Data-informed Stepped Care (DiSC) to Improve Adolescent HIV Outcomes (UH3):

A cluster randomized trial on a Data Informed Stepped Care intervention to improve retention among adolescents living with HIV

Protocol Number: STUDY00011096

National Clinical Trial (NCT) Identified Number: NCT05007717
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Sponsor: National Institutes of Health

Grant Title: Data-informed Stepped Care (DiSC) to Improve Adolescent HIV Outcomes

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Section 5.5	Change frequency of Caregiver Surveys from every 6 months to every 12 months	This data does not need to be collected as frequently; there was an instance of this language that was not corrected previously on pg. 26
Section 10.6.1	Reduce frequency of DSMB meetings	The frequency of DSMB meetings has been incorrectly stated as being semiannual; however, these meetings have occurred annually (in line with standards of NIH and the study's DSMB members)

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

Data-informed Stepped Care (DiSC) to Improve Adolescent HIV Outcomes (UH3): A cluster randomized trial on a Data Informed Stepped Care intervention to improve retention among adolescents living with HIV

Grant Number:

UH3 HD096906

Study Description:

The goal of this study is to develop, pilot and test a Data informed Stepped Care (DiSC) Intervention in a cluster randomized controlled trial (cRCT). The intervention is comprised of a system to assign adolescents living with HIV (ALHIV) to different levels of care, depending on their current and anticipated health care needs.

Objectives*:

Primary objective

Aim 1: To develop, adapt, pilot, and optimize implementation of a data-informed stepped care (DiSC) intervention for ALHIV HIV treatment management.

Aim 2: To evaluate effectiveness of the DiSC intervention on ALHIV retention in up to 24 high-volume HIV clinics in Homabay, Kisumu and Migori counties in Western Kenya.

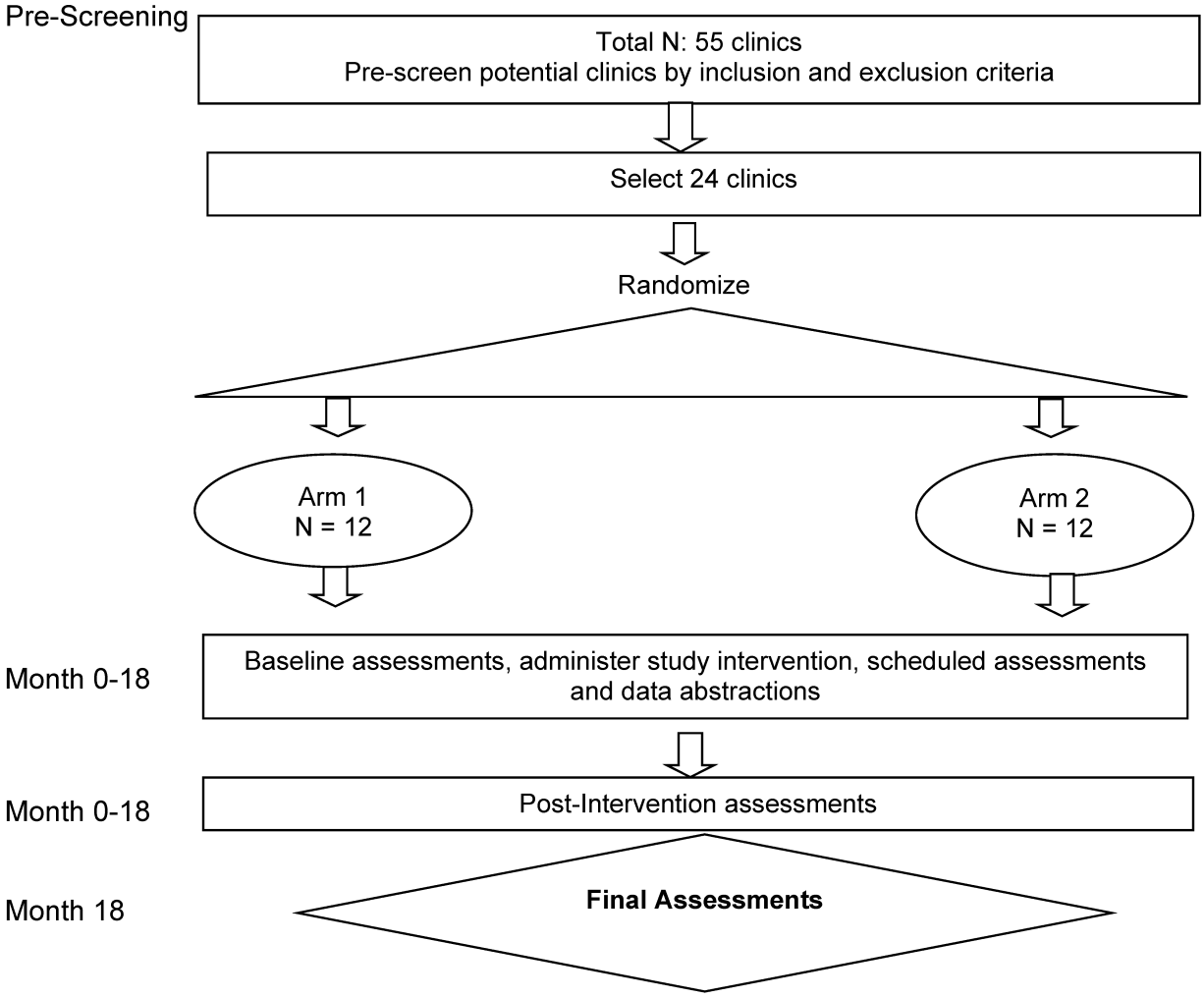
Secondary objectives

Aim 1: To determine acceptability, feasibility, adaptability and fidelity of the DiSC intervention

Aim 2: To evaluate the effectiveness of the DiSC intervention on ALHIV cascade outcomes (adherence, viral suppression) and adolescent self-efficacy, health service outcomes, implementation outcomes in high volume HIV clinics in Homabay, Kisumu and Migori counties.

Endpoints*:	**Primary Endpoint**:% retained at 6 and 12 months **Secondary Endpoints**:% virally suppressed at 6 and 12 months after ART initiation, proportion with >80% adherence since last refill, % retained at 18 and 24 months, adolescent self-efficacy and correlates of retention and viral suppression. **Secondary implementation outcomes**: intervention reach, adoption, fidelity, acceptability, feasibility, implementation and maintenance.
Study Population:	Up to 40 Health care workers (HCW), youth, policy makers and stakeholders in adolescent HIV care (aim 1 intervention development), HCW in 2 clinics in Kenya (aim 1 pilot) 6000medical records of adolescents and young adults ages 10-24 years enrolled in HIV care, and HCW in participating facilities, Approximately 3000 HIV positive adolescents and young adults,900 caregivers of HIV positive adolescents and young adults and a 200 HCWs. (Aim 2).
Phase* or Stage:	*Phase III Clinical Trial*
Description of Sites/Facilities Enrolling Participants:	Aim 1: 2 HIV clinics in Homa-bay, Migori or Kisumu. Aim 2: up to 24 HIV clinics in Homa-bay, Migori or Kisumu.
Description of Study Intervention/Experimental Manipulation:	Data-informed Stepped Care (DiSC) intervention is comprised of a system to assign ALHIV to different levels of care depending on their current and anticipated health care needs. The intervention will be delivered at the individual level by HCW providing routine care during routine HIV clinic visits.
Study Duration*:	24 months
Participant Duration:	24 months

1.2 SCHEMA


Pre-Screening
Total N: 55 clinics
Pre-screen potential clinics by inclusion and exclusion criteria
Select 24 clinics
Randomize
Arm 1
N = 12
Arm 2
N = 12
Month 0-18
Baseline assessments, administer study intervention, scheduled assessments and data abstractions
Month 0-18
Post-Intervention assessments
Month 18
Final Assessments

1.3 SCHEDULE OF ACTIVITIES

	Outcome assessed	Pre-screening (Pre-consent)	Enrollment	Enrollment Month 0±2	Month 6 Month 6±2	Month 12 Month 12±2	Unscheduled Visits
Clinic Eligibility		X					
Aim 2							
EMR data abstractions	Retention, viral non suppression		X	X	X	X	
Informed Consent (surveys)	NA		X				
Caregiver/adolescent surveys	Secondary outcomes		X		X	X	
HCW surveys	Health service & Implementation outcomes		X			X	
HCW implementation logs/surveys	Implementation outcomes						X
HCW implementation surveys, IDI /FGD (intervention sites only)	Implementation outcomes				X		
Facility surveys	Implementation outcomes		X			X	
Adolescent/caregiver satisfaction surveys (intervention only)	Implementation outcomes					X	
Adolescent FGDs	Implementation outcomes						
Randomization	NA	X					

2 INTRODUCTION

2.1 STUDY RATIONALE

UNAIDS '95-95-95' targets cannot be achieved without additional support for adolescents living with HIV (ALHIV) to increase retention in care and to support viral suppression. Risk prediction tools as well as a stepped care approach to care can support differentiation of ALHIV to different risk groups, and tailor care based on risk.

Our team has conducted formative work with ALHIV, caregivers, HCW and policy makers and has developed and validated a clinical prediction tool to identify ALHIV at highest risk of not being retained in care and poor viral suppression that could be adapted to identify adolescents who may need more support in their care. Understanding how best to use the risk prediction tool as well as how to tailor services based on risk may ultimately result in more efficient HIV care services, as well as adequate support for ALHIV at highest risk of poor outcomes.

This study aims to test a data informed stepped care approach to improve retention and viral suppression among ALHIV. We will also study implementation and service delivery outcomes.

2.2 BACKGROUND

B1. Adolescents are disproportionally affected by HIV

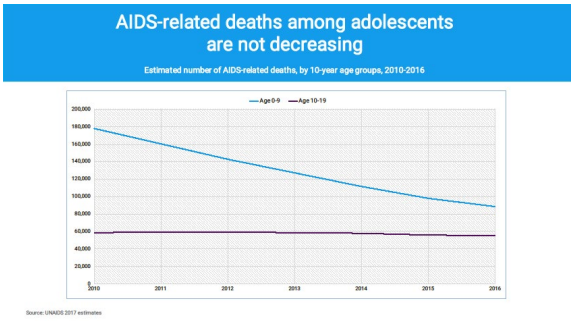


Figure 1: Static mortality among 10-19 year

Adolescents represent an estimated 40% of new infections worldwide,[2] and 84% of HIV-infected adolescents live in sub-Saharan Africa (sSA).[3] In Kenya, HIV incidence among adolescents has increased by 17% since 2013, while incidence has reduced by 19% in adults and 49% in children.[4]The majority (91%) of AIDS-related deaths among adolescents in the region have not declined (Figure 1).[5] A growing number of perinatally infected adolescents will need lifelong antiretroviral therapy (ART).[6, 7]**'90-90-90' targets cannot be achieved without substantially increasing engagement in care and viral suppression among adolescents.**

B2. Adolescent HIV care cascade outcomes are poor

Adolescents in African countries have lower retention, adherence to ART [8] and viral suppression compared to adults.[8-14] Loss to follow-up (LTFU) among adolescents within the first 12 months of treatment ranges from 15% to 83%.[12, 15, 16] Poor ART adherence is common and increases risk of HIV transmission and disease progression.[17, 18] The greatest gap in the adolescent care cascade is viral load, [19, 20] with >30% experiencing virologic non-suppression or failure after 12 months on ART.[7, 21-24]Lack of viral suppression among adolescents undermines progress in retention and adherence.

B3. Reasons for poor adolescent engagement in care are unclear and varied

Cofactors of viral suppression may be distinct in this age group. Male gender, poor mental health,[25] stigma, substance use,[25] fear of provider judgement, [26] lack of support,[27, 28] and school barriers [29] are risk factors for poor adherence and retention among adolescents, though data are limited.[30] Lack of age-disaggregated data in research and programs in high-burden settings remains a major barrier to responding effectively to the adolescent HIV epidemic.[31, 32]**Systematic cohort data on social, behavior, and clinical factors affecting retention and treatment outcomes are necessary to inform new HIV care interventions for adolescents.**

B4. Adolescence is a unique period of life, with specific challenges for HIV-infected adolescents

Adolescence is a time of rapid physical, cognitive, sexual, and social transition, characterized by increased autonomy, experimentation, growing peer influence, and identity formation.[33] These contexts and behaviors affect health outcomes in adulthood and next generations.[34, 35] Adolescents with HIV face unique challenges transitioning successfully to adulthood and achieving optimal health.[11, 36] Younger adolescents (10-14) are more likely to be perinatally infected, live at home, and have parental supervision. Many do not know their status or have been recently disclosed to.[37, 38] Older adolescents want more autonomy to make choices about relationships and health, but have decision-making challenges.[34, 39, 40] Adolescent females have added risk of poor adherence due to relationship violence[41] while gender norms and lack of targeted services are linked to lower male engagement in care.[42] **New interventions to optimize retention and clinical outcomes must be tailored to adolescents' developmental, health, and social needs.**

B5. Caregivers influence clinical outcomes in adolescents, but need support

Parents or non-parent caregivers are the primary sources of support, social norms, and supervision in early adolescence.[43] Caregivers have the potential to improve adolescent disclosure, treatment adherence, and retention, but feel ill-prepared for this role.[37, 38, 44] A trial conducted in Zimbabwe found that a community health worker-led intervention to train and support caregivers resulted in a significant reduction in viral non-suppression or mortality in their HIV-infected children.[45]**Caregiver perspectives are necessary to inform adolescent services and to improve clinical outcomes in adolescents.**

B6. 'Test and Start' will burden health systems in resource-constrained settings

Adoption of Test and Start models, where all persons living with HIV are rapidly initiated on treatment, addresses loss to follow-up in the pre-ART period as part of initiatives to reach 90-90-90 goals, with early evidence of success.[46]However, there are fears that increasing caseloads and HCW burden in already strained healthcare systems will result in difficulty accessing or poor quality of care.[47]Differentiated models of service delivery have been proposed as a client-centered approach that simplifies and adapts HIV services across the cascade to better serve those in care and to reduce unnecessary burdens on the health system.[48]Due to poor retention outcomes, Kenyan guidelines currently classify all adolescents as "unstable",[49] thus not able to access differentiated approaches, like community models or longer refill durations, which may benefit for this population.

B7. “Stepped care” as an evidence-based model for differentiated care

The stepped care model grounded in Stages of Change Theory,[50]has been used in mental health fields to organize provision of services; and to support clients, HCW, and caregivers to identify the most effective interventions (Figure 2).[51] Models typically start with a low-intensity, evidence-based treatment, and systematically progress to higher levels of care or intervention as clients fail to respond.[52] **A key feature of stepped care is outcome monitoring, giving both clients and HCWs feedback to inform care options and service delivery.** Early studies suggest improvements in access to care, client outcomes, and program efficiencies, including client volume.[53] A systematic review found effectiveness on 6-month depression outcomes,[54] and a randomized trial demonstrated reduced incidence of depression and anxiety among older adults.[55]

B8. Clinical prediction tools identify high-risk individuals for interventional support

Clinical prediction tools are useful to classify individuals into high and low risk groups, to identify those in need of intervention, and to deliver services more efficiently.[56-59] Studies among MSM in the United States [56, 59] and two studies in Kenya found that clinical characteristics were predictive of HIV risk.[58, 60]Tools validated in clinic cohorts of HIV-infected adults in the US [61] and in low resource settings [62] have shown to be predictive of virologic failure or mortality using minimal variables.[61-63]**Prediction tools could enable HCWs to provide better support to adolescents *at risk* for poor outcomes rather than waiting until poor outcomes occur.**

B9. Health systems interventions may improve adolescents care cascade and clinical outcomes

Despite nearly 15 years of research to improve retention outcomes in adults, there is lack of evidence of what works for HIV-infected adolescents.[64-66] Individual psychosocial interventions may improve ART adherence for adolescents at risk of treatment failure, [65] but alone are not sustainable in high-burden countries. Health systems interventions can empower HCWs to tailor services for their unique population needs and optimize limited resources.[48] A US study found that multidisciplinary care teams improve adolescent retention in care, [67] and the SAIA trial used a systems engineering approach to triple ART coverage for prevention of mother to child transmission in Africa.[68] **It is plausible that a health systems approach, using a data-driven, provider-led intervention to optimize adolescent HIV services, may result in health services efficiencies and improved adolescent HIV care engagement and clinical outcomes.**

C. INNOVATION

- A clinical prediction tool can identify adolescents at risk for loss to care before negative clinical outcomes occur. Simple, practical tools can be incorporated into routine data collection to identify adolescents at highest risk of disengagement ***before*** loss to care, providing an opportunity for health systems to intervene.
- Stepped care models paired with accurate risk identification can reach priority adolescents without increasing burden on the health system. There are great concerns about the capacity of health systems to manage care in the 'Test and Start' era. Stepped care models use programmatic data to target services to those most in need. This framework is highly aligned with international movements for differentiated care.
- Current Kenyan guidelines for differentiated care do not include adolescents. All HIV-infected adolescents are considered "unstable" and thus not eligible for differentiated HIV services under current Kenyan guidelines.[49] This approach masks heterogeneity and diverse needs. Carefully and systematically assessing individual risk can identify those who need heightened services, as well as those at lower risk, who may benefit from less intensive or frequent clinic visits according to differentiated care models.
- A health systems intervention can be widely applied across different settings. Despite national roll out of the Adolescent Package of Care (APoC) guidelines, large scale and local programs targeting adolescents with HIV are not uniform. A health systems approach can be applied across clinical facilities to enhance diverse interventions by matching them to client characteristics and specific health system compositions.
- Client-centered interventions that involve providers, families, and youth in design and implementation can maximize uptake and impact. Youth perspectives are critical to engagement in HIV research and programs and to determine what additional support might be needed.[69] Addressing legal and ethical considerations can maximize representative participation and better inform design and delivery.
- Effectiveness research is necessary to develop sustainable models for adolescent HIV care: We will evaluate the DiSC intervention by leveraging routine electronic medical record (EMR)data and clinic populations and engaging community stakeholders throughout the study lifecycle. By approximating real-world conditions, we maximize generalizability and sustainability of this modelin resource-limited settings.[70]
- Using an implementation-effectiveness hybrid design improves translation to practice: Our study is structured *a priori* to address both clinical intervention and implementation outcomes. Use of hybrid study designs may improve policy relevance and public health impact of new interventions.[71]

IMPACT: A data-driven, provider-led, health systems intervention can identify adolescents most at risk for loss to care, sub-optimal adherence, and viral failure. Our stepped care approach, combined with a clinical prediction tool, is a timely and flexible intervention in the context of differentiated care and numerous ongoing care initiatives. By improving adolescent engagement in care and optimizing provision of limited resources, this intervention can ultimately improve health and decrease HIV transmission risk among adolescents in Kenya.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWNPOTENTIAL RISKS

There are no medical interventions associated with the study, therefore we anticipate no risk of serious physical harm to participating HCWs, adolescents or caregivers. In all HIV research studies there is a non-negligible risk of loss of confidentiality of HIV status or other medical information. There is also risk of emotional discomfort when responding to sensitive personal questions. HCWs who are trained in the DiSC intervention may have concerns about job loss if they perform poorly in implementing the stepped care approach. There is a possibility for social harm (depression, violence after disclosure, abandonment) related to routine HIV treatment and management during clinical encounters with routine providers during the course of the study. However, the possibility of this social harm would exist if this intervention were not conducted. There is a possibility that during a clinical encounter with the more intensive care steps, an ALHIV may be more comfortable disclosing that they are suffering from previously undiagnosed mental health problems such as depression. Any patients with potential mental health problems will be referred for psychosocial support at the facility or nearest referral hospital, according to standard HIV care and treatment guidelines for adolescents at that clinic.

2.3.2 KNOWN POTENTIAL BENEFITS

Direct benefits:

Participants may benefit from enhanced HIV treatment services tailored to adolescents. This could result in better retention, adherence, and viral suppression. Clinics and HCWs may benefit from increased time and resources efficiencies from the stepped care approach.

Indirect benefits:

The study may produce data that will lead to improved interventions for treatment and care of adolescents with HIV, thus a benefit to society.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All adult study participants will have the study and relevant study procedures explained to them, their questions answered, and provide written consent for their enrollment.

Together, the UW, Nairobi, and Kisumu Study Team has more than 10 years' experience managing HIV-infected children and adolescents and in clinical trials and observational research and will take every precaution to protect participants' and their caregivers' confidentiality. All study staff will have been trained in the Protection of Human Subjects and new staff will receive similar training.

Procedures to minimize physical risks: There are no medical interventions associated with the study, therefore we anticipate no risk of serious harm to study participants.

Procedures to minimize confidentiality risks: All key personnel will be trained in the Protection of Human Subjects. The field team will take every precaution to protect participants' confidentiality. We will only collect personal identifiers for the purposes of identifying and contacting participants about the study. This information will include the names, telephone numbers and emails for those identified as interested in participating in the study. Personal identifiers will be used to contact stakeholders in aim 1 and HCWs to remind them of their scheduled study activities. This information will also be used to contact them again to verify the accuracy of the information

collected or to elaborate or clarify certain information provided during study procedures if they select the option to be re-contacted on the consent form.

All participants will be assigned a study identification number (ID). Participant identifiers will be linked to their study ID in a link-log document that will be stored separately from all other study data. Only necessary study staff will have access to this document and will not share this information with other study staff or with others outside of this study.

Procedures to minimize psychological risks: All participants will be assured that their participation is voluntary and that they may withdraw from the study at any time. Kenyan study personnel experienced in research with adolescents will be available for questions when participants take the surveys. While there is a risk of discomfort related to answering sensitive questions about sexual behavior, mental health, and stigma on the surveys, these questions are similar to what would be asked as part of routine HIV care for adolescents. Survey participants will be informed that they can skip any question or stop the interview at any time. Any participant who reports emotional distress, exposure to violence, or other threat will be offered support or referral to additional services, as appropriate, according to standard operating procedures. Some younger adolescents receiving HIV care and taking ART (which may be called 'medicine' and not HIV medicine) may not yet know their HIV status, because the caregiver is not ready for the child to learn this information. The ALHIV surveys will not include specific mention of HIV or ART unless a participant reports knowledge of their own HIV status on a screening question. This approach will minimize the possibility of involuntary disclosure to an ALHIV and maximize representative enrollment.

Procedures to minimize other risks: Study staff will be trained to take all precautions to ensure confidentiality of participation and data collected and will have standardized operating procedures (SOPs) to follow to minimize the risks of a participant's loss of confidentially. Risk of breach of confidentiality of study data is low, as all patient data collected will not include names and will be located on a password protected secure study server. ALHIV participants will be assured that their sensitive information will not be shared with anyone outside the study team, including a parent, caregiver, or partner who may be present. Study staff will be trained in the importance of confidentiality during training prior to study implementation. The community-driven process of adaption and optimization of the intervention to local context will ensure that the intervention is culturally sensitive before implementation in the pilot and RCT. All HCW participants will be assured that their participation will not affect their employment status.

Procedures to minimize unexpected events, including social harms, including violence: We will minimize social harms by training study staff on how to counsel participants on ways to avoid harm as per national guidelines, including not disclosing their HIV status to anyone who may harm them. We will also inform participants that they can contact study staff using the number provided on the consent form if they experience social harms. We will refer participants to the appropriate clinic staff, as needed.

There are no mandatory reporting requirements in Kenya for studies that ask about gender-based violence. If a participant reports directly to a study staff that they are experiencing violence or other threat, we will follow study SOPs to refer that person to a clinic staff person for appropriate follow-up services. If they report violence or other threat on the self-administered survey, a

message will appear that recommends a referral and that our study staff could help with that referral if they choose. As part of routine practice, HIV care clinicians are expected to ask adolescent clients about exposure to violence and are mandated to perform the relevant tests and offer care and referrals to legal and medical resources. There will be no mention of HIV on adolescent recruitment talking points or consent and assent forms for surveys. Adolescent surveys will not include specific mention of HIV or ART unless a participant reports knowledge of their own HIV status on a standardized set of screening questions. If we learn of social harms related to routine HIV care (and not this study), we will follow our standard operating procedures and clinic guidelines to offer referrals to the appropriate counseling or services.

Study justification
UNAIDS '95-95-95' targets cannot be achieved without additional support for ALHIV to increase retention in care and to support viral suppression. Risk prediction tools as well as a stepped care approach to care can support differentiation of ALHIV to different risk groups, and tailor care based on risk.

Our team has conducted formative work with ALHIV, caregivers, HCW and policy makers and has developed and validated a clinical prediction tool to identify ALHIV at highest risk of not being retained in care and poor viral suppression that could be adapted to identify adolescents who may need more support in their care. Understanding how best to use the risk prediction tool as well as how to tailor services based on risk may ultimately result in more efficient HIV care services, as well as adequate support for ALHIV at highest risk of poor outcomes.

A data-driven, provider-led, health systems intervention can identify adolescents most at risk for loss to care, sub-optimal adherence, and viral failure. Our stepped care approach, combined with a clinical prediction tool, is a timely and flexible intervention in the context of differentiated care and numerous ongoing care initiatives. By improving adolescent engagement in care and optimizing provision of limited resources, this intervention can ultimately improve health and decrease HIV transmission risk among adolescents in Kenya. Improved models of data-informed, client-centered care are urgently needed for this population and may translate to other programs in Kenya, and more generally in sub-Saharan Africa.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1: To develop, adapt, pilot, and optimize implementation of a data-informed stepped care (DiSC) intervention for ALHIV treatment management.	DiSC intervention	To provide intervention for the trial

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 2: To evaluate effectiveness of the DiSC intervention on ALHIV retention in care in up to 24 high-volume HIV clinics in Kenya.	Retention in care	Marker of successful HIV care
Secondary		
Aim 1: To determine acceptability, feasibility, adaptability and fidelity of the DiSC intervention	Pilot acceptability, feasibility, adaptability and fidelity	Pilot data to inform intervention adaptations
Aim 2: To evaluate effectiveness of the DiSC intervention on ALHIV cascade outcomes (adherence and viral suppression) and adolescent self-efficacy and correlates of outcomes in up to 24 high-volume HIV clinics in Kenya	ART adherence Viral suppression ALHIV self-efficacy	Markers of successful HIV care Covariate, mediator data
Aim 2: To evaluate effectiveness of the DiSC intervention on health service outcomes in care in up to 24 high-volume HIV clinics in Kenya	Client wait time Costs	Impact of intervention on service delivery
Aim 2: To evaluate effectiveness of the DiSC intervention on implementation outcomes in care in up to 24 high-volume HIV clinics in Kenya	Feasibility, acceptability, adaptation, fidelity, adoption, reach, maintenance	Intervention delivery data to support effectiveness data Mediator data

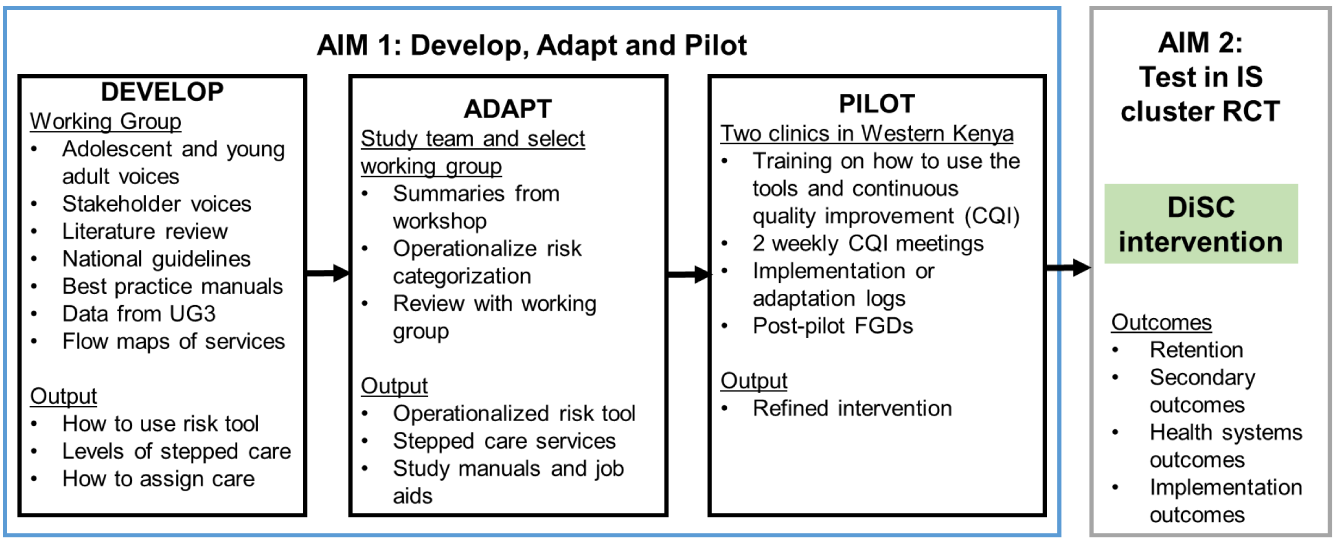
4 STUDY DESIGN

4.1 OVERALL DESIGN

In aim 1, with relevant stakeholders in adolescent HIV, we will collaboratively develop the DiSC intervention, then adapt and pilot test the intervention.

In aim 2, we will conduct a cluster randomized trial (cRCT) in up to 24 sites in western Kenya (12 randomized to intervention and 12 to control) (Figure 1).

Figure 1: Study design, main activities, and outcomes



Study hypothesis

- Primary and secondary outcomes: We hypothesize that the DiSC intervention will result in better retention, adherence and viral suppression among adolescents in the intervention sites compare to those in control sites. Hypothesized psychosocial outcomes will include better psychosocial and family support, mental health, family support and adolescent self-efficacy.

- We hypothesize the DiSC intervention will be associated with improved clinic efficiency (client wait time), and will be cost effective.

- The DiSC Intervention will be feasible, acceptable to HCW and adolescents but will require clinic specific intervention adaptations.

Randomization

Up to 24 clinics will be randomized in a 1:1 ratio using computer generated random numbers to either intervention or control, using restricted randomization to balance by county, aiming to balance the numbers of clinics from each county between arms. Timing of randomization will be prior to study start. Randomization will be done at the University of Washington by a biostatistician not involved in study procedures. A list of clinics with their allocation arms will be sent to the study team. We will perform individual substitutions of sites on a case by case basis, as needed (e.g. if the site no longer meets an eligibility criterion).The intervention is administered at the clinic-level; it is not possible to blind participating clinics or study team members.

Study intervention

The DiSC intervention is comprised of a system to assign adolescents to care based on their health needs and the different levels of care for each assignment group. Control sites will continue with standard of care approaches for adolescent clinic visits (usually 1-3 monthly visits) regardless of health care needs and additional support as needed.

Analysis

We do not plan for interim analysis. Subgroup analysis (age and gender) are planned as described in the statistical analysis section.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A cRCT design is appropriate because the intervention will be administered at the clinic level.

4.3 JUSTIFICATION FOR INTERVENTION

The intervention will be delivered by HCW during routine clinical visits; and works at improving clinic level effectiveness in care management. We anticipate at least 50 adolescents per site will be exposed to the intervention during the course of the study period. The intervention will be offered during regular clinic visits that are typically scheduled 1-6 monthly.

4.4 END-OF-STUDY DEFINITION

The definition of the end of the study is: completion of the 12-month follow-up assessment shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

Aim 1

Intervention development: Policy makers at national, county and care partner levels, HCW, ALHIV and caregivers as well as other stakeholders in HIV care will be invited to participate in an intervention development workshop.

HCWs in 2 facilities participating in the completed formative phase of the study will pilot the intervention in their clinics.

Aim 2

Cluster RCT: We will conduct this study at up to 24 HIV care and treatment facilities located in Kisumu, Homa-Bay, Migori County.

The population of interest is ALHIV age 10-24 enrolled in participating clinics, caregivers of adolescents and young adults and HCW offering services. The intervention will be administered by existing HCW, who will also participate in implementation surveys, interviews, and focus groups to assess health service and implementation outcomes. A cohort of ALHIV ages 10-24 years will also be enrolled to participate in longitudinal surveys. A subset of ALHIV and caregivers of ALHIV will also complete satisfaction surveys at the end of the trial.

5.1 INCLUSION CRITERIA

Aim 1	HCW	18 years or older
	Policymakers	18 years or older Employed currently or in past at national/county or partner level
	Other stakeholders	18 years or older Relevant experience with adolescents
All aims	Clinics	Approximately 150 adolescents in care Active EMR system Willing to participate in the study
	HCW	18 years or older Working with ALHIV in participating clinics Provision of informed consent Willing and able to give informed consent
Aim 1	Stakeholders in adolescent care	18 years or older Working in adolescent health Provision of informed consent Willing and able to give informed consent
Aim 2	Adolescents	Ages 10-24 years HIV-positive Enrolled in HIV care Provision of informed consent (intervention/surveys and FGDs/IDIs) Willing and able to give informed consent (intervention/surveys and FGDs or IDIs) AYA15-17 years that are considered mature/emancipated minors will provide informed consent without caregiver consent; For 10-17 year old AYA, provision of caregiver informed consent
	Caregivers	18 years or older Caregiver of 10-17 years ALHIV Provision of informed consent Willing and able to give informed consent

5.2 EXCLUSION CRITERIA

All aims	Clinics	Participating in other studies that could overlap procedures/clients
	Adolescents, HCW, caregivers, adolescent	Not able or willing to give informed consent

	stakeholders	

5.3 LIFESTYLE CONSIDERATIONS

NA

5.4 SCREEN FAILURES

Screen failures are defined as clinics that are not included in the final list of clinics for randomization. After randomization, we do not anticipate to re-screen or include additional facilities.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment

Intervention adaptation workshop

Policy makers at national and county level, adolescent representatives, frontline HCW, adolescent caregivers and representatives from HIV care partners will be purposively selected by the study team to participate in an intervention development workshop. Recruitment will be consecutive until at least 40 participants are reached. A script outlining talking points, purpose and scope of work will be used for recruitment. Written informed consent for participation and audio-recording of sections of the proceedings will be obtained.

Intervention optimization (pilot)

Following adaptation of intervention materials, HCWs from 2 clinics will pilot the adapted intervention for up to3 months using a modified quality improvement approach. The 2 HIV clinics will be purposively selected by the study team to participate in the pilot activities from a pool of HIV clinics involved in the formativephase of the study.

Cluster RCT

The sampling frame will consist of all55 clinics in participating counties that were part of the earlier phase of the study or that have been identified as potential clinics. Among those, up to 24clinics that meet eligibility criteria, have the highest AYA enrollment and whose leadership is willing to participate will be selected and randomized to intervention or control.

Adolescent and caregiver surveys

A proportion of ALHIV in participating facilities (~150per site) and caregivers (~45per site) will be enrolled to participate in surveys to determine ALHIV behavior, self-efficacy and co-factors of retention and viral suppression. Clinic staff members will refer ALHIV currently in HIV care to our trained study team for eligibility screening for the ALHIV longitudinal cohort. A standard recruitment script with talking points will be used. Recruitment will be conducted during different days and times of the week, during at least 2 school breaks and ‘youth friendly days’ to maximize enrollment. ALHIV who meet eligibility criteria will be invited to enroll in the cohort and complete

behavioral surveys at enrollment and every 6 months thereafter. Clinic staff members will refer to the study team a purposeful sample of caregivers of adolescents coming in for routine clinic visits. A large number of adolescents come to clinic alone; the study will only recruit caregivers who accompany adolescents. Caregivers who meet eligibility criteria will be invited to enroll and complete caregiver surveys at enrollment and at 12 months.

HCW surveys
HCW in participating sites working in the ALHIV clinic will be invited to participate in health service and implementation surveys. A script outlining talking points, purpose and scope of work will be used for recruitment. Written informed consent for participation will be collected from all participants prior to study activities.

Participant incentives
The study will provide reimbursement for transportation costs, accommodation and meals during the workshop and provide a per-diem allowance equal to current rates used by organizations or facilities where the HCWs work.
Adolescents and caregivers who participate in surveys will be reimbursed KSH 200 ($2.00 USD). HCW attending study related meetings and completing surveys will be reimbursed KSH 1000 (~10USD).

Population justification
This study will be conducted in ALHIV age 10-24 years old, who have a high risk of mortality, and require innovative client-centered strategies to improve retention, adherence, and viral suppression. The study will be conducted in Kenya, where 140,000 adolescents (ages 10-19) have HIV, and HIV is among the leading causes of mortality in this age group.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)ADMINISTRATION

6.1.1 STUDY INTERVENTIONOR EXPERIMENTAL MANIPULATIONDESCRIPTION

The Data-informed Stepped Care (DiSC) intervention is comprised of a system to assign ALHIV to different levels of care, or “steps”, depending on their current and anticipated health care needs. Stepped care is a model grounded in Stages of Change Theory and has been used in mental health fields to organize provision of services, and to support clients, HCWs, and caregivers to identify interventions tailored to individual need. HCWs at participating sites will assign ALHIV to different levels or intensity of HIV services. The trajectory of services moves from a relative position of ALHIV autonomy to more intensive service provision. Intervention steps could start with multi-month refills or community treatment delivery, then social support activities (support groups, life skills activities), progress to individualized services (text messaging, ‘big brother/sister’ older peer support, motivational interviewing), and ultimately a case management approach involving referrals to specialized care like mental health or gender-based violence services, individualized counseling, and active tracking of individual participation in support and care services. The stepped care framework is designed to be flexible, to accommodate variable

individual and social support services available at each facility. A sample of potential intervention steps is presented below:

Sample intervention steps

Levels	Criteria for eligibility	Regular care	Additional HCW provided	Additional clinic recommended
Stepped down care	Meets MoH criteria except age	-Differentiated care	None	-Support groups (optional)
Not retained	At risk for loss	-3 monthly visits	-Pre-clinic reminders (text) -Individual peer support -3 monthly adherence counseling	-Support group
Viral failure	At risk for viral failure OR VL under 1000 but detectable	-Monthly visits (6 weekly for school going)	-Monthly adherence counseling -Motivational interviewing (one round of several sessions) OR Coaching -Individualized ART pick-up strategies	-Support group -Caregiver or support person DOTS
Failed	Unsuppressed at last measure	-Monthly visits (6 weekly for school going)	-2 weekly adherence sessions (could make some on phone) -Accelerated repeat test timeline (3 month) -Prompt switch after second test -Case manager -DOTS by HCW (or caregiver/family)	-Support group -Special treatment failure support groups -Home visit by HCW -Viremia clinics

6.1.2 ADMINISTRATION AND/OR DOSING

The study team will conduct training for HCWs at intervention and control sites. At intervention sites, the training will focus on intervention use and data collection while in control sites, training will focus on data collection. At baseline, the study teams will assist HCWs to identify score categories for each step of care. The clinical tool will be uploaded onto handheld tablets or on paper tools, according to HCW preferences and will be used at ALHIV scheduled visits.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The intervention will be adapted and optimized prior to the RCT phase in an intervention development workshop and piloted in 2 HIV clinics. To optimize the tool for the Kenyan setting, we will invite stakeholder to an intervention development workshop. Existing services, the number of steps, as well as the system for assigning and re-assigning steps will be discussed.

The study team will develop job aids, training material and other identified tools to support intervention administration activities in the pilot phase and refine the material for the RCT phase. Intervention sites will be trained on how to deliver the intervention prior to implementation. As there will be varying skill and service delivery options across participating facilities, the study team

will work with HCWs to improve their ability to use the DiSC intervention during initial implementation period (about 3-6 months) during which an implementation/adaptation log will be used to track changes in implementation and HCWs will participate in twice-monthly planning and feedback meetings.

Surveys and tracking tools will be used to track implementation (see section 8).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization procedures are described in section 4.1.Blinding is not possible as the intervention will be delivered at the clinic level.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATIONADHERENCE

The study team will track ALHIV to determine if they received care as per assignment in the intervention sites using intervention adherence logs. These logs will be adapted based on the final intervention steps.

6.5 CONCOMITANT THERAPY

NA

6.5.1 RESCUE THERAPY

NA

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATIONDISCONTINUATIONAND PARTICIPANTDISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

We do not anticipate that clinics will discontinue participation or withdraw from the study after randomization. However, if this occurs, the study team will get permission from the clinic to use study data up until the time of discontinuation.

7.2 PARTICIPANTDISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in surveys or individual data collection procedures at any time upon request. Participants may also be discontinued if there is:

- Lostto Follow-up; unable to contact subject (see Section 7.3, Lost to Follow-Up)

- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and withdraw or discontinue may be replaced.

7.3 LOST TO FOLLOW-UP

Since the study primary outcome is retention, study staff will not contact caregivers or ALHIV who miss their appointments for longitudinal survey data collection. However, we will contact stakeholders and HCW as needed to schedule study related activities.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Intervention development workshop
The intervention development workshop will be led by study team members. Workshop material will be summarized and sent to participants prior to the workshop. Materials will include literature on the use of risk assessment tools, information on the risk tool from the formative phase of the study, proposed core elements of the risk tool, differentiated care services, best practices for adolescent care, national guidelines on HIV care, flow maps of existing services in clinics in the catchment area and proposed framework for stepped care levels including sample intervention tables. The workshop will begin with a review of all material shared before the workshop. Next, the risk prediction tool will be introduced and discussed in detail in small groups including performance, strengths, weaknesses, and proposed categories. HCWs will be encouraged to think about how the tool would work in their work setting, while incorporating the views of stakeholders. A framework of proposed intervention steps with different levels of care with increasing intensity will be presented. HCWs will discuss what interventions would work at the different levels of care, keeping in mind current practices in the facilities. HCWs will be encouraged to be participatory and as practical as possible, and to develop the most inclusive and simplest interventions that would work in the largest number of facilities in Kenya. Small working groups will present their discussions to the larger group, and the large group will work to come to consensus on a draft tool. The tool will continue to be refined after the workshop, incorporating the views and feedback of all stakeholders present. Selected workshop members will be contacted to review the refined tool after the workshop. The study will provide reimbursement for transportation costs, accommodation and meals during the workshop and provide a per-diem allowance equal to current rates used by organizations or facilities where the HCWs work.

Data Collection Procedures:

Small and large group discussions during the workshop will be audio recorded. Notes will be taken during discussions, and audio recordings will be transcribed as needed for team review. Prior to the intervention development workshop, HCWs will complete a short demographic form to collect socio-demographic information. Neither the transcribed notes from the workshop or transcripts will include any personal identifiers other than the participant's first name. Collected transcript data will be de-identified. The audio recordings of discussions will be destroyed after study participation and data analysis has been completed and no later than 6 years after the workshop took place. Audio files and English transcripts will be uploaded to a password protected secure website for back-up. A qualitative software program (ex: ATLAS.ti or Dedoose) will be used for data management and analysis.

Listed below are all the required procedures for the intervention development workshop

1) Invitation to participate in workshop
2) Collect locator information (phone number) and schedule meeting dates
3) Provide a copy of the materials to review prior to the meeting
4) Complete demographic surveys
5) Present results of qualitative work
6) Present the risk prediction tool
7) Discussion on how to use the risk tool
8) Present outline for proposed DiSC intervention
9) Group discussion on DiSC intervention components
10) Small group discussions to develop and refine steps in care
11) Whole group presentations with iterative refinement
12) Presentation of refined tool and risk categories
13) Post workshop review of refined tool

Intervention optimization (pilot)

HCWs and AYA in participating sites will consent to participate in the pilot phase which includes intervention administration, twice-monthly intervention adaptation meetings, as well as implementation surveys. At the start of the pilot, HCWs will complete a short demographic form to collect socio-demographic information. HCWs will be introduced to the adapted intervention materials, trained on how to use them, and encouraged to make small adaptations and changes to the way they implement the intervention throughout the pilot period. If a new HCW enters the facility during the pilot, they will also be trained on the intervention materials and have socio-demographic information collected. An implementation/adaptation log will be used to track changes in implementation and HCWs will participate in twice-monthly planning and feedback meetings. Meetings will be audio recorded and transcribed when necessary. Transcripts will not include HCW names. Routinely collected data at the facility, such as the number of adolescents attending and the number of adolescents exposed to the intervention, will be collected to monitor implementation outcomes of adoption and reach. Following the pilot period, HCWs from clinics who participated in the pilot will take part in individual in-depth interviews (IDIs) or focus group discussions (FGDs) to share their suggestions for optimizing the intervention based on their pilot experience. IDIs and FGDs will be audio recorded and will be transcribed verbatim. Transcripts and notes from twice-monthly meetings will be analyzed to identify themes related to how to revise intervention materials and implementation. After the pilot phase, the tool will be further refined with input from selected members who participated in the intervention development workshops prior to use in the RCT phase.

Cluster RCT
Intervention details, administration and assessments are described in the sections above (see section 6.1 and 6.2).

Program records: We will abstract ALHIV medical record data at baseline and regular intervals throughout the study. Data from all adolescents with at least 1 clinic record within the 12-month period prior to the first data abstraction date will be included. Data will be abstracted at the facility or at the office of the technical partner that supports the EMR system at the facility. The EMR system captures data on client anthropometric measures, demographics, HIV testing history, family members, clinical history, ART adherence data, laboratory data, CD4 count, transfers, and discontinuations. Routine viral load testing (done 6 months after ART initiation, then annually) will be abstracted from the EMR, if available, or NASCOP's laboratory database. If EMR data is unavailable, paper medical records will be abstracted using mobile REDCap which enables automatic upload of data to a secure, password-protected study server.

Adolescent behavioral surveys: Adolescent surveys will include questions on socio-demographics, health care use, stigma, sexual behavior, psychosocial support, mental health, personal health knowledge, HIV disclosure and medication adherence. Surveys will be administered every 6 months either in-person or over phone by a trained study staff. Survey visits will coincide with clinic visits as much as possible.

Caregiver behavioral surveys: Caregiver surveys will include questions on socio-demographics and family, caregiver roles, HIV disclosure, HIV care experience, disclosure, social support, mental health, HIV testing and awareness, personal health and HIV experience, HIV stigma, ART knowledge and adherence. Surveys will be administered every 12 months either in-person or over phone by a trained study staff. Survey visits will coincide with clinic visits as much as possible.

Data on health services and implementation outcomes will be collected as previously described (see section 6.2).

To track implementation, the following surveys will be conducted:

Facility surveys: Facility managers will complete baseline and annual facility surveys to understand baseline resource capacity to implement future interventions and modifiable and non-modifiable health system factors. Variables will include availability of youth-friendly services, management and referral systems, and differentiated care services available.

HCW surveys and FGDs/IDIs: Surveys with all HCWs at intervention and control sites who are willing to participate will be conducted at baseline and annually on demographic information, including training history and experience providing HIV care. HCWs at intervention sites will also complete an organizational readiness for change survey after training on the intervention, but prior to implementation at their clinic, and will participate in twice-monthly planning and feedback meetings during the first 6 months of implementation. We will conduct surveys, FGDs, and IDIs with HCWs in intervention sites at 6 months post-intervention implementation and at the end of the trial to evaluate barriers and facilitators of intervention implementation, overall implementation outcome measures using the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework as well as costs. Cost data will be collected from HCW or policy makers in adolescent health, published literature and government data. FGDs and IDIs with HCWs will

include a purposeful sample of those exposed to the intervention, stratified by clinic performance level during intervention implementation, cadre of HCW, and involvement in implementation. Exit surveys with HCWs at implementation sites will be conducted to determine experience with the DiSC intervention and barriers and facilitators for intervention utilization. Example validated tools that may be used to inform the surveys and measure each of the implementation outcomes include:

- Determinants of DiSC intervention feasibility and acceptability classified using the Consolidated Framework for Implementation Research (CFIR)
- Intervention adaptation classified according to the framework for reporting adaptations and modifications to evidence-based interventions (FRAME)
- Reach, Acceptability and Feasibility, measured by the Applied Mental Health Research (AMHR) validated implementation science measure[72]
- Adoption, measured using a 17-item validated survey to characterize intervention characteristics and likelihood of adoption[73]
- Implementation, measured using surveys to assess enthusiasm, self-efficacy and preparedness[74]
- Maintenance, measured using the Program Sustainability Assessment Tool (PSAT)

HCW implementation logs: These will be collected weekly and combined with information collected in annual HCW surveys to understand intervention and implementation processes in real time and service efficiency outcomes. We will specifically evaluate the percent of HCWs using the intervention, percent of adolescents in each step, percent of adolescents assigned to correct step, and percent of adolescents 'adherent' to services in each step. We will also collect basic information on numbers of adolescents attending clinic each week, and the number exposed to the intervention. In control sites, we will collect information on classification of adolescents as stable/unstable and offer for differentiated services.

ALHIV and caregiver satisfaction surveys: Surveys will be given to a random sample of adolescents and caregivers in intervention sites at the end of the study to evaluate satisfaction with their care.

ALHIV FGDs/IDIs: We will conduct FGDs/IDIs with adolescents in intervention sites at the end of the intervention period to determine acceptability, feasibility ad satisfaction with the intervention. FGD/IDI participants will be purposively selected from adolescents in intervention clinics. We will conduct FGDs/IDIs with up to 50 people per facility.

The table below summarizes study outcomes and definitions

Summary of outcomes and definitions

Aims	**Outcome type**	**Outcome**	**Definition**
Aim 1	Primary	Final optimized DiSC intervention	Modified DiSC intervention with input from workshop and pilot phase
	Secondary	DiSC intervention feasibility	Suitability for everyday use and practicality

		DiSC intervention acceptability	HCW satisfaction with the intervention
		DiSC intervention adaptation and fidelity	The degree with which the intervention is modified and implemented as planned
Aim 2	Primary	Retention in care	>30 days late for a scheduled visit at 6-month intervals
	Secondary	ART adherence	Proportion of days on ART based on last dispense date
		Viral suppression	<50 copies per milliliter and a second analysis using greater than lower limit of detection
		Co-factors of retention and viral suppression	School drop-out, relationships, depressive symptoms, substance use, social support, and satisfaction with care
		ALHIV self-efficacy	Self-efficacy scales from standard questionnaires
	Health service efficiency	Client wait time	Average ALHIV waiting time in clinic
		Costs	Direct and indirect costs of the intervention
		Differentiated care process	% of ALHIV correctly identified as stable or unstable
	Implementation outcomes	Intervention feasibility	Suitability for everyday use and practicality
		Intervention acceptability	HCW and ALHIV satisfaction with the intervention
		Intervention adaptation and fidelity	The degree with which the intervention is modified and implemented as planned
		Intervention adoption	The initial decision to take up a new intervention
		Intervention reach	The integration of the practice within the clinic

		Intervention maintenance	The longer-term ability to sustain or maintain intervention implementation

8.2 SAFETY ASSESSMENTS

We do not anticipate adverse events associated with the intervention, and therefore we will not actively monitor for adverse events. However, if any adverse events occur among participants enrolled in the study, we will report them as required by the regulatory bodies.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events will be defined as per the Division of AIDS (DAIDS) Table for grading the severity of adult and pediatric adverse events (grade 3-5 events).

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

We do not anticipate any significant adverse events to occur throughout this study. However, in the event that an adverse event occurs, participants will be given contact information for study team members and will contact study staff. Severity will be classified based on the DAIDS grading.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

We do not expect that adverse events will be related to the study intervention. However, all adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in HIV management will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

NA

8.3.5 ADVERSE EVENT REPORTING

All unanticipated problems, including adverse events, will be reported to the study sponsor, PIs, and ethics committee according to UW and Maseno University Ethics Review Committee guidelines.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event.

Reporting to Maseno University Ethics Review Committee (MUERC)
The investigator shall notify the secretariat by telephone (+ 254 57 351 622) within twelve (12) hours of the event. In addition, the adverse event(s) noted during the conduct of a study or project must be reported to the MUERC via email (muerc-secretariate@maseno.ac.ke) within twenty-four (24) hours after the applicant becomes aware of the event.The investigator must submit a completed adverse event form alongside a summary of the event. The hard copies of the report must be forwarded to the MUERC Secretariat within three (3) working days of the initial notification.

Reporting to University of Washington IRB:
Adverse events that meet the following criteria must be reported to the UW Human subjects division

a) AEs that were related to research procedures, serious, and unexpected (report immediately and within 10 business days)
b) AEs that were related to research procedures and expected, but more severe or occurred at a greater frequency than expected (report immediately and within 10 business days)
c) AEs that were related, non-serious, but unexpected (report annually)

Reporting to Study sponsor (NIH):
According to sponsor guidelines.

8.3.7 REPORTING EVENTS TO PARTICIPANTS
NA

8.3.8 EVENTS OF SPECIAL INTEREST
NA

8.3.9 REPORTING OF PREGNANCY
NA

8.4 UNANTICIPATED PROBLEMS.

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigators (PIs). The UP report will include the following information:

- Protocol identifying information: protocol title and version, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to MUERC and UW HSD. The investigator shall notify the MUERC secretariat by telephone (+ 254 57 351 622) within twelve (12) hours of the event. In addition, the adverse event(s) noted during the conduct of a study or project must be reported to the MUERC via email (muerc-secretariate@maseno.ac.ke) within twenty-four (24) hours after the applicant becomes aware of the event. UW HSD will also be notified within 10 business days.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

NA

9 STATISTICAL CONSIDERATIONS

A formal statistical analysis plan (SAP) will be developed and completed prior to database lock. The SAP will be posted at the clinical trials.gov site. The section below summarizes key aspects of the SAP.

9.1 STATISTICAL HYPOTHESES

Statistical hypothesis are described in section 4.1

9.2 SAMPLE SIZE DETERMINATION

Sample Size and Power for primary outcome

In our sample of HIV care facilities with >1,000 clients enrolled overall, we anticipate at least 10% will be eligible adolescents and young adults or about 100-200 AYA per clinic on average. Based on our UG3 data, we assume that 75% will be in care (not LTFU) and viral suppression of 64% (85% suppressed x 75% actively in care). Given a minimum of 20 facilities in the trial (minimum 10 per arm), we estimated the minimum average number of AYA per facility to detect a 15-20% change in retention using EMR data. We assumed 80% power, an a=0.05 and coefficient of

variation of 0.15. In table 3a below, we can detect a 17% percentage point different (75% to 93%) with an average of 100 AYA per facility and 20 facilities. The same estimates hold for as few as 50 AYA per arm and up to 170 per arm. Detecting less than a 17% percentage point difference would require more facilities per arm or at least 180 AYA per facility.

Secondary outcomes and assumptions:
Viral suppression: An average of 50 AYA VL records per facility and a minimum of 10 facilities per arm would be sufficient to detect a change from 64% to 81%, assuming 80% power, an a=0.05 and coefficient of variation of 0.15.

Cohort analyses: Based on UG3 enrollment data in the AYA cohort, we assume that about 50% of the total AYA clinic population to enroll in the cohort and set 50 as the average enrollment target per facility. Separate power and sample size calculations will be performed based on the specific exposure and outcome. When the intervention is the exposure, we will assume to have adequate power to detect at least a 17% percentage point difference in proximate outcomes (e.g. implementation and client outcomes)

Table 3a: Minimum Sample of AYA per Facility for the Primary ITT Analysis of Retention

	Retention % in the intervention arm	**n=100 AYA per facility**	**Facilities per arm**	**n=50 AYA per facility**	**Facilities per arm**
75%	90%	100	13	50	14
75%	92%	100	11	50	12
75%	**93%**	**100**	**10**	**50**	**10**

Table 3b: Summary of sample size estimates by outcome

Outcome	Source	Sample size	
		Intervention	Control
Retention	EMR data	3000	3000
Unsuppressed VL	EMR data	3000	3000
Mediators and secondary outcomes	Adolescent surveys	1500	1500
	Caregiver surveys	450	450
Implementation outcomes	HCW surveys	120	120
	HCW implementation logs	12	0
	HCW implementation assessment surveys and IDIs/FGDs	200	0
	Facility surveys per site	3	3
	Annual Adolescent/caregiver satisfaction surveys	500	0

9.3 POPULATIONS FOR ANALYSES

Intervention effectiveness will be assessed using an intent-to-treat analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A CONSORT diagram will show the number of clinics and ALHIV clients per clinic (cluster) randomized to each arm. We will report the number of clinics selected for inclusion, assignment to intervention or control, and the number of HCWs enrolled per site. Clinic-specific information, including ALHIV client volume, number of HCWs, and any pre-trial adolescent-specific services will be reported. Baseline characteristics of adolescents and participating HCWs will be presented in a descriptive table.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Mixed effects regression models will be used to compare the number of missed visits between arms, accounting for clustering by individual and clinic. LTFU will be compared using cox proportional hazards regression. Death or transfers will be censored. Sub-group analyses will be performed by gender and age-group. Facility factors, including concurrent adolescent-friendly services and high/low performance will be evaluated as moderators of intervention effectiveness.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Intervention effectiveness on secondary outcomes, including and the proportion virally suppressed at 6 and 12 months, proportion with >80% adherence since last refill, the proportion retained at 18 and 24 months, and proportion virally suppressed at 18 and 24 months, will be evaluated in separate regression models. Mediation analyses to understand mechanisms of intervention effectiveness will include whether intervention effectiveness is partially explained by ALHIV satisfaction and self-efficacy.

Intervention impact on systems efficiencies will be evaluated in regression models comparing intervention and control clinics on service outcomes including median client wait time. We will include selected costing indicators at all sites in consultation with the UW CFAR Health Economic Impact Study Team for future cost-modeling, although a complete cost-effectiveness analysis is beyond the scope of this application.

Implementation outcomes and health system outcomes will be evaluated using standard qualitative and quantitative analysis methods, corresponding to the type of data collected to measure each implementation outcome. The majority of implementation surveys will be evaluated using Likert scales, and data will be summarized using basic descriptive statistics. Qualitative data will be analyzed using thematic analysis approaches that account for the use of implementation frameworks (CFIR, FRAME). Themes will be organized based on selected frameworks. Adaptation of the intervention will include measuring micro-changes tested and evaluation of the results of these changes.

9.4.4 SAFETY ANALYSES

NA

9.4.5 BASELINE DESCRIPTIVE STATISTICS

NA

9.4.6 PLANNED INTERIM ANALYSES

NA

9.4.7 SUB-GROUP ANALYSES

Subgroup analysis will be performed by gender and age group for primary and secondary outcomes. As with the primary analysis, sub-group analysis will be adjusted to account for clustering.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed.

9.4.9 EXPLORATORY ANALYSES

NA

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol

Aim 1

- Stakeholder consent to participate in workshop
- HCW consent to participate in pilot study
- Adolescent consent to participate in facility-based intervention
- Consent for HCW post-pilot FGD

Aim 2

- Adolescent consent to participate in facility-based intervention
- Adolescent consent to participate in surveys (age 18+)
- Adolescent assent to participate in surveys (age under 18)
- Caregiver consent for adolescent surveys (age under 18)
- Caregiver consent for enrollment
- HCW consent to participate in IS activities
- HCW consent to participate in annual surveys
- Facility survey consent
- HCW consent for FGD and IDI (Intervention sites)

- Adolescent consent to participate in FGD and IDI (age 18+)
- Adolescent assent to participate in FGD and IDI (age under 18)
- Caregiver consent for adolescents to participate in FGD and IDI (age under 18)

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Prior to conducting consent, study staff will confirm eligibility. Adolescents and caregivers who are eligible will begin the consent/assent process. Study personnel will read through the consent or assent form with policy makers at national and county level, adolescent representatives, frontline HCW, adolescent caregivers and representatives from HIV care partners. During this process, potential participants will have the study and relevant study procedures explained to them, their questions answered, and provide written consent for their enrollment.

If ALHIV participants <18 are brought to clinic by a caregiver, the caregiver will provide written informed consent and the ALHIV will assent to participate in the study. However, adolescents <18 who meet the definition of emancipated minor (pregnant/has child, married/partnered, financially or otherwise independent of parents) or mature minor (age 15, living apart from parents, and managing own finances) under Kenyan law will be able to provide written consent as adults. We will request a waiver of parental permission for adolescents ages 15-17 who do not meet emancipated minor criteria and whose caregivers are not present. Caregivers will be informed that providing informed consent for their child does not permit them access to their child's survey responses. Adolescents and caregivers will be told that participation in the study will not affect their child's or their own personal care. Enrollment for adolescents less than 15 years of age will require caregiver consent.

Assessment of consent/assent understanding:

Comprehension will be assessed by asking the participant to repeat back what was explained and encourage them to ask questions. Study staff may ask the participant questions like the following to assess comprehension:

a. "Just so that I'm sure you understand what is expected of you, would you please explain to me what you think we're asking you to do?"
b. "Describe in your own words the purpose of the study."
c. "What more would you like to know?"
d. "What is the possible benefit to you of participating in this study? What are the possible risks?"

If the participant is unable to answer these questions, study staff will go through the consent form with them again. If a participant continues to be unable to understand the study procedures and risks and benefits, the staff person will thank them for their time and let them go without enrolling them into the study.

Children who become adults during the study (age 18) and whose caregivers had provide informed consent will be re-consented at their next visit.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to participating clinics, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study clinics and participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in a setting as private as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB) or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on a secure server hosted by the University of Washington, accessible by both Kenya and US based teams. The study data entry and study management systems used by clinical sites and by UW research staff will be secured and

password protected. At the end of the study, all study databases will be de-identified and archived at the UW.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Data may also be shared across studies in the PATC^{3}H program – composed of 8 research teams conducting clinical research to improve health outcomes among adolescents at risk for HIV. Data shared across the consortium members will not be considered public use.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

Our data storage, transfer, and ownership will conform to Kenya's Data Protection Policy (2018).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the UW. After the study is completed, the de-identified, archived data will be transmitted to and stored at the UW, for use by other researchers including those outside of the study. Permission to use data will be included in the informed consent.

When the study is completed, access to study data will be provided through the National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH) https://dash.nichd.nih.gov.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Principal Investigator**	**Site Principal Investigator**	
Pamela Kohler Associate Professor, Nursing, Global Health	Grace John-Stewart Professor, Medicine, Epidemiology, Pediatrics, Global Health	Kawango Agot Founder, Director, Impact Research & Development Organization (IRDO)	
University of Washington	University of Washington	IRDO	
Harborview Medical Center 325 9th Avenue, Box 359932 Seattle WA 98104 USA	Harborview Medical Center 325 9th Avenue, Box 359932 Seattle WA 98104 USA	Tuungane Hospital, Tom Mboya Estate Mito Jura Road, off Kisumu-Kakamega Highway P.O. Box 9171-40141 Kisumu, Kenya P.O Box 9171-40141, Kisumu, Kenya	
+1-206-616-7962	+1-206-543-4278	+254-727-688550	
pkohler2@uw.edu	gjohn@uw.edu	kawango@impact-rdo.org	

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including adolescent HIV, epidemiology, biostatistics and implementation science. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet annually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor/National Institutes of Health and regulatory bodies.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable,

and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be as follows:

- Monitoring for this study will be performed by Westat

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct and collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent: Study staff will review both the documentation of the consenting process as well as 100% of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source and the electronic documents data: Data will be directly entered into the study database (see Section10.1.9, Data Handling and Record Keeping).

Intervention Fidelity: Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in Section 6.2.1, Interventionist Training and Tracking.

Protocol Deviations: The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

10.1.9 DATA HANDLINGAND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study if needed. Data recorded

in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Survey data will be entered during client encounters into a REDCap database a 21 CFR Part 11-compliant data capture system provided by the UW. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.9.2 STUDY RECORDS RETENTION

Records retention will follow required IRB/ERC and sponsor guidelines.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonization, Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:
- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation. Protocol deviations will be sent to the reviewing IRB/ERC per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information

Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. In accordance with the NIH Data Sharing Policy, de-identified data will be stored in the National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH) (*https://dash.nichd.nih.gov*) indefinitely. Data from this study may be requested from other researchers through DASH. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NICHD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

NA

10.3 ABBREVIATIONS AND SPECIAL TERMS

AIDS	Acquired Immune Deficiency Syndrome
ALHIV	Adolescents Living With HIV
AMHR	Applied Mental Health Research
ART	Antiretroviral Therapy
CAB	Community Advisory Board
CEO	Chief Executive Officer
CFAR	Center For AIDS Research
CFIR	Consolidated Framework for Implementation Research
CRT	Cluster Randomized Trial
CCC	Comprehensive care clinic

DiSC	Data Informed Stepped Care
DSMB	Data Safety and Monitoring Board
EMR	Electronic Medical Records
ERC	Ethical Review Committee
FGD	Focus Group Discussion
GEE	Generalized Estimating Equations
HCW	Health Care Worker
HIV	Human Immunodeficiency Virus
HS	Health Systems
HSD	Human Subjects Division
IDI	In-Depth Interview
IRB	Institutional Review Board
IRDO	Impact Research and Development Organization
IS	Implementation Science
KNH	Kenyatta National Hospital
LTFU	Loss To Follow Up
MoH	Ministry of Health
NICHD	National Institutes of Child Health and Development
NIH	National Institutes of Health
NASCOP	National AIDS and STI Control Program
RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance
RCT	Randomized Controlled Trial
sSA	Sub-Saharan Africa
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
UW	University of Washington

VL	Viral load
WHO	World Health Organization

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.0	20-Dec-2020	Updated the protocol to address questions from MU ERC. These include updates to consent forms 05, 06, & 07; updated ages for providing consent;	To address comments from MU ERC.
3.0	13-May-2021	Asked for waiver of written consent for participation in intervention	MUERC did not approve for waiver of written consent
3.0	3-Aug-2021	Submitted additional consents for participation in intervention	MUERC approved additional consents for participation in intervention

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