HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

Contemp Clin Trials. 2023 April ; 127: 107123. doi:10.1016/j.cct.2023.107123.

Adapt for Adolescents: Protocol for a sequential multiple assignment randomized trial to improve retention and viral suppression among adolescents and young adults living with HIV in Kenya

Lisa L. Abuogi[1], **Jayne Lewis Kulzer**[2], **Eliud Akama**[3], **Thomas A. Odeny**[3,4], **Ingrid Eshun-Wilson**[4], **Maya Petersen**[5], **Starley B. Shade**[2], **Lina M. Montoya**[6], **Laura K. Beres**[7], **Sarah Iguna**[3], **Harriet F. Adhiambo**[3], **Joseph Osoro**[3], **Isaya Opondo**[3], **Norton Sang**[3], **Zachary Kwena**[3], **Elizabeth A. Bukusi**[3], **Elvin Geng**[4]

[1]Department of Pediatrics, University of Colorado, Denver, Aurora, CO, USA

[2]Department of Obstetrics, Gynecology, and Reproductive Sciences2, Institute for Global Health Science, University of California, San Francisco, CA, USA

[3]Center for Microbial Research, Kenya Medical Research Institute, Nairobi, Kenya

[4]School of Medicine, Washington University, St. Louis, MO

[5]Division of Biostatistics, School of Public Health, University of California, Berkeley

Corresponding Author: Lisa Abuogi, 13123 East 16th Avenue, Box 055, Aurora, CO 80045, Lisa.abuogi@cuanschutz.edu, 1-303-3585-61.

Author's contributions: LA, EA, and JLK drafted the manuscript. LA, EG, LMM, TAO, JLK, EA, SS, and MP conceptualized and designed the study and contributed to manuscript writing. SB, HA, EK, IEW, LB, SI, JO, IO, NS, ZK, and EAB have contributed to study design, implementation of study activities, and reviewed the manuscript. CO and EO made substantial contributions to study development and implementation and reviewed the manuscript. All authors read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests

Ethical approval: Ethical approval for this study has been obtained from all relevant Institutional Review Boards (IRBs). In the US, Washington University in St. Louis (IRB #202006141) is the single IRB of record and has reviewed and approved this study protocol, with the University of Colorado Denver and University of California San Francisco relying on Washington University in St. Louis. In Kenya, the protocol was reviewed by Kenya Medical Research Institute's (KEMRI) Scientific and Ethics Review Unit (SERU) (#3986). Protocol version 5.0 May 20, 2022. This is a low-risk study, with behavioral social interventions to enhance retention in HIV care using an adaptive approach, thus a formal Data Safety Monitoring Board is not required, and no formal stopping rules are planned.

Consent to participate: Eligible participants 18 years of age and older will undergo written informed consent. Caregiver consent and participant assent will be obtained for those less than 18 years of age and not emancipated (e.g., married or a parent).

Consent for publication: Not applicable

Availability of data and materials: The research will include data from approximately 880 adolescent and young adult (14–24 years of age) subjects enrolled in HIV care and treatment at clinics in Kisumu County, Kenya. The final dataset will include routine clinical data (visit history, health status, treatment initiation, pharmacy refills, and laboratory testing including viral load results) and self-reported demographic and behavioral data from surveys with the subjects. Upon completion of study analysis, the final dataset will be striped of identifiers prior to release for sharing

Code availability: Not applicable

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

[6]Department of Biostatistics, University of North Carolina at Chapel Hill

[7]Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

Abstract

Background: Adolescents and young adults living with HIV (AYAH) aged 14–24 years in Africa experience substantially higher rates of virological failure and HIV-related mortality than adults. We propose to utilize developmentally appropriate interventions with high potential for effectiveness, tailored by AYAH pre-implementation, in a sequential multiple assignment randomized trial (SMART) aimed at improving viral suppression for AYAH in Kenya.

Methods: Using a SMART design, we will randomize 880 AYAH in Kisumu, Kenya to either youth-centered education and counseling (standard of care) or electronic peer navigation in which a peer provides support, information, and counseling via phone and automated monthly text messages. Those with a lapse in engagement (defined as either a missed clinic visit by ≥ 14 days or HIV viral load ≥ 1000 copies/ml) will be randomized a second time to one of three higher-intensity reengagement interventions: (1) standard of care outreach and intensified counseling; (2) conditional cash transfers; and (3) in-person peer navigation. This study will evaluate which interventions and which dynamic sequence of interventions improve sustained viral suppression and HIV care engagement in AYAH at 24 months post-enrollment and assess the cost-effectiveness of successful strategies.

Discussion: The study utilizes promising interventions tailored to AYAH while optimizing resources by intensifying services only for those AYAH who need more support. Findings from this innovative study will offer evidence for public health programming to end the HIV epidemic as a public health threat for AYAH in Africa.

Trial registration: Clinicaltrials.gov NCT04432571, registered June 16, 2020.

Keywords

HIV; adolescents; youth; retention; viral suppression

INTRODUCTION

Despite the availability of highly efficacious antiretroviral therapy (ART) and global and local investment in HIV treatment programs, adolescents and young adults living with HIV (AYAH) aged 14–24 years are being left behind (1, 2). Population-based surveys show about three-quarters of AYA with HIV aged 15–24 years are virologically suppressed, compared to 90% of adults (3). Furthermore, AYAH are the only demographic groups in which HIV-related mortality continues to increase (4). AYAH treatment outcomes suffer in part because, compared to adults and younger children, AYAH face additional developmentally specific barriers to adherence and retention (5–8). With less control over resources, AYAH face greater structural barriers to care (e.g., lack of money for transportation) and unique clinic-based barriers such as lack of youth-friendly services. At the same time, AYAH face developmentally distinct psychosocial barriers such as desire for peer acceptance that exacerbates stigma and transition to adult care (9).

Scientific studies to identify interventions to engage AYAH, such as text messaging, peer support, and adolescent-friendly services, tend to examine single interventions for AYAH engagement with variable effectiveness (10–16). However, the diversity of barriers to AYAH engagement calls for innovative approaches. Any one intervention applied to all AYAH will be neither optimally efficient (not needed by all) nor optimally effective (not helpful to all who need help). Adaptive longitudinal strategies that tailor the intensity of interventions based on an individual response offer an alternative approach that resemble practice-based choices in service delivery, and therefore can advance the public health treatment response for AYAH.

In this study, we examine individual interventions and adaptive strategies using a sequential multiple assignment randomized trial (SMART) to address AYAH-specific barriers to HIV treatment success. Overall, we begin with initial preventive interventions which are low intensity and can be widely used for all to reduce lapses in care (17–19). We escalate to more intensive interventions among those who show evidence of missed visits or high viral load. This study design is intended to provide novel evidence for longitudinal clinical care that optimizes HIV care outcomes for AYAH.

METHODS

Study Design

This study will utilize a SMART design to compare adaptive strategies for engaging AYAH on treatment versus the standard of care, to prevent lapses in treatment (defined as either missed clinic visits or documented virological failure) and reengage those who have lapsed to achieve treatment success (viral suppression and care engagement) after two years. The SMART design represents an emerging, rigorous design for assessing adaptive strategies (18, 20). (Figure 1).

Our overall goal is to evaluate which individual interventions and dynamic sequence of combined interventions (e.g., strategies) improve sustained viral suppression and HIV care engagement in AYAH.

Specifically, the study aims to:

Aim 1: Assess the effectiveness of standard of care routine education and counseling (SOC-REC) versus standard of care plus electronic navigation (e-navigation) for preventing treatment lapses (defined as either virologic failure or missed appointments) for one year among AYAH in Kenya (Stage 1).

Aim 2: Assess the effectiveness of standard of care outreach and intensified counseling (SOC-OIC) versus 1) a conditional cash transfer; or 2) an in-person peer navigator to suppress AYAH six months after initial lapse, among AYAH who experience a lapse in the first year (Stage 2).

Aim 3: Assess the effectiveness and cost-effectiveness of six individualized strategies that begin with Stage 1 interventions (SOC-REC, e-navigation) and escalate based on participant response in Year 1 to Stage 2 interventions (SOC-OIC, conditional cash transfer, in-person

peer navigation) on viral suppression and engagement in care at the end of Year 2 of the study.

Setting

The study will be conducted at three public health facilities providing HIV care and treatment in Kisumu County, Kenya. Kisumu County is one of the highest HIV prevalence counties in Kenya (21). The clinics are in urban and peri-urban locations and were determined based on patient volume, availability of infrastructure, study logistics, and in consultation with facility management. Mobile phone access is high overall in Kenya and while not been systematically evaluated in youth, one report suggests 70% of urban youth have phone access (22). All clinics have youth-centered clinics and ART is provided free of charge. Viral load testing is available per Kenya national guidelines every 6 months (23). Elevated HIV RNA levels defined per national guidelines (initially ≥ 1000 copies/ml, updated in May 2022 to ≥ 200 copies/ml) trigger enhanced adherence counseling and a repeat test after three months of provider-determined good adherence (23, 24).

Participants

We will enroll AYAH on/initiating ART, 14–24 years of age, living >6 months in Kisumu County in previous year (to exclude temporary residents likely to migrate), have awareness of their HIV status or a caregiver who agrees to assisted disclosure, able to read or be read text messages, and willing to be contacted by clinic upon missed appointment. For those who share phones, disclosure of HIV status to the person sharing the phone will be required. Those without phone access will be automatically assigned to the standard of care in Stage 1, and then re-randomized per protocol for Stage 2.

Study Interventions

We describe all interventions using a modification of the framework by Proctor and colleagues (25), in which implementation strategies are described using the terms “actor” (who is carrying out the activity), “action” (describing the activities), “action dose” (describes when and how much), and “action target” (describes what the action is intended to change, Table 1). Combining Stage 1 and Stage 2, there are five possible sequenced strategies that we will compare versus the standard of care (Table 2 and Figure 2).

Study Procedures

Participatory Intervention Tailoring—To adapt and tailor the evidence-based interventions to optimize effectiveness in the study context prior to trial implementation, we conducted formative research including: 1) three Focus Group Discussions (FGDs) with 25 purposefully selected AYAH to identify key themes around AYA preferences, 2) a discrete choice experiment (DCE) to identify and quantify preferences for incentive distribution, and 3) a human-centered design (HCD) workshop to translate AYAH preferences into intervention activities. Formative study results contributed to intervention design decisions, for example, selection of acceptable wording for text messages, importance of including AYAH without phone access, amount and method of incentive delivery (Kenya Shilling 500 =~US $5), and training of peer navigators in how to address anticipated social support

needs.(26) Additionally, formative work, as well as experience delivering CCT for adults in Kenya, informed the incentive amount to ensure it is not coercive and limited the number of disbursements to reduce intentional lapses.

Randomization

The study will employ block randomization, generated by an independent statistician, stratified by participant age: 14–19 and 20–24 years of age. Study staff will receive treatment assignments in sequentially numbered sealed envelopes. Study staff and participants will not be blinded to study assignments, while the principal investigators and analyst will be. At Stage 1, participants without phone access will not be randomized but automatically placed in SOC-REC arm as delivery of electronic navigation will not be feasible. Participants with phones will be randomly assigned in a 1:1 ratio to one of the two initial arms (SOC-REC vs e-NAV). In Stage 2, those who have a lapse in care in the first year (missed visit of high viral load as defined above) will be re-randomized 1:1:1 to each of the three Stage 2 interventions (SOC-OIC, CCT, or IP-Nav). Those who meet the definition of lapse in care at enrollment will be immediately re-randomized to Stage 2 interventions. Participants with missed visits can be re-randomized "with contact" for those who return to clinic or are reachable by phone or "without contact" for those who are not reached. Those who do not have a lapse in Year 1 will continue in SOC-REC if they are already in SOC-REC or move to SOC-REC for those in e-NAV. (Figure 2)

Recruitment.—The study will approach potential AYAH/caregivers at routine clinic visits to conduct an eligibility screen and assess interest in study participation. Additionally, the study team will conduct targeted community-based recruitment for AYAH who have not attended a clinic visit for 90 days by tracing potential AYAH/caregivers at home and carrying out eligibility screening. If lapse in care is confirmed, and these AYAH enroll, they will qualify for immediate re-randomization to Stage 2 interventions.

Measures.—Patient measurements at baseline and follow up through two years are detailed in Table 3. The study measures allow for examination of response heterogeneity as well as enhance statistical efficiency (through secondary analyses to adjust for baseline and time-updated covariates). We will collect socio-demographic (e.g., age, sex) and clinical (e.g., date of enrollment, HIV and TB history, WHO stage, ART initiation date, pharmacy refill, visit dates, viral load, weight and height for BMI, pregnancy, and vital status) data captured routinely on MOH-issued clinical care forms. Data will be abstracted from medical charts.

In addition to routine clinical data, we will collect survey data from standardized and adapted surveys commonly used in sub-Saharan Africa at baseline, study lapse, 12- and 24-months post baseline. Surveys will capture additional socio-demographic information (e.g., household characteristics, school, income, sexual history/risk, health care access), food insecurity, general health (life events; social support; physical, emotional, and social well-being, health care utilization; clinical symptoms), ART adherence, depression, anxiety, alcohol and drug use, and trauma experiences. For intervention arm fidelity, we will capture session/delivery details including date, duration, if e-Nav or IP-Nav, session focus and

barrier progress and carry out in-depth interviews among a subset of patients in years 1–3 and conduct patient experience surveys at lapse, 12 and 24 months and in-depth interviews. Micro-costing data will be obtained through interviews with study and site staff, review of administrative records, and time and motion studies carried out with site-level staff at baseline and during Stage 1 and Stage 2 activities. For the primary outcome measures, visit adherence and viral load will be collected through routine clinical records and augmented with study viral load capture if there are gaps in routine viral load (e.g., reagent stock-out). For participants with missing viral loads and/or care status (e.g., on ART, out of care, lost to follow up etc.), an extended outcome ascertainment process will be used to determine study outcomes in Aims 2 and 3. The extended outcome process will include chart review and field tracing to further investigate, locate, and document viral load measurements and care status. In cases where viral load measures or care status continue to be outstanding, an adjudication process will be used to classify (viral load as unsuppressed, suppressed, or true missing, care status as lost to follow up, on ART) based on care and vital status identified during chart review and field tracing.

Statistical Analyses

The overall objective of the trial is to generate comparative effectiveness estimates for the six embedded adaptive strategies (including standard of care) on the primary outcome of sustained viral suppression and retention in care at 24 months after study enrollment (Aim 3), utilizing the SMART design. We will also conduct analyses of the two simple single time point randomized trials nested within the SMART (Aims 1 and 2) and carry out cost effectiveness analyses to parallel these aims.

The primary outcome for Aim 1 is engagement failure among AYA initially randomized in the trial (Stage 1). Aim 1 analysis will exclude participants without phone access. Engagement failure is defined as experiencing any of the following three events within the first year of follow-up: lapse in retention (defined as 14 days late for a scheduled visit) *or* viral failure (defined as a high viral load per national guidelines more than 3 months after ART initiation) *or* death (all causes). Primary analyses will use Targeted Maximum Likelihood Estimation (TMLE) to compare the risk of care engagement failure between arms, adjusting for baseline patient characteristics to improve precision (30). Secondary analyses will additionally adjust for informative censoring. Additional analyses will use a Kaplan Meier paired with a log rank test to compare time to first lapse between arms and examine alternative outcome definitions such as retention alone (mean visit adherence, visit constancy), medication possession ratio, and HIV RNA levels. Prespecified subgroup analyses (age 14–19 vs 20–24 years, sex, site, CD4 level) will be carried out to assess whether differences in the effect of adaptive strategies across these groups.

The primary outcome for Aim 2 will be viral suppression 6 months after rerandomization (Stage 2) among the subset of patients who lapse in Year 1 and will include all participants who are re-randomized. As in Aim 1, we will use TMLE to compare the proportion suppressed in the SOC-OIC, CCT and IP-Nav arms versus SOC-OIC arm, and secondary analyses will adjust for informative censoring. We will also explore secondary outcomes of time to return for the subset of patients with lapse due to missed visit during Stage 1 and

time to viral re-suppression for those who lapsed through an elevated viral load measured by end of Year 2. As with Aim 1, we will seek differential response by subgroups defined by age, sex, and CD4 level. In exploratory analysis we will treat the two components of the composite endpoint (failure to make visits, and high viral loads) as separate endpoints.

The primary outcome for Aim 3 is the primary outcome for the trial, the indicator of sustained viral suppression and engagement in care measured at the end of Year 2 of the study, under each of six strategies. Treatment success at the end of the trial is defined as viral load <200 copies/ml at 24 months (end of Year 2). Viral loads that are obtained within +/− 3 months of the 24-month end point will be included. We will also classify missing viral loads through a process of adjudication as described above. Sustained engagement in care will be defined as attending clinic visit within 14 days of scheduled visit at 24 months. Deaths will be classified as viral load failures and visit failures. Visits that are scheduled within +/− 3 months of the 24-month end point will be included. The primary analysis will be intention to treat and use longitudinal TMLE to estimate the probability of treatment success in each of the adaptive intervention strategies compared to the reference strategy (standard of care) (27, 28). In these analyses, a given person will contribute to the estimates of outcomes under each strategy-specific outcomes with which his or her treatment is compatible. For example, a participant who was initially randomized to e-Nav and did not experience an engagement failure would contribute data to the estimates of the outcome under three adaptive strategies (e.g., e-Nav plus SOC-OIC, e-Nav plus CCT, or e-Nav plus IP-Nav). Because Stage 2 intervention is randomized conditional on Stage 1 care engagement, use of Stage 1 engagement as the single time-dependent adjustment variable is sufficient to allow for unbiased estimation of these strategy-specific effects. However, further adjustment for patient characteristics at both baseline and at time of re-randomization/end of year 1 follow up will be used to potentially improve the precision of effect estimates (as well as, in secondary analysis, to adjust for potentially informative missing outcomes). Ensemble approaches to optimal dynamic regime estimation will be used to investigate the benefits of further tailoring adaptive intervention assignment based on baseline and time-varying patient characteristics (29, 30). For all analyses including viral load measures a sensitivity analysis will be conducted with and without adjudicated (extended outcome) viral load measures.

Overview cost-effectiveness analysis: We will compute unit cost for each intervention activity and use information on exposure to activities for each participant to compute intervention cost per participant for each intervention strategy. We will quantify *net costs* for each intervention strategy – i.e., intervention costs adjusted for added or averted patient and health care costs. Longer-term health care costs will be projected using clinical simulation modeling, based on observed changes in health status, combined with estimates from published studies. Population-level health will be quantified using directly measured health-related study outcomes (retention and viral suppression) and also using *disability-adjusted life years (DALYs)* which includes years of life gained and the collective disability effects of living with HIV. We use Markov modeling to estimate DALYs gained for the short term (during the trial) and the long-term (5, 10, and 20 years) using data from the trial, our own ongoing studies and published estimates of future retention in care, viral suppression, as well as morbidity and mortality attributed to un- or partially-treated HIV

disease. We will calculate efficiency and incremental cost-effectiveness for each intervention strategy as net cost per additional person retained, viral suppression achieved and per DALY gained. We will compute *incremental cost-effectiveness ratios (ICERs)* across intervention strategies to establish the relative cost-effectiveness of each intervention strategy. We plan robust univariable and multivariable sensitivity analyses to estimate the variability in costs, outcome, and cost-effectiveness as observed in the trial and within specified scale-up scenarios.

Sample Size

In Stage 1 of this SMART, we anticipate that 72% of 880 participants enrolled in the study will have a phone, and thus will be initialized randomized to either (1) SOC-REC or (2) E-Nav (approximately N = 634). Based on local program data, we anticipate approximately 5% attrition (including death, withdrawal, and transfer) by the end of Stage 1 of the study leaving a total of 836 evaluable patients for Stage 2. If 40% of patients in Stage 1 who are randomized to SOC and 25% who are randomized to E-Nav reach the failure endpoint, then approximately 300 patients will fail Stage 1 interventions and be re-randomized 1:1:1 to one of three Stage 2 interventions: (1) SOC-OIC, (2) CCT for re-establishment of care and re-suppression or (3) IP-Nav. (Figure 3) Sample size and power calculations for the primary outcome (Aim 3) were based on applying the *ltmle* R package to a multiple iterations of a simulated dataset (27) using a minimally sufficient adjustment set given the known treatment mechanism in the SMART design. The total sample size of 880 is based on estimates of the degree of precision we anticipate in our primary outcome if a given strategy were applied to the whole population. Simulation assumptions were based on proportion estimates of sustained viral suppression and engagement in care at 2 years under each prevention and treatment combination using preliminary data from study sites. We expect that 28% of patients enrolled will not have a phone at enrollment and deterministically be given SOC as their initial treatment. In addition, participants who were allocated to standard of care (followed with standard of care outreach upon initial lapse if any) will have a probability of sustained viral suppression and engagement in care of 45% at two years follow up, and a conservative estimate of 8% 2-year censorship annually due to transfer out or study withdrawal. Based on simulations, we anticipate that our estimate of the proportion virally suppressed and engaged in care 1 year after rerandomization among failures and 2 years after study enrolment for those who do not fail will fall within 2.5 percentage points of the truth with 95% confidence (i.e., the absolute difference between our estimate and the truth was less than 5% in 95% of iterations of the simulated experiment). This level of precision provides a strong basis for decision-making.

In addition, we will test the null hypotheses of no difference in proportion of sustained viral suppression and engagement in care between subjects followed with standard of care (including SOC-OIC upon initial lapse if any) and all 5 active adaptive strategies. We expect that subjects followed with standard of care throughout will have probability of 72% of sustained viral suppression and engagement at 2 years. Using 2-sided hypothesis tests, we anticipate approximately ≥80% power to detect the absolute difference ranging from 12 to 19% in probability of sustained viral suppression and engagement in care at 2 years in each of the navigator-based arms compared to SOC throughout. The absolute difference

will range from estimated 8–18% in CCT-based strategies compared to SOC strategy. Longitudinal TMLE that adjusts for covariates predictive of the outcome is expected to improve precision and power further.

Discussion

The Adapt for Adolescents (A4A) study seeks to advance the science of retention by contributing to a new class of evidence for clinical and public health practice. While research has identified a number of promising mHealth, peer support and incentive-based interventions to improve retention, none of these interventions alone have achieved global goals for HIV treatment success in AYAH (31–33). One avenue for scientific progress is to examine, with greater sophistication, the optimal sequence of individual interventions over time to achieve the best patient outcomes. To date, the vast majority of trials for engagement in HIV treatment randomize all patients in an arm to a single, fixed intervention (10–15, 34). A single trial of one or more interventions yields insights not immediately obvious from separate individual trials because intervention effects may depend on their deployment in a sequence and a representative population of those who have lapsed are difficult to recruit. Further, the fact that a given individual can contribute information about outcomes under more than one potential sequence enhances efficiency. Using a sequentially randomized study design, findings from this study will quantify the relative effectiveness and cost effectiveness of adaptive approaches aimed at improving HIV care engagement and viral suppression among AYAH. Such research on how to deploy behavioral tools mimics clinical practice in which providers work with patients over time and try different approaches, and thus this study may help advance implementation of supportive interventions of AYAH.

While the distinctive needs and disparate outcomes of AYAH have been increasingly recognized, effective approaches have been elusive (32). Youth-centered models of care such as designated “youth” days, youth-specific facilities, and youth-friendly have been found to be beneficial but not consistently effective in improving AYAH outcomes including retention in care and viral suppression (35–37). Cluver and colleagues identified several clinic-level factors associated with improved retention for AYAH in South Africa in a dose-response manner, including devoting sufficient time to adolescents and adolescent-friendly attitudes among health care workers (38). However, even when all factors were present, retention only reached 70% after 1–2 years. The A4A study will therefore test individual-level interventions that can be delivered in the context of facility-level youth-centered care approaches to further optimize engagement and viral outcomes among AYAH.

While we have developed a rigorous study approach responsive to the unique needs of AYAH with HIV, we recognize that several factors may impact our ability to conduct this study in Kenya. If fewer AYAH experience initial treatment lapses for example, we may be underpowered to evaluate our Stage 2 interventions. However, we have chosen conservative estimates based on real data from the clinics we will study. Another challenge may arise if we are unable to determine viral and care engagement outcomes for a large number of participants. Our group has extensive experience ascertaining vital status and care status in Africa (39, 40). Using a protocol of team-based intensive tracing of lost patients in the community, we have ascertained outcomes in over 90% of over 3,500 patients lost

to follow-up in 14 clinic sites in Uganda, Kenya and Tanzania which we will apply to this study to ensure sufficient outcome data are obtained. Further, we have pioneered an approach to adjudicating missing viral loads in adults on ART in Kenya. Some participants may be dissatisfied with their randomization arms and could theoretically "fail" on purpose in order to be re-randomized to a stage 2 intervention such as CCT. However, we believe have intentionally selected a modest cash incentive with stakeholder input to avoid this concern and inform all participants of the randomization process during informed consent procedures. Finally, we will limit follow up time to 1 year in Stage 1 and through 2 years in Stage 2. It is possible interventions will be effective in the longer term beyond these timepoints that will not be measured.

In conclusion, this study will contribute to ongoing efforts to improve the care and HIV outcomes of AYAH and provide valuable findings that can be applied in other similar settings in order to end the AIDS epidemic in youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors thank the study and facility staff, Director KEMRI, and HIV implementing partner the Center for International Health, Education and Biosecurity (CIHEB), University of Maryland for their support of this research.

Funding:

National Institute or Nursing Research, National Institutes of Health R01NR018801

References

1. Slogrove AL, Mahy M, Armstrong A, Davies MA. Living and dying to be counted: What we know about the epidemiology of the global adolescent HIV epidemic. J Int AIDS Soc 2017;20(Suppl 3):21520. [PubMed: 28530036]
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). In Danger: UNAIDS Global AIDS Update 2022. In: UNAIDS, editor. Geneva, Switzerland 2022.
3. Petersen M, Balzer L, Kwarsiima D, Sang N, Chamie G, Ayieko J, et al. Association of Implementation of a Universal Testing and Treatment Intervention With HIV Diagnosis, Receipt of Antiretroviral Therapy, and Viral Suppression in East Africa. JAMA : the journal of the American Medical Association 2017;317(21):2196–206. [PubMed: 28586888]
4. Ryscavage PA, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. JAIDS Journal of Acquired Immune Deficiency Syndromes 2011;58(2):193–7. [PubMed: 21826014]
5. Wong VJ, Murray KR, Phelps BR, Vermund SH, McCarraher DR. Adolescents, young people, and the 90–90-90 goals: a call to improve HIV testing and linkage to treatment. AIDS 2017;31 Suppl 3:S191–S4. [PubMed: 28665876]
6. Enane LA, Davies MA, Leroy V, Edmonds A, Apondi E, Adedimeji A, et al. Traversing the cascade: urgent research priorities for implementing the 'treat all' strategy for children and adolescents living with HIV in sub-Saharan Africa. J Virus Erad 2018;4(Suppl 2):40–6. [PubMed: 30515313]
7. Enane LA, Vreeman RC, Foster C. Retention and adherence: global challenges for the long-term care of adolescents and young adults living with HIV. Curr Opin HIV AIDS 2018;13(3):212–9. [PubMed: 29570471]

8. McHugh G, Simms V, Dauya E, Bandason T, Chonzi P, Metaxa D, et al. Clinical outcomes in children and adolescents initiating antiretroviral therapy in decentralized healthcare settings in Zimbabwe. J Int AIDS Soc 2017;20(1):21843. [PubMed: 28872269]
9. Ammon N, Mason S, Corkery J. Factors impacting antiretroviral therapy adherence among human immunodeficiency virus–positive adolescents in Sub-Saharan Africa: a systematic review. Public health 2018;157:20–31. [PubMed: 29501984]
10. Chung MH, Richardson BA, Tapia K, Benki-Nugent S, Kiarie JN, Simoni JM, et al. A randomized controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes. PLoS Med 2011;8(3):e1000422. [PubMed: 21390262]
11. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS. 2011;25(6):825–34. [PubMed: 21252632]
12. Baird S, Chirwa E, McIntosh C, Özler B. The short-term impacts of a schooling conditional cash transfer program on the sexual behavior of young women. Health economics 2010;19(S1):55–68. [PubMed: 19946887]
13. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 2010;376(9755):1838–45. [PubMed: 21071074]
14. Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, et al. Improving clinic attendance and adherence to antiretroviral therapy through a treatment supporter intervention in Uganda: a randomized controlled trial. AIDS Behav 2011;15(8):1795–802. [PubMed: 21424272]
15. Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M, et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. Aids 2010;24(9):1273–80. [PubMed: 20453627]
16. Goldstein M, Archary M, Adong J, Haberer JE, Kuhns LM, Kurth A, et al. Systematic Review of mHealth Interventions for Adolescent and Young Adult HIV Prevention and the Adolescent HIV Continuum of Care in Low to Middle Income Countries. AIDS Behav 2022:1–22.
17. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A “SMART” design for building individualized treatment sequences. Annu Rev Clin Psychol 2012;8:21–48. [PubMed: 22224838]
18. Murphy SA. An experimental design for the development of adaptive treatment strategies. Stat Med 2005;24(10):1455–81. [PubMed: 15586395]
19. Murphy SA, Collins LM. Customizing treatment to the patient: Adaptive treatment strategies. Drug Alcohol Depend 2007;88(Suppl 2):S1.
20. Murphy SA, Lynch KG, Oslin D, McKay JR, TenHave T. Developing adaptive treatment strategies in substance abuse research. Drug Alcohol Depend 2007;88 Suppl 2:S24–30. [PubMed: 17056207]
21. Kenya Ministry of Health. Kenya HIV Estimates 2018 Report In: National AIDS Control Council, editor. Nairobi, Kenya 2019.
22. Kharono B, Kaggiah A, Mugo C, Seeh D, Guthrie BL, Moreno M, et al. Mobile technology access and use among youth in Nairobi, Kenya: implications for mobile health intervention design. Mhealth 2022;8:7. [PubMed: 35178438]
23. Kenya Ministry of Health. Guidelines on Use of Antiretorivrals for Treating and Preventing HIV in Kenya In: National AIDS and STI Control Program, editor. Nairobi, Kenya: Kenya Ministry of Health; 2018.
24. National AIDS and STI Control Program. Kenya HIV Prevention and Treatment Guidelines, 2022 Nairobi,Kenya 2022.
25. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implementation Science 2013;8(1):139. [PubMed: 24289295]
26. Eshun-Wilson I, Akama E, Adhiambo F, Kwena Z, Oketch B, Obatsa S, et al. Adolescent and young adult preferences for financial incentives to support adherence to antiretroviral therapy in Kenya: a mixed methods study. Journal of the International AIDS Society 2022;25(9):e25979. [PubMed: 36109803]

27. Schwab J, Lendle S, Petersen M, van der Laan M, Gruber J Targeted Maximum Likelihood Estimation (TMLE) of treatment/censoring specific mean outcome or marginal structural model for point-treatment and longitudinal data 2020.
28. Montoya LM, Kosorok MR, Geng EH, Schwab J, Odeny TA, Petersen ML. Efficient and robust approaches for analysis of sequential multiple assignment randomized trials: Illustration using the ADAPT-R trial. Biometrics 2022.
29. Luedtke AR, van der Laan MJ. Statistical Inference for the Mean Outcome under a Possibly Non-Unique Optimal Treatment Strategy. Ann Stat 2016;44(2):713–42. [PubMed: 30662101]
30. Montoya LM, van der Laan MJ, Luedtke AR, Skeem JL, Coyle JR, Petersen ML. The optimal dynamic treatment rule superlearner: considerations, performance, and application to criminal justice interventions. Int J Biostat 2022.
31. Murray KR, Dulli LS, Ridgeway K, Dal Santo L, Darrow de Mora D, Olsen P, et al. Improving retention in HIV care among adolescents and adults in low- and middle-income countries: A systematic review of the literature. PLoS One 2017;12(9):e0184879. [PubMed: 28961253]
32. Okonji EF, Mukumbang FC, Orth Z, Vickerman-Delport SA, Van Wyk B. Psychosocial support interventions for improved adherence and retention in ART care for young people living with HIV (10–24 years): a scoping review. BMC Public Health 2020;20(1):1841. [PubMed: 33261566]
33. Ridgeway K, Dulli LS, Murray KR, Silverstein H, Dal Santo L, Olsen P, et al. Interventions to improve antiretroviral therapy adherence among adolescents in low- and middle-income countries: A systematic review of the literature. PLoS One 2018;13(1):e0189770. [PubMed: 29293523]
34. Aad G, Abbott B, Abdallah J, Abdel Khalek S, Abdinov O, Aben R, et al. Two-particle Bose-Einstein correlations in pp collisions at [Formula: see text] 0.9 and 7 TeV measured with the ATLAS detector. Eur Phys J C Part Fields 2015;75(10):466. [PubMed: 26457062]
35. Ojwang VO, Penner J, Blat C, Agot K, Bukusi EA, Cohen CR. Loss to follow-up among youth accessing outpatient HIV care and treatment services in Kisumu, Kenya. AIDS Care 2016;28(4):500–7. [PubMed: 26565428]
36. Reif LK, Bertrand R, Benedict C, Lamb MR, Rouzier V, Verdier R, et al. Impact of a youth-friendly HIV clinic: 10 years of adolescent outcomes in Port-au-Prince, Haiti. J Int AIDS Soc 2016;19(1):20859. [PubMed: 27389256]
37. Teasdale CA, Alwar T, Chege D, Fayorsey R, Hawken MP, Abrams EJ. Impact of Youth and Adolescent Friendly Services on Retention of 10–24-Year-Olds in HIV Care and Treatment Programs in Nyanza, Kenya. J Acquir Immune Defic Syndr 2016;71(2):e56–9.
38. Cluver L, Pantelic M, Toska E, Orkin M, Casale M, Bungane N, et al. STACKing the odds for adolescent survival: health service factors associated with full retention in care and adherence amongst adolescents living with HIV in South Africa. J Int AIDS Soc 2018;21(9):e25176. [PubMed: 30240121]
39. Chamie G, Kwarisiima D, Clark TD, Kabami J, Jain V, Geng E, et al. Leveraging Rapid Community-Based HIV Testing Campaigns for Non-Communicable Diseases in Rural Uganda. PLoS One 2012;7(8):e43400. [PubMed: 22916256]
40. Jain V, Liegler T, Kabami J, Chamie G, Clark TD, Black D, et al. Assessment of Population-Based HIV RNA Levels in a Rural East African Setting Using a Fingerprick-Based Blood Collection Method. Clinical infectious diseases 2013;56(4):598–605. [PubMed: 23243180]

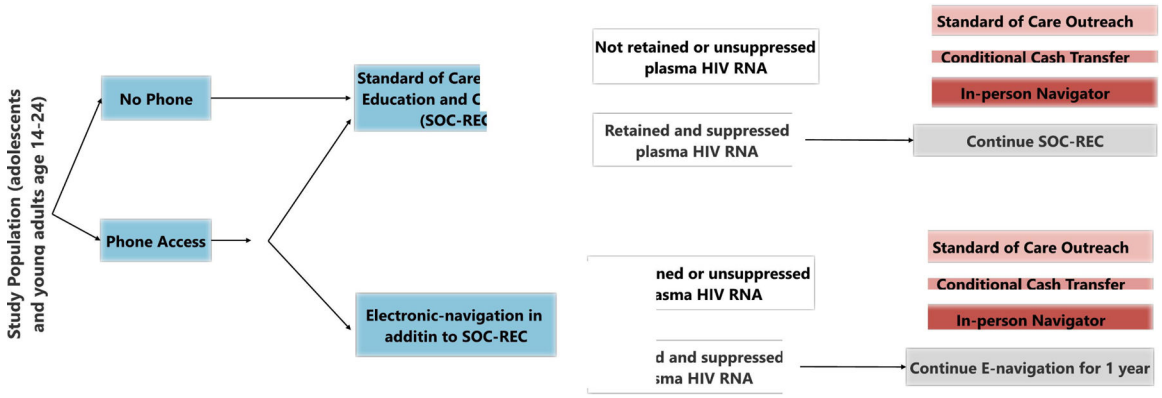

Figure 1.
Adapt for Adolescents study design Study aims

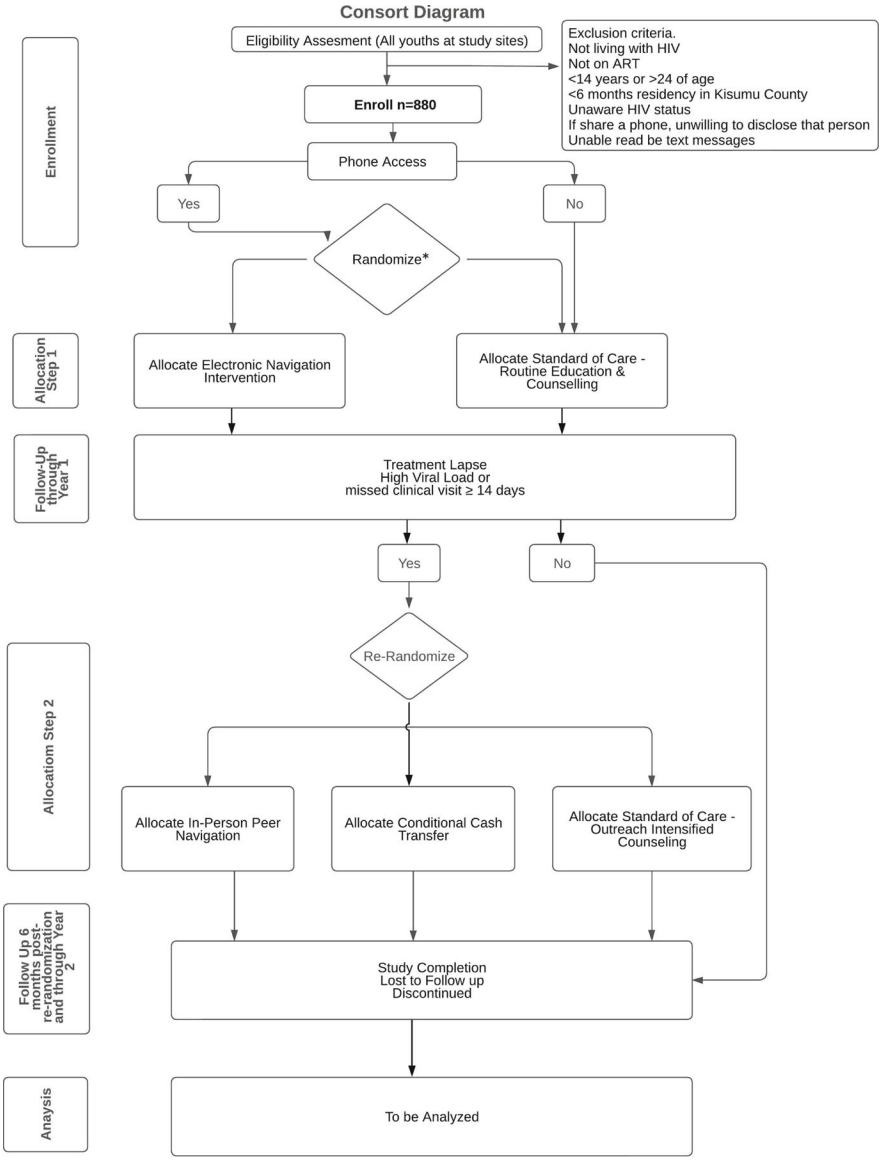

Figure 2.

Adapt for Adolescents flow diagram

*Participants who meet criteria for re-randomization at enrollment will be immediately re-randomized to Stage 2.

		STUDY PERIOD						
		Enrolment	Allocation		Post-allocation			Close -out
Description	Timepoint		Initial / baseline	*Lapse*	*6 m post-lapse*	*12 m post-baseline*	*12 m post-lapse*	*24 m post-baseline*
ENROLMENT								
	Eligibility screen	X						
	Informed consent/assent*	X						
	Random allocation		X[Stage 1]	X[Stage 2]				
INTERVENTIONS								
Stage 1	*SOC-REC – No Phone*	X				X		X
Stage 1	*Stage 1: SOC-REC*		X			X		
Stage 1	*Stage 1: E-Nav*		X			X		
Stage 2	*Stage 2: SOC-OIC*			X	X		X	X
Stage 2	*Stage 2: IP-Nav*			X	X		X	X
Stage 2	*Stage 3: CCT*			X	X		X	X
ASSESSMENTS								
BASELINE AND FOLLOW UP VARIABLES								
Demographics HIV history ART history TB history Pregnancy Visit attendance Refill attendance	*Clinical*	X		X	X	X		X
	Hospitalization	X		X	X	X		X
	Pregnancy	X		X	X	X		X
	Vital status	X		X	X	X		X
Demographics School attendance Household info Household SES Sexual history Healthcare access	*Socio Demographic*	X		X	X	X		X
Food access	*Food Insecurity*	X		X	X	X		X
General health		X		X	X	X		X

	General Health Assessment for Children (GHAC)						
Knowledge Preparedness Impact on life ART access ART adherence Mental well being COVID-19 status	*Coronavirus disease 2019 (COVID-19)*	X		X	X	X		X
Adherence	*Comprehensive ART Adherence Measurement for Pediatrics (CAMP)*	X		X	X	X		X
Depression	*Patient Health Questionnaire (PHQ-9)*	X		X	X	X		X
Anxiety	*General Anxiety Disorder (GAD)*	X		X	X	X		X
Alcohol use Drug use	*Alcohol Use Disorders Identification Test (AUDIT-10)*	X		X	X	X		X
Trauma	*Adverse Childhood Experience (ACES-IQ)*	X		X	X	X		X
Reasons for lost to follow up/ missed visits/viral failure	*HIV care barriers*	X		X				
E-Nav	*Intervention feedback – stage 1*			X		X		X
IP-Nav CCT	*Intervention feedback –stage 2*				X		X	X
	Costing	X				X		X
PRIMARY OUTCOME VARIABLES								
	HIV viral load	X		X	X	X		X
Clinic/refills	*Visit adherence*	X		X	X	X	X	X

Fig. 3.

An adaptive strategy for preventing and treating lapses of retention in HIV care for adolescents study measures and timepoints.

Table 1.

Intervention description using a modification of the Proctor framework(25)

	Intervention/ Mechanisms	Actor	Action	Action Dose	Action Target
Stage 1 interventions	**Standard of Care Routine Education and Counseling (SOC-REC)**	Facility staff including clinical officers, nurses, and peer educators trained in HIV and adolescent-friendly care.	Education and counseling about the importance of visit and medication adherence per the Kenyan National guidelines.	All AYAH receive 3 standard sessions of adherence counseling. "Booster" counseling is done at the discretion of facility staff. Phone and text reminders for visits and tracing for missed visits.	May increase HIV-related knowledge and motivation to adhere to medications and clinic visits.
	Electronic peer navigation (e-NAV)	Trained peer e-navigators (research staff) will provide support through mhealth modalities.	E-navigators will conduct an initial face-to-face introduction at the time of enrollment. Subsequently e-NAV will use phone calls or send messages at the participant's preferred time and mobile platform of choice (e.g., What's App, Snapchat) with a goal of creating a personal relationship to inform, influence and motivate patients.	Over the first two months, the e-NAV will make a minimum of bi-weekly calls followed by monthly calls. Communication can be more frequent if desired by patient. Face-to-face interactions are only allowed at the clinic. e-NAV contact will continue until either a patient misses a visit by > 14 days, has viremia > 1000 copies/ml or death for maximum of one year	Addresses AYAH barriers by reducing demotivation due to misinformation, depression and stigma and facilitating problem solving by providing (1) knowledge and positive social norms to counteract negative self-perceptions and stigma, (2) a therapeutic alliance to counter isolation and loneliness and (3) "expert patient" to address practical problem solving on clinic navigation.
Stage 2 interventions	**Standard of care outreach and intensified counseling (SOC-OIC)**	Facility-based clinical and lay staff	Per Kenyan guidelines, patients with missed visits and high viral loads are actively contacted by clinic staff and engaged in intensified adherence counseling.	At least one session of intensified counseling is provided and then as needed at the discretion of the facility staff.	May increase HIV-related knowledge and motivation to adhere to medications and clinic visits
	Conditional cash transfer (CCT) for re-engagement	Facility-based research staff will disburse cash.	The CCT will be dispensed in a private office and AYAH may choose to receive money in cash or mobile electronic cash transfer.	Cash or mobile money disbursed to patients upon presentation on the date of scheduled visits and separate disbursement for a suppressed viral load.	CCT's are anticipated to facilitate AYA capability to pay for transportation and provide motivation to seek care by counteracting prioritization of more immediate needs.
	In-person navigation (IP-NAV) for re-engagement	Trained peer navigators (research staff) will provide in person support.	The IP-Nav will act through in person interactions with patients, case management, and offering education and psychosocial support.	The IP-Nav will conduct an initial visit at home and then a minimum of monthly follow-up visits at location of preference, with more encounters as needed (maximum weekly).	IP-Nav will develop and leverage a longitudinal relationship with the patient and seek to influence motivation, capability, and opportunities to engage in care.

Table 2.

Adapt for Adolescents Study Interventions and Sequenced Strategies

Sequenced Strategies	Stage 1 Intervention	Possible Response	Stage 2 Intervention
Reference Strategy			
1.	Standard of Care- routine education and counseling	Succeed Fail	Standard of Care- routine education and counseling Standard of Care- Outreach and Intensified Counseling
Intervention Strategies			
2.	Standard of Care- routine education and counseling	Succeed Fail	Continue Standard of Care- routine education and counseling Conditional Cash Transfer
3.	Standard of Care- routine education and counseling	Succeed Fail	Continue Standard of Care- routine education and counseling In-person Navigation
4.	Electronic navigation	Succeed Fail	Standard of Care- routine education and counseling Standard of Care- Outreach and Intensified Counseling
5.	Electronic navigation	Succeed Fail	Standard of Care- routine education and counseling Conditional Cash Transfer
6.	Electronic navigation	Succeed Fail	Standard of Care- routine education and counseling In-person Navigation

Table 3:

Adapt for Adolescents (A4A) Study Interventions and Assessments by Time Period

		STUDY PERIOD						
		Enrolment	**Allocation**	**Post-allocation**				**Close-out**
Description	**Timepoint**		**Initial / baseline**	***Lapse***	***6 m post-lapse***	***12 m post-baseline***	***12 m post-lapse***	***24 m post-baseline***
ENROLMENT								
	Eligibility screen	X						
	Informed consent/ assent *	X						
	Random allocation		X^{Stage1}	X_2^{Stage}				
INTERVENTIONS								
Stage 1	*SOC-REC – No Phone*	X				X		X
Stage 1	*Stage 1: SOC-REC*		X			X		
Stage 1	*Stage 1: E-Nav*		X			X		
Stage 2	*Stage 2: SOC-OIC*			X	X		X	X
Stage 2	*Stage 2: IP-Nav*			X	X		X	X
Stage 2	*Stage 3: CCT*			X	X		X	X
ASSESSMENTS								
BASELINE AND FOLLOW UP VARIABLES								
Demographics HIV history ART history TB history Pregnancy Visit attendance Refill attendance	*Clinical*	X		X	X	X		X
	Hospitalization	X		X	X	X		X
	Pregnancy	X		X	X	X		X
	Vital status	X		X	X	X		X
Demographics School attendance Household info Household SES Sexual history Healthcare access	*Socio Demographic*	X		X	X	X		X
Food access	*Food Insecurity*	X		X	X	X		X
General health	*General Health Assessment for Children (GHAC)*	X		X	X	X		X
Knowledge Preparedness Impact on life ART access ART adherence Mental well being COVID-19 status	*Coronavirus disease 2019 (COVID-19)*	X		X	X	X		X
Adherence	*Comprehensive ART Adherence Measurement for Pediatrics (CAMP)*	X		X	X	X		X

		STUDY PERIOD						
		Enrolment	Allocation	Post-allocation				Close-out
Description	**Timepoint**		**Initial / baseline**	***Lapse***	***6 m post-lapse***	***12 m post-baseline***	***12 m post-lapse***	***24 m post-baseline***
Depression	*Patient Health Questionnaire (PHQ-9)*	X		X	X	X		X
Anxiety	*General Anxiety Disorder (GAD)*	X		X	X	X		X
Alcohol use Drug use	*Alcohol Use Disorders Identification Test (AUDIT-10)*	X		X	X	X		X
Trauma	*Adverse Childhood Experience (ACES-IQ)*	X		X	X	X		X
Reasons for lost to follow up/ missed visits/viral failure	*HIV care barriers*	X		X				
E-Nav	*Intervention feedback – stage 1*			X		X		X
IP-Nav CCT	*Intervention feedback – stage 2*				X		X	X
	Costing	X				X		X
PRIMARY OUTCOME VARIABLES								
Clinic/refills	*HIV viral load*	X		X	X	X		X
	Visit adherence	X		X	X	X	X	X

*Assent obtained ages 14–17 years;

m- month, SOC-REC- standard of care-routine education and counseling, E-nav- electronic navigation, SOC-OIC- standard of care- outreach and intensified counseling, IP-Nav- in-person navigation, CCT- conditional cash transfer, HIV- human immunodeficiency virus, ART-antiretroviral treatment, TB- tuberculosis, SES- socioeconomic status