Strategic Antiretroviral Therapy and HIV Testing for Youth in Rural Africa

The SEARCH Youth Study

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Sponsor: University of California, San Francisco

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
• 8.1.6	• Updated Assessment of Infant Outcomes section to include details on additional viral load testing of participating mothers and facilitation of standard care HIV testing of infants as needed.	• To include a final measurement of viral load suppression among this subset of participants and ensure their infants have completed all required HIV testing according to country programs.
• 8.1.7, 9.4.3.7	• Added Assessment of Mental Health procedures for participants in the RCT at both clinics and intervention sites, including the analytic approach for statistical analysis.	• To understand the effect of the intervention on participants' mental health and any major life events at the end of their study participation.
• Throughout protocol	• Minor typographical corrections.	• To make minor edits for to correct typographical errors.

CONFIDENTIALITY STATEMENT

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation 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.]

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.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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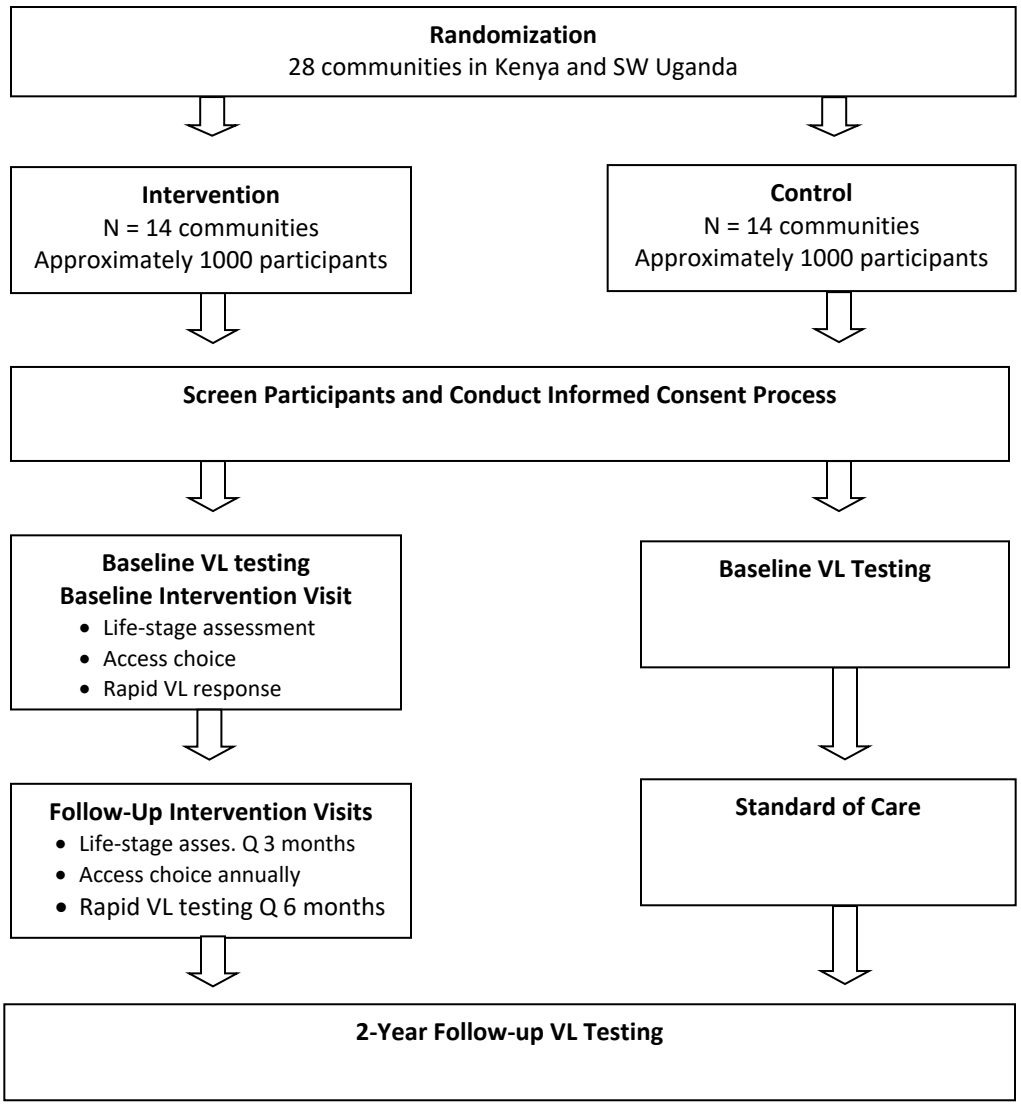
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Strategic Antiretroviral Therapy and HIV Testing for Youth in Rural Africa
Grant Number:	UG3 HD96915-01
Study Description:	A cluster randomized study to evaluate the effect on HIV viral suppression of a combination intervention designed to address the structural barriers, psychological and social needs of HIV-positive youth in rural Uganda and Kenya.
Objectives:	Primary Objective: To determine the effectiveness of the SEARCH Youth intervention in increasing long-term retention and virologic suppression Secondary Objectives: 1. To investigate barriers and facilitators of the SEARCH Youth intervention 2. To estimate incremental costs and gains of the SEARCH Youth intervention 3. To evaluate the effectiveness of the youth HIV testing and referral strategy to SEARCH youth clinics 4. To characterize alcohol use and its effect on viral suppression among HIV-positive youth 5. To evaluate the impact of SEARCH Youth intervention on HIV-free survival of infants born to participants
Endpoints:	Primary Endpoint: Proportion of study participants with virologic suppression (HIV RNA <400 c/mL) at 2 years of follow-up Secondary Endpoints include 1. Retention in care 2. Sustained viral suppression 3. Virologic failure 4. Cost of care delivery 5. Uptake and yield of community outreach to identify new HIV infections 6. Alcohol use 7. HIV-free survival among infants born to participants
Study Population:	Approximately 2000 HIV-positive youth, ages 15-24, in rural Uganda and Kenya
Phase or Stage:	Phase IV
Description of Sites/Facilities Enrolling Participants:	28 health centers in rural Southwestern Uganda and Western Kenya serving HIV-positive patients

Description of Study Intervention/Experimental Manipulation:	The intervention consists of 3 components: 1. Life-stage assessment tool and provider e-collaboratives 2. Structured choice clinic access 3. Rapid viral load (VL) feedback
Study Duration:	5 years
Participant Duration:	At least 2 years beyond enrollment until end of the study

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

	Baseline[1]	3 months[1]	6 months[1]	9 months[1]	12 months[1]	15 months[1]	18 months[1]	21 months[1]	24 months[1]	Every 3 months[1]
INTERVENTION AND CONTROL SITES										
Eligibility Screen	X									
Informed Consent	X									
Baseline Questions	X									
2-Year Follow-Up VL									X	
INTERVENTION SITES										
Life-Stage Assessment[2]	X	X	X	X	X	X	X	X	X	X
Structured Choice Clinic Access Review[3]	X				X					
Baseline VL and Rapid Feedback	X									
Follow-Up Rapid VL and Feedback[4]			X		X		X		X	Every 6 mo.
Provider Consultation via WhatsApp[5]	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed
CONTROL SITES										
Baseline VL	X									
Standard Care	X	X	X	X	X	X	X	X	X	X

1. Regular study visits in intervention and control sites will coincide with participants' standard care visit schedule, which is generally every 3 months
2. The Life-Stage Assessment will occur every 3 months, or more frequently as needed
3. The structured clinic access choice review will occur at least annually, but participant choice may be updated more frequently as needed
4. Rapid VL testing and feedback will occur every 6 months when the participant is suppressed; however participants with detectable VLs will be tested roughly every 2-4 weeks by clinician decision, with feedback and support, until suppression is achieved or until a time point that the participant is not amenable to changing adherence or medications as advised by the provider
5. Provider consultation and discussion via WhatsApp will occur for detectable VL test results and for any other issue or barrier to adherence identified by the study staff as requiring consultation, as needed

2 INTRODUCTION

2.1 STUDY RATIONALE

Adolescents and young adults with HIV (AYAH) represent a growing share of people living with the disease in sub-Saharan Africa (SSA). AYAH have lower HIV testing rates, engagement in care and viral suppression (VS) compared to adults.[1-5] We postulate that to achieve successful testing and longitudinal care of AYAH, interventions must be tailored to the dynamic social and cognitive needs of AYAH as they pass through life-stages, including both in- and out-of-health facility components. SEARCH Youth will be the first rigorously tested combination HIV intervention for AYAH in rural SSA that: a) incorporates youth in testing outreach, b) is grounded on contemporary understandings of social development with its life-stage approach, and c) includes AYAH new to care, re-engaging in care and already in care, d) has viral load (VL) as primary endpoint, and e) is designed to address the specific psychological, social, and gender needs of AYAH, in way that is cost effective and scalable for implementation in rural settings. Our proposed work is addressing 2 significant gaps: 1) Individual, clinic and/or community/ system level combination interventions to improve outcomes on the HIV care continuum for youth living with HIV), and 2) Implementation of youth friendly strategies to improve uptake of biomedical interventions (HIV testing and linkage for ART) for infected and/or at-risk youth.

2.2 BACKGROUND

An estimated 2.2 million adolescent and young adults are living with HIV in sub-Saharan Africa. In a study of 4 countries in SSA, the proportion of youth aged 15-24 years (n=53,244) who initiated ART by 1 year was only 25% compared to 46% among 25-54 year old adults (n=240,440).[1] Compared to adults, AYAH in SSA are 1.6-1.8 x more likely to be lost to follow up,[1,2] twice as likely to report lapsed adherence[3], and 1.5-3.2 times more likely to be viremic,[3-5] and adolescent girls and young women have four times the HIV prevalence of their male counterparts.[6] In rural settings where the burden of HIV among youth is substantial, additional challenges exist. In Kenya, 70% of people living with HIV reside in rural areas.[7] Mortality rates are higher among HIV- infected persons in rural vs urban SSA.[8,9] AYAH attending clinics outside of urban areas have higher attrition (RR: 1.2) 1 year after linkage.[1] Barriers in rural areas include distance to clinics[10] transportation costs,[11] decreased access to lab services[12] and other social influences.[13] Our strategic combination HIV intervention aims to engage, retain-in-care and increase VS among AYAH to reduce new infections and mortality in rural East Africa. We will generate evidence-based approaches aimed to direct resources towards what works and divert funding away from those that do not. We will additionally use mixed methods and costing studies to understand mechanisms of intervention components and to provide information for countries considering using this strategy for AYAH.

AYAH face barriers to HIV testing and long-term care that vary by life-stage, gender, and individual context. Between the ages of 10 and 24 years, AYAH go through a series of distinct life-stages that impact their decision making, healthcare-seeking behavior and outcomes. As described in the conceptual framework of Sawyer et al[14], and recently highlighted by the WHO,[15] cognitive and social role changes interact with social determinants to impact AYAH health behaviors and outcomes throughout this period (Table 1).

Table 1. Conceptual Framework of AYAH Life-Stage, Development, Events, and Barriers

Life-Stage	Cognitive Development	Social Development	Life Events	Barriers to HIV Testing and Care
Early Adolescence (10-14 years)	• Moving from concrete to abstract thought • Immediacy	• Struggle with identity • Worry about being normal • Conflict with parents • Desire for independence and privacy	• Lives at home or move to boarding school • Orphaned	• Concern for consequences of testing on identity • Worry that clinic attendance and medications leads to disclosure in school settings & stigma • Standard counseling based on long term life goals not effective
Late Adolescence (15-19 years)	• Abstract thinking • Goal setting • Moral reasoning	• Intense self-involvement • Distancing from parents and new responsibilities • Increasing influence of peers • increasing interest in sex	• Sexual debut; • Boarding school, first employment, migration • Marriage	• Shifting social and support systems from families, to peers, to partners means evolving needs for disclosure • Increased sexual activity and marriage lead to different counselling needs (STI to contraception to safe conception) • Change in daily schedules and residence– home / school / work - lead to shifts optimal timing and locations of clinic visits
Young Adulthood (20-24 years)	• Can delay gratification • Increasing concern for future	• Firmer sense of identity, increased concern for others, developing more serious relationships	• Marriage and then children, responsibility to others about life outcome	

Table adapted from Sawyer et al.[14]

Formative Research with AYAH in East Africa Has Identified Significant Barriers to HIV Care. In developmental research with AYAH in Uganda and Kenya, we interviewed AYAH to learn what they perceived as the barriers and facilitators to successful engagement in care and adherence (Table 2). We surveyed 20 clients aged 15-24 years. Respondents had a median age of 20.5 years, 16(80%) were female, 10(50%) were married, and 6(30%) were in school. Issues around stigma, particularly in the home environment, were prevalent barriers to clinic attendance and medication adherence. Several reported transport difficulties and distance to clinic were deterrents to visits. AYAH valued their relationships with providers, with 89% reporting they liked meeting with their providers when at clinic. Only 30% felt they had enough information about HIV; all expressed preference to learn more in conversations with their own provider.

Table 2. Barriers to Medication Adherence and Clinic Attendance

Barrier	AYAH Comments	SEARCH Youth Intervention Component	Mechanism of Action
Life-stage changes (marriage, school) that affect adherence	***Question: what makes taking medication HARDER?*** *"I am still young and most friends are not taking any drugs."* *"Eventually I got married and had to stop medication for the sake of my husband as I had not disclosed my status."* *"Sometimes I couldn't get time to go for the drugs without being seen. They still don't know my status."*	**Predisposing**: Life-stage specific counseling; facilitated disclosure	Structured re-evaluation of life-stage enables providers to promptly act when social structures and change
Structural barriers to care	***What makes attending appointments HARDER?*** *"People knowing that you are going to a HIV clinic."; "There is a long distance to clinic";" My school is very far from the clinic"* *"Sometimes I don't want other people to see me when I come on my day of convenience"; "It disrupts my work."* ***What makes attending appointments EASIER?*** *"Attending clinic in late evening"; A majority said that early and late hours would make attendance easier*	**Enabling**: Choice of clinic access 1. alternative-hours 2. option for phone visits 3. provider choice	Choice respects developing sense of autonomy among AYAH; multiple options allow clinic access be tailored to the case-specific pressures
Feedback/ motivation for adherence	***Do you think that knowing your viral load helps you take your medications better?*** *- 88% replied yes* *"It helps me because it gives me courage to take my medication"*	**Reinforcing**: Rapid VL feedback & Counseling	Prompt identification of adherence issues. Concept of viremia adapts to abstract thinking development.

The SEARCH Youth combination HIV intervention was developed using the proven PRECEDE Implementation Science Framework. To improve engagement in care and increase viral suppression we developed the SEARCH Youth combination HIV intervention structured on the empirically-validated PRECEDE model.[16] This model has shown that health promotion strategies are most effective when they address: (1) "predisposing factors" comprised of knowledge, attitudes or beliefs that affect behavior; (2) "enabling factors" that facilitate change by making the behavior "easier"; and (3) "reinforcing factors" which include anticipated consequences following a behavior. Use of a proven implementation science framework enhances both the scientific rigor of the intervention research and likelihood of success. Although this life-stage based approach using PRECEDE has not been tested in HIV care, there are data that multi-level interventions based on behavioral theories work in other diseases such as diabetes in youth[17].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The SEARCH Youth intervention works through provider behavior change, health systems changes: more flexible clinic hours and same day viral load testing – none of which pose significant risk to participants. Participants in our study all receive HIV antiretroviral therapy recommended by the ministries of health in Uganda or Kenya. There are neither "experimental" drugs nor un-recommended uses of standard medications in this study. Participants will have access to second and third line ART as per country guidelines. The primary immediate and long-term risk for youth is therefore loss of confidentiality. This could occur during testing, clinic-based care, or through the use of WhatsApp by the providers.

2.3.2 KNOWN POTENTIAL BENEFITS

AYAH enrolled at clinics randomized to the intervention arm might benefit from improved retention and virologic suppression from the components of the intervention, including increased access to clinic, access to ancillary services such as reproductive health, counseling based on the assessments and feedback from the more frequent viral load testing. Knowledge gained from this study could improve strategies for viral suppression and retention outcomes among AYAH.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

It is necessary to collect a minimal level of potentially sensitive information in order to practically conduct the study. We will seek to protect participants against the risk to confidentiality as follows:

Risk of HIV Status Disclosure: Given the sensitive and private nature of the HIV-status of participants of the randomized controlled trial (RCT), extra measures will be put in place to ensure maintenance of privacy, confidentiality and security of the data obtained. Contact mobile numbers will be re-checked to insure they are updated.

Use of WhatsApp: We are implementing a number of measures will protect the privacy of participants discussed on WhatsApp. First, participation in WhatsApp chats will be strictly limited to the providers participating in this study. As such, participant clinical information will remain within providers of the same health system, a practice generally considered acceptable when the goal is to improve medical care. Second, all participating providers will be required to attend a training in which they review and are tested on Standard Operating Procedures which outline specifically the acceptable and unacceptable information for discussion. For example, the use of names, birthdays, specific locations or any other potentially participant specific information is prohibited. Chats will be monitored by study staff to ensure that these guidelines are being adhered to. Finally, all transmissions of WhatsApp are encrypted, greatly reducing the risk that someone outside of the chat could intercept and read transmitted messages.

Data Security: All information will be recorded using study identification numbers, rather than participant names, and stored securely in locked offices at a study data center. All study computers will be password encrypted and kept in locked offices.

Institutional Review Board Approval: The proposed research study will be reviewed and approved by the IRBs of all the participating institutions in the U.S., Uganda and Kenya. This includes the UCSF Committee on Human Research (CHR), the Makerere University School of Medicine - Research and Ethics Committee (SOM-REC), the Uganda National Council of Science and Technology (UNCST), the Kenya Medical Research Institute (KEMRI).

Considering the minimal risk involved in this study and the potential benefit to health care providers and the scientific community, the investigators have determined that the potential information gained outweighs the risk of study participation.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the effectiveness of the SEARCH Youth intervention in increasing long-term retention and virologic suppression. We will compare the proportion of AYAH with virologic suppression (HIV RNA <400 c/mL) in each of the 14 clinics randomized to intervention versus those in 14 clinics randomized to the control condition, adjusting for clustering within clinics.	Proportion of study participants with virologic suppression (HIV RNA <400 c/mL) at 2 years of follow-up	This measure captures care outcomes that the combination SEARCH Youth intervention has been designed to achieve
Secondary		
1. **To investigate barriers and facilitators of the SEARCH Youth intervention,** we will use a mixed-methods approach of qualitative analysis of in-depth interviews (45 participants, 15-20 family members, 12-24 care providers and 6 key informants) at baseline and follow-up years combined with focus groups, quantitative process and fidelity data. In addition, focus groups and provider interviews will inform intervention development for HIV prevention among high risk youth.	1.a. Qualitative interview and focus group data 1.b Quantitative process measures	Understanding the perception of participants and providers will inform the future implementation and refinement of the intervention.
2. **To estimate incremental costs and gains of the SEARCH Youth**	2.a. Health facility level costs	Knowing which elements of the combined intervention

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
intervention over the continuum of care associated with the SEARCH Youth intervention using micro-costing and time-in-motion analyses.	2.b. Health gains (as per primary study outcome, disability-adjusted life years (DALYs)	were implemented with high fidelity might increase understanding of which are the most important to the primary outcome Quantitative cost and cost-effectiveness data will help inform stakeholder decision makers about the value and feasibility of the intervention
3. To evaluate the effectiveness of the youth HIV testing and referral strategy for ART.	3.a. Uptake of HIV testing (total number tested) 3.b. Yield (percentage of individuals testing HIV-positive with a new or out-of-care HIV diagnoses)	These are the key metrics generally used to assess the efficacy of testing programs
4. To characterize alcohol use and investigate its impact on viral suppression, we will measure alcohol use by self-report and blood-based biomarker and assess associated risk factors in participants randomized to the intervention at scheduled study visits	4.a. Self-reported alcohol use (by Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score) 4.b. Biomarker-measured alcohol use (by phosphatidylethanol (PEth))	Knowing the relative contribution of alcohol use to viral non-suppression may inform future implementation and refinement of the intervention
5. To evaluate the effect of the SEARCH Youth intervention on HIV-free survival among infants born to participants	5.a. Proportion of infants who remain alive and HIV-free at 1 and 2 years 5.b. Proportion of infants who complete country-specific testing programs for HIV-exposed infants	A larger portion of women deliver children during this age period. The SEARCH youth intervention could improve outcomes by reducing vertical transmission via higher rates of maternal virologic suppression, and increased participation in exposed infant follow up programs.

4 STUDY DESIGN

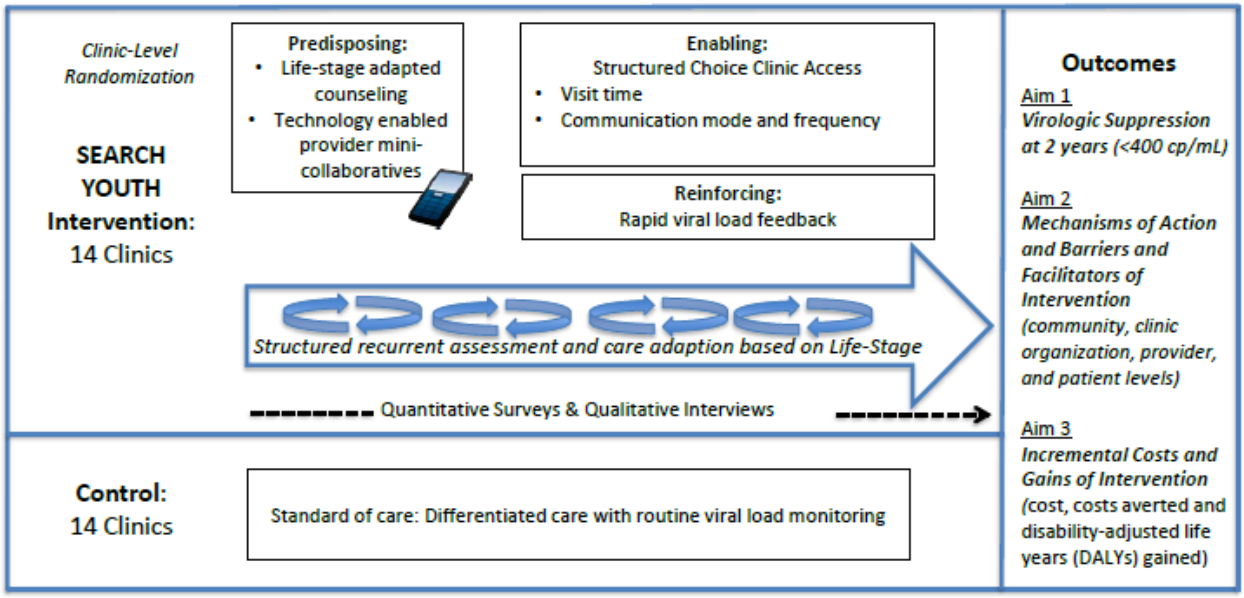
4.1 OVERALL DESIGN

The goal of this study is to evaluate the effect of the SEARCH Youth combination intervention on long-term HIV viral load (VL) suppression among HIV-infected adolescents/young adults 15-24 years of age in 28 HIV clinics in western Kenya and southwest Uganda. SEARCH Youth is a multi-level combination HIV intervention based on the PRECEDE model of behavioral change that is targeted towards adolescent and young adult behavior described above.

The study design is a cluster-randomized trial where the unit of randomization is the HIV clinic: 14 clinics randomized to the intervention and 14 to the optimized country standard of care (Differentiated ART care, standard clinic hours, routine VL monitoring, access to 2nd and 3rd line ART), balanced within country. Our target enrollment for the intervention is approximately 2000 (50-100 AYAH in each clinic).

The primary endpoint of the full RCT is the proportion of adolescents and young adults achieving VL suppression two years after the start of the intervention. Secondary endpoints include: a) Retention in care, and other virologic outcomes (sustained virologic suppression, virologic failure), b) costing and cost-effectiveness, and c) yield of community testing programs to identify persons with new HIV diagnosis.

Figure 1. RCT Study Design and SEARCH Youth Combination HIV Intervention Components



Clinics will be randomized using a stratified randomization with strata of total clinic participant load size (<300, ≥300) and region (Kenya or Uganda). Fourteen (14) clinics will be randomized to the intervention condition (SEARCH Youth intervention) and 14 clinics randomized to the control condition (optimized country standard of care).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The randomized-controlled trial design was chosen to avoid the potential confounding to which single arm observational trials of clinic-based outcomes are particularly vulnerable. The choice to cluster by clinic was made because implementing the components of the intervention on an individual participant level would be logistically challenging, not approximate the real-life implementation and risk contamination of the control arm as providers and participants in the same clinic would be aware of intervention vs control. It was felt important to have a true contemporaneous standard of care arm to demonstrate the costs and values added from the intervention, particularly in relation to any other changes that could occur over this period of time (e.g. changes in national treatment guidelines.)

4.3 JUSTIFICATION FOR INTERVENTION

To increase the feasibility and generalizability of the intervention, its elements (counseling, viral load testing) were designed to occur in accordance with standard clinical practice and visit frequencies in the participant countries. Because loss-to-follow up is part of the primary study outcome measure, it is difficult to state a "minimum acceptable" participation necessary to assess the intervention, but by that logic, the minimum could simply be considered completion of the enrollment visit.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as the completion of the last participant reaching the 2-year follow-up VL assessment among all participants in the SEARCH Youth intervention RCT.

5 STUDY POPULATION

The study population will consist of:

- HIV-infected youth taking part in the SEARCH Youth intervention RCT; a subset will also take part in in-depth interviews, focus group discussions, patient satisfaction surveys, or alcohol use surveys and alcohol blood-based biomarker measurement
- Community members who are tested as part of youth testing activities
- Family members/partners of a subset of HIV-infected youth taking part in the intervention RCT who will participate in an in-depth interview
- Care providers in clinics taking part in the intervention RCT or providing pre-exposure prophylaxis (PrEP) who will participate in an in-depth interview

- Community/regional health officers with responsibility for care at clinics taking part in the intervention RCT who will take part in an in-depth interview
- HIV-uninfected youth in the community who will take part in focus group discussions to elicit input on the concept and design of community-based PrEP delivery interventions to foster PrEP uptake and adherence
- Infants born to study participants during the study period

5.1 INCLUSION CRITERIA

In order to participate in the SEARCH Youth intervention RCT study, individuals must meet all of the following criteria:

1. HIV infection diagnosed according to country testing guidelines
2. Age 15-24 years
3. Enrolled in care in a study clinic
4. Ability and willingness to provide informed consent

Eligibility requirements for participants taking part in in-depth interviews and focus group discussions will meet minimal inclusion criteria described in the section 8.1.3.

Eligibility requirements for participants taking part in the alcohol sub-study will meet minimal inclusion criteria described in the section 8.1.5.

Eligibility requirements for infants are being born to a study participant, as described in section 8.1.6.

5.2 EXCLUSION CRITERIA

N/A.

5.3 LIFESTYLE CONSIDERATIONS

N/A.

5.4 SCREEN FAILURES

The entry criteria for inclusion in the SEARCH Youth intervention RCT or in-depth interviews will be determined prior to obtaining informed consent.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

A total of 28 rural clinics will participate in the study with 14 located in Uganda and 14 in Kenya. The clinics that will be chosen serve at least 10,000 people in their catchment area and are staffed typically by a medical doctor, a clinical officer, and a nurse. Study clinics will be selected with the cooperation of regional health directors for southwestern Uganda (outside Mbarara) and western Kenya (outside Homa Bay town) ensuring comparability in populations served, community HIV prevalence, HIV services and staffing within each region/country. Geographic location of clinics will be selected to reduce cross clinic "contamination."

Strategies for recruitment will be tailored to specific communities, such as youth-lead testing and linkage strategies, strengthening of efforts at clinics to reengage AYAH who have been lost to follow-up, and recruitment of AYAH engaged in care at the clinic. To reach youth at the highest risk of HIV infection, we will implement testing programs that take place outside of the clinic, or augment or coordinate with existing testing programs. High-risk populations include, but are not limited to, recently married women, adolescent girls, youth working in the casual sector (maids, motorcycle taxi drivers, field workers), school drop outs, men-who-have-sex-with-men (MSM), informal and commercial sex workers (SW). The community-tailored approaches to recruitment might include youth testing teams comprised of clinic providers and local youth leaders; youth testing programs such as PrEP "seed" youth to encourage testing among peers and youth club and public event mobile testing; and a mobile testing team resources to facilitate linkage.

Target enrollment will vary by clinic and community size, averaging approximately 50-100 AYAH in each of the 28 rural clinics, to achieve a total of approximately 2,000 participants overall.

Inclusion of children: Youth aged 15-24 years will be enrolled in the study, therefore minors <18 years of age will be included. The study is considered of minimal risk to participants, including minors. The Uganda National Council for Science and Technology (UNCST) has determined that individuals aged ≥ 14 years are able to provide independent consent for research if they have a sexual transmitted infection, and the National AIDS and STI Control Programme (NASCOP) and Kenya Medical Research Institute (KEMRI) state that individuals aged ≥ 12 years are able to provide independent consent for research. In both Uganda and Kenya, children of the age represented in this study can obtain HIV testing services and HIV care without parental consent, and including parental accompaniment could significantly inhibit youth from accessing these services. As with adults, AYAH <18 years will be given sufficient time to read or be read the consent form in their language and to ask any questions.

Infants of participants enrolled in the SEARCH Youth RCT at clinic sites randomized to the intervention and control, born during the study period, may also be enrolled in an assessment of outcomes via medical record data collection and maternal report. Women who have delivered will be approached for this data collection and, if interested, provide informed consent. Mothers <18 years will take according to the same guidelines described above.

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

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

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The randomized controlled trial (RCT) will evaluate the effect of the SEARCH Youth intervention on long-term HIV viral load (VL) suppression among HIV-infected adolescents/young adults.

SEARCH Youth Intervention Components

The components of the SEARCH Youth intervention might include the following:

Life-stage assessment tool**.** The "life-stage assessment tool," is a checklist-driven structured evaluation of life issues at the beginning of each visit that a) links to life-stage specific actions (Table 3), and b) puts subsequent medical discussions in an appropriate context.

a) Providers will receive initial or refresher training with country-approved curriculum on the development of youth from age 15 years, through adolescence and into adulthood and associated medical issues (e.g. contraception, alcohol use). After initial greetings, providers are prompted by the "life-stage" checklist to record: i) life status ii) major life events iii) support system iv) behaviors v) HIV disclosures. This checklist is updated at least every 6 months or more often as needed.

Table 3. Life-Stage Checklist Components

Life-Stage Assessment Area	*Examples of linked care action*
Life status: age strata, student, work, marital status, residence	Care coordination plan, school care transfer plan, family planning
Major life events: start or stop school or employment, financial strain, marriage, divorce or relationship strife, change in residence, new sexual partner or break-up, family death	Counseling, linkage to support groups and community services
Support system: supporting persons, feeling lonely or isolated, feeling bullied or ostracized	Counseling, peer support linkage
Behaviors: alcohol, STI risks	Alcohol counseling, reproductive health appointment and counseling
Completed and desired HIV disclosures: family, partner, friends	Facilitated Disclosure
Priority issues for participant: list	Issue specific action plans

Structured Choice Clinic Access.
To lower barriers to remaining in care, participants will also have a choice to schedule visits during routine clinic or before/after standard clinic hours, or in a location other than the clinic, as resources allow. There will be a minimum frequency of visits directed by medical needs and national standards. Participants can also elect to have phone-only visits between in-person visits.

Rapid VL Feedback. Participants will be provided with viral load results as soon as available, but always aiming to occur within 72 hours (to accommodate Friday-weekend visits and home visits for participants who don't have phones). Rapid viral load testing will be performed with technology such as the

Cepheid GeneXpert device to provide immediate feedback on their HIV suppression and engage AYAH in their overall health.

Provider E-Collaboratives Providers will also participate in "e-collaboratives," that comprises chat group using WhatsApp or similar secure messaging application. This gives providers an opportunity to solicit input about this new provider-participant approach and to provide suggestions for any challenging clinical situations. To ensure confidentiality of participants, providers are trained, and the use of names or any potentially identifying information is avoided.

6.1.2 ADMINISTRATION AND/OR DOSING

All intervention components will be conducted in clinics randomized to the intervention. Participants will meet with clinicians on a one-on-one basis and will not interact with other participants as part of the intervention.

Life-stage assessment tool: The life-stage assessment tool is designed to be performed at routine visits, typically every 3 months at routine visits.

Structured Choice Clinic Access: Initial selection visit time and location will occur at the first study visit. Participant preferences will be reviewed and, if needed, updated at least annually with each participant.

Rapid VL Feedback: Rapid VL testing will be performed at least every 6 months. Participants with detectable VL results will be tested roughly every 2-4 weeks according to clinician decision, until he or she is undetectable (according to the assay's lower limit of detection) or until a time point that the patient is not amenable to changing adherence or medications as advised by the provider.

Provider E-collaboratives: The WhatsApp e-collaboratives tool will be utilized as needed, for challenging issues including discussion of solutions to treatment barriers, detectable VL values, or other situations in which consultation with experts outside the clinic is needed.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will collect quantitative process and fidelity measures corresponding to each of the components of the intervention through chart review of medical records, study case report forms, survey, and review of administrative records, and archives of the WhatsApp secure messaging conversations. Survey measures may include brief survey questionnaires of patient satisfaction

Feedback on key recruitment, data collection and VL suppression metrics will be provided via regular data reports to study sites.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Clinics will be paired using clinic population size, socioeconomic, and geographic characteristics, then randomized using computer-generated randomization list with a random seed. Fourteen (14) clinics will be randomized to the intervention condition (SEARCH Youth intervention) and 14 clinics randomized to the control condition (optimized country standard of care).

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Because the intervention is primarily being implemented by providers, adherence will be encouraged by training at the outset of the study, and periodic monitoring of activity in clinics to ensure that the life stage counseling, rapid viral load assays with communication of results, and e-collaboratives are being utilized.

6.5 CONCOMITANT THERAPY

N/A.

6.5.1 RESCUE THERAPY

N/A.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Participants who discontinue from the SEARCH Youth intervention will also be discontinued from the overall study, however they may continue to receive care at the clinic according to country standard care guidelines. Section 7.2 describes participant discontinuation from the study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue a participant from the study for the following reasons:

- The participant meets a previously unrecognized exclusion criterion
- Significant non-compliance with the study
- Any event or situation that occurs such that continued participation would not be in the best interest of the participant

The reason for discontinuation and date of discontinuation will be documented on the SEARCH Youth Participant Withdrawal/Move case report form (CRF).

7.3 LOST TO FOLLOW-UP

A participant who misses clinic visits will not be considered lost to follow-up and can resume participation at any time while study activities are ongoing. If the participant fails to return to the clinic for a study visit, the study staff will attempt to contact the participant by telephone or via home tracking to reschedule the visit.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

8.1.1 COMMUNITY TESTING AND LINKAGE

Community-tailored youth testing and linkage strategies for ART will be implemented to recruit youth for the SEARCH Youth combination intervention RCT. Strategies to reach youth at the highest risk of HIV infection will be implemented. To enable evaluation of the effectiveness of these programs, we will collect data about the numbers of youth tested, the numbers of new diagnosis, and the number successfully linking to Care. Those individuals who test HIV-positive will be referred to the local clinic for HIV treatment services and, if they otherwise meet entry criteria, to the SEARCH Youth study for possible inclusion. Participants who are HIV-negative and who meet criteria for PrEP will be referred to PrEP services at the study clinic, if available.

8.1.2 SEARCH YOUTH INTERVENTION AND CLINICAL OUTCOMES

<u>Clinic Sites Randomized to SEARCH Youth Intervention</u>

- Participants will be screened to determine if they meet eligibility criteria. These participants may be already engaged in care, newly re-engaged or recently diagnosed participants, including those who have linked from youth testing activities. A waiver of consent will be obtained to confirm eligibility during the screening process.

- If participants meet eligibility criteria, they will be approached to discuss the study and, if interested, provide informed consent.
- Contact information will be collected, including home location and mobile phone number(s) if available.
- Baseline information will be collected including but not limited to education, occupation, and ART status.
- The SEARCH Youth Intervention will be provided (see section 6.1.1.):
    i. A Life-Stage Assessment will be performed at the initial visit and at subsequent care visits, generally every 3 months, or more often as needed
    ii. Participants will be offered visits during routine clinic hours or after standard hours, determined at the initial visit and updated at least annually
    iii. Participants will undergo VL testing at the baseline and every 6 months thereafter, via rapid point-of-care testing technology. Results will be provided to participants as soon as possible and ideally within 72 hours by mobile phone, via home tracking visits or by scheduled return clinic visit; undetectable results may be provided at the next clinic visit for participants who cannot be reached by mobile phone
    iv. As needed, providers and local investigators will participate in WhatsApp secure messaging to discuss approaches and solicit feedback for challenging participant-related situations, including but not limited to detectable VL results or barriers to adhering to clinic visits

Clinic Sites Randomized to Control

- Participants will be screened to determine if they meet eligibility criteria. These participants may be already engaged in care, newly re-engaged or recently diagnosed participants, including those who have linked from youth testing activities. A waiver of consent will be obtained to confirm eligibility during the screening process.
- If participants meet eligibility criteria, they will be approached to discuss the study and, if interested, provide informed consent.
- Participants will undergo VL testing at the initial visit, either by routine testing or performed by the study. The results from this testing will be provided to participants at their next routine visit as per standard clinic care.
- Data from participants' clinic medical records will be collected for at least a 2 year period following enrollment, including but not limited to VL results, ART medications, adherence, and illnesses.
- 2 years after enrollment and baseline VL, participants will undergo VL testing, either by routine testing or performed by the study.

8.1.3 IDENTIFICATION OF BARRIERS AND FACILITATORS OF THE SEARCH YOUTH INTERVENTION

Identification of barriers and facilitators may use qualitative interviews with AYAH participants and their family members, key stakeholders including care providers, administrators, HIV control program officers and community leaders, combined with focus groups, quantitative process measures and programmatic data. We will identify mechanisms of action and barriers and facilitators of SEARCH Youth study implementation at the community, clinic organization, provider and patient levels using mixed methods qualitative and quantitative assessments.

Qualitative Study Populations

We will compose six qualitative cohorts for in-depth semi-structured interviews and focus group discussions in select communities at baseline and/or at follow up years 1 or 2 after intervention start. A systematic approach to sampling research participants using probability methods will be undertaken prior to approaching potential participants.

1. Patient cohort:
    - *Initial interviews*: We will purposively select 45 patients in each region (Uganda and Kenya) (intervention n=30; control n=15), with sampling balanced by life-stage, gender, and treatment status (1. new diagnosis; 2. known diagnosis but out of care in past 6 months; and 3. known diagnosis, successfully engaged in care). The patient list will be randomly ordered, and participants will be systematically recruited and consented until the target number for each category is reached. Interviews will explore multiple domains of influence on HIV care engagement, including specific elements of the SEARCH Youth intervention for any interviews done in follow up years.
    - *Follow up interviews*: In the follow up year interviews, we will resample n=45 patients in each region (Uganda and Kenya) (intervention n=30; control n=15), with sampling by life-stage (age), gender, and treatment status in the control and in the intervention sampling by life-stage (age), gender, and viral suppression at follow up. We will maintain many of the baseline patients that fall within the new sampling criteria, and will recruit new patients to achieve our sampling categories.

2. Family member cohort:
    - *Initial interviews*: We plan to select a sample of 15-20 family members in each region Uganda and Kenya) of 45 AYAH in the patient cohort for in-depth interview in select communities to investigate influences of family members. Members of the patient cohort will be asked to provide a list of family members involved with their care seeking, and family members will be recruited. Interviews will explore attitudes toward AYAH (stigma, support), perceived needs of AYAH, attitudes towards HIV care and treatment.
    - *Follow up interviews*: We will sample 15-20 family members in each region (Uganda and Kenya) of 45 of the new AYAH in the patient cohort (at follow up). We will include family members of patients who have been successful at achieving viral suppression

as well as patients who are having challenges either achieving and/or maintaining viral suppression. These family interviews will explore AYAH support, perceived needs of AYAH, attitudes towards AYAH, care and treatment, and elements of the SEARCH Youth Intervention.

3. Provider cohort:
    - *Initial interviews*: We plan to perform in-depth interviews with a sample of 12-24 care providers in each region (Uganda and Kenya) from 3 intervention health facilities, with each including the SEARCH Youth provider clinical officer or nurse, the director or head of HIV care in the facilities this role exits, and peer navigators with one male and female peer where possible. Study staff will work with local partners to identify a cadre of personnel in study clinics to select the purposive sample. Attitudes towards AYAH patients, perceived burden, professional identity/intrinsic vs. extrinsic motivations, and specific elements of the SEARCH Youth intervention in any interviews done in follow up years.
    - *Follow up interviews*: We will conduct follow up in-depth interviews with all providers who were interviewed at baseline year, as well as any new additional providers that may have been hired and are providing care and/or support to AYAH in the SEARCH Youth study. Similar to the baseline year, interviews will explore provider perceptions of HIV/STIs and AYAH, provider views on providing care, perceived burden, professional identity/intrinsic vs. extrinsic motivations, and specific elements of the SEARCH Youth intervention.
    - *PrEP provider interviews*: We will conduct in-depth interviews with up to 10 clinicians that provide PrEP (up to 5 in Uganda and 5 in Kenya) in SEARCH Youth communities to discuss experiences in the provision of PrEP and elicit input on possible future PrEP delivery interventions.
4. Key informant cohort: Six community/regional health officers or leaders with responsibility for care at intervention sites may be selected at the beginning of the trial (3 Kenya and 3 Uganda) to obtain their perspectives on system-level barriers and facilitators, and sustainability of intervention elements.
5. Youth cohort with HIV focus group discussion: Beginning in follow up year 1, we will conduct annual focus group discussions (FGDs) with two cohorts of patients selected in intervention communities within each region (Uganda and Kenya) to assess the extent to which the intervention has affected care engagement. FGDs will take place with the following two groups: virally suppressed and virally unsuppressed. Further, within each FGD, we will ensure a balance by life stage (using age as a proxy) and treatment status (newly in care vs. previously in care), as well as a balance of current treatment status (engaged in care vs. lapsed care). The focus groups will explore individual, interpersonal, and social factor influencing care engagement and retention. Each FGD will have up to 15 participants.
6. HIV-uninfected youth cohort focus group discussion: We will conduct focus group discussions to understand the perspectives of young people on HIV prevention and elicit input on the design of future community-based PrEP delivery interventions (such as clubs)

to increase PrEP uptake and adherence, as well as desired concurrent health services and educational content. We will conduct up to 12 focus group discussions (6 in Uganda and 6 in Kenya), each with approximately 8-12 HIV-uninfected youth (ages 15-24 years), stratified by gender, who are recruited from SEARCH Youth communities, including clinics and testing events. Each focus group participant will also be asked to take part in a brief survey to collect information on demographics and prior PrEP use.

Interview Guides

The interview guides will seek to elicit responses to broad areas of inquiry, including across various guides, patients' attributions for their "success" or "failure" with HIV care engagement, family members' support and influence on AYAH care engagement, providers' perceptions of AYAH needs and perceived burdens and motivations for care-giving of AYAH, and barriers and facilitators of implementation of the intervention. Baseline guides establish key domains of influence on care engagement among AYAH, while follow up interview guides in select communities will investigate perceptions, experiences and reactions to each of the components of the SEARCH Youth intervention among each of the cohorts and samples, in addition to peer and social support and intimate partner/relationships areas of inquiry. The PrEP provider interview guides will focus on the experiences and opinions of clinicians providing PrEP.

Focus Group Discussion Guides

The focus group guides will seek to explore community norms and perceptions about HIV/STIs and adolescent sexual health. It will seek to surface norms, barriers, and potentially challenges are the community and peer level that may impact care seeking and engagement among AYAH. Further, the guides will explore youth's reasons for, barriers to, and facilitators of HIV care engagement, support of family/peers, and interactions with the SEARCH Youth intervention, including clinic spaces, providers, and other peer/network supports. The focus group guides for HIV-uninfected youth will seek to understand the community context and concerns about HIV, knowledge and experiences related to PrEP, and elicit input on the concept and design of PrEP delivery interventions to help youth initiate and adhere to PrEP.

WhatsApp Provider Survey

Providers involved in the study will be asked to complete an anonymous survey on advantages and disadvantages of engaging in WhatsApp group discussions to solicit input and provide suggestions for study participant clinical or social issues.

Patient Satisfaction Survey

We will also administer a brief patient satisfaction survey to all participants after 2-years of follow-up.

8.1.4 INCREMENTAL COSTS AND GAINS OF THE SEARCH YOUTH INTERVENTION

We will use rigorous methods to determine costs of the SEARCH Youth intervention and assess its efficiency and cost-effectiveness as cost per participant, cost per additional participant with viral suppression and cost per DALY gained. We will use standard micro-costing techniques and time-in-

motion (T&M) studies to measure the cost of optimized testing and each component of the SEARCH Youth intervention.

Costs Analysis

We will assess costs at least twice in each health facility: once before and once after adoption of the SEARCH Youth intervention, in order to estimate incremental costs of SEARCH Youth implementation and to compare costs of the intervention to standard of care. "Economic" costs (the true value of resources consumed or "opportunity cost") will be assessed by identifying the value of subsidized or donated resources with information from data bases (e.g. wage rates) and donors, and, as needed, three price quotes from appropriate market sources.

Health Effects

To quantify health effects, we will use directly measured health-related study outcomes (e.g. viral suppression). Second, we plan to integrate the health impact of achieving viral suppression using disability-adjusted life years (DALYs), including years of life gained and the collective disability effects of living with HIV. We might be estimated as DALYs gained for the short term (during the trial) and the long-term (5, 10, and 20 years) using data from the trial, as well as morbidity and mortality attributed to un- or partially- treated HIV disease.

8.1.5 ASSESSMENT OF ALCOHOL USE AND ITS EFFECT ON VIRAL SUPPRESSION

Assessment of alcohol use among SEARCH-Youth intervention participants may include use of surveys, validated alcohol self-report tools (e.g. AUDIT-C), and alcohol biomarker measurement (e.g. phosphatidylethanol [PEth], a blood-based biomarker). We will characterize alcohol use and assess the relationship with viral suppression, accounting for sex and life-stage using the data obtained in the SEARCH Youth intervention (see section 6.1.1).

Participants who are enrolled in the SEARCH Youth RCT at clinic sites randomized to the intervention will be eligible to participate. Potential participants will be approached to discuss the study and, if interested, provide informed consent.

Initial visit: We will administer a questionnaire that will measure alcohol use by self-report and will explore multiple domains of influence on alcohol use and related behaviors. We will collect a blood sample to measure PEth, a biomarker of alcohol use.

Subsequent visits: We will reassess alcohol use and/or risk factors by survey every 3 months for at least 12 months. We will collect blood samples for PEth measurement 12 months after the initial PEth sample is collected.

8.1.6 ASSESSMENT OF INFANT OUTCOMES

Infants of participants enrolled in the SEARCH Youth RCT at clinic sites randomized to either the intervention and control arms, born during the study period, will be eligible to participate. Women who have delivered will be approached for this data collection and, if interested, provide informed consent. A waiver of informed consent for recruitment purposes will be utilized in order to assess the completeness of standard care clinic records prior to meeting with participants. No data will be recorded before informed consent is obtained.

Infant outcomes will be characterized using data collected by the study team using the medical records of the child in the exposed infant care programs and by maternal report. They outcomes of interest include participation in scheduled visits in the HIV-exposed infant programs, receipt of antiretroviral medications as prophylaxis (drugs and duration), duration of breast feeding, HIV test results and mortality, at 1 and 2 years of life (for those who reach that duration during the study period).

In addition, viral load (VL) testing may be performed on participating mothers prior to transitioning off study if they do not have recent VL testing in the medical record. Staff may also help facilitate standard of care HIV testing of the infants if they have not completed the country's Early Infant Diagnosis (EID)/HIV Exposed Infant (HEI) program; there will be no extra testing of infants for the purpose of this study.

8.1.7 ASSESSMENT OF MENTAL HEALTH

A subset of study participants will take part in a one-time survey on symptoms of mental health and life event issues during a visit at the study clinic or by phone. The standard mental health assessment tool Patient Health Questionnaire (PHQ-9) will be administered to participants who take part, along with additional questions on major life events and pressures.

Potential participants will be approached to discuss the survey in the study clinic or by phone call and, if interested, be asked to provide verbal consent to take part. A subset of participants enrolled in the SEARCH Youth RCT at clinic sites randomized to either the intervention or control arms will be eligible to participate.

Participants with score ≥ 5 on the PHQ-9 portion of the survey, or those with a suicidal ideation, have moderate to severe symptoms and will need to be evaluated for therapy including pharmacological therapy. The study coordinator to arrange for urgent referral for mental health care to the regional referral hospital.

8.2 SAFETY ASSESSMENTS

Participants' VL results will be measured regularly as part of the SEARCH Youth intervention. All other safety assessments will be performed according to country standard of care.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

N/A.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems (UPs) 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 to the reviewing Institutional Review Board (IRB) and study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, 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

UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) or protocol violations will be reported to the IRBs within 7-10 working days of the investigator becoming aware of the event (see section 10.1.10 for individual IRB reporting timelines).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed of any UP that changes the study's risk/benefit ratio and/or requires modification to the informed consent. The nature of the UP will determine how and when participants will be notified.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint(s): Proportion of study participants with virologic suppression (HIV RNA <400 c/mL) at 2 years of follow-up.

The null hypothesis is there will be no difference in the proportion of participants with virologic suppression at 2 years, between participants who receive the SEARCH Youth intervention and participants in the control arm.

9.2 SAMPLE SIZE DETERMINATION

Because the intervention is delivered at the clinic-level (changing the policies and procedures of the clinic and all clinicians caring for AYAH within the clinic) randomization and evaluation must be done at the clinic-level and incorporate randomization of entire clinics. For the design and power calculations for this study we have taken the rigorous extra step of actually measuring the clustering effect on HIV virologic suppression of clinic level performance for AYAH in 16 clinics in Kenya and Uganda. Using a conservative estimate of the upper 95% CI bound on the measured ICC from the clinic using ICC estimates from both a one-way random-effects model and a one-way Analysis of Variance approaches (ICC=0.055) we have calculated that with 28 clinics (14 randomized to intervention and 14 to control) and an average cluster size of 50-100 AYAH our study would have a 83% or greater power to detect a significant difference between the control and intervention clinics if the proportion with HIV virologic

suppression among AYAH in the control clinics is 64% and the proportion with suppression in the intervention clinics is 88% In addition, if the study were to lose the ability to evaluate up to 2 clinics due to unforeseen events, the study would still retain 80% power to detect the 64% control vs. 88% intervention difference.

9.3 POPULATIONS FOR ANALYSES

Intervention Randomized Controlled Trial
AYAH ages 15-24 years enrolled in care at study clinic of ~ 2,000 participants, including ART-naïve and experienced participants.

Identification of Barriers and Facilitators
Sample of patient cohort participants, focus group participants, family members, care providers and clinic directors, and 6 community/regional health officers or leaders. Additionally, all participants will be asked to complete a brief Patient Satisfaction Survey.

Incremental Costs and Gains
AYAH trial participants and outcome data clinic administrative and financial records.

Effectiveness of the Youth HIV Testing and Referral Strategy
Young persons ages 15-24. The testing team will maintain a registry of tests performed and work with clinics to determine outcomes of linkage efforts. Interviews of key informant youth.

Alcohol Use and Impact on Viral Suppression
AYAH trial participants enrolled in care at study clinics randomized to the SEARCH Youth intervention who consent to additional questionnaires and alcohol biomarker testing

Infants outcomes
Infants born to women in intervention and control arms during the study period.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The primary analysis of the full RCT will be an adjusted comparison of the proportion of AYAH with HIV virologic suppression (HIV-1 RNA copies<400/mL) at 2 years on study between those enrolled at clinics randomized to the intervention condition (n=14 clinics) versus those enrolled at clinics randomized to the control condition (n=14 clinics). To identify mechanisms of action and barriers and facilitators of the study intervention implementation we will examine emergent qualitative themes (perceived benefits, acceptability, gender and life-stage issues, reduced burdens, improved communication, etc.), and for each

of the individual components of the intervention to identify which components worked and did not work and for whom. The incremental costs and gains associated with the intervention will be estimated using micro-costing, time-and-motion (T&M) studies, calculation of disability-adjusted life years (DALYs) gained, estimation of efficiency (cost per patient, costs per additional patient with viral suppression), cost-effectiveness analysis (cost per DALY gained). The efficacy of testing and linkage strategies will be estimated using yield and proportion who link to treatment clinics. Alcohol use patterns will be described and life-stage-specific, and sex-specific prevalence of each pattern will be calculated. The effect of alcohol use on viral non-suppression (HIV-1 RNA copies ≥400/mL) at 1 year will be estimated using causal inference techniques by comparing the proportion of AYAH with viral non-suppression between those with no alcohol use and those with various patterns of use. The effect of intervention on infants born to participants will be examined through (i) the proportion who remain alive and HIV-free at 1 and 2 years, and (ii) the proportion of who complete their testing programs for HIV-exposed infants.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary Outcome: Proportion of study participants with virologic suppression (HIV RNA <400 c/mL) at 2 years of follow-up

Primary Predictor: Clinic Randomized Arm (intent-to-treat), Intervention or Control.

Analytic Plan: The primary analysis of the full RCT will be an adjusted comparison of the proportion of AYAH with HIV virologic suppression (HIV-1 RNA copies <400/mL,) measured at 2 years on study between those enrolled at clinics randomized to the intervention condition (n=14 clinics) versus those enrolled at clinics randomized to the control condition (n=14 clinics). The primary analysis will restrict to participants enrolled prior to December 1, 2019; secondary analyses will include all participants. Viral suppression will be compared between arms using Two-Stage TMLE, an approach that appropriately accounts for the dependence of outcomes within clinics. In the first stage, viral suppression will be estimated for each clinic, using TMLE to adjust for possibly incomplete ascertainment of viral loads. In the second stage will use a cluster-level TMLE to estimate intervention effectiveness by comparing the clinic-specific endpoints between randomized arms, while accounting for the randomization scheme. We will test the null hypothesis that the intervention did not impact viral suppression with a two-sided test at the 5% significance level. To understand effect heterogeneity, we will repeat these analyses within the following pre-specified subgroups: country, baseline care status, baseline viral suppression status, gender, age group, and pregnancy or live birth during the study (among women).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

9.4.3.1 SECONDARY CLINICAL OUTCOMES

Secondary Outcomes include retention: Not more than 90 days late to scheduled visit; sustained virologic suppression (< 400 and < 200 c/mL), virologic failure, death, transfer to other medical facility and change to second line therapy.

Secondary Predictors include country, baseline care status, gender, age, pregnancy, education, occupation, marital status, alcohol use, mobility, and other variables captured in the Life-stage (assessment tool; intervention arm only).

Analytic Plan: The secondary clinical outcomes will be examined using analogous Two-Stage approach, described in section 9.4.2. In secondary analyses, we will also evaluate predictors of sub-optimal outcomes using TMLE (primary) and with univariate associations (secondary), overall and stratified by intervention arm. Based on our prior studies with HIV clinics and follow-up in the two regions we anticipate a 2-year LTFU rate of less than 8%. Regardless of the LTFU level, we will implement enhanced participant tracking procedures that have proven successful in our group at re-engaging participants in care.

Secondary Analyses for Exploring Intervention Component Mediation and Moderation: To explore mechanisms by which the multiple intervention components effect changes in study outcomes, secondary analyses will investigate whether measures of intervention component activities delivered to study participants listed in Table 4 mediate relationship between intervention group assignment (study arm) and viral suppression, and whether sex, age, and region moderate those associations. In line with recent NIH guidelines recommending consideration of sex as a biological variable, participant gender will be a key moderator in these analyses. Mediation and moderation will be assessed using the causal inference-based approach of Valeri and VanderWeele, which yields optimal estimates of indirect effects in the presence of non-continuous (e.g. binary) outcomes and moderator-mediator interactions.[20] M*plus* will be used to fit causal mediation models because it can adjust standard errors for clustering of participants within communities and clinics/providers, a feature of the proposed study, and because it can include multiple mediators simultaneously. [21,22] For each mediator, we will include the proportion of the total effect explained by the mediator.

Table 4. Intervention Component Mediators and Measures

Potential Mediators (Intervention Component)	Mediator Measures
SEARCH Youth-1 Predisposing • Life-stage identification and counseling	○ Life-Stage Tool Completeness (% visits w/ filled out tool) ○ % Life-Stage Events with Corresponding Plan or Counseling ○ % of Plans Enacted ○ # Life-Stage Events (total)
• Technology enabled e-collaboratives for providers	○ % Provider Engagement with Discussions ○ # Discussions with Provider Participation ○ # Discussion specific to Participant
SEARCH Youth-2 Enabling • Structured Choice Clinic Access	○ # Documented offers of clinic hours & provider choice ○ % Uptake of Structured Choice Options ○ # Provider changes

SEARCH Youth-3 Reinforcing • Rapid VL Feedback	○ # Visits with Receipt of Rapid- VL Testing & Counseling ○ Mean Participant Self-Report of VL Results Impact Score

9.4.3.2 IDENTIFICATION OF BARRIERS AND FACILITATORS

Analytic Approach: Mixed-methods approach of qualitative analysis of key informant interviews combined with quantitative process and fidelity measures and trial outcome data.

Primary Research Questions: Investigations will be focused on three main areas: 1) overall mechanisms of action of the intervention that result in success or failure (suppressed or unsuppressed at one and two years), 2) key issues impacting the effectiveness of individual components of the intervention, and 3) barriers and facilitators of implementation of the intervention from the care delivery side.

To identify mechanisms of action and barriers and facilitators of the SEARCH Youth intervention implementation we will examine emergent qualitative themes (perceived benefits, acceptability, gender and life-stage issues, reduced burdens, improved communication, etc.), and for each of the individual components of the intervention to identify which components worked and did not work and for whom.

We will look for evidence in qualitative data and quantitative process measures for each component to see if - and for which subgroups of AYAH - the proposed predisposing, enabling, and reinforcing mechanisms are supported by identified qualitative themes and are echoed in the quantitative utilization, success, and fidelity data. For qualitative data analysis translated data will be imported into Atlas.ti[24] guided by grounded theoretical approaches[23], in which research team members iteratively review , use theory as well as inductive analysis of empirical findings to develop a common set of codes describing patterns observed in the data, and iteratively refine codes as new themes emerge during the data collection process.

Table 5. Process Measures for Fidelity & Mechanisms of Action

Component	Process and Fidelity Measures
SEARCH Youth-1 Life Stage Identification & Plan WhatsApp E-collaboratives	• Proportion of trainings completed + attendance • Life-Stage tool use: frequency & completeness • Action plan: completeness, counseling & care changes made • Communication frequency: # messages & content (themes) • Participation measures: % of clinic providers initiating & involved • Action plan: completeness, counseling & care changes made
SEARCH Youth-2 Structured Choice Clinic Access	• Documentation of structured choice offer (off-hours and flexible location) • Off-hours visit utilization • Participant satisfactionsurvey • Number & frequency of phone visits
SEARCH Youth-3 Rapid viral Load & Counseling	• Time to viral load results communication to AYAH • Viral Load counseling received • Action plan: completeness, counseling & care changes made

9.4.3.3 INCREMENTAL COSTS AND GAINS

Primary Research Questions: In order to generate evidence that can address key questions concerning optimal resource allocation and provide guidance to policymakers, we will use rigorous methods to determine costs of the SEARCH Youth intervention and assess its efficiency and cost-effectiveness as cost per participant, cost per additional participant with viral suppression and cost per DALY gained. We will use standard micro-costing techniques and T&M studies to measure the cost of optimized testing and each component of the SEARCH Youth intervention.

Analytic Approach: Micro-costing, time-and-motion (T&M) studies, calculation of disability-adjusted life years (DALYs) gained, estimation of efficiency (cost per participant, costs per additional participant with viral suppression), cost-effectiveness analysis (cost per DALY gained).

Efficiency and Cost–effectiveness

We plan to calculate efficiency and cost-effectiveness (CE) ratios as net cost per additional person achieving viral suppression and net cost per DALY gained, with net costs equal to program costs adjusted for changes in health care costs due to the intervention. We plan to conduct extensive univariate and multivariate sensitivity analysis. Importantly, if the intervention yields net savings (i.e., negative net costs) as well as health benefits, the intervention is classified as “dominant” and no CE ratio is calculated.

9.4.3.4 EFFECTIVENESS OF THE YOUTH HIV TESTING AND REFERRAL STRATEGY FOR ART

Primary Research Questions: The effectiveness of strategies will be examined during the study and at the conclusion and shared with community testing teams to allow them to refine efforts.

Analytic Approach: Uptake of HIV testing (total number tested) and Yield (percentage of individuals testing HIV-positive with a new or out-of-care HIV diagnosis). Estimates of rates and proportions will be determined and compared using standard methods[25] within individual and across communities, examining predictors such as gender, age, marital status, employment and educational status. Mixed-methods approach of qualitative analysis of key informant interviews combined with quantitative process and fidelity measures and testing/linkage outcome data.

9.4.3.5 ASSESSMENT OF ALCOHOL USE AND ITS EFFECT ON VIRAL SUPPRESSION

Primary Research Questions: The developmental changes of youth influence risk-taking behavior and increase their likelihood of alcohol use, which may be a key contributor to poor HIV outcomes. However, there are substantial knowledge gaps on the scope, context, and impact of alcohol use on HIV outcomes among AYAH in SSA. Alcohol use among AYAH will be characterized and its longitudinal effects on viral suppression will be determined to allow further refinement of the intervention and identify potential foci of future interventions.

Analytic Approach: We will calculate the baseline prevalence of various alcohol use patterns, including life-stage-specific and sex-specific prevalence. We will summarize predictors of each alcohol use pattern and estimate the relative risks of any alcohol use associated with each predictor using targeted maximum likelihood estimation (TMLE). These analyses will be repeated varying definitions of alcohol use, incorporating both self-report (AUDIT-C) and biomarker measured use (PEth), to account for potential underreporting. We will estimate and compare the proportions of AYAH with viral non-suppression among non-drinkers versus baseline drinkers, using TMLE to account for potential confounders.

9.4.3.6 ASSESSMENT OF INFANT OUTCOMES

Primary Research Question: Does the SEARCH Youth intervention result in a higher rate of HIV-free survival? We will also investigate potential steps in the causal pathway, including participation in HIV-exposed infant care programs, receipt of antiretroviral medications, and duration of lactation.

Analytic Approach: We will compare the proportion of infants who remain alive and have HIV-free at 1 and 2 years of life between randomized arms using the Two-Stage approach, described in section 9.4.2. We will also investigate the intervention effects on elements of postnatal care including the rates of participation in HIV-exposed infant care programs, receipt of antiretroviral medications (agents and durations), and duration of lactation.

9.4.3.7 MENTAL HEALTH

Primary Research Question: Does the SEARCH Youth intervention result in a lower rate of depression? We hypothesize that additional engagement with providers would facilitate better identification and management of mental health issues like depression.

Analytic Approach: We will compare the proportion of participants with depression at the time of study end, using the PHQ-9 survey, between randomized arms using the Two-Stage approach, described in section 9.4.2. We also evaluate the association of depression with recent life events.

9.4.4 SAFETY ANALYSES

N/A.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention and control groups will be summarized on baseline characteristics including such features as age, gender, care status, and viral load suppression.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Subgroup analyses for primary and secondary endpoints will be performed by region, gender, age group, HIV care status, viral suppression status, and peripartum status (among women).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

N/A.

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

Informed consent will be obtained for the SEARCH Youth RCT participants and for participants of the qualitative in-depth interviews and focus groups to better understand youth attitudes and barriers to care. Both Uganda and Kenya allow individuals over the age of 14 to consent for participation in research, without involvement of their parents, if it concerns the treatment of a sexual transmitted disease. The Uganda National Council for Science and Technology (UNCST) has determined that individuals aged ≥ 14 years are able to provide independent consent for research if they have a sexual transmitted infection, and Kenya's National AIDS and STI Control Programme (NASCOP) states that individuals aged ≥ 12 years are able to provide independent consent for research while Kenya Medical Research Institute (KEMRI) allows mature minors to consent independently for research. For the qualitative activities, informed consent will be obtained from those interviewed or taking part in focus group discussions, including patient cohort participants, family members, providers or clinic directors

involved in the SEARCH Youth intervention and clinicians providing PrEP, community/regional health leaders, and members of focus groups among the patient cohort and HIV-non-infected youth.

The following informed consent form (ICF) materials will be used in this study:

- SEARCH Youth Intervention ICF
- SEARCH Youth Control ICF
- Testing Referral Verbal Consent Form
- Patient Qualitative Cohort ICF
- Provider Qualitative Cohort ICF
- Key Informant Qualitative Cohort ICF
- Family Member Qualitative Cohort ICF
- Focus Group Discussion Patient Cohort ICF
- PrEP Focus Group Discussion ICF
- PrEP Provider Interview ICF
- Alcohol Study Cohort ICF
- Infant Outcome ICF

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All consent forms will be translated into the local language and back translated into English to ensure correct use of language. Consent forms will be read aloud to participants by trained staff. The informed consent will describe the purpose of the study, all the procedures involved, and the risks and benefits of participation. Interviewers will ask participants to summarize the study and explain the reasons why they want to participate. Either a signature or a thumbprint (for those who cannot read) will be acceptable to confirm informed consent for participation in the study, in the case of written consent forms.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Notification documenting the reason for study suspension or termination will be provided to study participants, the funding agency, and regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. 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 as private a setting as possible.

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.

Data Security

All information will be recorded using study identification numbers, rather than participant names, and stored securely in locked offices at a study data center. All study computers will be password encrypted and kept in locked offices.

Risk of HIV Status Disclosure

Given the sensitive and private nature of the HIV-status of participants of the RCT, extra measures will be put in place to ensure maintenance of privacy, confidentiality and security of the data obtained. Contact mobile numbers will be re-checked to insure they are updated.

Use of WhatsApp

As described in section 2.3.3., participation in WhatsApp will be limited to providers taking part in the study, who will be required to attend an in service to review SOPs and be trained on appropriate information that can be included in the discussions. The chats will be encrypted and take place under the oversight of study staff to ensure compliance with confidentiality requirements. All mobile devices used in WhatsApp discussions will have security measures enabled to access the device and chats, and investigators will ensure discussions are deleted from individual devices when the study is complete or staff member leaves the study. Information shared in discussions will not include identifiers and will be limited to the minimum needed for productive exchanges of ideas.

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.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Samples for PEth testing will be collected after participants complete the initial alcohol survey and again 12 months later. These samples will be used to prepare dried blood spot cards at the designated in country laboratory facilities. Dried blood spot cards will be stored until shipment to the United States Drug Testing Laboratory (USDTL) in the United States. The DBS card will be tested for PEth level at USDTL using liquid chromatography-tandem mass spectrometry (LC/MS/MS). We will obtain a Materials Transfer Agreement to ship the DBS to the U.S.; no laboratories in Africa conduct this test. All samples will be labeled only with the participants' study ID number, initials, and the date of collection. A database that links these samples to other identifiers will be accessed only by study investigators and personnel and will be password protected. Any remaining specimen will be discarded.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Protocol Co-Chair	**Protocol Co-Chair**	**Protocol Co-Chair**
Diane Havlir, MD, Professor of Medicine	Moses R. Kamya, MBChB, MMed, PhD, Chair of the Department of Medicine	Theodore Ruel, MD, Associate Professor
University of California, San Francisco	Makerere University	University of California, San Francisco
UCSF Box 0874, San Francisco, CA 94143-0874, U.S.A.	P.O. Box 7072, Kampala, Uganda	Box 0434 550 16th Street, 4th Floor San Francisco, CA 94158-0434
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diane.havlir@ucsf.edu	mkamya@infocom.co.ug	Theodore.ruel@ucsf.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight in this minimal risk study will be led by the study investigators and by adherence to the quality management plan (QMP) described in section 10.1.8.

10.1.7 CLINICAL MONITORING

N/A.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data 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 a percentage 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.

Data

Data will be captured on source documents or entered directly onto electronic CRFs (see section 10.1.9). To ensure accuracy study staff will compare a representative sample of source data against the database, targeting key data points in that review. Reports based on recent data will be made available to study staff and investigators.

Intervention Fidelity

Consistent delivery of the study interventions will be monitored throughout the study. Procedures for ensuring fidelity of intervention delivery are described in section 6.2.1.

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.

As required, the investigators will provide direct access to all trial related sites, documents, and regulatory records for the purpose of monitoring and auditing by local regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data management for this study will be overseen by the Infectious Diseases Research Collaboration (IDRC) Data Management Center located in the main IDRC research complex in Nakasero, Kampala, Uganda. The Data Management Center (DMC) is also responsible for providing IT support to all staff members.

Data Management System

For any study components using paper data collection, IDRC has designed and developed a custom Data Management System that is used to manage the data, using Microsoft SQL Server as the backend for all data storage. MS Access is used for double data entry and SAS programs are used for comparing 1st and 2nd entry and generating discrepancy reports. In addition, the DMC has developed custom Visual Basic programming for direct survey and data entry of data in the field. Data Transformation Services/ SQL Server Integration Services (DTS/SSIS) packages are used to automatically import/export any new data and stored procedures written in T-SQL are used to automatically generate new data queries on a daily basis. There is a web interface to the whole system written in ASP.NET to allow users to view the data,

view reports, and even modify the data they are authorized to access. With regular backups and a full audit trail, the whole system is regulatory compliant (21 CFR Part 11).

Data Quality Assurance Process

The data management system is designed to collect, transfer and store data for Data Management Center studies. Data from any paper records will be 100% double entered into the system via Microsoft Access Databases or Web-based data entry screens. Locally collected data is compressed, password-protected, and then securely uploaded to a cloud based server (Network Solutions, Inc) using secure-FTP via the FileZilla application. Cloud-based uploads are downloaded daily to the Kampala DMC. After the data has been input into the Data Management Center server, it is electronically verified and is then written to the SQL database. Edit checks or queries are run nightly and the results are posted to a secure clinical trials website so that the sites can electronically address problems with the data the next day. The site corrects data via the website and the database is updated automatically.

In order to ensure data security and integrity, the following measures will be implemented:

- All members of the study team will be educated in the study protocol prior to the onset of the study.
- Detailed Standard Operating Procedures (SOPs) will be written for all project activities and be provided to relevant team members.
- Team members will be thoroughly trained on the SOP's.
- Where applicable, team members will receive additional training on the use of tablet computers.
- All data transcribed from paper will be double data entered or verified.
- All electronic data will be backed up regularly.
- All data will be transferred to the main Data Center in Kampala to the secure server. This sever is backed up on a daily basis and a monthly backup is stored off-site.
- All computers, including the tablets, will be password protected.
- All computers, including tablets, will be locked in a secure room each night.
- Any Log Books and CRF's will be locked in a secure room each night.

10.1.9.2 STUDY RECORDS RETENTION

Data archives will be kept for periods based upon the terms of the agreement between the funding organization and IDRC. Datasets that are required to be retained for periods as prescribed by law will also be kept following the respective durations as set in the enacted laws of Uganda. In general, study data will be kept electronically for a period of at least 5 years post completing of the study. Data will remain on the password secured IDRC servers and on the system of annual USB physical backup drives. After 5 years from the close of the study, all paper records will be destroyed and the electronic records will be removed from the server, but retained on Archival, password-protected USB drives.

10.1.10 PROTOCOL DEVIATIONS

It will be the responsibility of the site investigators and staff to use continuous vigilance to identify deviations or violations and report violations that meet the IRB definition of reportable events. Protocol violations that occur at UCSF will be reported to the UCSF CHR IRB within 10 working days of the PI's awareness. Protocol violations that occur on-site will be reported to the SOMREC IRB within 7 working days. SOPs will describe the process for communicating with study coordinators and investigators and the event reporting procedures.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The findings from this study may be published in a medical journal. No individual identities will be used in any reports or publications resulting from the study. The researchers will publish results of the study in accordance with NICHD, UCSF, UNCST, KEMRI and Makerere University guidelines.

10.1.12 CONFLICT OF INTEREST POLICY

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

N/A.

10.3 ABBREVIATIONS AND SPECIAL TERMS

ART	Antiretroviral Treatment
AYAH	Adolescents and Young Adults with HIV
CE	Cost Effectiveness
CFR	Code of Federal Regulations
CHR	Committee on Human Research (UCSF)
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DALY	Disability-Adjusted Life Year(s)
DMC	Data Management Center

eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDRC	Infectious Diseases Research Collaboration (Uganda)
IRB	Institutional Review Board
KEMRI	Kenya Medical Research Institute
LTFU	Lost to Follow-Up
NASCOP	National AIDS and STI Control Programme
NCT	National Clinical Trial
NICHD	National Institute of Child Health and Human Development (NIH)
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PEth	Phosphatidylethanol
PI	Principal Investigator
PrEP	Pre-Exposure Prophylaxis
Q	Every
QA	Quality Assurance
QC	Quality Control
QMP	Quality Management Plan
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOM-REC	School of Medicine Research and Ethics Committee (Makerere University)
SOP	Standard Operating Procedure
SSA	Sub-Saharan Africa
T&M	Time and Motion
UNCST	Uganda National Council on Science and Technology
UCSF	University of California, San Francisco
UP	Unanticipated Problem
US	United States
VL	HIV Viral Load

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.2	21-Dec-2018	Initial approved protocol version	N/A
2.0	21-Nov-2019	Updated with details on additional and revised qualitative activities, to add new and revised data collection instruments, and to clarify planned target enrollment.	To provide new and updated tools to understand barriers and facilitators to care and the study intervention, explore HIV prevention perspectives, and clarify enrollment targets.

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APPENDIX 1: RANDOMIZATION PRINCIPALS AND PROCEDURES

The location of the facility where the randomization event takes place should be a central venue that has been agreed upon by the local health leaders. The randomization strategy must be both scientifically valid and transparent to the community stakeholders and uses local idioms to make the concept of randomization easily understood by traditional leaders and community members. The random assignment within matched pairs of each site's communities to intervention or control status could employ a public lottery of community names to achieve maximum public acceptance of the randomization results by enhancing transparency and spreading ownership of the process. A computer randomly designates the randomization status for each pair of study communities only as the community name that would be 'picked up' or 'not picked up' in the public lottery. The lottery may be a public event with members of the CAB and local leadership present along with guests from other organizations with relationship to the health community.

The lottery could be conducted in a series of draws, one for each of the matched pairs of communities by their local leaders. For each drawing, the two clinic names are written on a separate piece of paper or card and folded in half to obscure the name from view. For the draw, the names of each matched pair could be placed in a sealed box with a hand hole cut out of the top of the box. A flip of a coin could be used to decide which of the two community leaders will pick the community name from the box. The unselected leader could be responsible for holding and shaking the selection box. The leader then draws a paper from the box without looking into the box and the picked-up community name was read aloud by both of the community leaders in turn. If the randomization protocol indicated that the "picked-up" community was to receive the intervention (i.e., the SEARCH Youth intervention components described in the protocol implemented for enrolled participants), then the host country Principal Investigator would announce the drawn clinic as an intervention clinic. If the protocol called for the "picked-up" clinic to be the control (i.e., community health campaigns and standard ART initiation), then the host-country PI would announce it as a comparison clinic. This process would assure equal chance of being randomized to the intervention or comparison arm, and eliminates any residual fears of bias or rigging.

APPENDIX 2: COSTING PRINCIPALS AND PROCEDURES

The costing team uses the standardized micro-costing workbook as the data collection tool to quantify the resources and associated unit costs to deliver the SEARCH Youth intervention components. These costs mainly consist of direct costs but also include some indirect costs such as infrastructure, administration, etc. Cost information will be gathered through examination of expenditure records, discussion with program staff and providers, care delivery logs, and other program documents. Each resource item used to deliver the SEARCH Youth intervention components will be enumerated under standard expenditure categories – personnel, recurrent goods (supplies), capital goods and equipment, services, and facility. The number of units consumed and unit cost of each resource item during the specified costing period will also be entered into the micro-costing workbook. The costing approach emphasizes resources used for service delivery and will include the value of all resources used even if not paid for by the SEARCH Youth study. The costing team will assign the full value to donated or subsidized resource items based on market price or existing data from similar costing analysis. The information sources (e.g., key informants and program documents) and the dates when the cost data were obtained are clearly documented in the micro-costing workbook. The costing team will also save relevant program documents and email communications for quality check and future references. The details of the costing process is outlined in a detailed SOP, which is used for training of staff and standardizing the process across all regions and clinics.

Costs Analysis

We will assess costs at least twice in each health facility: once before and once after adoption of the SEARCH Youth intervention, in order to estimate incremental costs of SEARCH Youth implementation and to compare costs of the intervention to standard of care. “Economic” costs (the true value of resources consumed or “opportunity cost”) will be assessed by identifying the value of subsidized or donated resources with information from data bases (e.g. wage rates) and donors, and, as needed, three price quotes from appropriate market sources.

Health Effects

To quantify health effects, we will use directly measured health-related study outcomes (e.g. viral suppression). Second, we plan to integrate the health impact of achieving viral suppression using disability-adjusted life years (DALYs), including years of life gained and the collective disability effects of living with HIV. We might be estimated as DALYs gained for the short term (during the trial) and the long-term (5, 10, and 20 years) using data from the trial, as well as morbidity and mortality attributed to un- or partially- treated HIV disease.