims to improve medication adherence for HIV-positive youth in Southern Uganda. The study is grounded in asset theory [50], which posits important developmental, psychological and social benefits for individuals and households as a result of owning assets; and informed by successful economic interventions previously tested among AIDS-affected youth in Southern Uganda [51–53]. Asset-theory predicts that an impoverished HIV + adolescent with no belief that he/she has the economic means to meet the specific needs associated with managing HIV as a chronic illness (e.g. nutritional

needs, costs associated with medical care, including transportation costs), is more likely to have high levels of depression, reduced self-efficacy, and is less likely to "bother" adhering to medication and other health behaviors. Based on asset-theory, we expect that children receiving an economic intervention (treatment arm), would have relatively stronger financial stability, strive to adhere to their HIV medication, have better health and mental health functioning, and avoid risk-taking behaviors (see Fig. 1).

3. Methods

3.1. Study aims

The specific aims are to: 1) Examine the impact of the *Suubi + Adherence* intervention on key adherence to HIV treatment regimen outcomes for HIV + adolescents including ability to access and refill prescribed medication, keep to prescribed daily medication routines, and keep CD4 count and HIV viral load schedules; 2) Explore the impact of the *Suubi + Adherence* intervention on potential mechanisms of protective health behaviors, knowledge, and beliefs (e.g. financial/economic stability, sexual risk-taking behavior, personal beliefs about medication, hopelessness, future plans and aspirations, adherence self-efficacy); and 3) Examine the costs associated with the *Suubi + Adherence* intervention.

3.2. Setting

Between 2012 and 2018, HIV + adolescents were recruited from clinic/health centers within the greater Masaka region, and where our collaborating institutions, Reach the Youth-Uganda (RTY) and Masaka Diocese, operate. The greater Masaka region is composed of seven political districts: Rakai, Masaka, Lwengo, Kalungu, Lyantonde, Kyotera and Bukomansimbi, and has the highest HIV prevalence rates of 12% compared to the national average [1,2]. For a clinic/health center to be included in the study, it had to be credited and provided ART. Using this criterion, 40 clinics were randomly selected. However, due to lack of proper operational license, one clinic was closed down by district health officials and subsequently dropped from the study's control arm before any study data were collected, leaving 39 clinics from which the study participants were recruited.

3.3. Study population, recruitment and retention

The study began with 728 participants from 40 clinics, and after disqualifying one clinic, a total of 702 HIV + adolescents enrolled in care at the 39 medical clinics were recruited. Youth inclusion criteria were: 1) HIV+, defined as an adolescent who has been tested with confirmation by medical report; 2) living within a family (defined broadly, not necessarily with biological parents); 3) between the ages of 10–16 years; and 4) prescribed ART. In the study clinics, the majority of adolescents in this age group are perinatally HIV-infected.

Recruitment procedures tested in our previous studies (Suubi Maka: R34MH081763 and Bridges to the Future: R01HD070727) were utilized. Participants were identified and recruited from the clinic/health centers associated with RTY and Masaka Diocese. Patients are seen at least annually and each patient on ART must have prescriptions filled monthly at each of the clinic/health centers. Although appointment days (not times) are provided, most patients arrive early in the morning on days that are convenient for them and wait for several hours before they are seen, providing an opportunity for recruitment through medical staff. A list of all eligible families was created from medical records by one of the medical staff. Each chart contained data on the patient's HIV status, age and family data. A clinic staff member reviewed the daily schedule, noting the eligibility of patients.

Providers presented the project to adult caregivers of eligible children during appointments. A research staff (who was on-site during clinic days) contacted interested caregivers and sought a verbal consent. After speaking with the research staff, interested caregivers provided written consent for child participation. Children were asked to provide written assent separately. Given the cultural context within which the study was undertaken, if multiple children in a family were eligible, they were all recruited, provided they met the inclusion criteria. This was intended to address any kind of envy or resentfulness that might happen when other children in the family who met the inclusion criteria were to be excluded.

The *Suubi + Adherence* study was implemented in a highly stable region of Uganda, where migrations are rare. Tracking procedures developed from our previous studies in Uganda that have resulted in very low attrition rates. Participants were asked to give their postal box number and telephone number (if they had one), and names, addresses and contact information of three people who always know how to reach them. In addition, contact with adolescent participants in both groups

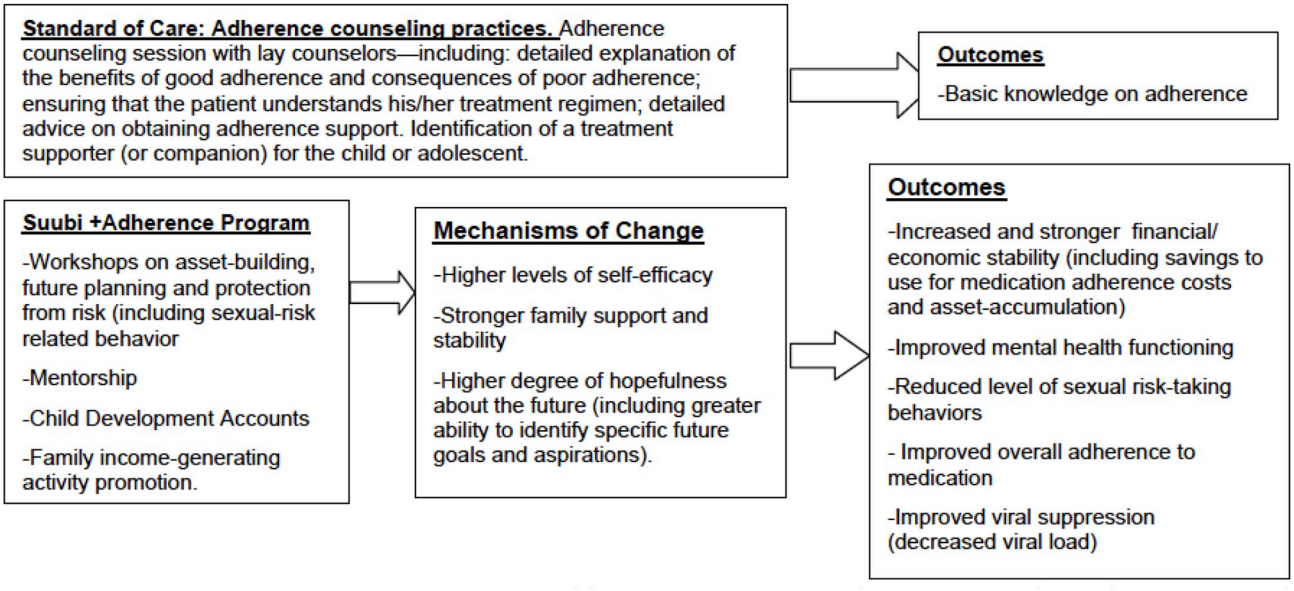

Fig. 1. Suubi+Adherence Study Design

was maintained through the healthcare clinics. Further, the in-country research collaborators (RTY and Masaka Diocese) have community workers who meet with all orphaned and vulnerable children (including HIV + adolescents) and their families frequently to deliver standard of care services. The records were used to track the location of study participants over time.

3.4. Ethics and consent

The research staff obtained written informed consent and assent from the adult caregivers and children, respectively prior to study enrollment. The consenting process for adults and children was done separately to avoid any coercion. Both consent and assent forms were translated into Luganda (the most widely spoken local language in the study region), and back-translated to English to ensure consistency. Both the assent and consent processes were conducted verbally in Luganda, given some caregivers and adolescents who were illiterate. The study team received training on Good Clinical Practices (GCP) so that sensitive research activities were handled appropriately. In addition, all interviewers completed the Collaborative Institutional Training Initiative (CITI) certificate and NIH certificate for protection of research participants. All study procedures were approved by Columbia University Review Board (AAAK3852), the home institution of the PI at the time of study initiation, and by the in-country local IRBs in Uganda: Makerere University School of Public Health Review Committee (Protocol # 210), and Uganda National Council of Science and Technology (UNCST, SS 2969).

In order to protect the confidentiality of the data, the following standard protocols are followed: (a) completed questionnaires, consent forms, and the file with linking data are kept separately; (b) during the data collection process, completed questionnaires, consent forms, and the file with linking data are kept separately in locked filing cabinets at the Suubi + Adherence's International Center for Children Health and Development (ICHAD) field office in Uganda; (c) at the ICHAD field office in Uganda, the locked filing cabinets with the completed questionnaires, consent forms, and the file with linking data are only accessible to the study PI, the Project Coordinator, and the data research team. Electronic data, not containing identifying information, is stored in a password-protected system, to which only the PI, the Co-Investigators, the Project Coordinator, Data manager, plus the individuals entering data have access.

The study maintains records of adverse events, any referrals for counseling, as well as copies of the consent and assent forms. All records are maintained in a locked filing cabinet at the ICHAD field office in Uganda, accessible only by the research team. The PI is responsible for data security and record keeping. The datasets that are used for analysis do not contain any identifying information—specifically, no names and no addresses of participants are included in the datasets for analysis. Identifiers for the participants will be disposed of not more than three years after study completion. To protect the participants' confidentiality, identifiers are only accessible by the PI and Project Coordinator, and are kept separate from other records with participants' responses.

3.5. Intervention description

The *Suubi + Adherence* study was designed as a two-arm cluster randomized-controlled trial (RCT), consisting of a control arm receiving bolstered standard of care, and a treatment arm receiving the child development accounts (CDA). Assessments were conducted at baseline, 12, 24, 36 and 48-months post baseline (see Fig. 2).

3.6. Control arm – bolstered standard of care (SOC)

All participants (both control and treatment arms) received medical and psychosocial support as part of bolstered standard of care. 1) Medical SOC**:** All public clinics, including our study sites follow procedures for pediatric ART initiation and monitoring, as outlined in the National Department of Health Guidelines for pediatric HIV care in Uganda [54]. Specifically, immediately after initiation, or if clinically unstable, youth are seen more frequently (weekly to monthly). Laboratory data (VL and CD4 counts) are collected every six months until the patient is stabilized and then annually. These data are collected in a standardized protocol by the hospitals using the National Health Laboratory Service. Blood work is sent daily to the lab using standardized protocols. ART is prescribed by medical doctors and dispensed monthly by a pharmacist at the clinic sites. For *Suubi + Adherence* study, data on VL, CD4 counts, and ART were collected from charts. 2) Psychosocial SOC: Primarily, lay counselors provide psychosocial support, trained in standardized ART adherence counseling. Typically, each patient is supposed to receive 2–4 sessions of adherence counseling at initiation and when non-adherence is identified. In addition to adherence support, during which information is provided and adherence monitored, lay counselors assist families with any other psychosocial needs that may arise.

However, we know that adherence counseling can vary substantially, thus usual care was bolstered with enhanced adherence sessions to ensure more standardized and sufficient adherence counseling. Because SOC can be delivered inconsistently, participants in the SOC condition received up to 6 sessions to review HIV, ART as well as ART resistance and adherence. In addition, materials devoted to family communication around these topics were adapted from the cartoon-based curriculum used in the CHAMP + SA study conducted in South Africa with HIV positive adolescents and their families [56]. Previous studies show that CHAMP + SA curriculum shows promise in promoting adherence for HIV + adolescents [55–58]. In the adapted version, the curriculum describes the lead characters (*Mabebeere* and *Kamperempe),* testing interactions with a nurse in which she describes how the HIV virus and ART work, and issues around adherence, including potential barriers. The materials were discussed with the participating child, and questions and barriers were identified. Through RTY, the implementation partner, lay counselors already in the clinic were trained to use these materials. The health clinics agreed to incorporate the curriculum into their practice.

3.7. Treatment arm – child development accounts (CDAs)

Participants in the treatment arm received bolstered SOC detailed

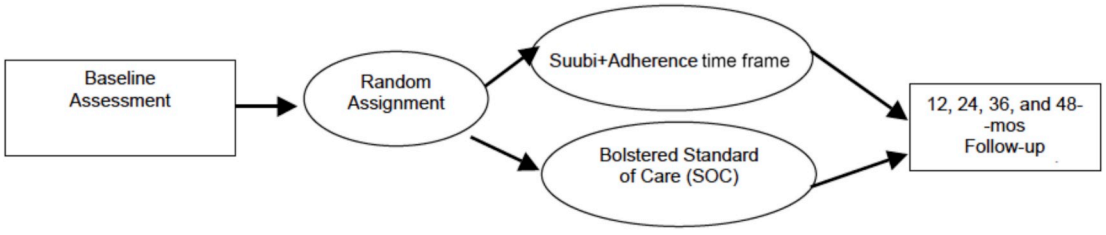

Fig. 2. Suubi+Adherence time frame

above, plus a 2-year economic intervention, consisting of three components:

1. Child Development Accounts (CDA): The central component of the *Suubi + Adherence* intervention is a savings account for each participant used for long-term saving goals. The study provided the initial deposit for each participant's account and matched his or her monthly savings at a ratio of 1:1. The accounts were housed at local financial institutions in the participants' communities and retained after the completion of the study. Parents and relatives of the child were encouraged to deposit money in the account to save for post-primary education or a family business. In accordance with the Uganda banking law which prohibits children below 18 years from independently entering into a binding agreement and operating a bank account, each account was opened in the child's name and his/her caregiver as a co-signer, until s/he turns 18 years of age, at which time a co-signer is no longer required.

2. Microenterprise workshops: Each participant and his/her family were invited to attend four sessions on financial management and training in starting family businesses. The small family business was intended to promote economic stability for the families in the study, and to enable the participating HIV + adolescents to meet the specific needs associated with managing HIV as a chronic illness. Moreover, since the study linked adolescents and their caregiving families to formal financial institutions, this was considered an important step that may allow them to establish modest savings and credit lines to be used in the longer-run.

3. Mentorship: Participants are given the opportunity to attend 12 educational sessions covering a wide range of issues including but not limited to financial planning, business development, saving, setting short and long-term goals, and avoiding risk-taking behaviors. Participants were paired with a peer-mentor to connect with for the duration of the intervention period.

4. Randomization, sample size and power analysis

Stratified random sampling was utilized to assign clinic/health centers to four strata based on two characteristics: 1) geographical location (rural vs urban), and 2) health clinic level (hospital vs health

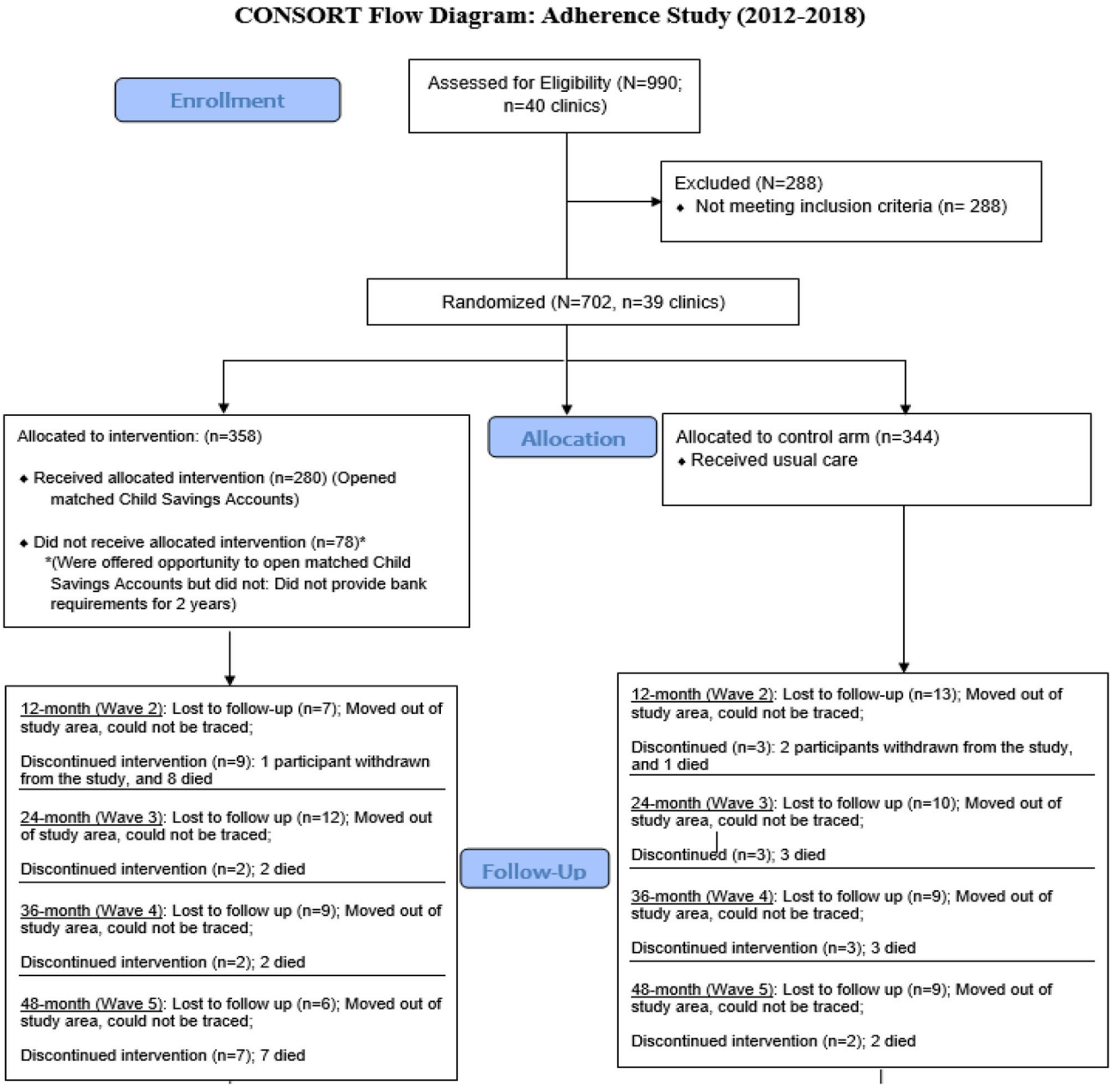

Fig. 3. CONSORT Flow Diagram – Suubi+Adherence

centers). The restricted randomization technique of Hayes and Moulton was implemented within the four strata to assure overall clinic/health center balance across the study arms [59]. Each of the original 40 clinics was randomly assigned to one of the two study arms, such that all selected HIV + adolescents in the same clinic/health center received the same intervention, to reduce contamination. In sum, of the 40 clinic/health centers, 20 clinics were randomly assigned to receive bolstered SOC, and the other 20 received economic intervention. However, one clinic was disqualified, resulting into 19 clinics in the treatment arm (see Fig. 3).

The starting *N* for each of the two study groups (SOC and *Suubi + Adherence)* was 368. Assuming n = 294 per group following 20% attrition, five repeated measurements, power was set at= .80, and α = .05, formulas found in Diggle et al., pg 26–32 [60]. were utilized to compute the minimum detectable effect sizes for two-group comparisons. For continuous outcomes like adherence self-efficacy, we computed the standardized mean difference *d* and the proportion increase for a binary outcome (e.g., adherence) was computed using the standardized proportion difference *h*. Therefore, minimum detectable effect sizes were estimated for binary outcomes with low (10%), moderate (25%), and substantial baseline proportions (50%) to cover a wide variety of possible analysis scenarios. The within-subject correlation *r* among the responses was also varied, as shown in Table 1 below. The effective sample size (ESS) was reduced by dividing the observed sample size (294 per condition*2 conditions = 588) by the design effect (DEFF). The DEFF represents the degree of variance inflation attributable to clustering of cases within higher order units such as clinics. The expected DEFF was conservatively set to 2.0 to account for clinic-level variance inflation, resulting in an effective total sample size of ESS = 588/2 = 294. Benchmarks were 0.20 and 0.50 for small and medium effect sizes, respectively [61], allowing for the detection of small to small-medium effects under a variety of analysis conditions.

4.1. Measures

The study aims at measuring ART adherence among HIV perinatally infected adolescents, potential mechanisms of protective health behaviors and cost associated with the intervention. These will be measured with several instruments including psycho social, technology based measures as well as bio markers. See Table 2 for a list of the study measures, the construct(s) they measure, and their internal consistency reliability (if applicable).

5. Data analysis

5.1. Data quality assurance and initial analyses

Data is currently being cleaned for analysis. Initial analyses will consist of one-way frequency tables for all variables and measures of central tendency and variability for continuous variables to perform range checks, quantify the amount of missing data, and yield valuable descriptive findings. In general, likelihood based method will be used to address incomplete data because it makes the relatively mild assumption that missing data arise from a conditionally missing-at-random process (MAR) [73]. Sensitivity analyses will be conducted with pattern-mixture models to assess the robustness of the MAR assumption [73].

Table 1
Minimum detectible effect sizes at varying levels of within-subject correlation.

Within-Participant *r*	Continuous *d*	Binary *h* – Low (10%)	Binary *h* – Medium (25%)	Binary *h* – High (50%)
.20	.20	6.7%	9.0%	9.8%
.40	.24	8.2%	10.8%	11.7%
.60	.27	9.6%	12.5%	13.3%
.80	.30	10.8%	13.9%	14.8%

Table 2
Variables, measures.

Variable	Measurement	Reliability
Demographics		
Age, socioeconomic status, family composition and structure, educational level of caregiver/parent, caregiver employment, residential moves, changes in child's educational placement, child's educational background (in-school or out-of-school).	Socio-demographic questionnaire	n/a
Moderators		
Gender		
Rural vs. urban/semi-urban		
Potential Mechanisms of Change		
Child/adolescent Age		
Self-efficacy	Questions adapted from the Tennessee Self-Concept Scale (TSCS-2) [62]	0.81
Family support	The Social Support Behaviors Scale (SS–B) [63]	0.77
	Krauss Interview [64] and Parent-Child Relationship Inventory (PCRI) [65] Frequency of talking about risky behavior	0.91
	Level of comfort talking about risky behavior	0.97
Family stability	Socio-demographic questionnaire	n/a
Hopelessness/hopefulness	Beck Hopelessness Scale [66]	0.79
Outcomes		
Financial/economic stability: (Savings and asset-accumulation)	MIS IDA, and American Dream Policy Demonstration [67]	
	Importance of savings	0.66
	Confidence of savings	0.82
Education	School enrollment and attendance; and attainment (National Primary Leaving Examination grades) obtained directly from students' schools (for those in school)	n/a
Sexual risk-taking behavior	Questions adapted from the Youth AIDS Prevention Project and the Aban Aya Project–as used in the CHAMP Family Study Program [68,69]	n/a
Intentions to engage in sexual risk behaviors	Questions adapted from Auslander et al. (1992) [70] and Slonim-Nevo et al. (1995) [71]	0.72
Mental health functioning (Depression)	Questions adapted from The Child Depression Inventory (CDI) [72]	0.65
Medication Adherence	Self-reports, CD4, Viral Load, Wise pill and Pill counts	

5.2. Inferential analyses to address specific aims 1 and 2

Participants in the *Suubi + Adherence* intervention group should exhibit beneficial changes in measured outcomes during the study period relative to participants in the standard of care (SOC) control group. For example, we hypothesize that over time participants in the intervention group should exhibit the following beneficial changes in adherence and clinical sequelae relative to the SOC control, as listed in specific aim 1: (a) an increased ability to access/refill prescribed medication and keep to the prescribed medication regimen; (b) increased mean health literacy and health behaviors (e.g. keeping medical appointments), and (c) show increased mean CD4 T-cell levels and lower mean levels of log10-transformed HIV viral load.

Similarly, we anticipate that the intervention will improve participants' mean levels of protective health behaviors, knowledge, and

beliefs, improve financial outcomes related to successful uptake of the microfinance-based principles of the *Suubi + Adherence* intervention, and lower negative health risk behaviors, as implied by specific aim 2. Relative to SOC control group participants, intervention participants should: (a) exhibit lowered mean levels of sexual risk behavior; (b) report increased levels of adherence self-efficacy and improved personal beliefs about medications; (c) report lowered levels of hopelessness and an increased amount of future plans and aspirations; and (d) increased financial/economic stability.

Multilevel random coefficient models (i.e., HLM) will be utilized to test the longitudinal hypotheses detailed above. These models incorporate random intercepts and slopes for each participant based upon the participant's multiple measurements captured over time, nested within an additional random intercept for the clinics [74]. Initial models will follow an intention-to-treat (ITT) approach and compare unadjusted means and proportions for the *Suubi + Adherence* intervention group vs. the SOC control group. A priori planned comparisons outlined above to address Hypotheses 1–2 will be evaluated at $\alpha = .05$; any subsequent post-hoc comparisons will be further adjusted via simulation-based stepdown methods [75] to maintain an appropriate Type 1 error rate. Subsequent secondary exploratory analyses will include demographic variables (specifically, age, gender and geographical location: rural vs. urban) and investigate their moderating effects on the intervention's efficacy. Secondary analyses will explore whether the potential mechanisms of change mediate the effects of the intervention on outcomes using the approach of Kenny for assessing mediation in the context of longitudinal random coefficient models [76].

Random coefficient models will be fitted to the data using SAS PROC MIXED [77] and SAS PROC GLIMMIX [78]. For linear mixed models fitted with PROC MIXED, adequacy of normality and constant variances assumptions will be evaluated by examining univariate histograms of model residuals for normality and plots of predicted values by Cholesky-scaled residuals [79], respectively. Inferences for models whose residual statistics do not fully meet assumptions will be generated via heteroskedastic-consistent estimators. All proposed analyses will include outlier and influential case screening via computation of the likelihood displacement index and Cook's D statistics [80,81] at both the individual and clinic levels to identify outlying responses at each level.

5.3. Proposed cost-analysis to address specific aim 3

Benefit-cost analysis of program interventions is generally the best guide to policy, but when critical benefits cannot be valued in dollar terms, cost effectiveness is a good guide to policy [82,83]. Because a four-year post-intervention initiation follow-up of 12–15 year old HIV + adolescents is too short to detect long-run increases in earnings—a critical long-run economic benefit—a benefit-cost analysis of *Suubi + Adherence* would be premature. We therefore propose a cost-effectiveness analysis of *Suubi + Adherence* and *Standard of Care.*

Cost effectiveness analyses measure the cost of achieving an agreed upon benefit, such as an additional year of schooling, employment, or a reduction in a disease. Following standard practice, we will measure costs on a per person basis. The costs of the intervention will include all program costs, including not just the savings match, but also all costs incurred for psychosocial counseling, financial management and business management training, and running the program. Research costs will not be included. Data on the savings match costs will be readily available from the management information system (MIS IDA). Data on costs of other program elements will be drawn from project administrative records. The per-person costs of *Suubi + Adherence* and SOC will then be divided by the relevant effect sizes to produce estimates of cost-effectiveness. For example, suppose that SOC and *Suubi + Adherence* costs per child were respectively $500 and $750 and on average increased the number of days participants adhere to their medication by 12 months for SOC and 24 months for *Suubi + Adherence,* the cost effectiveness of increasing years of adherence to treatment by one year for SOC and *Suubi + Adherence* would be respectively $500 and $750/2 = $375. Thus, in this *case,* although the *Suubi + Adherence* intervention is associated with an additional cost of a savings match which makes the cost potentially twice as high as that in SOC, the total cost of the program is not twice as much because other component costs are the same.. If *Suubi + Adherence* led to only 1.1 extra adherence years to treatment, however, it would be less cost effective than SOC–$500 compared to $750/1.1 = $682. As this example illustrates, the cost effectiveness of the alternative intervention arms depends not only on differences in costs but also upon how the different interventions affect outcomes. Because the alternative interventions are likely to differentially affect different outcomes, it is possible that SOC could be more cost effective for some outcomes and *Suubi + Adherence* more cost effective for other outcomes. Thus, similar analyses will be conducted for all of the outcomes.

The cost effectiveness estimates described above are, like the effect sizes from which they derive, point estimates. Confidence intervals based solely on effect size confidence intervals ignore the cost portion of cost effectiveness. But cost estimates are also only point estimates. We will calculate confidence intervals using two methods [84,85] Monte Carlo [86] and bootstrap [87]. Finally, for some outcomes, such as increases in adherence to treatment, education (where applicable) and health, we will be able to compare the cost-effectiveness of SOC and *Suubi + Adherence* to other interventions in developing country settings [88].

6. Discussion

This study aims to advance knowledge and to inform the development of the next generation of programs aimed at increasing adherence to HIV treatment for HIV + adolescents in low-resource regions such as SSA. To our knowledge, the proposed study is the first to integrate and test economic empowerment and stability-focused interventions in relation to ART adherence for HIV + adolescents in Uganda (and much of SSA). The study provides crucial evidence regarding the effects of an economic empowerment program on short, and long-term impacts, which is essential if such interventions are to be taken to scale. There are few evidence-based adherence interventions for adolescents growing up with HIV. ART adherence interventions that do exist have been tested in resource-rich settings, with well-established social welfare systems, requiring considerable resources and staff time, thereby precluding wide dissemination in resource-constrained settings. Indeed, in a review of 14 intervention studies, only 9 demonstrated modest improvements in adherence and three demonstrated some maintenance of effect [89,90]. Most interventions are based on cognitive-behavior models [89,90] and the effects of these psychosocial interventions are difficult to sustain.

Moreover, for resource-constrained settings, HIV-positive individuals may need interventions that focus beyond improving psychosocial individual-level factors. Thus, while psychosocial interventions have become an accepted strategy to manage the staggering numbers of HIV patients—registering small to moderate effect sizes at best [89,90]– a failure to explicitly incorporate an economic empowerment component, especially in the context of resource-constrained setting, into adherence treatment to address the well documented structural economic factors constitutes a major gap. Within this context, there is a need for innovative interventions that promote sustainable behavior change among HIV + adolescents and create the supports necessary to sustain these changes. In the context of resource-poor countries like Uganda, interventions that improve families' economic capabilities are likely to be particularly consequential. The proposed study represents the first study that incorporates economic empowerment, using savings-led microbusinesses for economic stability, into the commonly used/standard adherence counseling practices in Uganda.

Trial status

The study began in July 2012. The first six months was a preparation period for obtaining IRB approval, mobilizing financial institutions and recruitment of clinics and adolescents. Data collection in 39 clinics and implementation of the intervention in 19 clinics began in January 2014. Participant recruitment ended in December 2015. Data is being cleaned and finalized for analysis. This trial was registered with ClinicalTrials.gov (registration number: NCT01790373) on 13 February 2013.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Ethics approval and consent to participate

This study received approval from Columbia University Institutional Review Board #AAAK3852, Makerere University School of Public Health Ethics Committee Protocol # 210 and Uganda National Council of Science and Technology SS 2969. Both children and caregivers provided written assent and consent respectively to participate in this study.

Consent for publication

All publications from this study will be shared in academic journals and conferences in accordance with IRB guidelines.

Availability of data and material

The dataset from the study is being finalized for analysis and is available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflicts of interest.

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Authors' contributions

FS conceptualized, received funding for the study, and led and supervised all aspects of study implementation, WB, PN, OSB and FS drafted and edited the manuscript. MM, CM, FM and GN serve as co-investigators, TN is a statistical consultant, and FN and MM supervised study implementation in the field. All authors reviewed the final draft of the manuscript for intellectual property.

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