Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Havlir DV, Balzer LB, Charlebois ED, et al. HIV testing and treatment with the use of a community health approach in rural Africa. N Engl J Med 2019;381:219-29. DOI: 10.1056/NEJMoa1809866

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes. Please note, the original fully IRB-approved protocol is referred to as SEARCH protocol version 2.0.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

Sustainable East Africa Research in Community Health (SEARCH)

A Study of the:

Makerere University – University of California, San Francisco (MU-UCSF)
Research Collaboration

Protocol version: 2.0, November 30, 2012

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PROTOCOL SYNOPSIS

Overall Goal: The SEARCH study will quantify the health, economic and educational impact of early HIV diagnosis and immediate ART (antiretroviral therapy) using a streamlined care delivery system in rural communities in East Africa. The study intervention is designed to improve the entire continuum of care, to reduce structural barriers for all populations including those most "at risk" and build upon evidence based prevention interventions including adult male circumcision.

Study Hypothesis: ART initiation at any CD4 count with streamlined delivery compared to CD4-driven ART initiation will reduce cumulative 5-year HIV incidence and protect and improve health, economic and education outcomes in communities with annual HIV testing campaigns.

Study Partnerships: SEARCH is designed to inform governments and health policy makers and to benefit affected communities. To that end, SEARCH is a partnership with input and sponsorship from global and local health and development agencies, foundations, governments and the study communities. The National Institutes of Health is the scientific sponsor of the study.

Study Design: SEARCH is a cluster randomized community trial. Annual community health campaigns will be conducted in all study communities and will offer HIV testing and multi-disease prevention and treatment services. The intervention is ART independent of CD4 cell count delivered in a streamlined approach for all HIV infected adults and children. Components of streamlined care include ongoing HIV combination prevention strategies including male circumcision. Control communities will receive annual testing campaigns and ART will follow country guidelines for ART.

HIV incidence will be measured using an efficient community cohort design (ECCO) comprised of three key elements: A) baseline household community level census, B) annual community health campaigns (CHC) incorporating HIV testing that use unique identifiers to link individuals between successive waves of the intervention, and C) tracking and evaluation of individuals who do not participate in annual CHCs.

Study Population: Thirty-two communities with a population of approximately 10,000 persons each will participate in the following three regions: A) Mbarara/Western Uganda (n=10), B) Tororo/Eastern Uganda (n=10), and C) Southern Nyanza Province, Kenya (n=12). Randomization to intervention vs. control will occur in pairs of communities matched based on key health, geographic and ethnographic variables including: A) geographic region B) population density C) number of trading centers D) transportation index, and E) occupational mix.

Primary Endpoint: Cumulative 5-year HIV incidence in men and women ages ≥15 years.

Secondary Endpoints: The health-related secondary endpoints include: 1) mortality (overall, maternal, and infant mortality), 2) mother-to-child HIV transmission, 3) AIDS (WHO stage 4), 4)

tuberculosis, and 5) HIV drug resistance. The economic/education secondary endpoints include: 1) adult and child employment levels, 2) asset holdings, 3) school attendance levels, 4) programmatic costs, 5) health gains expressed in averted Disability Adjusted Life Years (DALY), and 6) cost effectiveness (e.g. cost per infection averted and per DALY averted).

Study Antiretroviral Treatment Regimen: The study intervention is provision of ART for all individuals at any CD4+ cell count. ART – the regimen of efavirenz, emtricitabine and tenofovir disoproxil fumurate – will be provided by the study for those who do not meet in-country guidelines to start ART. These individuals will be guaranteed 3 years of ART. After three years, these individuals will continue uninterrupted ART provided by their country of residence through agreements with the Ministry of Health.

Study Duration: The study will follow the communities for 5 years after the first community health campaign.

Statistics: We are powered to detect a 40% reduction in 5 year cumulative incidence in treatment versus control communities under conservative assumptions regarding plausible values for cumulative incidence in the control communities, baseline HIV prevalence, incomplete follow up, and between-community variation (matched pair coefficient of variation). Sample-based weights will be used to combine testing data from tracked individuals with testing data from the community health campaigns in order to obtain unbiased estimates of community-specific five year cumulative incidence. Primary analyses will consist of a) unadjusted pair matched community level analysis, and b) implementation of novel efficient targeted maximum likelihood estimators that adjust for individual and community level covariates in order to achieve effect estimates with greater precision.

GLOSSARY

3TC	Lamivudine
ABC	Abacavir
AFB	Acid-fast bacilli test
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ATV	Atazanavir
AZT	Zidovudine
BUN	Blood urea nitrogen
CO2	Bicarbonate
CBC	Complete blood count
CHC	Community health campaign
CHR	Committee on Human Research, UCSF
CI	Cumulative incidence
CK	Creatine kinase
CL	Chloride
DAIDS	Division of AIDS, NIH
DALY	Disability Adjusted Life Years
ECCO	Efficient community cohort design
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
FTC	Emtricitabine
GIS	Geographic information system
GPS	Global positioning system
HBV	Hepatitis B
HCG	Human chorionic gonadotropin pregnancy test
ICER	Incremental Cost-Effectiveness Ratio
IRB	Institutional Review Board
K	Potassium
KEMRI	Kenya Medical Research Institute
LPV	Lopinavir
MDRC	Modification of Diet in Renal Disease (formula)
MTCT	Mother-to-child transmission
MU	Makerere University
Na	Sodium
NDA	National Drug Authority in Uganda
NIAID	National Institute of Allergy and Infectious Diseases
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
RDT	Rapid diagnostic test
RNA	Ribonucleic acid (e.g., HIV-1 plasma RNA)
RTV	Ritonavir
SOM-REC	MU School of Medicine - Research and Ethics Committee
TB	Tuberculosis
TDF	Tenofovir disoproxyl fumarate
TMP/SMX	Trimethoprim/sulfamethoxazole
UNCST	Uganda National Council of Science and Technology
WHO	World Health Organization

1.0 STUDY CONTEXT

1.1 Background

The SEARCH study is designed to test the impact of a bold intervention in rural East Africa – treatment of all HIV-infected persons from near the onset of infection—on community health. The HIV epidemic has decimated health, education and economic gains that were made in Africa in the 1970s, leaving many countries with decreased life expectancy and mortality rates not seen in the US since the early 1900s [1]. HIV's effects on the population level are amplified by disabling the work force, damaging maternal health, increasing orphans and fueling the overlapping epidemics of TB and malaria [2-5]. The HIV epidemic represents one of the greatest public health challenges of all time.

The combination of prevention efforts and antiretroviral therapy (ART) has reduced the incidence of new HIV infections as well as mortality over the last decade. However, there were still over 2 million new HIV infections last year, and over 20 million individuals have died from HIV [1]. HIV is the leading cause of death among women of reproductive age in Sub-Saharan Africa. At the beginning of the 21st century, global approach to deploy ART to reduce AIDS mortality prioritized treatment for the most ill patients based on CD4 cell count. In Uganda and Kenya, ART is generally administered in adult patients when their CD4 count falls below 350 cells/mm^3, when they are diagnosed with a WHO Stage III or IV disease, and in other patients at high risk of HIV disease progression, including those with tuberculosis (TB). New data show that treating HIV *early* can prevent AIDS and prevent TB, a leading killer of HIV infected patients [6]. New data also show that ART can reduce HIV transmission by 96% in HIV sero-discordant couples [7]. These data illustrate a dual purpose for ART – prevent AIDS (including TB) in the HIV infected individual *and* prevent HIV transmission to the uninfected partner. The identification of HIV infection early and initiation of treatment thus has the potential to influence the overall health of the community as well as its economic and educational strength and viability.

The proposed community randomized trial will quantify the effect of an early HIV diagnosis and ART approach ("test and treat") on the health, economic productivity and educational outcomes of rural communities in East Africa. There have been several mathematical models, including a landmark publication by Granich et al and a subsequent economic analysis, showing frequent HIV testing and ART will reduce overall HIV incidence over a period of 5 to 10 years, and that the upfront investments required for such an approach result in net savings over 13 years in South Africa [8]. These models have generated heated debate within the scientific community based on various assumptions inherent in the models [9, 10]. These models may have also underestimated the benefits of ART because the evaluation framework did not include all the health benefits of ART, such as prevention of TB or the socioeconomic benefits of the preservation or return of good health afforded by ART. Thus it is time to test an early HIV diagnosis and treatment approach and to evaluate its cost and effects with an evaluation framework that includes health, economic and education metrics [11-13].

Inherent to the scale up of HIV treatment in general, and an important part of the SEARCH is the need to develop new models of chronic health care delivery at the community level that are

lower in resource needs and are sustainable. Finding patients earlier in HIV disease, keeping these individuals healthy with early ART, and delivering their care in a streamlined manner in fact may be the only viable path to deal with the health care worker shortage which is amplified by late HIV diagnosis, and the medical expertise and facilities needed to care for patients who present and are treated after HIV has significantly progressed.

Also inherent to the design of the SEARCH intervention is the recognition that a “test and treat” approach must find an overwhelming majority of HIV infected individuals, improve upon the entire continuum of care including participation of the most at risk populations and build upon prevention interventions known to work such as male circumcision [14, 15]. The SEARCH study is built upon biomedical evidence that is being applied and tested in a manner which incorporates social science evidence and approaches.

The SEARCH study is multicounty collaboration built upon expertise from a broad spectrum of scientific disciplines. It is grounded upon partnerships with scientific, health, and development global agencies. SEARCH is designed to inform the health sector, finance ministries, and the scientific and lay communities on the medical and economic effects of early antiretroviral therapy in rural East Africa.

1.2 Rationale

There is overwhelming evidence that the benefits of ART extend well beyond those originally appreciated, and those that are currently measured. ART reduces mortality among persons with HIV. The HPTN 052 study showed that ART reduces AIDS related illness even in persons with CD4 cell counts above thresholds of CD4 cell counts (i.e. 350 cells/mm3) currently used to initiate therapy [7]. ART also dramatically reduces TB risk both on the individual and the community level [6, 16, 17]; reduces the risk of malaria in individuals [18]; Reduces mother to child transmission (MTCT) of HIV; and reduces maternal and child mortality [19, 20].

ART is also a key component in a multilevel HIV prevention strategy. The HPTN 052 study shows definitively that ART reduces HIV transmission and preserves the health of the HIV infected persons receiving treatment [7]. These results build upon prior observational cohort studies showing reductions in HIV transmission by ART in HIV sero-discordant couples [21]. Biomedical interventions such as ART are likely to be highly complementary to proven interventions such as male circumcision and have an important role in reducing new HIV cases.

ART and the associated restoration of health also have important effects on socio-economic outcomes. Studies conducted in various settings in sub-Saharan Africa and South Asia have documented a significant improvement in the employment outcomes of adults following the initiation of ART [15, 22-25]. These studies have shown a large and rapid increase in labor supply and labor productivity, from levels that were initially very low to levels that were similar to those of HIV uninfected adults. In many cases, the increase in employment outcomes took place within 3-6 months of ART initiation, a result that is consistent with the rapid improvement in health and functional capacity due to ART. Furthermore, studies have found that the treated patients’ family members (particularly children) also benefit substantially when a working-age

adult becomes healthy and productive [26]. Following ART initiation in Kenya, there was a significant increase in the school attendance of children living with treated patients, as well as a reduction in child labor and improvement in nutritional status. These studies suggest that earlier ART initiation would *prevent* a decline in socio-economic status and help to protect living standards.

ART can contribute to prevention of new HIV infections and prevention of AIDS and TB, enhance economic productivity, and improve socio-economic outcomes more generally. A key question then is why is the ART "test and treat" strategy not being deployed?

First the strategy requires knowledge of HIV status, and globally, most individuals are not aware of their HIV status. *We aim to identify HIV status throughout the community through annual community health campaigns that we have piloted and refined in western rural Uganda*. Second, there is a stigma for participating in care that prevents even those with known HIV infection from getting treated. *This study will be conducted in communities where we have established ongoing community engagement work, and care delivery will be adapted to the community to promote participation and retention*. Third, there are few data in developing nations to prove or disprove that asymptomatic individuals will initiate and adhere to ART. *We are currently studying predictors of adherence in this population and will incorporate this knowledge into care delivery*. Non-adherence to ART has serious consequences for the HIV epidemic because it means that A) individuals will not immediately benefit, B) HIV can become resistant requiring new and more expensive medications, and C) resistant HIV can spread sexually and during mother to child transmission.

Community engagement strategies will be deployed in this study to maximize adherence. Finally, ART (despite 10-fold reductions in drug price over the last decade) is expensive to deliver. Providing it according to the current health delivery system might not be possible due to shortages in financial and human resources, particularly when doubts are expressed about the cost-effectiveness of such an intervention relative to many other priority health interventions. Thus data are needed to inform policy makers about the full range of benefits and risks of a test and treat ART strategy.

1.3 Antiretroviral therapy

The current WHO Antiretroviral Treatment Guidelines recommend ART for all adults with WHO stage III or IV disease, tuberculosis or CD4<350 cells/mm3. ART is recommended for all children less than 2 years of age, and subsequent ART is dependent on a variety of disease and CD4 specific criteria. The WHO recommends a variety of approaches of ART for HIV+ pregnant women who otherwise do not meet the adults guidelines for ART. The current specific country guidelines for ART treatment for countries participating in SEARCH as of October, 2011 are summarized in Table 1 below.

Table 1: Current ART treatment guidelines

Country	Population	ART initiation
Uganda[27]	Adults and children ≥5 years	CD4 count ≤350 cells/mm^3
	Adults and children co-infected with tuberculosis (TB), co-infected with hepatitis B (HBV), with WHO Stage III or IV disease, and pregnant women (prophylaxis)	Initiate ART irrespective of CD4 % or count
	Children 2 to <5 years	CD4 % <25% or CD4 count <750 cells/mm^3
	Children <2 years	Initiate ART irrespective of CD4 % or count
Kenya[28]	Adults and children ≥12 years	CD4 count ≤350 cells/mm^3
	Adults and children co-infected with tuberculosis (TB), co-infected with hepatitis B (HBV) with evidence of liver damage, with WHO Stage III or IV disease, with HIV-associated nephropathy, and pregnant women (prophylaxis)	Initiate ART irrespective of CD4 % or count
	Children 5 to 12 years	CD4 % <20% or CD4 count <500 cells/mm^3
	Children 2 to <5 years	CD4 % <25% or CD4 count <1000 cells/mm^3
	Children <2 years	Initiate ART irrespective of CD4 % or count

In this protocol, the intervention arm will provide antiretroviral therapy for all community members who otherwise do not meet the criteria for ART initiation. The selection of antiretroviral regimen for this study was based upon the following regimen characteristics: antiretroviral therapy efficacy, safety profile, monitoring requirements, pill burden, knowledge of HIV drug resistance that emerges under the drug use, prior use and experience within the study countries, consultation with in- country advisory board, consultation with in -country regulatory bodies The following regimens will be provided to the study populations below in the intervention arm that otherwise do not meet criteria for government supported ART.

Table 2: Study Treatment[1]

Population	First line regimen	Recommended substitutions/second line regimens
Adults and adolescents, 13 years and above	Emtricitabine, tenofovir disoproxil fumurate and efavirenz	Abacavir, lamivudine and atazanavir/ritonavir[2] or lopinavir/ritonavir[3]
Children 3-12 years	Abacavir, lamivudine, and efavirenz	Zidovudine, lamivudine and lopinavir/ritonavir
Children <3 years	Abacavir, lamivudine, and nevirapine	Zidovudine, lamivudine and lopinavir/ritonavir
Pregnant women and women attempting conception	Emtricitabine, tenofovir disoproxil fumurate and lopinavir/ritonavir. Women enrolled after the first trimester may take efavirenz	Abacavir, atazanavir/ritonavir[2] and nevirapine

1. Exceptions to the regimens can be made in accordance with in-country treatment guidelines
2. Substitutions for women of child-bearing potential with inadequate contraception and those who are attempting conception
3. Second-line therapy

2.0 STUDY OBJECTIVES

2.1 Primary Study Objective

To determine the effect of a strategy to start ART in HIV diagnosed persons at any CD4 count with streamlined delivery of HIV care compared to a country based ART guidelines on 5-year cumulative HIV incidence in rural communities with annual HIV testing.

2.2 Secondary Objectives – Health

2.2.1 To compare time from diagnosis to AIDS between the 2 study arms.

2.2.2 To compare incidence of AIDS-defining events between the 2 study arms.

2.2.3 To compare proportion of total TB and incident TB cases associated with HIV between the 2 study arms.

2.2.4 To compare mortality between the 2 study arms.

2.2.5 To compare maternal and child mortality between the 2 study arms.

2.2.6 To compare mother to child transmission between the 2 study arms.

2.2.7 To compare population HIV RNA metrics between the 2 study arms.

2.2.8 To determine the association between population HIV RNA metrics and HIV incidence.

2.2.9 To compare the prevalence of transmitted HIV drug-resistance mutations between the 2 study arms.

2.2.10 To compare rates of linkage to and retention in care for HIV between the 2 study arms.

2.2.11 To compare time to ART-initiation between the 2 study arms.

2.2.12 To characterize treatment outcomes in high CD4 count individuals (CD4>350) including: A) CD4 cell count recovery, B) rate of virologic suppression, C) treatment-associated toxicities and grade 3 and 4 adverse events, and D) HIV drug resistant mutations after 1 and 2 years of treatment.

2.2.13 To compare the five year cumulative incidence of internally derived HIV infections (infections genetically linked to a prior infection among members of the same community) between the 2 study arms.

2.3 Secondary Objectives – Economic and Education Outcomes

2.3.1 To compare the trends in average levels of adults' on- and off-farm employment between the 2 study arms.

2.3.2 To compare the trends in average levels of children's on- and off-farm employment (child labor) between the 2 study arms.

2.3.3 To compare the trends in average levels of children's time allocation to schooling and household activities between the 2 study arms.

2.3.4 To compare the trends in average asset holdings (durable good and livestock) between the 2 study arms.

2.3.5 To compare the trends in agricultural output and other economic production, such as fishing, between the 2 study arms.

2.3.6 To compare the trends in average levels of cash and in-kind transfers between the 2 study arms.

2.4 Secondary Objectives – Cost and Cost-Effectiveness

2.4.1 To compare costs of programming (campaigns, ART) between the 2 study arms: overall; per person identified, linked to care, and started on ART; and per ART-month, CD4 level recovered, and viral load suppressed.

2.4.2 To compare disease burden (expressed in disability adjusted life years, DALYs) between the 2 study arms, during and modelled beyond the study period.

2.4.3 To compare the savings from averted disease associated treatment costs between the 2 study arms.

2.4.4 To compare the occurrence and consequences of false positive HIV diagnosis (new).

2.4.5 To calculate the incremental cost-effectiveness of the intervention, as net cost per DALY averted.

3.0 STUDY DESIGN

SEARCH is a cluster randomized community trial. The primary study hypothesis is: ART initiation at any CD4 count with streamlined delivery compared to ART initiation according to country guidelines will reduce cumulative 5-year HIV incidence and protect and improve health, economic and education outcomes in communities with annual HIV testing campaigns. The primary study endpoint is cumulative 5 year HIV incidence in men and women ages $\geq$ 15 years. The study will be conducted in rural communities in Uganda and Kenya.

Annual community health campaigns will be conducted in all study communities and will offer HIV testing and multi-disease prevention and treatment services. The intervention is ART independent of CD4 cell count delivered in a streamlined approach for all HIV infected adults and children. This intervention will be applied in the context of ongoing HIV combination prevention strategies including male circumcision. Control communities will receive annual testing campaigns and ART will be provided by country programs according to their guidelines.

HIV incidence will be measured using an efficient community cohort design (ECCO) comprised of three key elements: A) baseline household community level census, B) annual community health campaigns that use unique identifiers to link individuals between successive waves of the intervention, and C) tracking and evaluation of individuals who do not participate in annual CHCs.

4.0 STUDY POPULATION

4.1 Community Level Inclusion Criteria

4.1.1 Non-adjacent geopolitical units in south-western and eastern Uganda and western Kenya.

4.1.2 Most recent census population between 9,000 and 11,000 individuals.

4.1.3 Served by an ART providing health center.

4.1.4 Community leader commitment for study participation and implementation.

4.1.5 Accessibility to health center via a maintained transportation route.

4.1.6 Community location with sufficient distance from other potential study communities to limit contamination of intervention or control conditions (buffer zone)

4.2 Individual Level Inclusion Criteria

4.2.1 Residency of individual in community, defined as present in household for at least 6 months of the calendar year.

4.3 Community Level Exclusion Criteria

4.3.1 Presence of ongoing community-based ART intervention strategies that provide treatment outside of the current in-country treatment guidelines.

4.3.2 An urban setting defined as a city with a population of 100,000 or more inhabitants.

4.3.3 Absence of a health center able to provide ART.

5.0 STUDY INTERVENTION

5.1 Antiretroviral Therapy

5.1.1 Intervention Arm Characteristics

ART intervention will be provided to participants in communities randomized to intervention who do not meet in-country treatment guidelines (Table 1). The study treatment will consist of a 3-drug ART regimen that will be provided to participants by the study (Table 2).

5.1.2 Regimen and Administration

<u>Adults and adolescents, 13 years and above</u>

First Line Regimen:	Truvada® (Emtricitabine [FTC] 200mg/Tenofovir disoproxil fumurate [TDF] 300mg), one tablet PO daily, administered as a fixed-dose combination, *PLUS*
	Efavirenz (EFV) 600mg, one tablet PO daily
Recommended Second Line Regimen:	Abacavir (ABC) 300mg, two tablets PO daily, *PLUS*
	Lamivudine (3TC) 150mg, one tablet PO twice daily, *PLUS EITHER*
	Atazanavir (ATV) 300mg and ritonavir (RTV) 100mg, once daily PO, *OR*
	Lopinavir/ritonavir (LPV/RTV) 200mg/50mg, two tablets PO twice daily, administered as a fixed-dose combination

<u>Children 3 – 12 years</u>

First Line Regimen:	Abacavir, *PLUS*
	Lamivudine, *PLUS*
	Efavirenz
Recommended Second Line Regimen:	Zidovudine (AZT), *PLUS*
	Lamivudine, *PLUS*
	Lopinavir/ritonavir, administered as a fixed-dose combination

Individual dosing information by weight can be found in Appendix E.

<u>Children < 3 years</u>

First Line Regimen:	Abacavir, *PLUS*
	Lamivudine, *PLUS*
	Nevirapine (NVP)
Recommended Second Line Regimen:	Zidovudine, *PLUS*
	Lamivudine, *PLUS*
	Lopinavir/ritonavir, administered as a fixed-dose combination

Individual dosing recommendations by weight can be found in Appendix E.

<u>Pregnant women and women attempting conception</u>

First Line Regimen:	Truvada® (Emtricitabine 200mg/Tenofovir disoproxil fumurate 300mg), one tablet PO daily, administered as a fixed-dose combination, *PLUS*
	Lopinavir/ritonavir 200mg/50mg, two tablets PO twice daily, administered as a fixed-dose combination

After the first trimester, women may switch to efavirenz 600mg, as described above for adults.

Recommended Second Line Regimen:	Abacavir 300mg, two tablets PO daily, *PLUS*
	Lamivudine 150mg, one tablet PO twice daily, *PLUS EITHER*
	Atazanavir 300mg and ritonavir 100mg, once daily PO, *OR*
	Nevirapine 200mg, one tablet PO daily for first 2 weeks, then one tablet PO twice daily

Based on variations of standard first- and second-line ART regimens suggested among in-country treatment guidelines, substitutions to the above can be made at the investigators' discretion.

5.1.3 Streamlined ART Delivery

In this study, participants in intervention communities will receive HIV therapy at ART providing health centers via "streamlined care," in order to maximize efficiency and clinic throughput, and engender the smallest impact of expanded ART access on current clinical sites, while maintaining treatment efficacy and safety. "Streamlined care" is defined as a method of enrolling ART-naïve participants, and initiating and sustaining ART delivery, in a manner consistent with

the principles of care outlined in Table 3, recognizing that both facilities and patterns of care will vary somewhat between sites. For participating health centers that do not currently offer ART in this streamlined fashion, study investigators will work with clinic staff to design and adapt existing procedures to this approach. During the course of the study, we will evaluate provider and patient attitudes and the implementation of streamlined and routine care.

Table 3. Features of "Streamlined" ART Delivery Model

ART Clinic	***Healthcare Team***	***ART Monitoring***
• Rapid ART initiation available with expedited counseling • Short throughput* for patients with no active issues • Targeted adherence support • Convenient ART refill process * = Throughput: time spent from clinic check-in to completion of visit	• Non-MD health care worker responsible for: 1. Screening for ART-related adverse events and toxicities 2. Dispensing, managing and altering ART regimens 3. Maintaining patient and drug accountability records • Back-up support for care and consultation by physician	• Streamlined visit schedule conducted by non-MD health care workers • Targeted laboratory evaluation schedule • Inclusion of viral load monitoring during ART • Back-up support for laboratory monitoring by physician

Study investigators and staff may provide additional support to ART providing health centers where needed. This may include assistance with staffing, operation of linkage to care procedures, and or oversight of study drug accountability.

5.1.4 Product Supply and Accountability

<u>Supply</u>

Each participant will be provided with treatment over the course of his or her participation. Truvada® and efavirenz will be provided by the study.

<u>Accountability</u>

Staff will maintain records of study drugs distributed according to standard guidelines. At most sites, lot number and the number of pills given to each participant at each visit will be recorded. A registry of study medications with current product labels, Certificates of Analysis, date received, lot number, expiration date, and date used will be maintained within the site regulatory binder for the study. Monthly inventory will be conducted.

6.0 COMMUNITY LEVEL STUDY EVALUATIONS

6.1 Baseline Household Community Level Census

Prior to the start of the study, study team members will meet with local officials and community representatives to discuss the study and plans for the census. Using a map of the boundaries of the selected communities, study staff will systematically cover the entire area within the boundaries to identify and enumerate all households. A head of the household will provide informed consent for the following information to be collected about household members:

- Name
- Relationship to head of household
- Mobile phone number
- Demographic information such as age, gender, occupation and marital status.
- A fingerprint of each household member over the age of 2 years will be collected with the use of a fingerprint biometric device.
- The household's location relative to the local health center will be mapped using hand-held GPS receivers.

At the time of the census, household members will be consented for participation in the community health campaign and for the census itself. Household members not present at the time of the census will be offered participation in the trial with consenting procedures offered at the first community health campaign.

6.2 Community Health Campaign (CHC)

6.2.1 Overview

Annual community health campaigns will be conducted in all study communities and will offer A) HIV testing, and B) multi-disease diagnostic, prevention, treatment, and referral services (such as malaria, deworming), tailored to the community. The CHCs will serve two primary purposes. First, the campaigns will allow for annual community-wide HIV testing and prompt linkage to HIV care – a critical aspect of care delivery for both intervention and control communities. Multi-disease service delivery in the context of a community health fair will encourage broad communication across all demographic groups and encourage HIV testing as a routine part of health care. Second, the campaigns will provide an evaluation framework for multiple study outcomes, including health, economic and education outcomes, such as HIV incidence, community HIV viral load, interval vital status and AIDS assessments for efficient community cohort participants.

6.2.2 CHC Procedures

Each community will have a campaign performed within 4 months after the census and performed annually. Roving CHC teams assigned to specific study communities will conduct the

campaigns. Campaign training will be performed at the start of the SEARCH study, and updated as needed.

6.2.2.1 Community mobilization

The primary goal of community mobilization will be to maximize CHC participation by informing the community of the purpose, dates and locations of the community health campaign days, and of the services that will be available. These activities will include meetings with village leaders throughout each study community, and may include poster and leaflet advertising, radio advertising and enlisting community-based volunteers to describe campaign activities and encourage participation in the CHCs. Community mobilization will incorporate the principles of a study community engagement plan.

6.2.2.2 CHC Services

The campaign will consist of a series of stations arranged so as to maximize participant privacy and flow through the campaign. Participants will proceed through stations such as those described below, but which could be adapted to the services provided in the individual communities.

Welcome Station

At the start of each campaign, participants will review the services offered at the campaign with campaign staff. If participants have not taken part in census activities prior to the campaign, informed verbal consent will be obtained from all adults for themselves and their children to participate in the campaign and to take part in census activities. The verbal consent form will be read to them in the local language, and their fingerprint biometric will be recorded on tablet computers as affirmation of their agreement to participate. Identifying information will be collected from each community member. Identification of participants will be based on the following: name, village of residence, age, gender, and fingerprint biometric. Campaign staff will provide each participant with a campaign results card to record their screening results. Participants will then initiate campaign activities.

Health and Socioeconomic Interview Station

Health and socioeconomic questionnaires will be performed for each participant annually, in order to collect updated information about health and economic status, including interim births, illnesses, hospitalizations; changes in employment or educational attainment over the past year; and migration patterns and social network. Staff will interview women of child-bearing age regarding any births and deaths of children over the past year.

Pre-test Counselling Station

Prior to undergoing diagnostic testing in the campaign field laboratory, group pre-test counselling will take place to inform and update participants on the diagnostic services offered and answer questions.

Campaign Field Laboratory

Multiple diagnostic services will be offered in the field laboratory. Some will be offered at all campaigns, and others will be recommended but not required, depending on country guidelines and local resources.

a. All participants:
    i. HIV Antibody testing for all participants >18 months as follows:
        1. Initial rapid HIV test
        2. All negative results will be informed of their HIV-negative status
        3. All positive results will be confirmed with a second rapid HIV test, performed either in series or in parallel with the first test.
        4. Discordant results (first test positive, second test negative): participants with discordant rapid tests will undergo a third "tie-breaker" HIV rapid test. Participants with a positive "tie-breaker" test will be informed that they are HIV positive. Participants with a negative "tie-breaker" test will be told that their results were inconclusive and a recommendation will be given for repeat testing in 6-8 weeks.
    ii. Dried Blood Spot on filter paper for all participants, including children <18 months
    iii. *Recommended:* Finger-stick blood glucose measure
    iv. *Recommended:* Syphilis screening (RPR) for all >15 years
    v. *Recommended:* Blood pressure measurement for all >18 years
b. HIV-infected participants:
    i. Point-of-care CD4 cell count testing
    ii. HIV RNA, by fingerprick or phlebotomy
c. Children (<18 years)
    i. *Recommended:* Anthropomorphic Measures: Height and weight
    ii. Malaria rapid diagnostic test (RDT) for children <10 years old reporting fever in the past 24 hours

Post-test Counselling

All adult participants, regardless of test results, will receive post-test counselling. Child participants will receive post-test counselling with a parent or guardian. On-site malaria treatment will be available at this station as well. All malaria RDT positive children will be offered on-site malaria treatment, according to Ugandan or Kenyan standard of care for non-severe

malaria. Cases of severe malaria will be offered transportation the nearest in-patient health center for hospital-based treatment.

Linkage Station

Post-test counsellors will direct any participants with a positive screening test (i.e. HIV, hypertension, diabetes, etc.) to the referral station in order to meet disease-specific clinical staff and to schedule intake appointments for the appropriate clinic(s). Campaign staff at the referral station will focus on three aspects of linkage-to-care:

a. Patient education: All participants will receive information regarding early treatment and the benefits and importance of linking to disease-specific care after diagnosis.
b. Patient Navigation: A clinician will meet with each participant not already in care in order to introduce him or herself and answer questions regarding the referral clinic. Following this introduction, a study assistant will schedule an intake appointment.
c. Incentives: HIV-infected participants will receive transportation vouchers redeemable for transportation expenses *after linking to care* for their first visit. SEARCH linkage vouchers will be collected by a research assistant at the clinic to which the participant is referred at the time of linkage to HIV-specific care. HIV-infected participants will also receive a one-month supply of TMP/SMX.

Distribution Station/Campaign Exit

In the final step of each CHC, participants will have their fingernails marked with permanent ("voting") ink, to prevent persons from repeating campaign activities during a CHC period, and receive several additional services:

a. All children ≥12 months and ≤5 years of age will be provided with Mebendazole (one 500 mg tablet).
b. All children ≥ 6 months and ≤5 years of age will be provided with Vitamin A supplementation (one 200,000 IU capsule)
c. Distribution of male condoms

Documenting Participation

Upon completion of every campaign, each community's baseline census enumeration will be compared to the list of campaign attendees using all identifying information collected at the Welcome Station (including electronic fingerprint). After the first CHC, all community members (defined by enumeration in the baseline census and including HIV-infected and uninfected residents) who did not attend the CHC will be tracked and evaluated. After each subsequent CHC, a random sample of CHC non-attendees will be tracked and evaluated. The size of the random sample to be tracked will be based on the number of CHC non-attendees.

6.2.2.3 CHC Procedures Intervention Arm

Participants in all communities who are newly diagnosed with HIV will be encouraged to visit their local health center for care. Participants in intervention communities who do not meet country guidelines to start ART will be asked to visit the study supported ART providing health center for their community, where they will be introduced and consented to the ART Intervention study. Participants will receive transportation vouchers, which can be redeemed at the health center. The value of the transportation voucher will depend on the distance from the participant's home to the clinic.

6.2.3 Supplemental Testing

Existing testing services in intervention communities will be assessed at baseline, and SEARCH will partner with these services to ensure linkage to the streamlined care delivery system, including ART at all CD4 counts for individuals diagnosed in these locations. In addition, the CHC will be used to assess unmet need for testing of most at risk populations (MaRPs), and testing services will be supplemented accordingly.

6.2.4 Tracking CHC non-participants

<u>Tracking Procedure</u>

Locator information collected during the baseline census enumeration will be used to locate CHC non-participants. The community tracker then records the outcome of the patient after tracking in the community.

<u>Tracking Evaluation</u>: Evaluation will consist of at least the following:

- Vital status with verbal autopsy in the event of a reported death, to capture cause of death (e.g. trauma, illness, suicide, childbirth) whenever possible.
- Field HIV antibody rapid testing according to the testing algorithm (with confirmation and tie-breaker testing) used in the CHC
- CD4 cell count and HIV RNA testing among HIV+ participants
- A health, economic and educational interview, similar to the interview conducted during CHCs.
- Trackers will also evaluate reasons for not coming to the recent CHC, and investigate incentivizes for participation in the subsequent CHC.
- For people who cannot be tracked: reasons for not finding the person (e.g. emigration out of the study community, migration within the study community, or other reasons).
- *Recommended*: The collection of Dried Blood Spots on filter paper, finger-stick blood glucose measures, syphilis screening (RPR) for all above 15 years, and blood pressure measurement for everyone 18 years and older.

6.3 Mortality and HIV and TB Disease Surveillance

To maximize ascertainment of SEARCH study secondary outcomes, we will conduct community-based surveillance for key study outcomes in the one-year period between annual community health campaigns (CHCs).

6.3.1 Mortality Surveillance

Deaths and births within each study community will be ascertained using a combination of data from the CHC, post-CHC tracking and local death registries.

a) CHC data: Following every CHC, research assistants will update each community's baseline census to reflect interim deaths and causes of death (when known) of study community members. Information (including electronic fingerprint and residence information) on all children born to members of the study community will be added to the updated census.
b) Post-CHC Tracking: We will update each community's baseline census based on the birth and mortality data collected during post-CHC tracking (see above).
c) Local Death Registries: Study staff will work with government officials to build capacity to maintain ongoing lists of deaths as they occur in their community. Study staff will review these local death registries periodically and incorporate the information into the study census for that community.

Immediately prior to each CHC, study staff will produce an updated community census based on all birth and death data collected in the past year. The updated census will represent the target community, including documentation of CHC participation and tracking of CHC non-attendees.

6.3.2 Morbidity/Disease Surveillance

Health Center Surveillance: Study staff will regularly collect information available from routine encounters at local health centers and, where needed, hospitals within the community. This information will be available in the clinic's standard visit forms and recorded by staff for data entry. The following information will be collected:

- Visit date and identifying information, including name, age, gender, village of residence, and fingerprint, will be collected on all clinic attendees at the time of clinic visit.
- Diagnosis
- Laboratory results
- Medications
- Hospitalizations
- Mortality

TB Surveillance: Staff will visit all clinics providing TB therapy at regular intervals throughout the year. The government is the sole supplier of anti-tuberculosis antibiotics in Uganda and Kenya,

and therefore TB therapy is only available through government-run or associated clinics and hospitals. All TB clinic dispensaries keep government registries with diagnostic and treatment-related outcomes for every case, including name, age, HIV status and residence information. Staff will enumerate all clinics providing TB therapy at baseline. At the start of the SEARCH study and during regular visits to TB clinics, staff will collect the following information, as available:

- Overall interval number of TB cases reported to the clinic, with name, age, residence, and acid-fast bacilli (AFB) smear results
- TB treatment: Data on treatment status of each case at initiation of anti-TB therapy (new TB cases, retreatment TB, and TB treatment defaulters)
- TB treatment completion and failure rates.
- All-cause TB case fatality rates: the proportion of TB patients who died on TB treatment each year, excluding those cases that left the community during treatment.

6.4 Feedback of CHC Process and Clinical Data

The CHC implementation team for each community will be provided with data on CHC operations, including linkage to care, determine what, if any, alterations will need to be made to outreach, testing, tracking and surveillance procedures to make them more effective. These modifications will be incorporated into subsequent campaigns in an ongoing effort to improve community trial efforts throughout the five-year study period. This will allow the CHC procedures in each community to evolve in response to data. Individual plasma HIV-1 RNA levels measured at the CHC as part of this research study will be provided to clinics for subjects on ART.

7.0 CLINCAL AND LAB EVALUATIONS IN ART INTERVENTION ARM

7.1 Recruitment

At the time of first awareness of HIV infection, either during a community health campaign or any other location, participants in intervention communities will be asked to visit the study supported ART providing health center in their community, where they will be introduced to the study. All patients who do not meet in-country treatment guidelines will be offered to be screened for the study. Participants will receive a transportation voucher at the campaign site or testing facility, which can be redeemed at the ART providing health center.

7.2 Selection of Participants in Intervention Arm

7.2.1 Inclusion Criteria

7.2.1.1 HIV-1 infection diagnosed by a rapid HIV test or any licensed ELISA test kit. For patients diagnosed in a setting other than study-conducted community health campaigns, HIV status will be re-verified at the time of study screening.

7.2.1.2 Most recent CD4+ cell count ≥ 350 cells/uL, performed within the past 6 months.

7.2.1.3 Willing to initiate ART.

7.2.1.4 The following laboratory values obtained at the screening visit:

- Hemoglobin ≥ 7.0 g/dL
- ALT (SGPT) ≤ 5 times greater than the upper limit of normal
- Estimated glomerular filtration rate (eGFR) of ≥ 60 mL/minute by the Modification of Diet in Renal Disease (MDRD) formula:

$$eGFR = 186 * \text{Serum creatinine}^{-1.154} * \text{Age}^{-0.203} * [1.21 \text{ if African}] * [0.742 \text{ if female}]$$

7.2.1.5 Ability to swallow oral medications.

7.2.1.6 Ability and willingness of participant to give informed written consent.

7.2.2 Exclusion Criteria

7.2.2.1 Currently taking ART.

7.2.2.2 Allergy or sensitivity to prescribed ART.

7.2.2.3 Active World Health Organization (WHO) HIV stage III or IV disease.

7.2.2.4 Any other clinical condition that, in the opinion of the site investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements.

7.3 Informed Consent and Enrollment

Written informed consent to participate in the study will be obtained from all participants. Consent forms will be translated from the original English to the language(s) spoken in the community. The consent form will be read to participants in their local language.

After consent, participants will undergo screening procedures to determine eligibility by clinical evaluation and laboratory testing. Once eligibility is verified, participants will proceed to the local health care center for enrollment procedures and to receive ART medications, where their identify will be confirmed by name and electronic fingerprint.

7.4 Schedule of Evaluations

Table 4: Schedule of Evaluations

Procedure or Evaluation	Screen	Baseline	Study Week						
			4	12	24	36	48	Every 12 weeks	144
Demographic information	X						X		X
Medical history	X								
Targeted physical exam	X								
Tuberculosis screen	X	X	X	X	X	X	X	X	X
Vital signs	X								
Symptom screen	X	X	X	X	X	X	X	X	X
Dispense medications		X	X	X	X	X	X	X	X
Adherence assessment			X	X	X	X	X	X	X
Documentation of HIV infection	X								
Pregnancy	X				X		X	X[1]	X
Complete blood count (CBC)	X			X			X		X
Liver function tests[2]	X			X			X		
Serum chemistries[3]		X					X		
Blood urea nitrogen (BUN) and creatinine	X			X			X	X[4]	X
Glucose		X					X		X
Tuberculosis	X								
CD4 count	X[5]								
Plasma HIV-1 RNA		X			X		X	X[1]	X

[1] Repeat every 24 weeks between Week 48 and Week 144.
[2] ALT at timepoints shown above. AST, total and direct bilirubin, alkaline phosphatase as indicated.
[3] Na, K, Cl, CO2
[4] Repeat at Week 96 only.
[5] Only if not available within the past 6 months.

7.5 Timing of Evaluations

- The baseline visit must be performed within 4 weeks of screening evaluations.
- Weeks 4 through 144 must occur +/- 7 days from the protocol-specified target date.

7.6 Definitions of Evaluations

7.6.1 Demographic information

The following information will be collected: age, sex, place of residence, presumed route of HIV infection (opposite-sex contact, same-sex contact, injection drug use, MTCT), current marital status, current employment status, access to transportation, and the time spent reaching the clinic.

7.6.2 Medical history

A medical history will be collected including current health complaints and allergies to medications.

7.6.3 Targeted physical exam

Participants will undergo a physical exam covering the following systems: oropharynx, heart, lungs, skin and abdomen. Cervical cancer screening may be done in clinics where this is part of standard care.

7.6.4 Vital signs

Weight, temperature, pulse and blood pressure will be recorded

7.6.5 Symptom screen

Participants will be asked whether they currently have any active symptoms.

7.6.6 Dispense medications

Study medications will be dispensed to participants in intervention arm.

7.6.7 Adherence assessment

Participants will be asked to perform a 3-day adherence recall.

7.6.8 Documentation of HIV-1 infection

HIV-1 infection determined by previous testing will be documented at the time of study screening.

7.6.9 Pregnancy testing

Women of child-bearing potential will be tested by urine HCG (human chorionic gonadotropin). This testing will be repeated every 24 weeks between Weeks 48 and 144, or sooner if clinical suspicion of pregnancy exists.

7.6.10 Complete blood count

This will consist at minimum of a white blood cell count (WBC), WBC differential, absolute neutrophil count, hemoglobin and hematocrit, and platelet count.

7.6.11 Liver function tests

ALT will be performed at Screen, Week 12 and Week 48. AST, total and direct bilirubin, and alkaline phosphatase may also be performed as clinically indicated.

7.6.12 Serum chemistries

This will consist of Na, K, Cl, and CO2.

7.6.13 BUN and creatinine

At screening, estimated glomerular filtration rate (eGFR) will be calculated by the Modification of Diet in Renal Disease (MDRD) formula, which is as follows:

$$eGFR = 186 * Serum\ creatinine^{-1.154} * Age^{-0.203} * [1.21\ if\ African] * [0.742\ if\ female]$$

7.6.14 Glucose

Blood glucose will be measured.

7.6.15 Tuberculosis

Tuberculosis screening will be performed according to each clinic's standard of care.

7.6.15 CD4/CD8 counts

CD4 counts will be measured at Screen only if a result is not available within the past 6 months.

7.6.16 Plasma HIV-1 RNA

This will consist of a quantitative determination of the HIV-1 plasma RNA level (in copies/mL). This testing will be repeated every 24 weeks between Weeks 48 and 144.

8.0 ART TOXICITY GRADING AND MANAGEMENT FOR INTERVENTION ARM

8.1 Toxicity Screening

At each follow-up study visit, staff will ask participants about any new symptoms. Depending on the results of this screen, staff may refer the participant to a clinician for further evaluation. Laboratory testing will be done according to the Schedule of Evaluations (Section 7.1) and results will be assessed for evidence of laboratory values indicating possible grade 3 or 4 toxicity according to the DAIDS Toxicity Table, December 2004.

8.2 Management of Laboratory Toxicities

8.2.1 Grade 1 or 2 Toxicities

Participants who develop grade 1 or 2 adverse events or toxicities may continue study medications without alteration of dosage. Participants experiencing such events will be managed at the discretion of the site investigator and staff.

8.2.2 Grade 3 Toxicities

Participants will be referred to a clinician for immediate evaluation. If there is evidence that the adverse event or toxicity is NOT associated with the study drug, dosing may continue. If adverse event/toxicity IS thought to be related to study drug, ART may be withheld or switched at the clinician's discretion. Participants should be re-evaluated every 1-2 weeks if possible and if patient is able to return for follow-up on that schedule, until the adverse event returns to ≤ grade 2 or until stabilized and no longer in need of frequent monitoring, to be determined by the site investigator. ART, if withheld, may be re-introduced anytime at the discretion of the site investigator.

8.2.3 Grade 4 Toxicities

If a symptomatic grade 4 adverse event or toxicity develops, ART should be withheld or switched at the discretion of the site investigator, and the patient should be monitored frequently until the adverse event returns to ≤ grade 2 or until stabilized and no longer in need of frequent monitoring, to be determined by the site investigator.

If an asymptomatic grade 4 adverse event or toxicity develops, ART may be continued or discontinued or switched at the discretion of the site investigator.

8.3 Management of Specific Clinical Syndromes

Patients will be managed according to local standard care general guidelines, including use of the targeted management described below.

8.3.1 Rash

<u>In general</u>:

- Patients will be evaluated for the severity, location, and characteristics of any rash. If any concern exists about serious medical conditions that feature a rash, such as Stevens-Johnson syndrome, clinicians will consult with the site investigator to determine the best course of action.

Issues related to EFV:

- Any rash while on efavirenz (EFV) should prompt suspicion and evaluation for non-nucleoside reverse transcriptase inhibitor (NNRTI) hypersensitivity rash. This should include clinical evaluation for systemic symptoms (fever, arthralgias, myalgias), and laboratory evaluation for suggestive findings (AST/ALT >2x upper limit of normal, peripheral eosinophilia).

- Participants felt to be experiencing an NNRTI hypersensitivity reaction should not be rechallenged with the suspected causal agent.

- An isolated rash while taking EFV does not constitute and should not raise concern for NNRTI hypersensitivity.

For any serious rash (e.g., exfoliation, mucosal involvement, target lesions [erythema multiforme] or evidence of Stevens-Johnson syndrome):

- Participants should discontinue all ART, and staff will confer with investigators as to proper management. Upon resolution to grade 1 or resolved, rechallenge with EFV ART versus restarting with a different ART can occur at the discretion of site investigator.

Issues related to ABC:

- Abacavir (ABC) hypersensitivity is characterized by symptoms of rash (maculopapular or urticarial, but sometimes absent), fever, gastrointestinal symptoms, respiratory symptoms, and malaise. If ABC hypersensitivity is suspected, participants should undergo a clinical and laboratory evaluation. Elevated AST/ALT, CK or creatinine, or decreased lymphocytes, are often present.

- Participants felt to be experiencing ABC hypersensitivity reaction should stop ABC immediately. They should not be rechallenged and should instead restart ART with an alternate NRTI.

8.3.2 Nausea and Diarrhea

Nausea and diarrhea are fairly common side effects patients experience during the first few weeks of ART, but usually subside and resolve promptly. Participants can be encouraged to take medicines with food, or to take anti-emetic symptomatic therapy. For diarrhea, unless an infectious cause is suspected, antidiarrheal agents may be used for symptomatic relief.

8.3.3 AST/ALT Elevation

If a participant's AST and/or ALT are elevated >5x the upper limit of normal, they will be referred to a clinician for evaluation. Toxicity management will proceed according to the plan for grade 3 or 4 events.

8.3.4 Creatinine Increase and/or Creatinine Clearance Decrease

If a participant's glomerular filtration rate is found to be <60 mL/minute by the MDRD formula, they will be referred to a clinician for evaluation for the need to switch ART regimen.

8.3.5 Hyperbilirubinemia

For isolated grade 3 or 4 unconjugated hyperbilirubinemia attributed to atazanavir (ATV), the drug should be continued unless associated with jaundice or scleral icterus that presents an intolerable cosmetic concern to the participant. For events that cannot be attributed to ATV or a non-study drug-related cause, clinicians will consult with the site investigator and all study medications will be held pending evaluation of etiology.

8.3.6 Management of Pregnancy

For women who become pregnant, EFV will be discontinued and replaced with lopinavir/ritonavir (LPV/RTV). EFV can replace LPV/RTV after the first trimester of pregnancy is complete at the discretion of the site investigator.

8.3.7 ART Substitutions

Recommendations for alternative ART regimens are outlined in Table 2.

8.4 Sentinel Sites Clinical Event Grading

In addition to laboratory adverse event grading, sentinel sites (Section 12.5) will grade all clinical events occurring within their local health centers according to the DAIDS Toxicity Table for Adults and Children (Appendix A). Management and grading of clinical adverse events will be performed as follows:

8.4.1 Grade 3 Toxicities

Participants will be referred to a clinician for immediate evaluation. If there is evidence that the adverse event or toxicity is NOT associated with the study drug, dosing may continue. If adverse event/toxicity IS thought to be related to study drug, ART may be withheld or switched at the clinician's discretion. Participants should be re-evaluated every 1-2 weeks if possible and if patient is able to return for follow-up on that schedule, until the adverse event returns to ≤ grade 2 or until stabilized and no longer in need of frequent monitoring, to be determined by the site investigator. ART, if withheld, may be re-introduced anytime at the discretion of the site investigator.

8.4.2 Grade 4 Toxicities

If a symptomatic grade 4 adverse event or toxicity develops, ART should be withheld or switched at the discretion of the site investigator, and the patient should be monitored frequently until the adverse event returns to ≤ grade 2 or until stabilized and no longer in need of frequent monitoring, to be determined by the site investigator.

If an asymptomatic grade 4 adverse event or toxicity develops, ART may be continued or discontinued or switched at the discretion of the site investigator.

9.0 ECONOMIC AND EDUCATION EVALUATIONS

9.1 Overview

A longitudinal household survey will be conducted among a random sample of adult participants in order to record information about the socio-economic status of participants and their households. These surveys will provide information needed to assess the effects of the intervention on a number of outcomes related to the economic and educational status of community members.

9.2 Recruitment and Enrollment of Study Participants

9.2.1. Recruitment

Participants will be recruited after the annual community health campaigns. Recruitment will be from those who offered consent for participation in the campaign. In each of the 32 communities, all HIV-positive campaign participants and 100 randomly selected HIV-negative participants will take part in the household survey. Selected participants' homes will be visited after the campaign using geographic data collected during the baseline household census. Participants will be asked whether they would be willing to take part in a household socio-economic survey and their identity will be confirmed by name and electronic fingerprint.

9.2.2. Informed Consent and Enrollment

Informed consent for participation in the Household Socio-Economic Survey will be conducted the participant's home shortly after the annual health campaign. Consent will be conducted in the appropriate language with the study candidates; translators will be used if necessary. The informed consent will be available in local languages and will be read aloud to the study candidates. Enrollment will be limited to adult participants in the annual community health campaigns.

9.3 Procedures

9.3.1 Household Survey

Participants will be visited at their homes by trained interviewers and consent will be obtained from those agreeing to take part. Community elders and local chiefs will be informed about the survey prior before interviewers begin visiting households. The interviewers will begin by locating the participant at the location described in the baseline household survey. We will attempt to arrange for respondents to be interviewed by somebody of the same sex. If the participant is not present, one additional re-visit to the household will be conducted at a later time. The household survey questionnaire will have a modular format, with each module covering a different topic. SOPs will be developed to provide further instructions on how the surveys will be administered. Quantitative information will be collected on various topics, such as:

- Demographic characteristics of households, such as age and sex of household members

- Health and education of household members
- Marital characteristics of household members
- Income and employment of household members
- Housing characteristics and asset ownership of households
- Transfers, gifts, and loans to and from the household
- Subjective expectations about future health and income
- Height and weight information for children, if not available from the community health campaign
- Food insecurity
- Consumption and spending patterns
- Health care utilization

The household survey will be administered in a private area so that the respondent can answer questions freely. Information about the schooling, employment and income will be collected from a knowledgeable household member in cases where the respondent is not able to provide accurate information.

9.3.2 Duration of Survey

The household survey will last approximately 2.0 hours, as is standard for comprehensive household surveys that contain multiple modules.

9.3.3 Follow-up Visits

Households that participate in the annual community health campaigns will be revisited least at years 2 and 5, and up to annually, in order to measure changes in socio-economic outcomes. A similar household survey questionnaire will be used during each visit, with additional modules that will record changes in household composition. Reasons for entry and exit of household members will be recorded.

9.3.4 Linkage to Community Health Campaign Data

Information collected in the household socio-economic survey will be linked to the data from the community health campaign by the CHC ID number of the participant who was recruited for the household survey. The linked community health campaign data will provide information on the HIV status of the participant as well as measures of the CD4 cell count and viral load of HIV-positive participants.

10.0 HEALTH CARE COSTING EVALUATIONS

10.1 Overview

We will undertake a micro-costing of the resources needed to carry out the activities contemplated in achieving this project's primary objectives. Activities to be costed include both the community health campaigns, and the provision of ART including pMTCT to both the intervention and control communities. The unit costs of the full range of services provided will be calculated. When combined with incidence data for HIV, as well as all-cause mortality and morbidity, these data will be used to estimate the incremental cost-effectiveness of the intervention.

10.2 Recruitment and Enrollment of Study Participants

As described in section 7.1, either during a community health campaign or upon testing at a health care facility, participants in intervention communities will be asked to visit the ART distributor main facility for their community where they will be introduced and enrolled into the study. The medical care resources required by each enrolled patient will be assessed as follows. A cost analysis will be carried out at each of the participating government health facilities that provides ART to enrolled patients and at that and other facilities that provide non-ART care to study patients for malaria, TB and the chronic diseases that the community campaigns seek to mitigate. We expect to complete the cost analysis at the health facilities providing ART within the study communities.

10.3 Procedures

To assess the costs of the additional activities assessed in this study, we will conduct incremental unit cost analyses using standard micro-costing techniques [29]. Incremental unit cost comparisons will be completed, based on the costs of implementing the community campaigns and the five-year costs of providing ART.

10.3.1 Cost Data Teams

Incremental costs of the interventions will be assessed using a uniform cost data collection protocol for gathering expenditure data at each of the study sites. We will work in close consultation with staff at each site to complete this protocol retrospectively in 6-monthly intervals over the 5 years of follow-up. Following training and instrument piloting to be conducted prior to study initiation, the data collection effort will carried out by three teams, one in each study area Each team will consist of a medically trained person coupled with a person trained in finance, economics or accounting. They will be supervised by a senior in-country expert who will coordinate and communicate with the SEARCH economics team. We anticipate that the initial visit to each site will require 5 days to complete the cost instruments but that this will drop to 2 – 3 days during the subsequent visits.

10.3.2 Organization of Cost Data

Expenditures will be classified in one of four categories; (i) personnel (including fringe benefits); (ii) recurring supplies and services; (iii) capital and equipment; and (iv) facility space (as

appropriate). We will also collect retrospective expenditure data to document program start-up costs. The costs of each program activity will be identified through interviews with administrative, finance and human resources officers, supplemented by direct observation in a limited number of formal time and motion studies. The costing approach will emphasize resources utilized, rather than out-of-pocket costs. For example, where expenditures do not fully reflect the opportunity cost of the resources used (e.g., donations or transfer payments), we will adjust the valuations accordingly. Costs for capital items will be amortized on a straight-line basis over their expected useful life, and assuming no salvage value. Facility space required by the interventions, will be valued at the market rental rate. Following assignment of expenditures to these four broad categories, we will further allocate each expenditure item across three areas, (i) service delivery; (ii) staff training directly related to service delivery; (iii) indirect costs consisting of intervention overhead and administration.

10.3.3 Personnel Costs and the Allocation of Overhead Across Activities

Overhead and administrative costs will be allocated to the programs in proportion to the full-time equivalent staff (FTEs) that study intervention service providers constitute of all service provider FTEs at the study sites [30]. We expect that the preponderance of intervention costs will be personnel time. The appropriate approach to measuring personnel time will depend upon the way services are organized at the study sites. For example, if dedicated staff is hired specifically for these interventions, costs can be obtained directly from compensation data. In the more likely case that service providers have multiple responsibilities, the time dedicated to these interventions can be obtained via interviews supplemented by direct “time and motion” observations, including completion by staff of logs recording major activities, for one week periods approximately six months apart.

10.3.4 Measuring Unit Costs

Outputs (denominator of the unit cost) include the numbers of patients receiving each type of study-supported services. Unit costs are defined as the relevant program costs divided by each of these outputs, respectively. To supplement this information, we will also collect information on patient-level contact hours, to allow us to examine the importance of participant and intervention-level factors related to variation in unit cost. We will also assess the variation in unit costs across the study sites and identify the major determinants of that variation. If possible, we will document changes in unit cost over time as programs potential achieve greater scale and administrative efficiency. These findings are intended to provide program managers with insights into costs structures that may be used to enhance program efficiency. We will calculate the cost per added person receiving ART and pMTCT interventions, based on other study findings.

10.3.5 Health Care Utilization and Spending by Households

The household survey mentioned in section 9.3.1 will include a section on health care utilization, using short term (1 month) recall for care sought for illness episodes and longer term (6 months) for inpatient hospital care. These questions will identify the range of health care providers used, the frequency, and family expenditures.

11. STATISTICAL PLAN

11.1 Overview of Study Design

This is a Phase III community-level cluster randomized controlled trial, in which 32 communities in three sites in East Africa (two in Uganda and one in Kenya) will be randomized to either an intervention arm, consisting of annual community-health campaigns including voluntary counseling and testing for HIV along with a strategy of HIV antiretroviral therapy for all HIV infected persons regardless of CD4 cell count (Universal ART) coupled with a streamlined ART delivery system for individuals with less advanced HIV disease, or to a control arm, consisting of annual community-health campaigns including voluntary counseling and testing for HIV and the current country standard guidelines for the initiation of HIV antiretroviral therapy for HIV infected persons (Standard ART). As the study is testing a community-level strategy, communities – rather than individuals – are the unit of randomization. An individually randomized trial could be used to study the effect of standard ART compared to ART at all CD4 counts on individual outcomes. In contrast, our interest is in the impact of a community-wide universal ART strategy, as compared to a standard ART strategy, on HIV incidence and a range of secondary community level health, economic, and educational outcomes, in the setting of annual community-based HIV testing.

Randomization will take place within pair-matched communities. Communities will be matched on site region and major factors influencing HIV transmission dynamics and health care delivery system structure. The primary outcome measure is five year cumulative HIV incidence. This will be measured for each community using an efficient community cohort design, in which a) community members are enumerated using a baseline household based census; b) individuals are serially assessed for HIV status at annual community health campaigns; and, c) a random sample of individuals failing to participate in each community health campaign are tracked and receive home-based HIV testing. Community-level cumulative HIV incidence will be evaluated 5 years after the date of community randomization.

a. <u>Target Population of Communities</u>
   The target population that we wish to generalize the results of this research to are rural and semi-rural African communities with moderate levels of HIV prevalence and incidence and served by health centers within or adjacent to the community. We are targeting communities of approximately 10,000 persons, a size which fosters social familiarity and connectedness, and which are organized as one or two adjacent geopolitical units served by a common health center. Community has in past work been defined as groups of individuals who live next to one another and participate in common practices; depend on one another; make decisions together; identify themselves as part of something larger than the sum of their individual relationships; and commit themselves to the group's well-being [31, 32]. Our target communities for this study represent units of organization that reflect these dimensions of communality.

b. <u>Selection of Countries</u>
   The two countries participating in this study (Uganda and Kenya) were chosen to meet the criterion that HIV incidence could be used as the primary endpoint, and that shared

common features of HIV/TB co-infection, and general levels of maternal and child mortality and economic and educational structure and productivity. We chose the participating sites so that the average baseline annual incidence across all communities in the study is likely to reach at least 2%.

c. Selection of Site Regions

We determined, on the basis of the power analysis, that 32 communities are needed to test the primary study hypothesis (see Section 11.5.5). The study will be conducted within three site regions in two countries, in an effort to balance feasibility and cost concerns with generalizability and protection against potential regional instability. We have chosen two site regions in Uganda – Western Uganda centered on the Mbarara District, Eastern Uganda centered on the Tororo District and in Kenya – Western Kenya centered on southern Nyanza Province. Each of the two Uganda site regions (Western, Eastern) will have 10 study communities each and within Kenya, the Nyanza Province will have 12 study communities. With 10-12 study communities per site, a central study operations center may efficiently serve these widely separated rural study communities.

d. Sample of communities from target population

We identified a subset of 54 candidate communities from the target population based on the following criteria:

i. Inclusion criteria:

1) Most recent census population between 9,000 and 11,000 individuals.
2) Served by a government health center already providing ART or a highly functioning health center at one organizational level below those generally providing ART
3) Community leaders' consent to ethnographic mapping.
4) Accessibility to health center via a maintained transportation rout
5) Community location with sufficient distance from other potential study communities to limit contamination of intervention or control conditions (buffer zone).

ii. Exclusion Criteria:

1) Presence of ongoing community-based ART intervention strategies that provide treatment outside of the current in-country treatment guidelines.
2) An urban setting defined as a city with a population of 100,000 or more inhabitants.
3) National government not willing or opposed to support commodities needed for Community Health Campaign, if provided by an outside organization.

e. Rationale for Selection of Study Communities and Use of Matched Pairs

Fifty-four communities were chosen using the systematic selection criteria listed in section 11.1.d. Our study design calls for the creation of 16 matched community pairs within which study randomization will take place. The rationale for matching in this

setting is three-fold: 1) matching can increase study power and the precision of effect estimates if communities are matched well on factors closely associated with the study outcome of interest; 2) we propose to match on more community level drivers of HIV transmission than can be accommodated by the alternative approach of stratified randomization (given the sample size of 32 communities); and, 3) prior experience from HPTN-043 has shown a high community acceptability of the matched pair design and allows for the utilization of validated procedures and community preparedness protocols from Project Accept.

f. Criteria for Community Pair Matching
Communities will be matched based on the following criteria: 1) site region, 2) population density, 3) number of trading centers in the community, 4) major occupational mix category (mixed agricultural, mining, tea plantation, fishing), and 5) migration index (measure of mixture with outside communities). The top 16 pairs of matched communities will be selected.

11.2 Primary Outcome Measurement

The primary outcome measure for this community cluster-randomized trial is community specific 5-year HIV cumulative incidence (CI). The general framework for measuring cumulative incidence is a community cohort of HIV uninfected persons identified at baseline in each community. Community membership will be identified through a community-wide, brief household enumeration done at baseline. HIV status of individuals in the cohort will be assessed at baseline and annually through HIV testing at a community health campaign with tracking and home-based HIV testing for individuals failing to participate in the community health campaign. Each of these steps is described in greater detail below.

a. Baseline Household Enumeration
At baseline in each community we will perform a simplified community-wide, brief household enumeration to identify community members. Staff in cooperation with community volunteers will conduct an enumeration of households in the community at GPS coordinates will be recorded. Each household will be approached, and a head of the household will be provided with an explanation of the study. A minimum of 2 repeat visits to the household will be made until contact with a head of the household is made. An enumeration of the members of the household will be conducted with a head of household listing the names, age, sex, relationship to head of household, occupation, length of residence, and general travel history/frequency for each household occupant. Inclusion and exclusion criteria for eligible participants in the community cohort are:

i. Inclusion Criteria:
1) Stable residency of individual in community, defined as present in household for at least 6 months of the calendar year
2) Able and willing to provide verbal informed consent.
3) For legal minors and children-consent of legal parent or guardian.

b. Cohort Participant Identification

To aid in the identification of community participants over time, eligible persons in the household will be approached for consent to participate in the community health campaign and tracking activities. Information to be collected includes names, alternate contact information such as nearby relatives or mobile phone numbers, and a unique biometric identifier generated electronically from the individual's fingerprint using a portable computer.

c. HIV Testing in Community Health Campaign

HIV testing for community cohort participants will be conducted as follows: Identity confirmation using biometric fingerprint identifier will be conducted for all subjects. For those who have not participated in biometric identification, consent and fingerprint ID will be performed along with collection of tracking information as in the baseline household census. All participants will answer a brief questionnaire regarding prior HIV testing. Rapid HIV testing using a serial HIV testing algorithm will be performed using an initial rapid HIV test. All negative results will be informed of their HIV-negative status. All positive results will be confirmed with a second rapid HIV test, performed either in series or in parallel with the first test. Discordant results (first test positive, second test negative): participants with discordant rapid tests will undergo a third "tie-breaker" HIV rapid test. Participants with a positive "tie-breaker" test will be informed that they are HIV positive. Participants with a negative "tie-breaker" test will be told that their results were inconclusive and a recommendation will be given for repeat testing in 6-8 weeks at a local health center. At participating sites, we will obtain a dried blood spot on filter paper on all tested subjects and a rapid CD4+ T-cell count test and a capillary tube plasma collection on all participants with positive rapid HIV-antibody tests.

d. Definition of Baseline HIV Uninfected Community Cohort

Individuals who have HIV tested as being HIV uninfected and are eligible per the criteria from the baseline household enumeration will be considered to be part of the Baseline HIV Uninfected Community Cohort. Persons who subsequently migrate into the community following the baseline enumeration will have data collected but not be considered as part of the Community Cohort for purposes of measurement of community specific 5 year HIV cumulative incidence (although data on these individuals will still be collected and can be used in secondary analyses).

e. Tracking and HIV Testing for CHC Non-Participants

Biometric identifiers will be used to identify those community members enumerated during the baseline census who fail to attend the baseline CHC. These individuals will be tracked by the community tracker using locator information collected during the baseline census enumeration

When located, if alive an HIV antibody rapid test will be performed, and if positive the individual will be referred to care in accordance with treatment arm. At following subsequent CHCs, the identical procedures will be performed among a random sample of non-participants.

11.3 Randomization of Community Pairs

11.3.1 Randomization Strategy

We will utilize an established randomization strategy that is 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 [33]. Community randomization is conceptualized as an ongoing part of the community preparedness process in partnership with the community leaders and community individuals. An example of this strategy is described below:

To explain the concept of a randomized controlled trial (RCT) to community groups such as Community Advisory Board (CAB) members, we may use a supplementary feeding analogy that the communities are already familiar with, likening randomizing each matched pair of communities to a set of twins from one family who end up attending two different schools, only one of which offers an indigenous energy drink during the morning break to supplement the child's lunch box from home. To explain the random allocation of communities, we will also use local language idioms that would resonate with traditional leaders, such as words meaning 'by chance', 'luck of the draw', and 'lottery'.

For the random assignment within matched pairs of each site's communities to intervention or control status we 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. For each study site area, the computer will randomly designate 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 (see sample randomization scheme in Table 5.)

Table 5: Sample Study Site Community Pair Lottery Randomization Scheme

Matched Pair #	**Community Names**	**Picked-Up at Public Lottery**	
		Picked-Up	**Not Picked-Up**
1	Atiri Mukuju	Intervention	Control
2	Malaba Koitangiro	Control	Intervention
3	Paya Nawire	Control	Intervention
4	Mulanda Mwello	Control	Intervention
5	Nabuyoga Pawanga	Intervention	Control

The lottery could be a public event with members of the CAB and local leadership present along with guests from other community-based organizations and the general public to witness the lottery conducted by local chiefs or leaders.

The lottery could be conducted in a series of draws, one for each of the matched pairs of

communities by their local chiefs or community leaders. For each drawing, the two community 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 would be responsible for holding and shaking the selection box. The selected chief or leader will then draw 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., community health campaigns and ART initiation regardless of CD4 cell count), then the host country Principal Investigator (PI) would announce the drawn community as an intervention community. If the protocol called for the "picked-up" community to be the control (i.e., community health campaigns and standard ART initiation), then the host-country PI would announce it as a comparison community. This process would assure equal chance of being randomized to the intervention or comparison arm, and eliminates any residual fears of bias or rigging.

11.4 Primary Analyses

11.5.1 Target Causal Parameter

In this section we describe the analytic plan for estimating the effect of Universal ART, as compared to Standard ART on cumulative incidence of HIV five years after study initiation. Specifically, we aim to estimate the difference in counterfactual cumulative incidence of HIV infection (probability of becoming HIV infected within five years given HIV negative at baseline) if all communities had received the treatment versus the control level of the intervention. This target causal parameter is referred to as the average treatment effect.

11.4.2 Data Structure

a. <u>Baseline Community-Level Data</u>
   For each community in the sample, baseline variables will be measured with census data (including population size, summaries of demographic data such as age and sex distribution, and occupational mix), and ethnographic mapping (including proximity to trucking routes and trade centers, and health care infrastructure). We denote these characteristics E.

b. <u>Longitudinal Individual Data</u>
   For each community in the sample, the J stable members of the community will be enumerated at baseline. We define stable as subjects who spent at least 9 months of the previous year as residents in that community. Note that J is itself a community level random variable. We assume throughout that J is included in E. We measure the following individual level data at baseline ($t = 0$) including: age, sex, occupation, location of residence, and marital status. Denote these covariates $W(0)$.

   In addition, each year during the duration of the study ($t = 1, \ldots, 6$), we measure on each individual an indicator of whether he or she attended the CHC ($\Delta^*(t)$) and an

indicator of whether he or she had data collected at time t. The latter indicator is equal to one if an individual attended the CHC or if he or she was subsequently tracked ($\Delta(t) = \Delta^*(t) + I(tracked)$).

We will aim to track and measure baseline HIV status on all stable community residents included in the baseline enumeration who do not attend the first CHC ($t = 1$). At subsequent time points $t = 2, \ldots, 6$, a known proportion of subjects with $\Delta(1) = 1$ (either seen at the first CHC or tracked) who do not attend the CHC at time t and have not already been documented to have died or seroconverted will be randomly selected for tracking.

We first present our analysis plan under the assumption of 100% success tracking selected individuals at each time point. Tracking success is defined as locating a subject and, for those not previously seen to seroconvert, performing an HIV test. We then discuss estimation under the realistic scenario in which outcomes for a non-random subset of the individuals selected for tracking are not successfully ascertained.

For individuals who either came to the CHC or were tracked at time t ($\Delta(t) = 1$), we measure HIV status at time t ($Y(t)$), and additional individual specific covariates including changes in any of the baseline enumeration variables (residence, occupation, marital status), and any travel or time spent in other communities and occupation while there. Denote these covariates ($W(t)$). (We also measure additional covariates on HIV positive individuals; these are discussed under secondary analyses, below.)

Let $\mathrm{X}(t) = (Xj(t), j = 1, \ldots, J)$ denote the community wide vector of an individual (j-specific) variable at time t. Let

$$\mathrm{L} \equiv \left(\Delta^*(t), \Delta(t), \Delta(t)\big(\mathrm{W}(t), \mathrm{Y}(t)\big)\right) : t = 2, \ldots, 5$$

denote intermediate data collected between assignment of the intervention and the final CHC.

c. <u>Observed Data</u>

The observed data for a randomly sampled community included in the study consist of

$$(E, \mathrm{W}(0), \Delta^*(1), \Delta(1), \Delta(1)\big(\mathrm{W}(1), \mathrm{Y}(1)\big), A, \mathrm{L}, \Delta^*(6), \Delta(6), \Delta(6)(\mathrm{W}(6), \mathrm{Y}(6))).$$

We note that only a subset of these data $(\mathrm{Y}(1), A, \Delta^*(6), \Delta(6), \Delta(6)\mathrm{Y}(6))$ are needed to identify the causal effect of interest under the assumption of 100% tracking success. The additional data collected can, however, be used to improve the precision of effect estimates, to identify the causal effect of interest under less than 100% tracking success (under additional non-testable assumptions), and for secondary analyses, including estimation of the impact of the intervention on cumulative incidence of HIV at earlier time points. We discuss each of these uses in greater detail below.

Rather than a simple random sample of this data structure, under the matched study design A is randomly allocated within a matched pair, and the matched pairs selected for inclusion in the study are based on applying a matching algorithm to the baseline sample. In other words, the underlying data generating distribution is described by an experiment in which one:

1. Draws 54 communities from the marginal distribution of E, to generate a sample of 54 i.i.d. copies of E.
2. Applies a matching algorithm to the sampled values E_k, $k = 1, \ldots, 54$ and identifies the best 16 matched pairs. Note that the algorithm may only use a subset of the variables in E. Let $M = f_n(E)$ denote the random variable whose levels define these matched pairs. Here we use the notation f_n to make clear that the random variable M is a function of the actual realized values of E in the sample.
3. Draws $E^c = (\mathrm{W}(0); \Delta^*(1), \Delta(1), \Delta(1)\big(\mathrm{W}(1), \mathrm{Y}(1)\big))$ for each of the 32 communities selected by the matching algorithm conditional on *E*.
4. Randomly assigns the treatment level of the intervention, $A = 1$, to one community in each pair, and assigns the control level, $A = 0$, to the remaining community.
5. Draws $\mathrm{L}, \Delta^*(6); \Delta(6); \Delta(6)(\mathrm{W}(6); \mathrm{Y}(6))$ for each of the 32 communities conditional on E^c, A.

We note that in practice the intervention will be randomly assigned prior to the first CHC and thus prior to $(\Delta^*(1), \Delta(1), \Delta(1)(\mathrm{W}(1), \mathrm{Y}(1))$ in order to allow HIV cases diagnosed at the first CHC to be referred to the appropriate intervention-specific treatment and care services. However, we assume that treatment arm A does not affect the values of these baseline variables – a reasonable assumption since changes to treatment and care services due to the intervention should only occur after the first CHC has taken place.

Let the observed data on a given community generated by this experiment be denoted O; the observed data thus consist of O_i, $i = 1, \ldots, 32$. (In fact, the observed data also include 22 copies of E measured on those communities included in the ethnographic mapping sample but not selected by the matching algorithm. Data from these communities might be incorporated into an effect estimator; however, in the interest of simplicity we do not discuss this in the current protocol.) Note that due to the matching process O_i is not an i.i.d. random variable.

Let P_0 be the true probability distribution of O. We assume a semi parametric statistical model, which restricts the set of possible distributions P_0 by only assuming that A is randomly allocated within each matched pair, and that the probability of collecting data on an individual at time t is 1 if the subject attended the CHC, and is otherwise equal to the known tracking probability $p(t)$ $(P(\Delta_j(t) = 1|Past) = I(\Delta_j^*(t) = 1) + I(\Delta_j^*(t) = 0)p(t))$. Below, we relax the latter assumption.

11.4.3 Community Level Analysis

Our primary analysis will estimate the average treatment effect of the intervention by comparing the estimated 5 year cumulative incidence of HIV in the treatment versus control communities. This requires first estimating the cumulative incidence in each community; this is the community level outcome, which we denote Y^c. We acknowledge that not all individuals in the community have their baseline and final HIV status measured. Therefore, we first describe estimation of the community level outcome under the assumption that all individuals who fail to come to a CHC and are subsequently selected for tracking are located and tested. We then discuss how this assumption will be relaxed to allow for incomplete tracking success.

a. <u>Estimation of the community level cumulative incidence</u>

The community level outcome of interest Y^c is the proportion of stable residents in a given community who become HIV infected by year 6 given that they are HIV negative at year 1 (the time of the first CHC). If all stable residents had their HIV status measured at years 1 and 6, then this cumulative incidence could be calculated directly, without need for estimation. Similarly, if those subjects with HIV status known at both years 1 and 6 were a simple random sample of the enumerated baseline population, then Y^c could be estimated straightforwardly. In practice, however, the individuals attending the CHC are anticipated to be a biased sample of the underlying population. Tracking a random sample of individuals included in the baseline enumeration who do not attend the CHC allows us to recover from this bias, but estimation of Y^c now requires adjustment for non-random missingness.

In other words, we aim to estimate, for each community, $Y^c = \frac{1}{J}\sum_{j=1}^{J} P(Y_j(6) = 1 | Y_j(1) = 0)$. Given that the J participants within a community are assumed exchangeable, this conditional probability is constant in j. Therefore, for the remainder of this subsection, to simplify notation we suppress the individual level subscript j.

The parameter $P(Y(6) = 1 | Y(1) = 0)$ is not yet written in terms of the observed data. The baseline HIV status $Y(1)$ will always be observed (under the assumption of complete tracking success) since all subjects in the baseline enumeration who do not attend the first CHC will be tracked $(\Delta(1) = 1)$. However, $Y(6)$ is only directly observed if a subject attends the final CHC, or is randomly selected for tracking after failing to attend the final CHC. (Final HIV status, $Y(6)$ is also known if a subject was observed to seroconvert at an earlier time point; we discuss incorporation of this data below). The fact that subjects who are not seen at the CHC are tracked with some known probability gives us the following identifiability result:

Let $Y^* = Y(6) - Y(1)$ denote an indicator that a subject acquires HIV during the course of the study. We have that $(Y(6) = 1 | Y(1) = 0) = \frac{P(Y^*=1)}{P(Y(1)=0)}$. Here, $P(Y(1) = 0)$ is already a parameter of the observed data distribution (assuming all subjects in the

baseline enumeration who do not attend the first CHC are tracked). It can thus be estimated straightforwardly as the proportion of subjects in the baseline enumeration who are HIV negative. Given final CHC attendance $(\Delta^*(\quad))$, Y^* is known by design to be independent of observation status $\Delta(6)$, and thus,

$$P(Y^* = 1) = E\left(\frac{I(\Delta(6)=1)}{P(\Delta(6)=1|\Delta^*(6))}\, Y\right), \qquad (1)$$

where the RHS is now a function of the observed data distribution. As a result, the probability of seroconverting during the course of the study $P(Y^* = 1)$ can be estimated as a weighted average of the outcome Y^*, with subjects seen at the final CHC receiving a weight of 1, those who are tracked receiving a weight of 1 over the tracking probability $p(6)$, and the remainder receiving a weight of 0. Finally, the community level outcome can be estimated as the estimated probability of sero-conversion, divided by the proportion of subjects who are HIV negative at year one.

While (1) non-parametrically identifies the community level cumulative incidence, the inverse probability weighted estimator described does not make full use of the available data and will be inefficient. Instead, by incorporating data on each individual's past prior to year 6, including past HIV test results, we have the potential to improve the efficiency of our estimate of the community specific outcome. Specifically, let $Pa(\Delta(6))$ denote all variables measured on a subject prior to $\Delta(6)$:

$$Pa(\Delta(6)) \equiv (W(0), \Delta^*(1), \Delta(1), \Delta(1)\big(W(1), Y(1)\big), L, \Delta^*(6)).$$

Equation (1) can equivalently be written

$$P(Y^* = 1) = E_{Pa(\Delta(6))} E[Y^*|\Delta(6) = 1, Pa(\Delta(6))].$$

To the extent that $Pa(\Delta(6))$ predict final HIV status beyond $\Delta^*(6)$, adjusting for the full $Pa(\Delta(6))$ should result in a more efficient estimate of the community specific HIV cumulative incidence than an estimator that only adjusts using sampling weights that treat the missingness mechanism as known. Because $Pa(\Delta(6))$ is a high dimensional covariate, the NPMLE of (2) will not be well defined. Thus given our semiparametric statistical model, we will apply targeted maximum likelihood estimation [34] to generate an efficient estimator of the community specific outcome, adjusting for the measured past prior to final tracking.

Modification of estimator of Y^c to incorporate incomplete tracking success. The above approach can also be applied in the more realistic scenario in which not all individuals selected for tracking are successfully located at $t = 6$. In this case, identification of our target parameter will rely on additional non-testable assumptions that the measured covariates are sufficient to control for the likely non-random nature of this

missingness with respect to an individual's HIV status. Specifically, for the case where tracking is incomplete at time 6, we will assume

$$Y\ (6)\ \perp\!\!\!\perp\ \Delta(6)|Pa(\Delta(6))$$

(previously, this assumption was known to hold by design). A similar approach can be employed in response to incomplete tracking success at time $t\ =\ 1$, where now we assume

$$Y\ (1)\ \perp\!\!\!\perp\ \Delta(1)|W(0),\Delta^{*}(1).$$

The estimator of Y^{c} is modified accordingly to incorporate adjustment for potentially informative missingness at time $t\ =\ 1$ in both the estimate of $E(Y^{*})$ and the estimate of $E(Y\ (1))$.

For the purposes of the primary analysis, incomplete tracking success at times $t\ =\ 2,\ldots,5$ simply affects the richness of the observed intermediate covariates that can be used to improve estimator efficiency and to help improve the plausibility that the needed missing at random assumption holds for time 6. The approach proposed can also be adapted to secondary analyses aimed at estimating the cumulative incidence of HIV for years 2 through 5. In this case, estimators can be used that fully respect the interval censored nature of the outcome, such that a subject who, for example, is known to be HIV negative at time 6 is also known to be HIV negative at time 5, whereas a subject who is HIV positive at time 6 and HIV negative at time 2, and who is not seen at times 3-5 is known to be infected at some point during that interval [35].

b. <u>Unadjusted Analysis</u>

Given an estimate of the community level outcome Y^{c}, the effect of the intervention can now be estimated using a community level analysis. In a slight abuse of notation, in this and the following section we use Y^{c} to refer to the estimated community specific outcome rather than its underlying true value.

We aim to estimate the difference in the expected counterfactual outcome in the treated versus control communities if all communities were assigned to the treatment versus control arm of the intervention. Because the intervention is randomly allocated within matched pairs, this target causal parameter corresponds to the expected difference in community level outcome within matched pairs: $E(Y^{c1}-Y^{c0})$ (where Y_{l}^{ca} denotes the estimated 5 year cumulative incidence of the community in the lth pair with intervention level a and where the expectation is taken over the matched pairs of communities.) This estimate can be estimated as the empirical mean of the difference in estimated cumulative incidence within matched pairs:

$$\frac{1}{16}\sum_{l=1}^{16}(Y_l^{c1} - Y_l^{c0}).$$

A paired t-test can be used to test the null hypothesis of no difference in 5 year cumulative incidence between the treatment and control communities within matched pairs.

c. <u>Adjusted Analysis</u>

Randomization of the intervention ensures that the unadjusted estimator will be unbiased for the causal effect of interest. However, the unadjusted estimator does not make full use of the observed data on each community and thus will not be efficient. We will thus also conduct an analysis adjusted for baseline community level covariates.

Let E^c denote all community level characteristics measured prior to the intervention

$$E^c = (E, \mathrm{W}(0), \Delta^*(1), \Delta(1), \Delta^*(1)(\mathrm{W}(1), \mathrm{Y}(1))).$$

In adjusting for covariates E^c, we will apply both a standard approach to the analysis of pair matched cluster randomized trials (e.g. two-stage adjustment, as described in Hayes and Moulton p.238, [31]), as well as an adjustment strategy based on new results for the analysis of pair matched trials, such as SEARCH, in which the matched pairs are created by applying an algorithm to a sample of communities (as opposed to a design that samples independent pairs). These results suggest an alternative approach to covariate adjustment, described in greater detail below.

We first discuss an unmatched design, where the intervention is assigned to a randomly selected 50% of sampled communities, and then return to modification of the estimator for the matched experiment described above. The following simplified data are measured on each randomly sampled community: (E^c, A, Y^c). (To simplify presentation, we suppress the additional data measured between assignment of the intervention and the outcome: $(\mathrm{L},\ \Delta^*(6), \Delta(6), \Delta(6)(\mathrm{W}(6))$. These variables will be used in estimation of Y^c as discussed above, as well as in estimation of other outcomes, but once Y^c is estimated will not otherwise contribute to the primary community level analysis.) The unmatched design corresponds to drawing 16 independent samples of $E^c,\ Y^c$ given $A = 1$ and 16 independent samples of $E^c,\ Y^c$ given $A = 0$.

Adjusted analysis under an unmatched design corresponds to estimating the following target parameter

$$E_{E^c}[E(Y^c|E^c, A = 1) - E(Y^c|E^c, A = 0))]. \qquad (3)$$

A common approach to estimating this parameter in randomized trials is to fit regress the community level outcome on the intervention and covariates, using a general linear model, with the intervention A included as a single main term or in an interaction. Such an approach provides both a consistent and asymptotically normal estimator of the average treatment effect, even if the parametric regression model is misspecified [36].

Under the matched design used in SEARCH, the intervention is randomly allocated within matched pairs of communities, where the matched pairs themselves are generated based on applying some algorithm to a sample of communities. The experiment is similar to one in which the treatment is randomly allocated within strata of some pre-determined baseline variable; however, it is complicated by the fact that the random variable M used to create the strata in which the treatment is randomized is itself a function of the sample (in particular, of the baseline community characteristics to which the matching algorithm is applied). As a result, dependence is introduced by the matching process and the observed data on the 32 communities in the sample do not correspond to 32 i.i.d copies of a random variable; nor do they correspond to 16 i.i.d. copies of a random variable. To address this challenge, we propose to apply recent work that investigates this dependence and develops estimators under this design [37]. An adjusted community level analysis to estimate the average treatment effect in such a design can be implemented by estimating $E_{E^c}(E(Y^c|A, E^c)$ as for the unmatched design, treating the data as i.i.d.. Consistent estimation of the variance requires, however, consistent estimation of the true conditional mean of Y^c given A, E^c. The point estimate, but not the variance estimate, is robust to misspecification of the regression model used for adjustment. However, a variance estimator that treats the data as i.i.d. will provide a conservative estimate of the variance under general conditions.

11.4.4 Individual Level Analysis

The community level analyses described above will generate robust estimates of the average effect of the intervention. We will also implement complimentary individual level analyses. Individual level analyses may help us to further improve the precision of our effect estimates, by making use of individual level working models for the dependence of the expectation of the individual level outcome Y_j on covariates and treatment. The individual level approach described below can also be extended to estimate alternative target parameters, including those aiming to answer secondary research questions including:

1. Investigation of individual level characteristics that modify the impact of the intervention.
2. Estimation of the effect of individual level exposure to various components of the intervention on individual risk of HIV acquisition, and the extent to which the community level impact is mediated by individual uptake of various intervention components.

Specification of an efficient estimator based on individual level analysis is complicated by a) the hierarchical nature of the data; b) the pair matched design; c) the fact that there are a variable number of individuals per community (J is a random variable); and d) the fact that final and

baseline HIV status are only measured on a subset of individuals. We propose the following estimator to
address these challenges. We focus on the unmatched case, noting that the results for analysis studies with the type of dependent pair matching employed by SEARCH, discussed in the prior section, provide a means of adapting the resulting estimator to the particular matched pair design pursued in SEARCH.

Let

$$O_j = (E, W_j(0), \Delta_j^*(1), \Delta_j(1), \Delta_j(1)\left(W_j(1), Y_j(1)\right), A, L_j, \Delta_j^*(6), \Delta_j(6), \Delta_j(6)Y_j(6))$$

be the longitudinal observed data structure on the j-th subject in the enumerated community specific population for a randomly sampled community.

The observed data on the randomly sampled community is the collection of these measurements across the J individuals:

$$O = (O_j : j = 1, \ldots, J).$$

Let P_0 be the true probability distribution of O, and let $P_{0,j}^I$ be the probability distribution of O_j. Since the J subjects are assumed exchangeable, we have that $P_{0,j}^I = P_0^I$ is constant in j. We used sup-script I to index that it is a probability distribution for the individual component O_j.

Let $O_j^{1,a,1}$ denote the counterfactual value of O_j under an intervention to ensure measurement at time 1 $(\Delta_j(1) = 1)$, treatment assignment $A = a$, and measurement at time 6 $(\Delta_j(6) = 1)$. We know by design that A is randomly assigned. In the case that tracking is 100% successful, we further know that $\Delta(t)$ is only a function of whether a subject was seen at the CHC and a known tracking probability. The sequential randomization assumption (stating that each intervention node $(\Delta_j(1), A, \text{ and } \Delta_j(6))$ is independent of the counterfactual $O_j^{1,a,1}$ given its parents [38, 39]) is thus known to hold. In the case that tracking is not 100% successful, baseline and or final HIV status will be missing on a subset of individuals selected for tracking. In this case, the sequential randomization assumption for the missingness processes is no longer known to hold by design, and we make the non-testable assumption that the measured past is sufficient to adjust for the informative missingness process (analogous to the approach described for estimation of Y^c under less than 100% tracking success).

Under the sequential randomization assumption, the post-intervention distribution of O_j under an intervention $(1, a, 1)$ is identified by the longitudinal G-computation formula [38]. The statistical target parameter for the distribution of O_j is given by

$$\Psi_j(P_j^I) = \frac{E_{P_j}(Y_j^{1,a=1,1}(6) - Y_j^{1,a=0,1}(1))}{P(Y_j^{\delta_j(0)=1}(1) = 0)}.$$

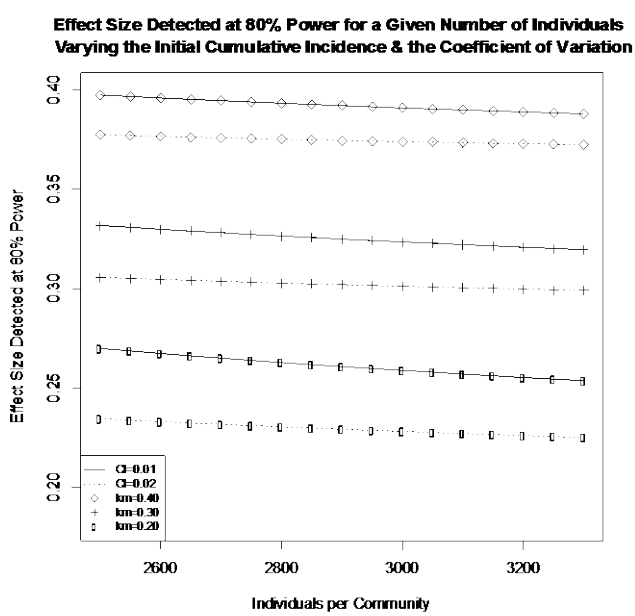
This corresponds to the probability that individual j becomes infected over the course of the study, given he or she is not infected at baseline. We target $\Psi_{ja}(P_j^I) = E_{P_j^I} Y_j^{1,a,1}$ and $\Psi_{j2}(P_j^I) = P(Y_j^{\delta_j(0)=1}(1) = 0)$, which then yields $\Psi_j(P_j^I) = \frac{\Psi_{j1}(P_j^1 - \Psi_{j0}(P_j^I)}{\Psi_{j2}(P_j^I)}$. Let $\Psi_j(P_j^I) = (\Psi_{j0}(\Psi_j^I), \Psi_{j1}(P_j^I), \Psi_{j2}(P_j^I))$ be this tri-variate target parameter.

In order to estimate this target parameter, a j-specific individual level TMLE can be applied to a pooled data set, in which each community generates a random number J of individual longitudinal data structures. The number of subjects in a given community, J, will be treated as a random variable included in E. Because g is known, a conservative estimate of the variance of the estimator can be based on an estimate of the variance of the efficient influence curve.

11.4.5 Power and Sample Size

The trial is being conducted in 20 community pairs in Uganda and 12 community pairs in Kenya, each with a population of approximately 5000 stable adults residents. We assume a baseline HIV prevalence of 10%, HIV status measured at baseline among 80% of residents, and 75% of the approximately 3600 of those HIV negative at baseline with an outcome observed at year 6. This yields approximately 2700 residents per community who are HIV negative at baseline and have their HIV status known at year 6. We note that the exact number of residents per community will vary; if the actual sample size per community is at least 2700 individuals then the following calculations can be considered conservative. We further note that moderate deviations from this number of individuals are not expected to have a strong effect on power (Figure 1).

Figure 1



We calculated the number of matched pairs of communities needed to provide at least 80% power to detect a 40% reduction in 5 year cumulative incidence of HIV infection in the treatment versus control communities, using a two sided test at a 5% level of significance. We based our sample size calculations on the simple unadjusted effect estimator; this approach should provide a conservative effect estimate given the potential for covariate adjustment to improve precision. Sample size calculations were thus based on the formula in Hayes and Bennet for an unadjusted comparison of proportions in a matched trial [40].

Our sample size calculations assumed a 1% five year cumulative incidence in the control communities. This estimate is conservative based on the available literature, which suggests that HIV transmission rates are approximately 0.5 to 2% [41-43]. For example, assuming a current incidence density of 0.5 cases per 100 person years, and allowing for a 10% decline in transmission rate per year in the absence of the intervention (due to concurrent prevention activities), the incidence density method would suggest a five year cumulative incidence of approximately 2%. Figure 1 shows the effect size we are powered to detect under the less conservative assumption that the control proportion is 2%.

We further assumed a matched pair coefficient of variation (km) of no greater than 0.4. This corresponds to an assumption that, in the absence of the intervention, community specific cumulative incidence would vary between 20% and 180% of the unknown pair specific value [31] (assuming a normal distribution of the pair-specific community level cumulative incidences). Considered from a different angle, an unmatched coefficient of variation of 0.4 would imply that the true cumulative incidence in the control arms would vary between approximately 1.8% and 0.2% and the true cumulative incidence in the treatment arms would vary between 1.08% and 0.12% (again, assuming normality). If this degree of variation in the true between community cumulative incidences is considered plausible or conservative, then use of a matched pair coefficient of variation equal to this unmatched parameter should result in conservative sample size estimates. We note that, while ideally external data would be available to inform choise of km, 1) km values depend (among other things) on which covariates are matched on, how close a match is achieved, and the strength of association between these covariates and the outcome, limiting generalizability between studies; and 2) recent work has demonstrated the instability of estimates of km based on empirical data [32]. We note that prior studies performed in similar settings have assumed a km of closer to 0.25 (Project ACCEPT, Mwanza Trial as discussed in Hayes and Moulton 1999 [31]); in the case that this more optimistic km holds we will be powered to detect a smaller (approximately 30%) reduction in cumulative incidence. Figure 1 shows a graph of the percent reduction we will be powered at 80% to detect under a range of deviations from the assumptions above, including variation in the number of individuals per community who are HIV negative at baseline and have known HIV status at year 6, a range of five year cumulative incidence values, and a range of km values (for 16 matched pairs, and following recommendation of Hayes and Moulton to correct for the loss of degrees of freedom when using a paired t-test, page 115 [31]).

a. <u>Simulations investigating performance of sample size formula under plausible deviation form assumptions</u>

Because the sample size formula employed rely on assumptions including normality (potentially concerning with small sample sizes), homogeneity in effect size, and a constant coefficient of variation in treatment and control groups, we also performed simulations to investigate the performance of these sample size formula under data generating distributions similar in basic respects to SEARCH, under plausible deviations from these assumptions. Specifically, we generated study data for 5,000 trials, each consisting of n=32 communities, with a true mean outcome of the community level outcome Y^c equal to 0.01 in the control communities and 0.06 in the treatment communities (corresponding to a 40% reduction in cumulative incidence of infection).. For each community, we sampled two baseline characteristics, one from a normal distribution and the other a uniform distribution. We also drew the number of individuals per community from a uniform distribution and thereby explored the effect of heterogeneous cluster sizes. The intervention was then randomized within matched pairs and the outcome for each individual drawn from a Bernoulli distribution. The probability of an individual seroconverting depended on the intervention as well as the community covariates, including community size. We also included various interactions between the intervention and community covariates in order to investigate heterogeneity in the effect size. By this method of simulation, the coefficient of variation in an unmatched design would depend on the treatment assignment. For each of the 5,000 trials, we calculated the unadjusted effect estimator and its standard error estimate. From these values, we determined if the null hypothesis of no effect was rejected at $\propto = 0{:}05$ significance level and constructed 95% confidence intervals. The attained power was determined by the proportion of trials where the null was rejected. Likewise, the attained confidence interval coverage was determined by the proportion of intervals containing the true parameter value. Despite deviations from the assumptions, the simulations suggested that the sample size formula provided by Hayes and Moulton accurately predicted the power achieved under these scenarios.

11.5 Secondary Analyses

11.5.1. Secondary Health Outcomes

a. <u>Overview.</u>

In addition to estimating the impact of the treatment on expected 5 year cumulative incidence of HIV among adults, we will also estimate the average treatment effect for the set of secondary outcomes detailed in section 2.2. Key secondary outcomes include: vertical transmission; adult, maternal and pediatric mortality; plasma HIV RNA levels; antiretroviral resistance; AIDS; tuberculosis and opportunistic infections; and, linkage, time to ART initiation, and retention in care for HIV-infected subjects. Given a community level estimate for each of these secondary outcomes, statistical analysis to evaluate the intervention's effect on each of these outcomes will follow the general approach described for evaluation of the primary outcome, based on unadjusted and adjusted comparison of treatment and control communities. In the following subsections we outline the data that will be collected to estimate each secondary outcome.

b. Mortality

While our study design includes investment to strengthen existing local death registries, we acknowledge that death reporting may remain incomplete. However, as with HIV incidence, our study design will allow us to generate unbiased estimates of mortality rates in each community. Specifically, unreported deaths will be ascertained via tracking in a random sample of non-returnees. Estimation of mortality outcomes will thus employ the tracking-based estimators described above. We will estimate all-cause mortality among adults, children < 1 year of age (infant mortality), children < 5 years of age (pediatric mortality), and women who are pregnant or within 42 days of termination of pregnancy (pregnancy-related mortality).

c. Mother to Child Transmission of HIV

We will evaluate the effect of the intervention on the proportion of live births still alive and HIV uninfected at two years, among all birth and among births to HIV-infected mothers. We focus on the outcome among infants two years after birth to capture the interventions effect on transmission prenatally, during transmission, and during breastfeeding. Evaluating HIV-free survival among all births, and not only among HIV-infected mothers will allow us to capture the effect of the intervention on vertical transmission rates due to its effect on decreasing the prevalence of HIV infected mothers, and not only any effect due to reducing the probability of a mother who is HIV infected transmitting the virus to her baby.

Estimation of 2 year HIV free survival rates for each community will be performed analogously to estimation of cumulative incidence of HIV among adults. Crucially, the use of annual CHCs, combined with tracking of non-attendees will provide us with a birth cohort that is representative of the entire community (and not only of those mothers who engage with antenatal care). Specifically, an infant will enter the cohort when his or her mother is seen at the CHC or tracked and the birth reported.

d. Plasma HIV RNA levels, CD4 Cell Count, and Antiretroviral Resistance

Dried blood spots from CHC attendees, together with dried blood spots from non-returnees who are tracked, will provide data from which to estimate HIV RNA level metrics, including geometric and arithmetic mean and median HIV RNA level and proportion with HIV RNA level below the limit of detection among all HIV-infected individuals.

Drug resistance among HIV-infected individuals will be measured by assaying dried blood spots collected during the CHC and at tracking for the mutations K103N, M184V, and K65R. We will estimate proportion of newly diagnosed individuals with each and with any of these three mutations as a marker of transmitted resistance in each community. As markers of acquired resistance, we will also estimate proportion of HIV infected individuals with resistance mutations among those individuals who initiated treatment one and two years prior.

Finally, point of care CD4 cell count testing at the CHC and among tracked subjects will allow us to estimate CD4 cell count recovery rates.

Importantly, the use of the CHC plus tracking will provide us with estimates of each of these metrics among all HIV-infected individuals, regardless of whether they are retained in care. In addition to comparing these community level metrics between treatment and control communities, we also perform individual level analyses to assess how these outcomes vary as a function of CD4 at antiretroviral initiation, including estimating these metrics in the subpopulation of subjects who initiate therapy at CD4 >350 cells/uL.

e. Linkage, Retention, and Time to ART Initiation

Use of the CHC combined with tracking of a random sample of non-returnees (irrespective of HIV status), and linkage of resulting data to clinic records will allow us to generate unbiased estimates of linkage and retention rates among all HIV infected individuals. Specifically, we will estimate for each community over time the proportion of newly diagnosed HIV infected individuals who successfully link to care (defined as any visit to clinic), as well as the proportion retained in care (defined as at least two visits in the past 12 months) each year following HIV diagnosis. In addition, we will estimate the average time from first HIV diagnosis to ART initiation for each community.

f. Internally Derived HIV Infections

Data: Viral consensus sequences will used to estimate phylogenetic relationships and genetic distances between HIV viruses sampled during the study. These data, together with additional reference sequences, will be used to classify incident HIV infections among community cohort members as linked or not linked to previously documented infections among community members [44].

Analysis: Internally derived incident HIV infection will be defined as an incident HIV infection in a study participant classified, based on sequence analysis, as linked to a virus previously measured from a member of the same community. Externally derived incident HIV infection will be defined as infection with a virus classified as unlinked to a previously measured virus in a member of the same community. Let G_j equal an indicator that an HIV infection was internally derived.

The community specific outcome for this secondary analysis will be the probability of becoming infected over the course of the study by an internally derived virus. Externally derived infection will be treated as a competing risk for this outcome of interest. Specifically, this secondary community level outcome will be defined as $Y^{*c} = \frac{1}{J}\sum_{j=1}^{J} P(Y_j\,(6) = 1, G_j = 1 | Y_j(1) = 0)$. The decision to treat externally derived infection as a competing risk is based on the fact that a) the identifiability assumptions needed to treat external infection as a censoring event are highly implausible; and, b) randomization arm is deemed unlikely to have a major impact on risk of externally derived infection (other than via its effect on internally derived infection). This outcome

will be estimated for each community, incorporating tracking data to address informative missingness, and compared between treatment arms in community as well as individual level analysis, analogous to analyses described for the primary outcome.

g. Additional Health Outcomes

AIDS-defining events, TB, and treatment-associated toxicities and adverse events will not be diagnosed at either the CHC or during tracking. Measurement of these outcomes will thus rely on passive surveillance systems and secondary data sources, as described in section 6.3.2, with analytic methods used whenever possible to reduce resulting bias in estimates of the underlying population parameters.

Confirmed active TB cases will be identified using existing registries and clinic data. HIV status of confirmed cases will be based on a) HIV status as recorded in the registry and b) linkage with SEARCH study HIV status based on name and demographic information (following an initial feasibility study).

AIDS-defining events among HIV-infected individuals will be measured by obtaining WHO Stage IV diagnoses recorded in clinic. Other information may be obtained from community health campaigns, tracking or hospital records. Note that measurement at the clinic will rely on retention of HIV infected patient in care. The resulting outcome data will thus be subject to potentially informative interval censoring under a non-monotone missingness pattern (i.e. patient will be seen at clinic intermittently, some not for long intervals, and detection of these outcomes will only be possible when they are seen). Individual level longitudinal inverse probability weighting and targeted maximum likelihood estimation will be applied to estimate these community level outcomes, accounting for the informative clinic visit process to the extent possible given observed covariates.

11.5.2 Economic and Education Evaluations

Our analysis will compare changes in socio-economic outcomes of households in intervention and comparison communities. It will also examine the relationship between socio-economic status and HIV status of respondents. For the sample of HIV-positive study participants who are also part of the household survey, we will analyze changes in socio-economic status as a function of CD4 cell count and viral load. Analyses will be performed using STATA 11.0 statistical software.

Sample Size

All HIV-positive participants will be recruited for the household survey and 100 HIV-negative participants will be randomly selected using a sampling method that selects every 10th person who provides consent for participation in the Community Campaign.

Estimation Strategy

The study objectives will be met by comparing changes in the main outcomes between intervention and comparison communities. The following outcome variables will be studied: adults' on- and off-farm employment; children's on- and off-farm employment (child labor); children's time allocation to schooling and household activities; asset holdings (durable good and livestock); agricultural output; cash and in-kind transfers.

For each outcome, a regression model of the following form will be estimated:

$$Y_{ijt} = \beta_0 + \beta_1 INTERVENTION_j + \sum_{t=1}^{5} \pi_t \, (YEAR_t * INTERVENTION_j + \sum_{t=1}^{5} \delta_t + X_i\beta_2 + V_j\beta_3 + \mu_{ijt}$$

$Y_{ijt} = \pi_0 + \pi_1 INTERVENTION_j * YEAR2_t + \pi_2 INTERVENTION_j * YEAR5_t + X_i\pi_3 + V_j\pi_4 + \pi_5 YEAR5_t + \pi_6 YEAR5_t + \mu_{ijt.}$

Y_{ijt} is the outcome of interest for household *i* in community *j* at time *t* (with *t* equal to either 0-5 at baseline, 1 year, 2 years, 3 years, 4 years and 5 years, respectively), while the binary variable $INTERVENTION_j$ indicates whether community *j* is an intervention community or not. X_i is a vector of individual characteristics including age, gender, and household composition while V_j is a vector of community characteristics including average age, percent male/female, and HIV prevalence. The model will control for trends in the comparison communities by allowing outcomes in each year to differ from those at baseline; this will be captured by the time trends δ_t. The parameters π_1- π_5 will be the coefficients of interest, as they will indicate whether changes in the intervention communities differed from those in the comparison communities.

11.5.3 Health Care Costing Evaluations

<u>Costs</u>

Costs will be assessed both from the health care system analytic perspective, and from the patient's perspective. During the five-years of cost data collection, costs will be measured using empirical data as described in section 10.3 above. However, because important health effects of ART and the treatment of other chronic disease extends beyond this period, we will model the consequences of early versus later ART initiation using the best available data on disease progression and the health states and associated medical care costs.

<u>Unit Cost Measures</u>

We will calculate several measures of the cost per programmatic goal achieved, from proximate to distal. The proximate measures will be cost per HIV+ person identified, linked to care, and started on ART. The intermediate measure will be cost per ART-month (person on ART for a month). The distal efficiency measures will focus on surrogate biological markers of ART success: cost per CD4 level recovered and viral load suppressed.

Health Status

We will translate observed and projected health events into a standard metric of disease burden, Disability Adjusted Life Years (DALYs). The calculated DALYs occurring will reflect health benefits (e.g., added years of life from ART) estimated from the morbidity and mortality measured during the study, plus future health effects of HIV incidence measured during the trial, using our published methods to project future health burden of HIV adjusted for ART access.

Cost-Effectiveness

Finally we will estimate incremental cost-effectiveness. This is the net added cost per health outcome, e.g., per DALY averted. Both the numerator and the denominator represent the difference between study arms. Thus, the **numerator** will reflect differences in the cost of ART use and in savings from averted disease. (Both arms have a community testing campaign.). The **denominator** will represent the difference in DALYs due to the clinical benefits of ART, HIV infections averted, and any other observed disease effects. The **ratio** is the ICER (incremental cost-effectiveness ratio), in dollars per DALY averted. If the intervention saves money and improves health ("dominant" in cost-effectiveness parlance), no ICER will be calculated (since there is no cost-health tradeoff); results will be expressed as economic savings and health gains.

Sensitivity Analyses

To estimate the impact of uncertainty in inputs, we will conduct extensive one-way and two-way sensitivity analyses. We will also using Monte Carlo multi-variable simulations to estimate the confidence intervals associated with the base-case incremental cost-effectiveness ratios.

12. DATA COLLECTION AND MONITORING

12.1 Data and Safety Monitoring Plan

The SEARCH project will employ a multi-tiered approach to monitoring the progress of the trial for ethics, safety, efficacy, and futility. Monitoring will take place at the levels of the community, the host country, and study-wide through defined groups and processes (see Table 6).

Table 6: SEARCH Trial Monitoring Information Sources and Responsibilities

Information Tier	Organization Unit	Responsibilities
Community	Community Advisory Boards (CAB)	Experiences and concerns of community members of the study communities and agencies.
Host Country	Local Advisory Boards (LAB)	Ethical and policy issues and developments potentially impacting the conduct and rationale of the trial within the host country.
Science & Ethics	Scientific Advisory Board (SAB)	Scientific and ethical issues and potentially impacting the conduct and rationale of the trial.
Study Data	Data Safety Monitoring Board (DSMB)	Study progress including incidence of significant adverse events, interim efficacy and futility analyses, and issues from community and scientific advisory boards.

Information on the conduct and acceptance of the study will be obtained at the community level through the local Community Advisory Boards who are charged with representing the experiences and concerns of community members of the study communities. Issues and concerns about the conduct and impact of the trial on the community will be communicated in writing from local CAB to study investigators and presented in summaries to the study Data Safety Monitoring Board (DSMB). Likewise, scientific and policy issues and developments potentially impacting the conduct and rationale of the trial at the host country level will be assessed by the study-wide and host-country site Scientific Advisory Boards and communicated in writing to study investigators and presented in summaries to the study DSMB. Finally, study progress including incidence of significant adverse events and interim efficacy and futility analyses will be presented to the study DSMB and study statisticians in written form and in person at annual or ad-hoc DSMB meetings.

12.1.1 Data and Safety Monitoring Board

Pursuant to the NIH policy for Data and Safety Monitoring: a Data Safety and Monitoring Board will be convened to provide oversight of the SEARCH trial. The role of the DSMB will be to review implementation and progress of the trial and to review the accumulating data from the study to detect early, significant benefit or harm for communities and persons while the trial is in

progress. In consultation with the NIH and the study sponsors, the study team will convene the DSMB consisting of at least 5 members with expertise in the following 5 areas: 1) the specific disease(s) under study, 2) biostatistics, 3) epidemiology, 4) ethics/patient advocacy, and 5) clinical trials. Board membership should consist of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. The DSMB will convene annually to review study progress and safety and may be called into ad hoc sessions as the Board sees fit or at the request of the study Principal Investigator or NIH. At the annual meeting, the study Statistician and Principal Investigator will present summaries of issues and concerns from the local and study-wide advisory boards and the trial progress and safety and efficacy data, including the results of any planned interim analyses, to the DSMB for consideration. Following its meetings, the DSMB will present its recommendations in writing to continue, modify, or terminate the trial to NIH, study sponsors and the study Principal Investigator.

12.1.2 Interim Reports and Study Stopping Guidelines

An interim report to the DSMB will be prepared two and four years after the first community is randomized. Interim reports will contain information on community and advisory board issues and concerns and on study progress and data quality (including community health campaign testing, ART initiation and distribution) and safety data (serious adverse events and deaths). For stopping guidelines, the protocol team recommends that an exceptional difference (in either direction) in deaths between the study arms could justify early termination of the study. It is recognized that this is a randomized comparison; however a thorough investigation of potential confounding factors that may be mal-distributed by randomization will be needed prior to any recommendation to terminate the study. For the purposes of this study, an exceptional difference in death rates with an incidence rate ratio of 3 or greater that is statistically significant according to Peto-Haybittle criteria and remains that large and significant in analyses that adjust for potential confounding factors.

The protocol team does not recommend stopping the trial for early indications of intervention efficacy. The rationale for continuation in the setting of early significant evidence of efficacy is the need to evaluate the magnitude and durability of the intervention over the full study period. Another rationale is the need for complete data on the economic impact of the intervention (work productivity, reduced health care expenditures for serious HIV illnesses) and the beneficial effect on the other health conditions and children's education. It is desirable to balance the impact evaluation with the ethics of withholding a beneficial intervention from the control group. If the trial were to be stopped for early efficacy the likelihood that the control communities (and the rest of East Africa) would receive the intervention under study in a timely fashion as delivered by their governments and HIV funders is expected to be small. On balance the protocol team believes continuing to evaluate the full effect of the intervention is ethical and warranted.

12.1.3 Study Discontinuation

This study may be discontinued at any time by the NIH, respective Institutional Review Boards (IRBs) or other governmental agencies in the United States, Uganda or Kenya as part of their duties to ensure that research subjects are protected.

12.2 Baseline Household Community Level Census

Household Census data will be collected by teams using hand-held computers (tablets). Prior to conducting the census, the census questionnaire will be programmed into the hand-held computers. Programming will include range checks, structure checks and internal consistency checks. Before leaving the household, the completed questionnaire will be checked for mistakes and completeness, ensuring each household has a unique identifier. Data from these devices will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

Each household location will be mapped using a hand-held GPS receiver. Readings will be taken from the door of the household, if possible, or from a point that is most representative of the household. The GPS coordinates for each household will also be recorded in the tablet computer at the time of administering the census questionnaire. GPS data will be synchronized from the GPS to a Microsoft Access database daily and then transferred via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

A digital biometric identifier based on an electronic fingerprint of each household member over 2 years old will be captured in an electronic database on the hand-held computer and linked to the household member name. A portable fingerprint reader will be connected to the tablet computer via a USB port and the biometric identifier will be saved into the electronic database on the tablet. The database will be transferred daily via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.3 Community Health Campaign

12.3.1 Welcome Station

The first stop for participants during most Community Health Campaign will be the Welcome Station. There will be an electronic database of all the biometric identifiers collected during the Census Survey available at the Welcome Station. Staff members will verify participant's fingerprint biometric identifier against the database to ensure they have a biometric identifier in the system. If a participant did not have a biometric identifier taken during the Census Survey, a biometric identifier based on his or her digital fingerprint will be taken at the Welcome Station and added to the database. Once the participant's biometric identifier is verified, the participant will be given a bracelet with a unique identifier on it. The unique identifier will be added to the biometric identifier database and linked to the participant's biometric identifier. The participant will then be tracked through the Community Health Campaign with the unique identifier on the bracelet.

12.3.2 Health and Socioeconomic Interview Station

During most campaigns, health and socio-economic data will be collected by trained staff members electronically using tablet computers. Prior to conducting the Health and Socioeconomic Interview, the interview will be programmed into the tablet computers. Programming will include range checks, structure checks and internal consistency checks. The unique identifier on the participant's bracelet will be used to link the participant to their interview data. Data from the tablet computers will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

12.3.3 Other CHC Stations

During the campaign, all information recorded at each of the stations will be recorded in Log Books by staff members. The unique identifier on the participant's bracelet will be used to link the participant to their data in the Log Books. Afterwards, the Log Books will be entered directly into an electronic database. Data Integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. All data will be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.3.4 Tracking CHC Non-Participants

Apart from the verbal autopsy questionnaire, data collected during evaluation of non-participants will be collected using hand-held computers (tablets). Prior to conducting the evaluation, the questionnaire will be programmed into the hand-held computers. Programming will include range checks, structure checks and internal consistency checks. Data from these devices will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

The verbal autopsy questionnaire will be recorded on paper forms.

12.3.5 Morbidity/Disease Surveillance

Study staff will regularly collect information available from routine encounters at local health centers and, where needed, hospitals within the community. This information will be available in the clinic's standard visit forms and recorded by staff for data entry.

Afterwards, the surveillance forms will be entered directly into an electronic database. Data Integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. All data will be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.4 ART Intervention

All data will be obtained from encounter forms at local health centers and recorded onto standardized case record forms by study staff. Afterwards, the forms will be entered directly into an electronic database. Data Integrity checks will be written into the database to limit the

entry of incorrect data and ensure entry of data into required fields. All data will be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.5 Grade 3 and 4 Adverse Event and Serious Adverse Event Monitoring

Grade 3 and 4 adverse events (AEs) and serious adverse events (SAEs) will be monitored in 3 paired sentinel cohorts. We will utilize the DAIDS Toxicity Table for Adults and Children grading scale (Appendix A) for reported symptoms and laboratory monitoring. The sentinel cohorts will be composed of persons in the intervention arm with CD4 ≥350 cells. These individuals will be matched on CD4 to individuals not receiving ART and evaluated semi-annually through chart review supplemented by tracking visits.

Adverse events at the sentinel sites which are definitely, probably, or possibly related to study procedures or study participation **AND** serious or unexpected will be reported. AEs which are clearly not related to research will be documented, referenced, and retained in the study files for follow-up. The following definitions for serious or unexpected adverse events will be followed:

A Serious Adverse Event (SAE) is any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event occurring in a gene therapy study
- Event that changes the risk/benefit ratio of the study.

An Unexpected Adverse Event is defined as being unexpected if the event exceeds the nature, severity, or frequency described in the protocol, consent form and investigator brochure (when applicable). An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the study protocol

Adverse events in sentinel sites will be reported to individual IRBs according to the table below:

Institution	Type of Adverse Events	When to Report
UCSF-CHR	• Definitely, Probably, or Possibly related **AND** Serious* or Unexpected±	• Within 10-working days of awareness
MU SOMREC	• All Serious* or Unexpected± events irrespective of relationship	• Fatal or life-threatening events within 3 working days of awareness • All other SAEs within 10 working days of awareness
UNCST	• All Serious* or Unexpected± events irrespective of relationship	• Within 7-calendar days of awareness • All other reportable events within 15-calendar days of awareness
NDA	• All serious and Unexpected events irrespective of relationship	• Within 7-calendar days of awareness
KEMRI ERC	• All Serious* or Unexpected± events irrespective of relationship	• Study-related events within 24 hours of awareness • Unrelated events within 10 working days of awareness
Gilead Sciences	• Definitely, Probably, or Possibly related **AND** Serious* or Unexpected± • Only AEs in participants taking Truvada	• Within 10-working days of awareness

12.6 Household Socio-Economic Survey

Household Socio-Economic Survey data will be collected by teams using hand-held computers (tablets). Prior to conducting the survey, the questionnaire will be programmed into the hand-held computers. Programming will include range checks, structure checks and internal consistency checks. Before leaving the household, the completed questionnaire will be checked for mistakes and completeness, ensuring each household has a unique identifier. Data from these devices will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

12.7 Health Care Costing Evaluations

Each health facility will be identified using a code. Health facility time in motion data will be recorded on paper and transferred to a database by study staff. Cost data will be collected in Microsoft Excel and imported to a database (Microsoft Access or FileMaker) for storage and manipulation. Although there is no confidential patient information in the cost data, it will be integrated with standard secure methods used for other data in the study. The data files will be regularly backed up on secure servers

12.8 Data Security and Integrity

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 GPS devices.
- Where applicable, team members will receive additional training on the use of tablet computers.
- All data transcribed form paper will be double data entered.
- All electronic data will be backed up on a daily basis.
- 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.
- All Log Books and CRF's will be locked in a secure room each night.

13. HUMAN SUBJECTS

13.1 Ethical Considerations

13.1.1 ART Intervention

In this study, ART will be initiated at CD4 ≥ 350 cells/uL, which is higher than the national guidelines defining standard of care in Uganda. We must therefore consider the potential benefits and risks of ART at higher CD4 counts to ensure that the key intervention of this study (ART initiation) meets the strictest ethical guidelines. We submit that initiation of ART at CD4 ≥ 350 meets and exceeds ethical standards by several criteria:

1) ART is routinely initiated in HIV-positive patients throughout many countries at CD4 ≥ 350.

2) ART initiation at CD4>350 is now recommended by many professional HIV medicine societies. For example, ART at CD4<500 (and consideration of ART initiation in <u>all</u> patients with CD4>500) is now formally recommended by the United States Department of Health and Human Services. ART initiation at CD4<500 (and consideration of ART initiation in <u>select</u> patients with CD4>500) is now recommended by the International AIDS Society (IAS). Furthermore, ART at CD4<500 is also recommended by the European AIDS Clinical Society (EACS).

3) Accumulating evidence indicates that there may be substantial clinical benefit to initiating ART at CD4>350 (i.e., earlier in disease). This benefit may accrue from reductions in immune activation and systemic inflammation, as well as limitation of the size of the latent reservoir of HIV. These pathophysiologic discoveries have been partially responsible for the changes in clinical practice guidelines detailed above.

4) The additional amount of time a patient will take ART if initiated at CD4 ≥ 350 compared to if they initiate after CD4 < 350 (i.e., following country-specific guidelines) is relatively small. Accumulated data on the speed of HIV progression (i.e., the time taken for CD4 to decline to 350 cells/uL from the time of infection) indicates that this may take, on average, 2-3 years in most patients. This study, therefore, will bridge this length of treatment administration, after which point participants will be allowed to continue ART provided by the local government's country-specific guidelines.

13.2 Institutional Review Board (IRB) and Informed Consent

13.2.1 Obtaining Consent

This protocol, all procedures and consent forms, and any subsequent modifications must 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 Uganda National Drug Authority

(NDA), the Kenya Medical Research Institute (KEMRI) Ethics Review Committee and the Kenya Pharmacy and Poisons Board.

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 or their parents 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 or their parents/guardians 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.

Verbal consent will be obtained from adults to participate in the Baseline Household Community Level Census and, for those not available during the Census, at the initial Community Health Campaign. Consent will obtained for adults and their children, by reading the approved consent script and documenting agreement by recording their fingerprint biometric on portable, password-protected computers. Written consent will be obtained from adults to participate in the Household Socio-Economic Survey and ART Intervention. In addition, children 13 years or older will provide consent to participate in ART Intervention, with parental co-signature; written assent will be obtained from children 8 to 12 years old, with parental co-signature; and parental written consent will be obtained for children less than 8 years old. In addition, a letter of commitment will be obtained from community leaders for their site's participation in the study. See Appendix B for further details.

14. PUBLICATION OF RESEARCH FINDINGS

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 NIAID, UCSF, UNCST, KEMRI and Makerere University guidelines.

REFERENCES

1. *UNAIDS Report on the global AIDS epidemic 2010*, 2010, UNAIDS.
2. Hogan, M.C., et al., *Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5.* Lancet, 2010. **375**(9726): p. 1609-23.
3. Beegle, K., J. De Weerdt, and S. Dercon, *The intergenerational impact of the African orphans crisis: a cohort study from an HIV/AIDS affected area.* Int J Epidemiol, 2009. **38**(2): p. 561-8.
4. Kublin, J.G., et al., *Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study.* Lancet, 2005. **365**(9455): p. 233-40.
5. Havlir, D.V., et al., *Opportunities and challenges for HIV care in overlapping HIV and TB epidemics.* Jama, 2008. **300**(4): p. 423-30.
6. Lawn, S.D. and A.D. Harries, *Reducing tuberculosis-associated early mortality in antiretroviral treatment programmes in sub-Saharan Africa.* Aids, 2011. **25**(12): p. 1554-5; author reply 1556.
7. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy.* N Engl J Med, 2011. **365**(6): p. 493-505.
8. Granich, R.M., et al., *Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.* Lancet, 2009. **373**(9657): p. 48-57.
9. Wagner, B. and S. Blower, *Costs of eliminating HIV in South Africa have been underestimated.* Lancet, 2010. **376**(9745): p. 953-4.
10. Wagner, B.G., J.S. Kahn, and S. Blower, *Should we try to eliminate HIV epidemics by using a 'Test and Treat' strategy?* Aids, 2010. **24**(5): p. 775-6.
11. Dieffenbach, C.W. and A.S. Fauci, *Thirty years of HIV and AIDS: future challenges and opportunities.* Ann Intern Med, 2011. **154**(11): p. 766-71.
12. Weber, J., R. Tatoud, and S. Fidler, *Postexposure prophylaxis, preexposure prophylaxis or universal test and treat: the strategic use of antiretroviral drugs to prevent HIV acquisition and transmission.* Aids, 2010. **24 Suppl 4**: p. S27-39.
13. Dodd, P.J., G.P. Garnett, and T.B. Hallett, *Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings.* Aids, 2010. **24**(5): p. 729-35.
14. Wawer, M.J., et al., *Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial.* Lancet, 2009. **374**(9685): p. 229-37.
15. Rosen, S. and M.P. Fox, *Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review.* PLoS Med, 2011. **8**(7): p. e1001056.
16. Middelkoop, K., et al., *Antiretroviral therapy and TB notification rates in a high HIV prevalence South African community.* J Acquir Immune Defic Syndr, 2011. **56**(3): p. 263-9.
17. Zachariah, R., et al., *Reduced tuberculosis case notification associated with scaling up antiretroviral treatment in rural Malawi.* Int J Tuberc Lung Dis, 2011. **15**(7): p. 933-7.
18. Flateau, C., G. Le Loup, and G. Pialoux, *Consequences of HIV infection on malaria and therapeutic implications: a systematic review.* Lancet Infect Dis, 2011. **11**(7): p. 541-56.
19. Fowler, M.G., et al., *Perinatal HIV and its prevention: progress toward an HIV-free generation.* Clin Perinatol, 2010. **37**(4): p. 699-719, vii.
20. Schouten, E.J., et al., *Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach.* Lancet, 2011. **378**(9787): p. 282-4.

21. Donnell, D., et al., *Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis.* Lancet, 2010. **375**(9731): p. 2092-8.
22. Thirumurthy H, Goldstein M, and Graff Zivin J, *The economic impact of AIDS treatment: labor supply in western Kenya.* Journal of Human Resources, 2008. **43**(June 20): p. 511-552.
23. Habyarimana, J., B. Mbakile, and C. Pop-Eleches, *The Impact of HIV/AIDS and ARV Treatment on Worker Absenteeism: Implications for African Firms* J. Human Resources, 2010. **45**(September 21): p. 809-839.
24. Rosen, S., et al., *Economic outcomes of patients receiving antiretroviral therapy for HIV/AIDS in South Africa are sustained through three years on treatment.* PLoS One, 2010. **5**(9): p. e12731.
25. Thirumurthy, H., et al., *Two-year impacts on employment and income among adults receiving antiretroviral therapy in Tamil Nadu, India: a cohort study.* Aids, 2011. **25**(2): p. 239-46.
26. Graff Zivin, J., H. Thirumurthy, and M. Goldstein, *AIDS treatment and intrahousehold resource allocation: Children's nutrition and schooling in Kenya.* Journal of Public Economics, 2009. **93**(7-8): p. 1008-1015.
27. *Integrated National Guidelines on Antiretroviral Therapy, Prevention of Mother to Child Transmission of HIV and on Infant & Young Child Feeding*, 2011, Ministry of Health, Republic of Uganda.
28. *Guidelines for Antiretroviral Therapy in Kenya, 4th edition 2011*, 2011, Ministry of Medical Sciences, Republic of Kenya.
29. Muennig, P.A. and K. Khan, *Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults.* Clin Infect Dis, 2001. **33**(11): p. 1879-85.
30. Marseille, E.A., et al., *Case management to improve adherence for HIV-infected patients receiving antiretroviral therapy in Ethiopia: a micro-costing study.* Cost Eff Resour Alloc, 2011. **9**: p. 18.
31. Hayes, R.J. and L.H. Moulton, *Cluster Randomized Trials* 2009: Chapman and Hall.
32. Pagel, C., et al., *Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomized controlled trials in low and middle-income countries; results and methodological implications.* Trials, 2011. **12**: p. 151.
33. Chingono, A., et al., *Balancing science and community concerns in resource-limited settings: Project Accept in rural Zimbabwe.* Clin Trials, 2008. **5**(3): p. 273-6.
34. Van der Laan, M.J. and S. Rose, *Targeted Learning: Causal Inference for Observational and Experimental Data* 2011: Springer, Berlin Heidelberg New York.
35. Carone, M., M.L. Peterson, and M.J. Van der Laan, *Targeted minimum loss-based estimation of causal effect using interval-censored time-to-event data*, in *Peace Interval-Censored Time-to-Event Data: Methods and Applications*, D. Chen, J. Sun, and KE, Editors. 2012, Chapman and Hall.
36. Rosenblum, M. and M.J. van der Laan, *Simple, efficient estimators of treatment effects in randomized trials using generalized linear models to leverage baseline variables.* Int J Biostat, 2010. **6**(1): p. Article 13.
37. van der Laan, M.J., L. Balzer, and M.L. Petersen, *Adaptive matching in randomized trials and observational studies.* U.C. Berkeley Division of Biostatistics Working Paper Series, 2012(296).
38. Robins, J.M., *A new approach to causal inference in mortality studies with sustained exposure period application to control of the healthy worker survivor effect.* Math Mod, 1986. **7:13931512**.
39. Robins, J.M., *Addendum to: A new approach to causal inference in mortality studies with a sustained exposure periodapplication to control of the healthy worker survivor effect.* Comput Math Appl, 1987. **14**(912): p. 923-45.

40. Hayes, R.J. and S. Bennett, *Simple sample size calculation for cluster-randomized trials.* Int J Epidemiol, 1999. **Apr; 28**(2): p. 319-26.
41. Guwatudde, D., et al., *Relatively Low HIV Infection Rates in Rural Uganda, but with High Potential for a Rise: A Cohort Study in Kayunga District, Uganda.* PloS One, 2009. **4**(1): p. e4145.
42. Shafer, L.A., et al., *HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989-2005.* AIDS, 2008. **22**: p. 1641-49.
43. Gray, R.H., et al., *Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial.* Lancet, 2007. **369**: p. 657-66.
44. Campbell, M.S., et al., *Viral linkage in HIV-1 seroconverters and their partners in an HIV-1 prevention clinical trial.* PLoS One, 2011. **6**(3): p. e16986.

Appendix A Guidelines for Adverse Event Grading – DAIDS Toxicity Table for Adults and Children

Selected portion of the of Division of AIDS [DAIDS] Table for Grading the Severity of Adult and Pediatric Adverse Events, version Dec. 2004.

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
SKIN – DERMATOLOGICAL				
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
RESPIRATORY				
Dyspnea or respiratory distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute neutrophil count (ANC)	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Hemoglobin (Hgb) **Adult and Pediatric ≥ 57 days** (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bilirubin (Total)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*

Appendix B Table of Study and Consent and Commitment Procedures

Study component	No. of participants in Mbarara district, Uganda	No. of participants in Tororo district, Uganda	No. of participants in Kenya	Procedures	Timeline	Consent or commitment process
Community Leader	10	10	12	Meet with local community leaders representing each of the 32 selected communities	Prior to the first Household Census and Community Health Campaign in each selected community	Obtain letter of commitment from leader of each selected community
Baseline Household Community Level Census	All individuals in selected communities	All individuals in selected communities	All individuals in selected communities	Census of all community members to collect identifier and location information	Prior to first Community Health Campaign in each selected community; also at Campaign for those not previously consented	Verbal consent of head of household for themselves and other household members; fingerprint biometric will be recorded as consent documentation
Community Health Campaign	All individuals in selected communities	All individuals in selected communities	All individuals in selected communities	• Tests and measurements including rapid HIV testing, malaria testing on children and other health evaluations • Education and referral to local health services • Distribution of anti-malaria medications and vitamin A in children, and male condoms	Prior to first Community Health Campaign in each selected community; also at Campaign for those not previously consented	Verbal adult consent for themselves and their children to participate in Campaign; fingerprint biometric will be recorded as consent documentation
Household Socio-Economic Survey	200 x 10 communities, 100 HIV+ & 100 HIV- (n = 2,000)	200 x 10 communities, 100 HIV+ & 100 HIV- (n = 2,000)	200 x 12 communities, 100 HIV+ & 100 HIV- (n = 2,400)	A survey to collect demographic, health and education information of household members	2-4 weeks after each Campaign	• Written consent, adults, conducted at Community Health Campaign
ART Intervention	All HIV+ individuals who do not meet in-country treatment guidelines	All HIV+ individuals who do not meet in-country treatment guidelines	All HIV+ individuals who do not meet in-country treatment guidelines	Distribution of ART and routine testing in a streamlined model of care	144 weeks from ART initiation for each participant	• Written consent, adults • Parental written consent, children <8 years • Written assent, children 8-12 years, with parental written consent • Written consent, children ≥13 years, parental co-sign

Appendix C Uganda Antiretroviral Therapy Guidelines

Selected portion of The Integrated National Guidelines on Antiretroviral Therapy, Prevention of Mother to Child Transmission of HIV and Infant & Young Child Feeding, Ministry of Health, Uganda.

ART Initiation in Adults

We now recommend that anyone with a CD4 cell count of 350 and below should be initiated on ART whether symptomatic or not. Those with a count above 350 should start on ART as provided below.

It is recommended to initiate Antiretroviral Therapy in Adults with documented HIV infection and;

- CD4 cell count of 350 cells/mm^3 and below
- CD4 cell count above 350 cells/mm^3 in those:
  - All who are co-infected with tuberculosis (TB),
  - Who are co-infected with HBV
  - Women who are pregnant (prophylaxis use only)
- WHO Stage III and IV disease irrespective of CD4 cell count

Tables C.1 and C.2 outline the criteria for initiating antiretroviral therapy.

Table C.1: WHO clinical staging and immunological criteria for initiating ART

Clinical Stage	**CD4 cell count**	**Comments**
I	CD4 guided	Treat if ≤350
II	CD4 guided	Treat if ≤350
III	Treat	Treat
IV	Treat	Treat

Table C.2: CD4 cell count criteria for initiation of ART

CD4+ count (cells/uL)	**Actions**
<350	Treat irrespective of clinical stage
350-500	Consider treatment in patients who are symptomatic (WHO Stage III or IV), have TB, HBV co-infected or are pregnant (prophylaxis)
>500	Do not initiate treatment unless TB-co-infected, HBV co-infected or pregnant (prophylaxis), or stage III or IV

Eligibility criteria for initiating art in infants and children

Three parameters guide the decision making process for initiation of ART in infants and children; these are the age, immunological status and WHO clinical Staging. However ART can also be started in children under 18 months of age presumptively (*as will be described in the next section.*) The following criteria is used to initiate infants and children on ART (see table a for summary of initiation criteria)

1. All infants and children under 2 years of age should be started on ART irrespective of WHO clinical stage or CD4 % or count. All children with WHO clinical stage 3 or 4 disease should be started on ART irrespective of the CD 4 count (see appendix 2 for the WHO clinical staging Chart for guidance on how to stage)
2. All children aged 2 years and under 5 years should be started on ART if the CD4 % is less than 25% or CD4 count is <750 cells/mm^3
3. All children above 5 years should be started on ART is CD4 count is less than 350 cells/mm^3
4. All infants under 18 months of age with presumptive diagnosis of HIV

Table C.3: When to Initiate ART in Children

All HIV-positive children should be clinically staged and receive a CD4 test when possible to determine the eligibility for ART, except for children <u>under 2 years of age</u> who should <u>initiate ART immediately irrespective of clinical or immunological stage</u>			
Age	Criteria for Initiating ART		
	Who Clinical Staging	CD4%	CD4 Count
Under 2 years	Initiate ART if child is confirmed HIV Positive, regardless of CD4 or Clinical Staging		
2 to < 5 years	Initiate ART if Stage III or Stage IV	< 25%	< 750
5 years and above		N/A	< 350

Appendix D Kenya Antiretroviral Therapy Guidelines

Selected portion of the Guidelines for Antiretroviral Therapy in Kenya, 4th Edition.

When to Initiate Antiretroviral Therapy in Adults and Adolescents

The following are the recommendations/indications for initiating ART in HIV-infected adults and adolescents with documented HIV infection.

Table E.1: Criteria for Initiation of ART in Adults and Adolescents

Who stage/Clinical condition	CD4 cell count (cells/mm^3)	
	≤350	>350
1 & 2	Start ART	Defer ART
3 & 4[1]	Start ART	Start ART
TB disease	Start ART	Start ART
HIV/HBV co-infection with evidence of active/chronic liver disease	Start ART	Start ART
HIV-associated nephropathy[2]	Start ART	Start ART

1. Patients with WHO stage III or IV disease should be started on ART irrespective of availability of CD4
2. HIV-associated nephropathy is characterized by proteinuria and impaired kidney function with or without peripheral edema.

When to start antiretroviral therapy in children

Any child diagnosed to have HIV infection (as outlined above) who fulfills any of the criteria shown below should start ART as soon as possible:

Clinical criteria:

Age <24 months:

- Children with positive DNA PCR should start ART regardless of WHO clinical stage, CD4 count or CD4%.

Age 24 months and above:

The indications for starting ART in children aged above 24 months are the following:

- Children in WHO stage III or IV disease regardless of CD4 count.
- Age related CD4 count as shown in table 12.1

Viral load is not recommended as a criterion for ART initiation as it is highly variable in young children, and levels that predict rapid disease progression are not well defined in children.

Table E.2: Recommendations for When to Start ART in Infants and Children

Age	Who clinical stage	CD4%	CD4 count (cells/mm$^{3)}$
≤24 months	ALL	ALL	ALL
25-59 months	3 or 4	<25%	<1000
5-12 years	3 or 4	<20%	<500

Use of antiretroviral drugs for treating HIV-positive pregnant women for their own health (those eligible for ART)

When to start antiretroviral therapy

The criteria for initiating ART for pregnant women are similar to that for non-pregnant women (Table 16.2). In pregnant women who meet the criteria for antiretroviral therapy for their own health, it is also the most effective method of preventing MTCT. By improving the general health of the mother; ART also offers the best chance of survival to children born to HIV-positive women. Recent evidence has demonstrated that these group of women account for about 80% of MTCT hence making it critical to identify and treat them.

- Lifelong ART in eligible pregnant women should be initiated as soon as feasible irrespective of gestational age and continued throughout pregnancy, during delivery, breastfeeding and throughout life
- Though ART should be initiated expeditiously in eligible pregnant women; adequate patient preparation through patient education, counseling and support is important to avoid non-adherence and treatment failure. Many of these patients are likely to be relatively healthy; the motivation to deliver a healthy baby means that patient preparation can be successfully fast-tracked.

Table E.3: When to Initiate ART in Pregnant Women

Who clinical stage	CD4 testing not available	CD4 testing available
1	Offer efficacious ARV prophylaxis	Treat if CD4 <350 mm^3
2		
3	Treat with ART	Treat with ART
4	Treat with ART	Treat with ART

Appendix E Sample Pediatric ART Dosing Chart

		3 - 5.9 kg	6 - 9.9 kg	10 - 13.9 kg	14 - 19.9 kg	20 - 20.9 kg	25 - 25.9 kg
Tablets/Capsules	EFV 200 - 100 - 50mg	NR	NR	200mg daily	300mg daily	300mg daily	400mg daily
	ABC 300mg	NR	NR	NR	0.5 BID	1 AM/0.5 PM	1 BID
	ABC 60mg	1 BID	1.5 BID	2 BID	2.5 BID	3 BID	Use adult
	3TC 150mg	NR	NR	NR	0.5 BID	1 AM/0.5 PM	1 BID
	LPV/r 100/25mg	NR	NR	2 AM/1 PM	2 BID	2 BID	3 BID
	LPV/r 200/50mg	NR	NR	NR	1 BID	1 BID	2 AM/1PM
	AZT 300mg	NR	NR	NR	0.5 BID	1 AM/0.5 PM	1 BID
	NVP 200mg	NR	NR	NR	1 AM/0.5 PM	1 AM/0.5 PM	1 BID
	NVP 50mg	1 BID	1.5 BID	2 BID	2.5 BID	3 BID	Use adult
Oral Solutions	ABC 20mg/ml	3ml BID	4ml BID	6ml BID	NR	NR	NR
	3TC 10mg/ml	3ml BID	4ML BID	6ml BID	NR	NR	NR
	LPV/r 80/20 mg/ml	3-3.9kg: 1ml BID 4-5.9kg: 1.5ml BID	1.5ml BID	2ml BID	2.5ml BID	3ml BID	3.5ml BID
	AZT 10mg/ml	6ml BID	9ml BID	12ml BID	NR	NR	NR
	NVP 10mg/ml	5ml BID	8ml BID	10ml BID	NR	NR	NR

Sustainable East Africa Research in Community Health (SEARCH)

A Study of the:

Makerere University – University of California, San Francisco (MU-UCSF)
Research Collaboration

Protocol version: 6.0, October 1, 2015

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PROTOCOL SYNOPSIS

Overall Goal: The SEARCH study will quantify the health, economic and educational impact of early HIV diagnosis and immediate ART (antiretroviral therapy) using a streamlined care delivery system in rural communities in East Africa. The study intervention is designed to improve the entire continuum of care, to reduce structural barriers for all populations including those most "at risk" and build upon evidence based prevention interventions including adult male circumcision.

Study Hypothesis: ART initiation at any CD4 count with streamlined delivery compared to CD4-driven ART initiation will reduce cumulative 5-year HIV incidence and protect and improve health, economic and education outcomes in communities with annual HIV testing campaigns.

Study Partnerships: SEARCH is designed to inform governments and health policy makers and to benefit affected communities. To that end, SEARCH is a partnership with input and sponsorship from global and local health and development agencies, foundations, governments and the study communities. These include the ministries of health in Uganda and Kenya, the National Institutes of Health, the World Bank, and PEPFAR.

Study Design: SEARCH is a cluster randomized community trial. Community health campaigns will be conducted in all study communities at baseline and will offer HIV testing and multi-disease prevention and treatment services. The intervention is annual and targeted HIV testing and ART independent of CD4 cell count delivered in a streamlined approach for all HIV infected adults and children. Components of streamlined care include ongoing HIV combination prevention strategies including male circumcision. Control communities will follow country guidelines for ART.

HIV incidence will be measured using an efficient community cohort design (ECCO) comprised of three key elements: A) baseline household community level census, B) community health campaigns (CHC) incorporating HIV testing that use unique identifiers to link individuals between successive waves of the intervention, and C) tracking and evaluation of individuals who do not participate in CHCs.

Study Population: Thirty-two communities with a population of approximately 10,000 persons each will participate in the following three regions: A) Mbarara/Western Uganda (n=10), B) Tororo/Eastern Uganda (n=10), and C) Southern Nyanza Province, Kenya (n=12). Randomization to intervention vs. control will occur in pairs of communities matched based on key health, geographic and ethnographic variables including: A) geographic region B) population density C) number of trading centers D) transportation index, and E) occupational mix.

Primary Endpoint: Cumulative 5-year HIV incidence in men and women ages ≥15 years.
Secondary Endpoints: The health-related secondary endpoints include: 1) mortality (overall, maternal, and infant mortality), 2) mother-to-child HIV transmission, 3) AIDS (WHO stage 4), 4)

tuberculosis, and 5) HIV drug resistance. The economic/education secondary endpoints include: 1) adult and child employment levels, 2) asset holdings, 3) school attendance levels, 4) programmatic costs, 5) health gains expressed in averted Disability Adjusted Life Years (DALY), and 6) cost effectiveness (e.g. cost per infection averted and per DALY averted). Other secondary endpoints include: cumulative 3-year HIV incidence in men and women ages ≥15 years; implementation of the HIV, hypertension and diabetes care cascades including testing, linkage and retention to care; and attitudes of community, patients and providers on care delivery in control and intervention communities.

Study Antiretroviral Treatment Regimen: The study intervention is provision of ART for all individuals at any CD4+ cell count. ART – the regimen of efavirenz, emtricitabine and tenofovir disoproxil fumurate or equivalent – will be provided by the study for those who do not meet in-country guidelines to start ART. These individuals will be guaranteed 3 years of ART. After three years, these individuals will continue uninterrupted ART provided by their country of residence through agreements with the Ministry of Health.

Study Duration: The study will follow the communities for 5 years after the first community health campaign.

Statistics: We are powered to detect a 40% reduction in 5 year cumulative incidence in treatment versus control communities under conservative assumptions regarding plausible values for cumulative incidence in the control communities, baseline HIV prevalence, incomplete follow up, and between-community variation (matched pair coefficient of variation). Estimation of cumulative incidence within each community will account for incomplete attendance at the community health campaign and tracking. Primary analyses will consist of pair matched community level analysis.

GLOSSARY

3TC	Lamivudine
ABC	Abacavir
AFB	Acid-fast bacilli test
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ATV	Atazanavir
AZT	Zidovudine
BUN	Blood urea nitrogen
CO2	Bicarbonate
CBC	Complete blood count
CHC	Community health campaign
CHR	Committee on Human Research, UCSF
CI	Cumulative incidence
CK	Creatine kinase
CL	Chloride
DAIDS	Division of AIDS, NIH
DALY	Disability Adjusted Life Years
ECCO	Efficient community cohort design
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
FTC	Emtricitabine
GIS	Geographic information system
GPS	Global positioning system
HBV	Hepatitis B
HCG	Human chorionic gonadotropin pregnancy test
ICER	Incremental Cost-Effectiveness Ratio
IRB	Institutional Review Board
K	Potassium
KEMRI	Kenya Medical Research Institute
LPV	Lopinavir
MDRC	Modification of Diet in Renal Disease (formula)
MTCT	Mother-to-child transmission
MU	Makerere University
Na	Sodium
NDA	National Drug Authority in Uganda
NIAID	National Institute of Allergy and Infectious Diseases
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
RDT	Rapid diagnostic test
RNA	Ribonucleic acid (e.g., HIV-1 plasma RNA)
RTV	Ritonavir
SOM-REC	MU School of Medicine - Research and Ethics Committee
TB	Tuberculosis
TDF	Tenofovir disoproxyl fumarate
TMP/SMX	Trimethoprim/sulfamethoxazole
UNCST	Uganda National Council of Science and Technology
WHO	World Health Organization

1.0 STUDY CONTEXT

1.1 Background

The SEARCH study is designed to test the impact of a bold intervention in rural East Africa – treatment of all HIV-infected persons from near the onset of infection—on community health. The HIV epidemic has decimated health, education and economic gains that were made in Africa in the 1970s, leaving many countries with decreased life expectancy and mortality rates not seen in the US since the early 1900s [1]. HIV's effects on the population level are amplified by disabling the work force, damaging maternal health, increasing orphans and fueling the overlapping epidemics of TB and malaria [2-5]. The HIV epidemic represents one of the greatest public health challenges of all time.

The combination of prevention efforts and antiretroviral therapy (ART) has reduced the incidence of new HIV infections as well as mortality over the last decade. However, there were still over 2 million new HIV infections last year, and over 20 million individuals have died from HIV [1]. HIV is the leading cause of death among women of reproductive age in Sub-Saharan Africa. At the beginning of the 21st century, global approach to deploy ART to reduce AIDS mortality prioritized treatment for the most ill patients based on CD4 cell count. In Uganda and Kenya, ART is generally administered in adult patients when their CD4 count falls below 350 cells/mm^3, when they are diagnosed with a WHO Stage III or IV disease, and in other patients at high risk of HIV disease progression, including those with tuberculosis (TB). New data show that treating HIV *early* can prevent AIDS and prevent TB, a leading killer of HIV infected patients [6]. New data also show that ART can reduce HIV transmission by 96% in HIV sero-discordant couples [7]. These data illustrate a dual purpose for ART – prevent AIDS (including TB) in the HIV infected individual *and* prevent HIV transmission to the uninfected partner. The identification of HIV infection early and initiation of treatment thus has the potential to influence the overall health of the community as well as its economic and educational strength and viability.

The proposed community randomized trial will quantify the effect of an early HIV diagnosis and ART approach ("test and treat") on the health, economic productivity and educational outcomes of rural communities in East Africa. There have been several mathematical models, including a landmark publication by Granich et al and a subsequent economic analysis, showing frequent HIV testing and ART will reduce overall HIV incidence over a period of 5 to 10 years, and that the upfront investments required for such an approach result in net savings over 13 years in South Africa [8]. These models have generated heated debate within the scientific community based on various assumptions inherent in the models [9, 10]. These models may have also underestimated the benefits of ART because the evaluation framework did not include all the health benefits of ART, such as prevention of TB or the socioeconomic benefits of the preservation or return of good health afforded by ART. Thus it is time to test a population-based approach to early HIV diagnosis and treatment approach and to evaluate its cost and effects with an evaluation framework that includes health, economic and education metrics [11-13].

Inherent to the scale up of HIV treatment in general, and an important part of the SEARCH is the need to develop new models of chronic health care delivery at the community level that are

lower in resource needs and are sustainable. Finding patients earlier in HIV disease, keeping these individuals healthy with early ART, and delivering their care in a streamlined manner in fact may be the only viable path to deal with the health care worker shortage which is amplified by late HIV diagnosis, and the medical expertise and facilities needed to care for patients who present and are treated after HIV has significantly progressed.

Also inherent to the design of the SEARCH intervention is the recognition that a “test and treat” approach must find an overwhelming majority of HIV infected individuals, improve upon the entire continuum of care including participation of the most at risk populations and build upon prevention interventions known to work such as male circumcision [14, 15]. The SEARCH study is built upon biomedical evidence that is being applied and tested in a manner which incorporates social science evidence and approaches.

The SEARCH study is multicounty collaboration built upon expertise from a broad spectrum of scientific disciplines. It is grounded upon partnerships with scientific, health, and development global agencies. SEARCH is designed to inform the health sector, finance ministries, and the scientific and lay communities on the medical and economic effects of early antiretroviral therapy in rural East Africa.

1.2 Rationale

There is overwhelming evidence that the benefits of ART extend well beyond those originally appreciated, and those that are currently measured. ART reduces mortality among persons with HIV. The HPTN 052 study showed that ART reduces AIDS related illness even in persons with CD4 cell counts above thresholds of CD4 cell counts (i.e. 350 cells/mm3) [7]. ART also dramatically reduces TB risk both on the individual and the community level [6, 16, 17]; reduces the risk of malaria in individuals [18]; Reduces mother to child transmission (MTCT) of HIV; and reduces maternal and child mortality [19, 20].

ART is also a key component in a multilevel HIV prevention strategy. The HPTN 052 study shows definitively that ART reduces HIV transmission and preserves the health of the HIV infected persons receiving treatment [7]. These results build upon prior observational cohort studies showing reductions in HIV transmission by ART in HIV sero-discordant couples [21]. Biomedical interventions such as ART are likely to be highly complementary to proven interventions such as male circumcision and have an important role in reducing new HIV cases.

ART and the associated restoration of health also have important effects on socio-economic outcomes. Studies conducted in various settings in sub-Saharan Africa and South Asia have documented a significant improvement in the employment outcomes of adults following the initiation of ART [15, 22-25]. These studies have shown a large and rapid increase in labor supply and labor productivity, from levels that were initially very low to levels that were similar to those of HIV uninfected adults. In many cases, the increase in employment outcomes took place within 3-6 months of ART initiation, a result that is consistent with the rapid improvement in health and functional capacity due to ART. Furthermore, studies have found that the treated patients’ family members (particularly children) also benefit substantially when a working-age

adult becomes healthy and productive [26]. Following ART initiation in Kenya, there was a significant increase in the school attendance of children living with treated patients, as well as a reduction in child labor and improvement in nutritional status. These studies suggest that earlier ART initiation would *prevent* a decline in socio-economic status and help to protect living standards.

ART can contribute to prevention of new HIV infections and prevention of AIDS and TB, enhance economic productivity, and improve socio-economic outcomes more generally. A key question then is why is the ART "test and treat" strategy not being deployed?

First the strategy requires knowledge of HIV status, and globally, most individuals are not aware of their HIV status. *We aim to identify HIV status throughout the community through annual community health campaigns that we have piloted and refined in western rural Uganda*. Second, there is a stigma for participating in care that prevents even those with known HIV infection from getting treated. *This study will be conducted in communities where we have established ongoing community engagement work, and care delivery will be adapted to the community to promote participation and retention*. Third, there are few data in developing nations to prove or disprove that asymptomatic individuals will initiate and adhere to ART. *We are currently studying predictors of adherence in this population and will incorporate this knowledge into care delivery*. Non-adherence to ART has serious consequences for the HIV epidemic because it means that A) individuals will not immediately benefit, B) HIV can become resistant requiring new and more expensive medications, and C) resistant HIV can spread sexually and during mother to child transmission.

Community engagement strategies will be deployed in this study to maximize adherence. Finally, ART (despite 10-fold reductions in drug price over the last decade) is expensive to deliver. Providing it according to the current health delivery system might not be possible due to shortages in financial and human resources, particularly when doubts are expressed about the cost-effectiveness of such an intervention relative to many other priority health interventions. Thus data are needed to inform policy makers about the full range of benefits and risks of a test and treat ART strategy. During the course of the study, we will also use social science approaches to understand how the attitudes of the community, patients and providers influence the results of the study.

1.3 Antiretroviral therapy

The 2010 WHO Antiretroviral Treatment Guidelines recommended ART for all adults with WHO stage III or IV disease, tuberculosis or CD4≤350 cells/mm3. ART was recommended for all children less than 2 years of age, and subsequent ART is dependent on a variety of disease and CD4 specific criteria. The WHO recommended a variety of approaches of ART for HIV+ pregnant women who otherwise do not meet the adults guidelines for ART. The specific country guidelines for ART treatment for countries participating in SEARCH starting in October, 2011 are summarized in Table 1 below.

Table 1: 2010 ART treatment guidelines

Country	Population	ART initiation
Uganda[27]	Adults and children ≥5 years	CD4 count ≤350 cells/mm^3
	Adults and children co-infected with tuberculosis (TB), co-infected with hepatitis B (HBV), with WHO Stage III or IV disease, and pregnant women (prophylaxis)	Initiate ART irrespective of CD4 % or count
	Children 2 to <5 years	CD4 % <25% or CD4 count <750 cells/mm^3
	Children <2 years	Initiate ART irrespective of CD4 % or count
Kenya[28]	Adults and children ≥12 years	CD4 count ≤350 cells/mm^3
	Adults and children co-infected with tuberculosis (TB), co-infected with hepatitis B (HBV) with evidence of liver damage, with WHO Stage III or IV disease, with HIV-associated nephropathy, and pregnant women (prophylaxis)	Initiate ART irrespective of CD4 % or count
	Children 5 to 12 years	CD4 % <20% or CD4 count <500 cells/mm^3
	Children 2 to <5 years	CD4 % <25% or CD4 count <1000 cells/mm^3
	Children <2 years	Initiate ART irrespective of CD4 % or count

In 2013, the WHO revised ART initiation guidelines, recommending antiretroviral therapy for persons with CD4+≤500 cells/ml, all pregnant women , HIV serodiscordant couples and other most at risk populations.. These recommendations are summarized at http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. These guidelines were adopted in Uganda and Kenya in 2014. In this protocol, the intervention arm will provide antiretroviral therapy for all community members who otherwise do not meet the country criteria for ART initiation. The selection of antiretroviral regimen for this study was based upon the following regimen characteristics: antiretroviral therapy efficacy, safety profile, monitoring requirements, pill burden, knowledge of HIV drug resistance that emerges under the drug use, prior use and experience within the study countries, consultation with in- country advisory board, consultation with in -country regulatory bodies The following regimens will be provided to

the study populations below in the intervention arm that otherwise do not meet criteria for government supported ART.

Table 2: Study Treatment[1]

Population	First line regimen	Recommended substitutions/second line regimens
Adults and adolescents, 13 years and above	Emtricitabine or lamivudine, plus tenofovir disoproxil fumurate and efavirenz	Abacavir or zidovidine plus lamivudine plus atazanavir/ritonavir or lopinavir/ritonavir[2]
Children 3-12 years	Abacavir, lamivudine, and efavirenz	Zidovudine, lamivudine and lopinavir/ritonavir
Children <3 years	Abacavir, lamivudine, and nevirapine	Zidovudine, lamivudine and lopinavir/ritonavir
Pregnant women and women attempting conception[3]	Emtricitabine or lamivudine, plus tenofovir disoproxil fumurate and efavirenz.	Abacavir plus lamivudine plus atazanavir/ritonavir or lopinavir/ritonavir or nevirapine

1. Exceptions to the regimens can be made in accordance with in-country treatment guidelines
2. Second-line therapy
3. Women may receive ART via in-country program (not study intervention) if ART is started immediately and lifelong (option B plus)

2.0 STUDY OBJECTIVES

2.1 Primary Study Objective

To determine the effect of a strategy to start ART in HIV diagnosed persons at any CD4 count with streamlined delivery of HIV care compared to a country based ART guidelines on 5-year cumulative HIV incidence in rural communities with annual HIV testing.

2.2 Secondary Objectives – Health

2.2.1 To compare the three year cumulative incidence of HIV infections between the 2 study arms.

2.2.2 To compare time from diagnosis to AIDS between the 2 study arms.

2.2.3 To compare incidence of AIDS-defining events between the 2 study arms.

2.2.4 To compare proportion of total TB and incident TB cases associated with HIV between the 2 study arms.

2.2.5 To compare mortality between the 2 study arms.

2.2.6 To compare maternal and child mortality between the 2 study arms.

2.2.7 To compare mother to child transmission between the 2 study arms.

2.2.8 To compare population HIV RNA metrics between the 2 study arms.

2.2.9 To determine the association between population HIV RNA metrics and HIV incidence.

2.2.10 To compare the prevalence of transmitted HIV drug-resistance mutations and pharmacologic measures of ART between the 2 study arms.

2.2.11 To compare rates of linkage to and retention in care for HIV between the 2 study arms.

2.2.12 To compare time to ART-initiation between the 2 study arms.

2.2.13 To characterize treatment outcomes in high CD4 count individuals (CD4>350) including: A) CD4 cell count recovery, B) rate of virologic suppression, C) treatment-associated toxicities and grade 3 and 4 adverse events, and D) HIV drug resistant mutations after 1 and 2 years of treatment.

2.2.14 To compare the five year cumulative incidence of internally derived HIV infections (infections genetically linked to a prior infection among members of the same community) between the 2 study arms.

2.2.15 To evaluate attitudes of community, patients and providers on care delivery in control and intervention communities.

2.2.16 To evaluate implementation of other disease care cascades (hypertension, diabetes, women and children health services) including testing, linkage and retention to care.

2.3 Secondary Objectives – Economic and Education Outcomes

2.3.1 To compare the trends in average levels of adults' on- and off-farm employment between the 2 study arms.

2.3.2 To compare the trends in average levels of children's on- and off-farm employment (child labor) between the 2 study arms.

2.3.3 To compare the trends in average levels of children's time allocation to schooling and household activities between the 2 study arms.

2.3.4 To compare the trends in average asset holdings (durable good and livestock) between the 2 study arms.

2.3.5 To compare the trends in agricultural output and other economic production, such as fishing, between the 2 study arms.

2.3.6 To compare the trends in average levels of cash and in-kind transfers between the 2 study arms.

2.4 Secondary Objectives – Cost and Cost-Effectiveness

2.4.1 To compare costs of programming (campaigns, ART) between the 2 study arms: overall; per person identified, linked to care, and started on ART; and per ART-month, CD4 level recovered, and viral load suppressed.

2.4.2 To compare disease burden (expressed in disability adjusted life years, DALYs) between the 2 study arms, during and modelled beyond the study period.

2.4.3 To compare the savings from averted disease associated treatment costs between the 2 study arms.

2.4.4 To compare the occurrence and consequences of false positive HIV diagnosis (new).

2.4.5 To calculate the incremental cost-effectiveness of the intervention, as net cost per DALY averted.

2.4.6 To evaluate streamlined vs. non-streamlined care including time in motion studies for staff and clients.

3.0 STUDY DESIGN

SEARCH is a cluster randomized community trial. The primary study hypothesis is: ART initiation at any CD4 count with streamlined delivery compared to ART initiation according to country guidelines will reduce cumulative 5-year HIV incidence and protect and improve health, economic and education outcomes in communities with annual HIV testing campaigns. The primary study endpoint is cumulative 5 year HIV incidence in men and women ages $\geq$ 15 years. The study will be conducted in rural communities in Uganda and Kenya.

Community health campaigns will be conducted in all study communities at baseline and will offer HIV testing and multi-disease prevention and treatment services. The intervention is ART independent of CD4 cell count delivered in a streamlined approach for all HIV infected adults and children. This intervention will be applied in the context of ongoing HIV combination prevention strategies including male circumcision. In control communities ART will be provided by country programs according to their guidelines.

HIV incidence will be measured using an efficient community cohort design (ECCO) comprised of three key elements: A) baseline household community level census, B) community health campaigns that use unique identifiers to link individuals between successive waves of the intervention, and C) tracking and evaluation of individuals who do not participate in annual CHCs.

4.0 STUDY POPULATION

4.1 Community Level Inclusion Criteria

4.1.1 Non-adjacent geopolitical units in south-western and eastern Uganda and western Kenya.

4.1.2 Most recent census population between 9,000 and 11,000 individuals.

4.1.3 Served by an ART providing health center.

4.1.4 Community leader commitment for study participation and implementation.

4.1.5 Accessibility to health center via a maintained transportation route.

4.1.6 Community location with sufficient distance from other potential study communities to limit contamination of intervention or control conditions (buffer zone)

4.2 Individual Level Inclusion Criteria

4.2.1 Residency of individual in community, defined as present in household for at least 6 months of the calendar year.

4.3 Community Level Exclusion Criteria

4.3.1 Presence of ongoing community-based ART intervention strategies that provide treatment outside of the current in-country treatment guidelines.

4.3.2 An urban setting defined as a city with a population of 100,000 or more inhabitants.

4.3.3 Absence of a health center able to provide ART.

5.0 STUDY INTERVENTION

5.1 Antiretroviral Therapy in a Streamlined Care Delivery

5.1.1 Streamlined ART Delivery

In this study, all HIV+ participants in intervention communities will be offered HIV therapy at ART providing health centers via "streamlined care," in order to maximize efficiency and clinic throughput, and engender the smallest impact of expanded ART access on current clinical sites, while maintaining treatment efficacy and safety. "Streamlined care" is defined as a method of enrolling ART-naïve participants, and initiating, monitoring, and sustaining ART delivery, in a manner consistent with the principles of care outlined in Table 3, recognizing that both facilities and patterns of care will vary somewhat between sites. In addition, intervention sites will employ enhanced services for linkage and retention. These include provision of provider cell phone number for referral clinic; cell phone reminder before appointments; standardized tracking for linkage from CHC to clinic and missed visits; and accelerated ART start for patients not on treatment. For participating health centers that do not currently offer ART in this streamlined fashion, study investigators will work with clinic staff to design and adapt existing procedures to this approach. During the course of the study, we will evaluate provider and patient attitudes and the implementation of streamlined and routine care.

Table 3. Features of "Streamlined" ART Delivery Model

ART Clinic	***Healthcare Team***	***ART Monitoring***
• Rapid ART initiation available with expedited counseling[#] • Short throughput* for patients with no active issues • Targeted adherence support • Convenient ART refill process *Throughput: time spent from clinic check-in to completion of visit [#]ART initiation may begin at CHC	• For stable, high CD4 patients, non-MD health care worker responsible for: 1. Screening for ART-related adverse events and toxicities 2. Dispensing, managing and altering ART regimens 3. Maintaining patient and drug accountability records • Back-up support for care and consultation by physician	• Streamlined visit schedule conducted by non-MD health care workers • Targeted laboratory evaluation schedule • Viral load monitoring at 6 months after ART start and then at least yearly. Provider counseling with client on all viral load results. Back-up support by physician

Study investigators and staff may provide additional support to ART providing health centers where needed. This may include assistance with staffing, training on good clinical practices and HIV care and non-communicable disease management, operation of linkage to care procedures, and or oversight of study drug accountability.

5.1.2 Provision of ART to persons who do not qualify for treatment by country guidelines

ART study medication will be provided to participants in communities randomized to intervention who do not meet in-country treatment guidelines. The study treatment will consist of a 3-drug ART regimen that will be provided to participants by the study (Table 2).

5.1.2.1 Regimen and Administration

<u>Adults and adolescents, 13 years and above</u>

First Line Regimen:	Tenofovir disoproxil fumurate (TDF) 300mg, *PLUS*
	Efavirenz (EFV) 600mg, *PLUS EITHER*
	Emtricitabine (FTC) 200mg, *OR*
	Lamivudine (3TC) 150mg
Recommended Second Line Regimen:	Abacavir (ABC) 300mg, *PLUS*
	Lamivudine (3TC) 150mg, *PLUS EITHER*
	Atazanavir (ATV) 300mg and ritonavir (RTV) 100mg, *OR*
	Lopinavir/ritonavir (LPV/RTV) 200mg/50mg, administered as a fixed-dose combination

<u>Children 3 – 12 years</u>

First Line Regimen:	Abacavir, *PLUS*
	Lamivudine, *PLUS*
	Efavirenz
Recommended Second Line Regimen:	Zidovudine (AZT), *PLUS*
	Lamivudine, *PLUS*
	Lopinavir/ritonavir, administered as a fixed-dose combination

Individual dosing information by weight can be found in Appendix E.

<u>Children < 3 years</u>

First Line Regimen:	Abacavir, *PLUS*

Lamivudine, *PLUS*

Nevirapine (NVP)

Recommended Second Line Regimen: Zidovudine, *PLUS*

Lamivudine, *PLUS*

Lopinavir/ritonavir, administered as a fixed-dose combination

Individual dosing recommendations by weight can be found in Appendix E.

<u>Pregnant women and women attempting conception*</u>

First Line Regimen: Tenofovir disoproxil fumurate (TDF) 300mg, *PLUS*

Efavirenz (EFV) 600mg, *PLUS EITHER*

Emtricitabine (FTC) 200mg, *OR*

Lamivudine (3TC) 150mg

Or if patient provider desire: Tenofovir disproxil fumerate, *PLUS EITHER*

Emtricitabine (FTC) *OR* Lamivudine (3TC),
PLUS

Lopinavir/ritonavir 200mg/50mg, two tablets PO twice daily, administered as a fixed-dose combination. After the first trimester, women may switch to efavirenz 600mg, as described above.

* Women may receive ART via in-country program (not study intervention) if ART is started immediately and lifelong (option Bplus)

Recommended Second Line Regimen: Abacavir 300mg, two tablets PO daily, *PLUS*

Lamivudine 150mg, one tablet PO twice daily, *PLUS EITHER*

Atazanavir 300mg and ritonavir 100mg, once PO daily, *OR*

Nevirapine 200mg, one tablet PO daily for first 2 weeks, then one tablet PO twice daily

Based on variations of standard first- and second-line ART regimens suggested among in-country treatment guidelines, substitutions to the above can be made at the investigators' discretion.

5.1.2.2 Product Supply and Accountability

Supply

Each participant will be provided with ART treatment over the course of his or her participation. Truvada® and efavirenz, if prescribed, will be provided by the study; other medications will be provided by their country of residence through agreements with the Ministry of Health.

Accountability

Staff will maintain records of study drugs distributed according to standard guidelines. At most sites, lot number and the number of pills given to each participant at each visit will be recorded. For Gilead provided study medications, current product labels, Certificates of Analysis, date received, lot number, expiration date, and date used will be maintained within the site regulatory binder for the study. Monthly inventory will be conducted.

6.0 COMMUNITY LEVEL STUDY EVALUATIONS

6.1 Baseline Household Community Level Census

Prior to the start of the study, study team members will meet with local officials and community representatives to discuss the study and plans for the census. Using a map of the boundaries of the selected communities, study staff will systematically cover the entire area within the boundaries to identify and enumerate all households. A head of the household will provide informed consent for the following information to be collected about household members:

- Name
- Relationship to head of household
- Mobile phone number
- Demographic information such as age, gender, occupation and marital status.
- A fingerprint of each household member will be collected with the use of a fingerprint biometric device.
- The household's location relative to the local health center will be mapped using hand-held GPS receivers.

At the time of the census, household members will be consented verbally for participation in the community health campaign and for the census itself. Household members not present at the time of the census will not be excluded from participation in community health campaigns.

6.2 Community Health Campaign (CHC)

6.2.1 Overview

A baseline community health campaign will be conducted in all study communities and will offer A) HIV testing, and B) multi-disease diagnostic, prevention, treatment, and referral services (such as malaria, deworming), tailored to the community. The CHCs will serve two primary purposes. First, the campaigns will allow for community-wide HIV testing and prompt linkage to HIV care – a critical aspect of care delivery for both intervention and control communities. Multi-disease service delivery in the context of a community health fair will encourage broad communication across all demographic groups and encourage HIV testing as a routine part of health care. Second, the campaigns will provide an evaluation framework for multiple study outcomes, including health, economic and education outcomes, such as HIV incidence, community HIV viral load, interval vital status and AIDS assessments for efficient community cohort participants. CHCs will be conducted annually in the intervention communities. CHCs will be conducted at baseline and after 3 and 5 years of follow up in the control communities. Adults who do not attend the campaigns will have follow up "tracking" visits to ascertain HIV status and offer ART start for infected persons.

6.2.2 CHC Procedures

Each community will have a baseline campaign performed within 4 months after the census and performed up to annually. Roving CHC teams assigned to specific study communities will conduct the campaigns. Campaign training will be performed at the start of the SEARCH study, and updated as needed.

6.2.2.1 Community mobilization

The primary goal of community mobilization will be to maximize CHC participation and linkage to care by informing the community of the purpose, dates and locations of the community health campaign days, and of the services that will be available. These activities will include meetings with village leaders throughout each study community, and may include poster and leaflet advertising, radio advertising and enlisting community-based volunteers to describe campaign activities and encourage participation in the CHCs and linkage to care. Community mobilization will incorporate the principles of a study community engagement plan which may include incentives at the CHC, such as a raffle for prizes, supported by the community.

6.2.2.2 CHC Services

The campaign will consist of a series of stations arranged so as to maximize participant privacy and flow through the campaign. Participants will proceed through stations such as those described below, but which could be adapted to the services provided in the individual communities. Examples of other activities that could be included are: vaccines, referral stations for adult male circumcision, women and children health services, tuberculin skin testing, urgent care station, men's health services, and dermatological screening and services.

<u>Welcome Station</u>

At the start of each campaign, participants will review the services offered at the campaign with campaign staff. If participants have not taken part in census activities prior to the campaign, informed verbal consent will be obtained from all adults for themselves and their children to participate in the campaign and to take part in census activities. The verbal consent form will be read to them in the local language, and their fingerprint biometric will be recorded on tablet computers as affirmation of their agreement to participate. Identifying information will be collected from each community member. Identification of participants will be based on the following: name, village of residence, age, gender, and fingerprint biometric. Campaign staff will provide each participant with a campaign results card to record their screening results. Participants will then initiate campaign activities.

<u>Health and Socioeconomic Interview Station</u>

Health and socioeconomic questionnaires will be performed for each participant, in order to collect updated information about health and economic status, including interim births, illnesses, hospitalizations; changes in employment or educational attainment over the past year; and migration patterns and social network. Staff will interview women of child-bearing age regarding any births and deaths of children over the past year.

Pre-test Counselling Station

Prior to undergoing diagnostic testing in the campaign field laboratory, group pre-test counselling will take place to inform and update participants on the diagnostic services offered and answer questions.

Campaign Field Laboratory

Multiple diagnostic services will be offered in the field laboratory. Some will be offered at all campaigns, and others will be recommended but not required, depending on country guidelines and local resources.

a. All participants:
    i. HIV Antibody testing for all participants >9 months (Kenya) or >18 months (Uganda) according to country policy at the baseline CHC. In subsequent years, HIV testing will be optional for persons ≤10 years of age, depending on epidemiology of region:
        1. Initial rapid HIV test
        2. Participants with a negative result will be informed that they are HIV-negative
        3. Participants with an initial positive result will undergo a second rapid HIV test. If the result is positive, participants will be informed of their HIV-positive status.
        4. Participants with discordant rapid test results (first test positive, second test negative) will undergo a third "tie-breaker" HIV test. Participants with a positive "tie-breaker" test will be informed that they are HIV positive. Participants with a negative "tie-breaker" test will be informed that they are HIV-negative.
        5. At follow up years 3 and 5, an additional confirmatory HIV test will be performed for research measurement confirmation of HIV infection and not for clinical management. At follow up year 2, this test will also be performed for a subset of communities in Uganda and Kenya for quality control of the confirmatory assay.
    ii. Dried Blood Spot on filter paper for all HIV-positive participants
    iii. At the baseline CHC, HIV testing (for HIV DNA) on Dried Blood Spots may be performed on either:
        a) <u>all</u> infants ≤9 months (Kenya) or ≤18 months (Uganda) of HIV positive or HIV status unknown mothers; or
        b) on infants of ≤18 months old who test rapid HIV Antibody positive, according to routine country policy.
    iv. *Optional:* Malaria rapid diagnostic test (RDT) for participants with a temperature taken at the CHC of $\geq 38^{o}C$
    v. *Recommended:* Finger-stick blood random plasma glucose measure for all participants ≥13 years and/or HB A1c screening when available
    vi. *Recommended:* Syphilis screening (RPR) for all >15 years

vii. *Recommended:* Blood pressure measurement for all ≥18 years*Optional:* Tuberculosis screening: Communities may be randomized to receive participant TB screening as part of the CHC
viii. *Optional*: Malaria screening: Communities may be randomized to collect filter paper blood spots for genotyping

b. HIV-infected participants:
   i. Point-of-care CD4 cell count testing
   ii. HIV RNA, by fingerprick or phlebotomy
c. Children (<18 years)
   i. *Recommended:* Anthropomorphic Measures: Height and weight
   ii. *Recommended*: Malaria rapid diagnostic test (RDT) for children <10 years old with a recorded temperature ($\geq 38^{o}$C) at the CHC

Post-test Counselling

All adult participants, regardless of test results, will receive standard post-test counselling per country guidelines, including participants newly diagnosed with HIV. For known HIV+ participants already engaged in care, counselling will be adapted to meet their needs. Child participants will receive post-test counselling with a parent or guardian. On-site malaria treatment will be available at this station as well. All malaria RDT positive participants will be offered on-site malaria treatment, according to Ugandan or Kenyan standard of care for non-severe malaria. Cases of severe malaria will be offered transportation the nearest in-patient health center for hospital-based treatment.

Linkage Station

Post-test counsellors will direct any participants with a positive screening test (i.e. HIV, hypertension, diabetes, etc.) to the referral station in order to meet disease-specific clinical staff and to schedule intake appointments for the appropriate clinic(s). Campaign staff at the referral station will focus on three aspects of linkage-to-care:

a. Patient education: All participants will receive information regarding early treatment and the benefits and importance of linking to disease-specific care after diagnosis.
b. Patient Navigation: A clinician will meet with each participant not already in care in order to introduce him or herself and answer questions regarding the referral clinic. Following this introduction, a study assistant will schedule an intake appointment, or arrange immediate linkage to the clinic if available and the participant agrees. Participants who tested HIV-negative at their prior CHC or home-based testing who are newly diagnosed with HIV may be provided with specialized counseling, including targeted information on the benefits of linking to care and addressing participants' specific fears. Participants may also be offered immediate counseling from study clinic leadership by mobile phone.
c. Structural barrier to Linkage: Transportation costs to clinics represent a major barrier to linkage to care in this study population. HIV-infected participants will

receive transportation vouchers redeemable for transportation expenses *after linking to care* for their first visit at baseline in all communities and subsequently in intervention communities. SEARCH linkage vouchers will be collected by a research assistant at the clinic to which the participant is referred at the time of linkage to HIV-specific care. HIV-infected participants may also receive a one-month supply of TMP/SMX. Some patients may also be started on ART at the CHC if agreements have been arranged with the local clinic for assurance of continued care. For HIV, hypertension and diabetes, linkage may include tracking of participants who did not link to care.

Distribution Station/Campaign Exit

In the final step of each CHC, participants will have their fingernails marked with permanent ("voting") ink, to prevent persons from repeating campaign activities during a CHC period, and receive several additional services:

a. All children ≥12 months and ≤5 years of age will be provided with Mebendazole (one 500 mg tablet).
b. All children ≥ 6 months and ≤5 years of age will be provided with Vitamin A supplementation (one 200,000 IU capsule)
c. Distribution of male condoms

Documenting Participation

Upon completion of every campaign, each community's baseline census enumeration will be compared to the list of campaign attendees using all identifying information collected at the Welcome Station (including electronic fingerprint). After each CHC, all community members (defined by enumeration in the baseline census and including HIV-infected and uninfected residents) who did not attend the CHC will be tracked and evaluated.

6.2.2.3 CHC Procedures Intervention Arm

Participants in all communities who are newly diagnosed with HIV will be encouraged to visit their local health center for care. Participants in intervention communities who do not meet country guidelines to start ART will be asked to visit the study supported ART providing health center for their community, where they will be introduced and consented to the ART Intervention study. Participants will receive transportation vouchers, which can be redeemed at the health center. The value of the transportation voucher will depend on the distance from the participant's home to the clinic. Patients may be started at ART at the CHC at the discretion of the local health care center.

6.2.3 Targeted/Supplemental HIV Testing

Existing testing services in intervention communities will be assessed at baseline, and SEARCH will partner with these services to ensure linkage to the streamlined care delivery system,

including ART at all CD4 counts for individuals diagnosed in these locations. In addition we will use HIV prevalence and incidence data from CHC testing campaigns and national HIV information to identify important most at risk populations (MaRPs) for supplemental HIV testing at time periods in between community health campaigns. Supplemental HIV testing for MaRPs will be tailored to the needs of the individual MaRP population and may include the following strategies:

- Chain referral contact (sometimes called snowball or respondent driven sampling) to access hard to reach populations. In chain referral contact "seed" members of MaRP populations are used to recruit their contacts that are also members of the MaRP risk group for supplemental HIV testing and those tested persons are then asked to recruit their MaRP contacts in a similar fashion. Each successive recruit is asked to participate in recruiting his or her MaRP contacts for testing. Numbered invitation cards and incentives may be used to enhance recruitment and testing uptake.
- Private location or home-based testing will be utilized where MaRP populations have issues of confidentiality and public stigma.
- Venue based recruiting (such as brothels or bars) will be employed where appropriate to identify MaRPs for referral to supplemental testing at an offsite private location/home or to clinic-based or community HIV testing services.
- For MaRP populations with elevated HIV incidence we may employ rapid HIV testing technologies that are able to identify individuals with acute HIV infection prior to HIV antibody responses by testing for the presence of HIV p24 antigen.
- Engagement of the leadership of social or business organizations with significant MaRP membership may be used to provide access to opportunities for recruitment for supplemental HIV testing for the organizations' members. Recruitment may take the form of personal or group invitations at meetings, numbered invitation cards and incentives, or co-location of mobile HIV testing services at group functions as needed.
- Non-cash incentives may be used where appropriate to enhance recruitment and uptake of HIV testing among MaRPs. Appropriateness of type and amount of incentive will be informed through discussions with the study community advisory boards and key informant members of MaRP populations. Incentives may include mobile phone air time cards, transport reimbursement, or a liter of fuel for transport drivers, that does not have a value of more than $5 USD.

6.2.4 Tracking CHC non-participants

<u>Tracking Procedure</u>

Locator information collected during the baseline census enumeration will be used to locate CHC non-participants. The community tracker then records the outcome of the patient after tracking in the community. Data of new household members including immigrants will be captured as well.

<u>Tracking Evaluation</u>: Evaluation will consist of at least the following:

- Vital status with verbal autopsy in the event of a reported death, to capture cause of death (e.g. trauma, illness, suicide, childbirth) whenever possible.
- Field HIV antibody rapid testing according to the testing algorithm (with confirmation and tie-breaker testing) used in the CHC
- CD4 cell count and HIV RNA testing among HIV+ participants
- A health, economic and educational interview, similar to the interview conducted during CHCs.
- Trackers will also evaluate reasons for not coming to the recent CHC, and investigate incentivizes for participation in the subsequent CHC.
- For people who cannot be tracked: reasons for not finding the person (e.g. emigration out of the study community, migration within the study community, or other reasons).
- *Recommended for consideration*: The collection of Dried Blood Spots on filter paper, finger-stick blood glucose measures, syphilis screening (RPR) for all above 15 years, and blood pressure measurement for everyone 18 years and older.

6.3 Mortality and New Births, and HIV and TB Disease Surveillance

To maximize ascertainment of SEARCH study secondary outcomes, we will conduct community-based surveillance for key study outcomes in the one-year period between annual community health campaigns (CHCs).

6.3.1 Mortality and New Births Surveillance

Deaths and births within each study community will be ascertained using a combination of data from the CHC, post-CHC tracking and local death and birth registries. Depending on the location, staff may also work with government sponsored village health teams, village elders or community leaders, or their equivalent to obtain this information.

a) CHC data: During the CHC, research assistants may update each community's baseline census to reflect interim deaths and causes of death (when known) of study community members. Information (including electronic fingerprint and residence information) on all children born to members of the study community will be added to the updated census.
b) Post-CHC Tracking: We will update each community's baseline census based on the birth and mortality data collected during post-CHC tracking (see above).
c) Local Death Registries: Study staff may work with government officials to build capacity to maintain ongoing lists of deaths as they occur in their community, depending on the desires of the village representatives. Study staff will review these local death registries periodically and incorporate the information into the study census for that community.

Immediately prior to each CHC, study staff will produce an updated community census based on all birth and death data collected in the past year. The updated census will represent the target community, including documentation of CHC participation and tracking of CHC non-attendees.

6.3.2 Morbidity/Disease Surveillance, Infant Diagnosis and Care Delivery

Health Center Surveillance: Study staff will regularly collect information available from routine encounters at local health centers and, where needed, hospitals within the community. The following information will be collected but not limited to:

- Visit date and identifying information, including name, age, gender, village of residence, and fingerprint, will be collected on all clinic attendees at the time of clinic visit.
- Diagnosis
- Laboratory results
- Medications
- Hospitalizations
- Mortality

Study staff will also work with implementing partners and health facilities to ascertain HIV status of children born to HIV+ women at the heath facility.

A sample of health provider and patients will be surveyed using standard instruments on a) patient satisfaction, b) provider satisfaction, c) perception of empathy and respect in order to assess qualities of the patient-provider interaction in care delivery.

TB Surveillance: Staff will visit all clinics providing TB therapy at regular intervals throughout the year. The government is the sole supplier of anti-tuberculosis antibiotics in Uganda and Kenya, and therefore TB therapy is only available through government-run or associated clinics and hospitals. All TB clinic dispensaries keep government registries with diagnostic and treatment-related outcomes for every case, including name, age, HIV status and residence information. Staff will enumerate all clinics providing TB therapy at baseline. At the start of the SEARCH study and during regular visits to TB clinics, staff will collect the following information, as available:

- Overall interval number of TB cases reported to the clinic, with name, age, residence, and acid-fast bacilli (AFB) smear results
- TB treatment: Data on treatment status of each case at initiation of anti-TB therapy (new TB cases, retreatment TB, and TB treatment defaulters)
- TB treatment completion and failure rates.
- All-cause TB case fatality rates: the proportion of TB patients who died on TB treatment each year, excluding those cases that left the community during treatment.

6.4 Feedback of CHC Process and Clinical Data

The CHC implementation team for each community will be provided with data on CHC operations, including linkage to care, determine what, if any, alterations will need to be made to outreach, testing, tracking and surveillance procedures to make them more effective. In addition, the study team will evaluate how the intervention is affecting the community: describe

attitudes, beliefs and social norms surrounding HIV testing, disclosure, and ART; and describe experiences of HIV stigma and disclosure, experiences with engagement in HIV care and ART, and sexual behavior, among HIV-positive individuals. These modifications will be incorporated into subsequent campaigns in an ongoing effort to improve community trial efforts throughout the five-year study period. This will allow the CHC procedures in each community to evolve in response to data. Individual plasma HIV-1 RNA levels measured at the CHC as part of this research study will be provided to clinics for subjects on ART.

7.0 CLINCAL AND LAB EVALUATIONS IN ART INTERVENTION ARM

7.1 Recruitment

At the time of first awareness of HIV infection, either during a community health campaign or any other location, participants in intervention communities will be asked to visit the study supported ART providing health center in their community, where they will be introduced to the study. All patients who do not meet in-country treatment guidelines for ART will be offered to be screened for the study. The remainder of this section refers only to patients who will receive ART from the SEARCH study because they do not meet ART guidelines.

7.2 Selection of Participants in Intervention Arm

7.2.1 Inclusion Criteria

7.2.1.1 HIV-1 infection diagnosed by a rapid HIV test or any licensed ELISA test kit. For patients diagnosed in a setting other than study-conducted community health campaigns, HIV status will be re-verified at the time of study screening.

7.2.1.2 Most recent CD4+ cell count > 350 cells/uL, performed within the past 6 months.

7.2.1.3 Willing to initiate ART.

7.2.1.4 Ability to swallow oral medications.

7.2.1.5 Ability and willingness of participant to give informed written consent.

7.2.2 Exclusion Criteria

7.2.2.1 Currently taking ART.

7.2.2.2 Allergy or sensitivity to prescribed ART.

7.2.2.3 Active World Health Organization (WHO) HIV stage III or IV disease.

7.2.2.4 Any other clinical condition that, in the opinion of the site investigator, would make the participant unsuitable for the study, unable to comply with dosing requirements or qualify the participant for ART initiation according to in-country treatment guidelines.

7.3 Informed Consent and Enrollment

Written informed consent to participate in the study will be obtained from all participants. Consent forms will be translated from the original English to the language(s) spoken in the community. The consent form will be read to participants in their local language.

After consent, participants will undergo screening procedures to determine eligibility by clinical evaluation and laboratory testing. Once eligibility is verified, participants will undergo baseline procedures and to receive ART medications. Screening and baseline procedures may be done

on the same day. Patients may be re-screened for participation according to patient-provider discussions.

7.4 Schedule of Evaluations

Table 5: Schedule of Evaluations

Procedure or Evaluation	Screen	Baseline	Study Week						
			4	12	24	36	48	Every 12 weeks	144
Demographic information	X						X		X
Medical history	X								
Targeted physical exam		X							
Tuberculosis screen		X	X	X	X	X	X	X	X
Vital signs		X							
Symptom screen		X	X	X	X	X	X	X	X
Dispense medications		X	X	X	X	X	X	X	X
Adherence assessment			X	X	X	X	X	X	X
Documentation of HIV infection	X								
Pregnancy		X			X		X	X[1]	X
Hemoglobin		X					X		X
Liver function tests[2]		X[6]			X				
Creatinine		X			X		X[6]	X[3]	X
Glucose		X					X		X
CD4 count	X[4]								
Plasma HIV-1 RNA[5]		X[4]			X		X[5]	X[5]	X[5]
HIV seroconversion questionnaire			X[7]						

[1] Repeat every 24 weeks between Week 48 and Week 144.
[2] ALT at timepoints shown above. AST, total and direct bilirubin, alkaline phosphatase as indicated.
[3] Repeat at Week 96 only.
[4] Only if not available within the past 6 months. CHC viral load collection fulfils this criteria.
[5] Viral loads will be measured annually. Samples collected ruing annual CHC attendance, home-based testing during tracking or clinic visits will qualify for this viral load measurement.
[6] As clinically indicated.
[7] Optional; may be performed any time within the first 6 months of enrolment at the discretion of the clinician.

7.5 Timing of Evaluations

- The baseline visit must be performed within 4 weeks of screening evaluations.
- Weeks 4 through 144 must occur +/- 21 days from the protocol-specified target date.

7.6 Definitions of Evaluations

7.6.1 Demographic information

The following information will be collected: date of birth, sex, clinic ID (if applicable) and place of residence.

7.6.2 Medical history

A medical history will be collected including current health complaints and allergies to medications.

7.6.3 Targeted physical exam

Participants will undergo a physical exam covering the following systems: oropharynx, heart, lungs, skin and abdomen. Cervical cancer screening may be done in clinics where this is part of standard care.

7.6.4 Vital signs

Weight, temperature, pulse and blood pressure (in participants ≥18 years) will be recorded.

7.6.5 Symptom screen

Participants will be asked whether they currently have any active symptoms.

7.6.6 Dispense medications

Study medications will be dispensed to participants in intervention arm. The standard interval for dispensing medications is 12 weeks, but this may be extended at the discretion of the investigator for persons whose travel makes the follow up appointment not possible. It will be the responsibility of the SEARCH staff to maintain and document contact with the patient at the routine 12 week interval.

7.6.7 Adherence assessment

Participants will be asked to perform a 3-day adherence recall.

7.6.8 Documentation of HIV-1 infection

HIV-1 infection determined by previous testing will be documented at the time of study screening.

7.6.9 Pregnancy testing

Women of child-bearing potential will be tested by urine HCG (human chorionic gonadotropin). This testing will be repeated every 24 weeks between Weeks 48 and 144, or sooner if clinical suspicion of pregnancy exists.

7.6.10 Hemoglobin

This will consist of a hemoglobin measurement.

7.6.11 Liver function tests

- ALT will be performed at Baseline, Week 24 and as clinically indicated. AST, total and direct bilirubin, alkaline phosphatase will be performed as clinically indicated.

7.6.12 Creatinine

At Baseline, estimated glomerular filtration rate (eGFR) will be calculated by the Modification of Diet in Renal Disease (MDRD) formula, which is as follows:

$$eGFR = 186 * Serum\ creatinine^{-1.154} * Age^{-0.203} * [1.21\ if\ African] * [0.742\ if\ female]$$

7.6.13 Glucose

Blood glucose will be measured.

7.6.14 Tuberculosis

Tuberculosis screening will be performed according to each clinic's standard of care.

7.6.15 CD4 counts

CD4 counts will be measured at Screen only if a result is not available within the past 6 months.

7.6.16 Plasma HIV-1 RNA

This will consist of a quantitative determination of the HIV-1 plasma RNA level (in copies/mL) at study specified intervals or as clinically indicated.

7.6.17 HIV seroconversion interview

An optional interview to be completed by the study staff within the first 6 months of enrollment which will include questions to newly HIV infected subjects on their sexual partner history, prevention strategies, HIV testing experience and preferences and related issues.

7.6.18 Pharmacokinetic evaluations

In addition to the evaluations described in Table 5, pharmacologic measurements of ART levels may be performed on collected hair samples at one or more visits after Week 0.

7.6.19 Stigma questionnaire

A random subset of community members will be asked to complete a questionnaire related to HIV stigma in their community.

8.0 ART TOXICITY GRADING AND MANAGEMENT FOR INTERVENTION ARM

8.1 Toxicity Screening

At each follow-up study visit, staff will ask participants about any new symptoms. Depending on the results of this screen, staff may refer the participant to a clinician for further evaluation. Laboratory testing will be done according to the Schedule of Evaluations (Section 7.1) and results will be assessed for evidence of laboratory values indicating possible grade 3 or 4 toxicity according to the DAIDS Toxicity Table, December 2004.

8.2 Management of Laboratory Toxicities

8.2.1 Grade 1 or 2 Toxicities

Participants who develop grade 1 or 2 adverse events or toxicities may continue study medications without alteration of dosage. Participants experiencing such events will be managed at the discretion of the site investigator and staff.

8.2.2 Grade 3 Toxicities

Clinicians will evaluate all grade 3 toxicities at the time of awareness. If there is evidence that the adverse event or toxicity is NOT associated with the study drug, dosing may continue. If adverse event/toxicity IS thought to be related to study drug, ART may be withheld or switched at the clinician's discretion. Participants should be re-evaluated every 1-2 weeks if possible and if patient is able to return for follow-up on that schedule, until the adverse event returns to ≤ grade 2 or until stabilized and no longer in need of frequent monitoring, to be determined by the site investigator. ART, if withheld, may be re-introduced anytime at the discretion of the site investigator.

8.2.3 Grade 4 Toxicities

If a symptomatic grade 4 adverse event or toxicity develops, ART should be withheld or switched at the discretion of the site investigator, and the patient should be monitored frequently until the adverse event returns to ≤ grade 2 or until stabilized and no longer in need of frequent monitoring, to be determined by the site investigator.

If an asymptomatic grade 4 adverse event or toxicity develops, ART may be continued or discontinued or switched at the discretion of the site investigator.

8.3 Management of Specific Clinical Syndromes

Patients will be managed according to local standard care general guidelines, including use of the targeted management described below.

8.3.1 Rash

<u>In general</u>:

Patients will be evaluated for the severity, location, and characteristics of any rash. If any concern exists about serious medical conditions that feature a rash, such as Stevens-Johnson syndrome, clinicians will consult with the site investigator to determine the best course of action.

Issues related to EFV:

Any rash while on efavirenz (EFV) should prompt suspicion and evaluation for non-nucleoside reverse transcriptase inhibitor (NNRTI) hypersensitivity rash. This should include clinical evaluation for systemic symptoms (fever, arthralgias, myalgias), and laboratory evaluation for suggestive findings (AST/ALT >2x upper limit of normal, peripheral eosinophilia).

Participants felt to be experiencing an NNRTI hypersensitivity reaction should not be rechallenged with the suspected causal agent.

An isolated rash while taking EFV does not constitute and should not raise concern for NNRTI hypersensitivity.

For any serious rash (e.g., exfoliation, mucosal involvement, target lesions [erythema multiforme] or evidence of Stevens-Johnson syndrome):

Participants should discontinue all ART, and staff will confer with investigators as to proper management. Upon resolution to grade 1 or resolved, rechallenge with EFV ART versus restarting with a different ART can occur at the discretion of site investigator.

Issues related to ABC:

Abacavir (ABC) hypersensitivity is characterized by symptoms of rash (maculopapular or urticarial, but sometimes absent), fever, gastrointestinal symptoms, respiratory symptoms, and malaise. If ABC hypersensitivity is suspected, participants should undergo a clinical and laboratory evaluation. Elevated AST/ALT, CK or creatinine, or decreased lymphocytes, are often present.

Participants felt to be experiencing ABC hypersensitivity reaction should stop ABC immediately. They should not be rechallenged and should instead restart ART with an alternate NRTI.

8.3.2 Nausea and Diarrhea

Nausea and diarrhea are fairly common side effects patients experience during the first few weeks of ART, but usually subside and resolve promptly. Participants can be encouraged to take medicines with food, or to take anti-emetic symptomatic therapy. For diarrhea, unless an infectious cause is suspected, antidiarrheal agents may be used for symptomatic relief.

8.3.3 AST/ALT Elevation

If a participant's AST and/or ALT are elevated >5x the upper limit of normal, including the baseline measurement, they will be referred to a clinician for immediate evaluation. Toxicity management will proceed according to the plan for grade 3 or 4 events.

8.3.4 Creatinine Increase and/or Creatinine Clearance Decrease

If a participant's glomerular filtration rate is found to be <60 mL/minute by the MDRD formula, including the baseline measurement, they will be referred to a clinician for evaluation for the need to switch ART regimen.

8.3.5 Hyperbilirubinemia

For isolated grade 3 or 4 unconjugated hyperbilirubinemia attributed to atazanavir (ATV), the drug should be continued unless associated with jaundice or scleral icterus that presents an intolerable cosmetic concern to the participant. For events that cannot be attributed to ATV or a non-study drug-related cause, clinicians will consult with the site investigator and all study medications will be held pending evaluation of etiology.

8.3.6 Management of Pregnancy

For women who become pregnant, EFV will be continued in accordance with country guidelines. EFV may also be discontinued and replaced with lopinavir/ritonavir (LPV/RTV). EFV can replace LPV/RTV after the first trimester of pregnancy is complete at the discretion of the site investigator.

8.3.7 ART Substitutions

Recommendations for alternative ART regimens are outlined in Table 2.

9.0 ECONOMIC AND EDUCATION EVALUATIONS

9.1 Overview

A longitudinal household survey will be conducted among a random sample of adult participants in order to record information about the socio-economic status of participants and their households. These surveys will provide information needed to assess the effects of the intervention on a number of outcomes related to the economic and educational status of community members.

9.2 Recruitment and Enrollment of Study Participants

9.2.1. Recruitment

Participants will be recruited after the annual community health campaigns. In each of the 32 communities, 100 HIV-positive campaign participants and 100 randomly selected HIV-negative participants will take part in the household survey from both campaign attenders and non-attenders. Selected participants' homes will be visited after the campaign using geographic data collected during the baseline household census. Participants will be asked whether they would be willing to take part in a household socio-economic survey and their identity will be confirmed by name and electronic fingerprint.

9.2.2. Informed Consent and Enrollment

Informed consent for participation in the Household Socio-Economic Survey will be conducted the participant's home shortly after the annual health campaign. Consent will be conducted in the appropriate language with the study candidates; translators will be used if necessary. The informed consent will be available in local languages and will be read aloud to the study candidates. Enrollment will be limited to adult participants in the annual community health campaigns.

9.3 Procedures

9.3.1 Household Survey

Participants will be visited at their homes by trained interviewers and consent will be obtained from those agreeing to take part. Community elders and local chiefs will be informed about the survey prior before interviewers begin visiting households. The interviewers will begin by locating the participant at the location described in the baseline household survey. We will attempt to arrange for respondents to be interviewed by somebody of the same sex. If the participant is not present, one additional re-visit to the household will be conducted at a later time. The household survey questionnaire will have a modular format, with each module covering a different topic. SOPs will be developed to provide further instructions on how the surveys will be administered. Quantitative information will be collected on various topics, such as:

- Demographic characteristics of households, such as age and sex of household members

- Health and education of household members
- Marital characteristics of household members
- Income and employment of household members
- Housing characteristics and asset ownership of households
- Transfers, gifts, and loans to and from the household
- Subjective expectations about future health and income
- Food insecurity
- Consumption and spending patterns
- Health care utilization
- HIV RNA testing (if not done within the past 3 months) and plasma for HIV drug resistance testing will be performed on persons identified as HIV+
- Anthropometric measurements may be collected as performed in the baseline CHC
- CD4 testing (optional)

The household survey will be administered in a private area so that the respondent can answer questions freely. Information about the schooling, employment and income will be collected from a knowledgeable household member in cases where the respondent is not able to provide accurate information. We will also offer tuberculin skin testing to measure latent tuberculosis infection on a population level at sites in Uganda as agreed upon with National TB Control programs. This is will be voluntary test that individuals may choose to opt out. Compensation for time to participate in the HSE survey will be made up to the amount of $10 USD per household and paid directly to the index case identified during the randomization process.9.3.2 Duration of Survey

The household survey will last approximately 2.0 hours, as is standard for comprehensive household surveys that contain multiple modules.

9.3.3 Follow-up Visits

Households that participate in the annual community health campaigns will be revisited least at years 2 and 5, and up to annually, in order to measure changes in socio-economic outcomes. A similar household survey questionnaire will be used during each visit, with additional modules that will record changes in household composition. Reasons for entry and exit of household members will be recorded.

9.3.4 Linkage to Community Health Campaign Data

Information collected in the household socio-economic survey will be linked to the data from the community health campaign by the CHC ID number of the participant who was recruited for the household survey. The linked community health campaign data will provide information on the HIV status of the participant as well as measures of the CD4 cell count and viral load of HIV-positive participants.

10.0 HEALTH CARE COSTING EVALUATIONS

10.1 Overview

We will undertake a micro-costing of the resources needed to carry out the activities contemplated in achieving this project's primary objectives. Activities to be costed include both the community health campaigns, and the provision of ART including pMTCT to both the intervention and control communities. The unit costs of the full range of services provided will be calculated. When combined with incidence data for HIV, as well as all-cause mortality and morbidity, these data will be used to estimate the incremental cost-effectiveness of the intervention.

10.2 Recruitment and Enrollment of Study Participants

As described in section 7.1, either during a community health campaign or upon testing at a health care facility, participants in intervention communities will be asked to visit the ART distributor main facility for their community where they will be introduced and enrolled into the study. The medical care resources required by each enrolled patient will be assessed as follows. A cost analysis will be carried out at each of the participating government health facilities that provides ART to enrolled patients and at that and other facilities that provide non-ART care to study patients for malaria, TB and the chronic diseases that the community campaigns seek to mitigate. We expect to complete the cost analysis at the health facilities providing ART within the study communities.

10.3 Procedures

To assess the costs of the additional activities assessed in this study, we will conduct incremental unit cost analyses using standard micro-costing techniques [29]. Incremental unit cost comparisons will be completed, based on the costs of implementing the community campaigns and the five-year costs of providing ART. This will also include time in motion studies.

10.3.1 Cost Data Teams

Incremental costs of the interventions will be assessed using a uniform cost data collection protocol for gathering expenditure data at each of the study sites. We will work in close consultation with staff at each site to complete this protocol retrospectively over the 5 years of follow-up. Following training and instrument piloting to be conducted prior to study initiation, the data collection effort will carried out by three teams, one in each study area Each team will consist of a medically trained person coupled with a person trained in finance, economics or accounting. They will be supervised by a senior in-country expert who will coordinate and communicate with the SEARCH economics team. We anticipate that the initial visit to each site will require 5 days to complete the cost instruments but that this will drop to 2 – 3 days during the subsequent visits.

10.3.2 Organization of Cost Data

Expenditures will be classified in one of four categories; (i) personnel (including fringe benefits); (ii) recurring supplies and services; (iii) capital and equipment; and (iv) facility space (as appropriate). We will also collect retrospective expenditure data to document program start-up costs. The costs of each program activity will be identified through interviews with administrative, finance and human resources officers, supplemented by direct observation in a limited number of formal time and motion studies. The costing approach will emphasize resources utilized, rather than out-of-pocket costs. For example, where expenditures do not fully reflect the opportunity cost of the resources used (e.g., donations or transfer payments), we will adjust the valuations accordingly. Costs for capital items will be amortized on a straight-line basis over their expected useful life, and assuming no salvage value. Facility space required by the interventions, will be valued at the market rental rate. Following assignment of expenditures to these four broad categories, we will further allocate each expenditure item across three areas, (i) service delivery; (ii) staff training directly related to service delivery; (iii) indirect costs consisting of intervention overhead and administration.

10.3.3 Personnel Costs and the Allocation of Overhead Across Activities

Overhead and administrative costs will be allocated to the programs in proportion to the full-time equivalent staff (FTEs) that study intervention service providers constitute of all service provider FTEs at the study sites [30]. We expect that the preponderance of intervention costs will be personnel time. The appropriate approach to measuring personnel time will depend upon the way services are organized at the study sites. For example, if dedicated staff is hired specifically for these interventions, costs can be obtained directly from compensation data. In the more likely case that service providers have multiple responsibilities, the time dedicated to these interventions can be obtained via interviews supplemented by direct “time and motion” observations, including completion by staff of logs recording major activities, for one week periods approximately six months apart.

10.3.4 Measuring Unit Costs

Outputs (denominator of the unit cost) include the numbers of patients receiving each type of study-supported services. Unit costs are defined as the relevant program costs divided by each of these outputs, respectively. To supplement this information, we will also collect information on patient-level contact hours, to allow us to examine the importance of participant and intervention-level factors related to variation in unit cost. We will also assess the variation in unit costs across the study sites and identify the major determinants of that variation. If possible, we will document changes in unit cost over time as programs potential achieve greater scale and administrative efficiency. These findings are intended to provide program managers with insights into costs structures that may be used to enhance program efficiency. We will calculate the cost per added person receiving ART, NCD and pMTCT interventions, based on other study findings.

10.3.5 Health Care Utilization and Spending by Households

The household survey mentioned in section 9.3.1 will include a section on health care utilization, using short term (1 month) recall for care sought for illness episodes and longer term (6 months)

for inpatient hospital care. These questions will identify the range of health care providers used, the frequency, and family expenditures.

11. STATISTICAL PLAN

11.1 Overview of Study Design

This is a community-level cluster randomized controlled trial, in which 32 communities in three sites in East Africa (two in Uganda and one in Kenya) will be randomized to either an intervention arm, consisting of annual community-health campaigns including voluntary counseling and testing for HIV along with a strategy of HIV antiretroviral therapy for all HIV infected persons regardless of CD4 cell count (Universal ART) coupled with a streamlined ART delivery system, or to a control arm, consisting of baseline community-health campaigns including voluntary counseling and testing for HIV and the current country standard guidelines for the initiation of HIV antiretroviral therapy for HIV infected persons (Standard ART). As the study is testing a community-level strategy, communities – rather than individuals – are the unit of randomization. An individually randomized trial could be used to study the effect of standard ART compared to ART at all CD4 counts on individual outcomes. In contrast, our interest is in the impact of a community-wide universal ART strategy, as compared to a standard ART strategy, on HIV incidence and a range of secondary community level health, economic, and educational outcomes.

Randomization will take place within pair-matched communities. Communities will be matched on site region and major factors influencing HIV transmission dynamics and health care delivery system structure. The primary outcome measure is five year cumulative HIV incidence. This will be measured for each community using an efficient community cohort design, in which a) community members are enumerated using a baseline household based census; b) individuals are serially assessed for HIV status at community health campaigns; and, c) individuals failing to participate in each community health campaign are tracked and receive home-based HIV testing. Community-level cumulative HIV incidence, together with all secondary outcomes for which sufficient data are available, will be evaluated 3 and 5 years after the first community health campaign.

a. <u>Target Population of Communities</u>
   The target population that we wish to generalize the results of this research to are rural and semi-rural African communities with moderate levels of HIV prevalence and incidence and served by health centers within or adjacent to the community. We are targeting communities of approximately 10,000 persons, a size which fosters social familiarity and connectedness, and which are organized as one or two adjacent geopolitical units served by a common health center. Community has in past work been defined as groups of individuals who live next to one another and participate in common practices; depend on one another; make decisions together; identify themselves as part of something larger than the sum of their individual relationships; and commit themselves to the group's well-being [31, 32]. Our target communities for this study represent units of organization that reflect these dimensions of communality.

b. <u>Selection of Countries</u>
   The two countries participating in this study (Uganda and Kenya) were chosen to meet the criterion that HIV incidence could be used as the primary endpoint, and that shared

common features of HIV/TB co-infection, and general levels of maternal and child mortality and economic and educational structure and productivity.

c. Selection of Site Regions

We determined, on the basis of the power analysis, that 32 communities are needed to test the primary study hypothesis (see Section 11.5.5). The study will be conducted within three site regions in two countries, in an effort to balance feasibility and cost concerns with generalizability and protection against potential regional instability. We have chosen two site regions in Uganda – Western Uganda centered on the Mbarara District, Eastern Uganda centered on the Tororo District and in Kenya – Western Kenya centered on southern Nyanza Province. Each of the two Uganda site regions (Western, Eastern) will have 10 study communities each and within Kenya, the Nyanza Province will have 12 study communities. With 10-12 study communities per site, a central study operations center may efficiently serve these widely separated rural study communities.

d. Selection of communities from target population

We identified a subset of 54 candidate communities from the target population based on the following criteria:

i. Inclusion criteria:

1) Most recent census population between 9,000 and 11,000 individuals.
2) Served by a government health center already providing ART or a highly functioning health center at one organizational level below those generally providing ART
3) Community leaders' consent to ethnographic mapping.
4) Accessibility to health center via a maintained transportation route
5) Community location with sufficient distance from other potential study communities to limit contamination of intervention or control conditions (buffer zone).

ii. Exclusion Criteria:

1) Presence of ongoing community-based ART intervention strategies that provide treatment outside of the current in-country treatment guidelines.
2) An urban setting defined as a city with a population of 100,000 or more inhabitants.
3) National government not willing or opposed to support commodities needed for Community Health Campaign, if provided by an outside organization.

e. Rationale for Selection of Study Communities and Use of Matched Pairs

Fifty-four communities were chosen using the systematic selection criteria listed in section 11.1.d. Our study design calls for the creation of 16 matched community pairs within which study randomization will take place. The rationale for matching in this setting is three-fold: 1) matching can increase study power and the precision of effect estimates if communities are matched well on factors closely associated with the study

outcome of interest; 2) we propose to match on more community level drivers of HIV transmission than can be accommodated by the alternative approach of stratified randomization (given the sample size of 32 communities); and, 3) prior experience from HPTN-043 has shown a high community acceptability of the matched pair design and allows for the utilization of validated procedures and community preparedness protocols from Project Accept.

f. Criteria for Community Pair Matching
Communities will be matched based on the following criteria: 1) site region, 2) population density, 3) number of trading centers in the community, 4) major occupational mix category (mixed agricultural, mining, tea plantation, fishing), and 5) migration index (measure of mixture with outside communities). The top 16 pairs of matched communities will be selected.

11.2 Primary Outcome Measurement

The primary outcome measure for this community cluster-randomized trial is community specific 5-year HIV cumulative incidence (CI). The general framework for measuring cumulative incidence is a community cohort of HIV uninfected persons identified at baseline in each community. Community membership will be identified through a community-wide, brief household enumeration done at baseline. HIV status of individuals in the cohort will be assessed at baseline and after 3 and 5 years of follow up through HIV testing at a community health campaign with tracking and home-based HIV testing for individuals failing to participate in the community health campaign. Each of these steps is described in greater detail below.

a. Baseline Household Enumeration
At baseline in each community we will perform a simplified community-wide, brief household enumeration to identify community members. Staff in cooperation with community volunteers will conduct an enumeration of households in the community and GPS coordinates will be recorded. Each household will be approached, and a head of the household will be provided with an explanation of the study. A minimum of 2 repeat visits to the household will be made until contact with a head of the household is made. An enumeration of the members of the household will be conducted with a head of household listing the names, age, sex, relationship to head of household, occupation, length of residence, and general travel history/frequency for each household occupant. Inclusion and exclusion criteria for eligible participants in the community cohort are:

i. Inclusion Criteria:
1) Stable residency of individual in community, defined as present in household for at least 6 months of the calendar year
2) Able and willing to provide verbal informed consent.
3) For legal minors and children-consent of legal parent or guardian.

b. Cohort Participant Identification
To aid in the identification of community participants over time, eligible persons in the household will be approached for consent to participate in the community health

campaign and tracking activities. Information to be collected includes names, alternate contact information such as nearby relatives or mobile phone numbers, and a unique biometric identifier generated electronically from the individual's fingerprint using a portable computer.

c. HIV Testing in Community Health Campaign

HIV testing for community cohort participants will be conducted as follows: Identity confirmation using biometric fingerprint identifier will be conducted for all subjects. For those who have not participated in biometric identification, consent and fingerprint ID will be performed along with collection of tracking information as in the baseline household census. All participants will answer a brief questionnaire regarding prior HIV testing. Rapid HIV testing using a serial HIV testing algorithm will be performed using an initial rapid HIV test. All negative results will be informed of their HIV-negative status. All positive results will be confirmed with a second rapid HIV test. Discordant results (first test positive, second test negative): participants with discordant rapid tests will undergo a third "tie-breaker" HIV rapid test. Participants with a positive "tie-breaker" test will be informed that they are HIV positive. Participants with a negative "tie-breaker" test will informed that they are HIV-negative.

At participating sites, we will obtain from participants with positive rapid HIV antibody test results 1) a rapid CD4+ T-cell count test, 2) dried blood spots, and 3) blood plasma.

d. Definition of HIV Uninfected Community Cohort

Individuals who are 15 years of age or older, have HIV tested HIV seronegative and are eligible per inclusion criteria (stable residency and informed consent) will be considered to be part of the HIV Uninfected Community Cohort. Persons who subsequently migrate into the community following the baseline enumeration will have data collected but not be considered as part of the Community Cohort for purposes of measurement of community specific HIV cumulative incidence (although data on these individuals will still be collected and can be used in secondary analyses). Participants with evidence of HIV care (as recorded on Ministry of Health records) prior to the date of the baseline CHC will be excluded from the incidence cohort. In order to ensure non-differential application of this exclusion criteria, enumeration data from all SEARCH participants (including name, sex, age, and parish/sub-county) will be matched to existing data from all primary SEARCH clinics (Uganda) and the FACES OpenMRS system (Kenya).

e. Tracking and HIV Testing for CHC Non-Participants

Biometric identifiers will be used to identify those community members enumerated during the baseline census who fail to attend the baseline CHC. These individuals will be tracked by the community tracker using locator information collected during the baseline census enumeration

When located, if alive an HIV antibody rapid test will be performed, and if positive the individual will be referred to care in accordance with treatment arm. At following subsequent CHCs, the identical procedures will be performed among all enumerated community members who fail to attend the CHC.

11.3 Randomization of Community Pairs

11.3.1 Randomization Strategy

We will utilize an established randomization strategy that is 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 [33]. Community randomization is conceptualized as an ongoing part of the community preparedness process in partnership with the community leaders and community individuals. An example of this strategy is described below:

To explain the concept of a randomized controlled trial (RCT) to community groups such as Community Advisory Board (CAB) members, we may use a supplementary feeding analogy that the communities are already familiar with, likening randomizing each matched pair of communities to a set of twins from one family who end up attending two different schools, only one of which offers an indigenous energy drink during the morning break to supplement the child's lunch box from home. To explain the random allocation of communities, we will also use local language idioms that would resonate with traditional leaders, such as words meaning 'by chance', 'luck of the draw', and 'lottery'.

For the random assignment within matched pairs of each site's communities to intervention or control status we 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. For each study site area, the computer will randomly designate 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 (see sample randomization scheme in Table 5.)

Table 6: Sample Study Site Community Pair Lottery Randomization Scheme

Matched Pair #	**Community Names**	**Picked-Up at Public Lottery**	
		Picked-Up	**Not Picked-Up**
1	Atiri Mukuju	Intervention	Control
2	Malaba Koitangiro	Control	Intervention
3	Paya Nawire	Control	Intervention
4	Mulanda Mwello	Control	Intervention
5	Nabuyoga Pawanga	Intervention	Control

The lottery could be a public event with members of the CAB and local leadership present along with guests from other community-based organizations and the general public to witness the lottery conducted by local chiefs or leaders.

The lottery could be conducted in a series of draws, one for each of the matched pairs of

communities by their local chiefs or community leaders. For each drawing, the two community 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 would be responsible for holding and shaking the selection box. The selected chief or leader will then draw 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., community health campaigns and ART initiation regardless of CD4 cell count), then the host country Principal Investigator (PI) would announce the drawn community as an intervention community. If the protocol called for the "picked-up" community to be the control (i.e., community health campaigns and standard ART initiation), then the host-country PI would announce it as a comparison community. This process would assure equal chance of being randomized to the intervention or comparison arm, and eliminates any residual fears of bias or rigging.

11.4 Primary Analyses

11.4.1 Overview of Analyses for HIV Incidence Outcomes

Estimation of the impact of the intervention on five year cumulative incidence will be based on a two stage analysis. In the first stage, we will estimate cumulative incidence of HIV for each community. The community level cumulative incidence will then be compared between treatment and control arms, adjusting for a measure of population HIV RNA or baseline prevalence, with the adjustment variable chosen using a pre-specified algorithm, and accounting for the pair matched design.

In our primary analysis death will be treated as a right censoring event. In the estimation of the community specific five year cumulative incidence we will adjust in the first stage to allow for potentially informative incomplete tracking success and right censoring.

11.4.2 Data Structure

a. <u>Baseline Community-Level Data</u>
   For each community in the sample, baseline variables will be measured by the census (including population size, summaries of demographic data such as age and sex distribution, and occupational mix), and in ethnographic mapping.

b. <u>Longitudinal Individual Data</u>
   For each community in the sample, the J stable members of the community will be enumerated. We define stable as subjects who spent at least 6 months of the previous year in that community. Note that number of stable residents J is itself a community level random variable. We measure individual level data at time of census ($t=0$), including age, sex, occupation, location of residence, and marital status.

In addition, in the intervention arm in each year during the duration of the study ($t=1,\ldots,6$), we measure on each individual an indicator of whether he or she attended the CHC and an indicator of whether he or she was tracked at time t. In the control arm, we collect analogous data at baseline and after 3 and 5 years ($t=1,4,6$). We will aim to track all stable community residents included in the baseline enumeration who do not attend the each CHC and have not already been documented to have died.

For individuals who come to the CHC at time t, we measure HIV status, and individual – specific covariates, the intervention assignment, including changes in any of the baseline enumeration variables (residence, occupation, marital status) and secondary outcomes as specified elsewhere in the protocol. For subjects who are tracked at time t, we ascertain their vital status and if alive measure HIV status and the individual-specific variables measured at the CHC.

c. Observed data

The observed data for a given community consist of baseline community level covariates, and J copies of the individual level data structure above. We observe this community level data structure on 32 pair matched communities, where one community in each pair receives the treatment and one community the control level of the intervention.

11.4.3 Estimation of Community Specific Cumulative Incidence.

a. First Stage Target Parameter

In our primary analysis, we define our HIV negative cohort as those individuals in the baseline enumeration who are alive, stable residents, ≥ 15 years of age, and HIV negative at the first CHC (or at subsequent tracking). As we aim to track and test 100% of CHC non-attendees at baseline, this cohort should be highly representative.

b. Estimation

The outcome of interest, HIV status at follow up years 3 and 5, is not observed for all subjects in our negative cohort due to incomplete CHC attendance with partial tracking of non-attendees, and due to right censoring. In the control arm there is an increased potential for informative missingness due to the longer intervals between serial testing. To address the potential bias from differential measurement of HIV between the study arms, we will use baseline and year three data for estimation of the three year cumulative incidence, and baseline, year three, and year five data for estimation of the five year cumulative incidence in both study arms. By using equivalent data in intervention and control communities, under most plausible scenarios this approach reduces bias and in simulations results in close to nominal confidence interval coverage and type I error control. In secondary analyses we will employ a mixed approach that makes full use of the annual data available in the intervention communities.

In primary analysis we will adjust for potentially informative missingness in both arms to the extent possible given measured individual level covariates using a targeted

maximum likelihood estimator[34]. Controlling for individual level covariates isexpected to reduce bias to the extent that missingness of the outcome is dependent on HIV status due to incomplete tracking success or informative censoring, and conditioning on some larger subset of the observed past removes some of this dependence. Further, adjustment for a larger subset of the past may improve efficiency, to the extent that the observed past is strongly predictive of final status. However, a larger adjustment set also runs the risk of an increased finite sample variance that outweighs any bias gains. Therefore we will also conduct secondary analysis without individual level adjustment for informative missingness.

11.4.4 Estimation of Intervention Effect.

a. Second Stage Target Parameter.
We will evaluate the effect of the intervention on HIV cumulative incidence, defined as the difference in the cumulative incidence of HIV if all communities in the sample had received the intervention versus all communities in the sample had not received the intervention. This definition provides inference for the study communities, treating them as fixed rather than randomly sampled from some hypothetical target population.

b. Accounting for the Matched Design
Under the matched design used in SEARCH, the intervention is randomly allocated within matched pairs of communities, where the matched pairs themselves are generated based on applying an algorithm to a set of candidate communities. The experiment is thus complicated by the fact that the strata (matched pairs) within which the intervention is randomized are a function of the entire sample (in particular, of the baseline community characteristics to which the matching algorithm is applied). As a result, dependence is introduced by the matching process and the observed data on the 32 communities in the sample do not correspond to 32 i.i.d copies of a random variable; nor do they correspond to 16 i.i.d. copies of a random variable. To address this challenge, we propose to apply recent work that investigates this dependence and develops estimators under this design[35].

c. Adjusted Analysis
Randomization of the intervention ensures that an unadjusted estimator will be unbiased for the causal effect of interest. However, imbalances between treatment and control communities may occur by chance, and adjustment for baseline community level covariates, which include aggregates of baseline individual level covariates, can improve efficiency and confidence interval coverage without jeopardizing unbiased estimation[35]. In particular, both baseline prevalence and population HIV RNA levels will be measured on each community at the time of the first CHC and are known to affect incidence, but are not available for matching.The limited number of communities restricts the size of the possible adjustment set, and it is not known *a priori* which baseline covariate will result in the greatest efficiency gain. We will therefore use leave-one-out cross-validation to select one baseline variable for adjustment. Our primary analysis will adjust for this community-level covariate using a targeted maximum likelihood estimator.

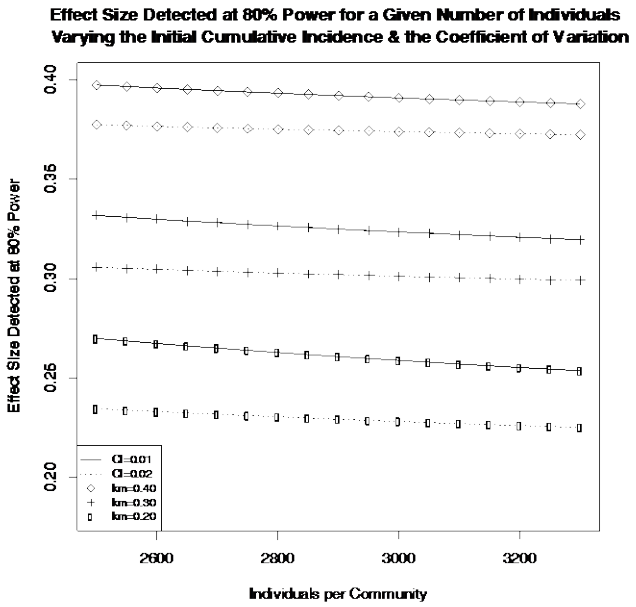
Inference will be based on the estimated influence curve[36]. This approach has been shown in simulations to result in excellent confidence interval coverage and type I error control while resulting in potentially substantial increases in power for testing the null hypothesis of no intervention effect.

d. Unadjusted Analysis
As a secondary analysis, we will obtain an unadjusted estimate as the mean difference in the community level outcomes in the treatment versus the control communities within matched pairs. We will use the standard variance estimator the sample variance of the pairwise differences. A paired t-test with appropriate degrees of freedom will be used to test the null hypothesis of no difference in cumulative incidence between the treatment and control communities.

11.4.4 Power and Sample Size

The trial is being conducted in 20 community pairs in Uganda and 12 community pairs in Kenya, each with a population of approximately 5000 stable adult residents. We assume a baseline HIV prevalence of 10%, HIV status measured at baseline among 80% of residents, and 75% of the approximately 3600 of those HIV negative at baseline with an outcome observed at year 5 (t=6). This yields approximately 2700 residents per community who are HIV negative at baseline and have their HIV status known at year 5 (t=6). We note that the exact number of residents per community will vary; if the actual sample size per community is at least 2700 individuals then the following calculations can be considered conservative. We further note that moderate deviations from this number of individuals are not expected to have a strong effect on power (Figure 1).

Figure 1



We calculated the number of matched pairs of communities needed to provide at least 80% power to detect a 40% reduction in 5 year cumulative incidence of HIV infection in the treatment versus control communities, using a two sided test at a 5% level of significance. We based our sample size calculations on the simple unadjusted effect estimator; this approach should provide a conservative effect estimate given the potential for covariate adjustment to improve precision. Sample size calculations were thus based on the formula in Hayes and Bennet for an unadjusted comparison of proportions in a matched trial [37].

Our sample size calculations assumed a 1% five year cumulative incidence in the control communities. This estimate is conservative based on the available literature, which suggests that HIV transmission rates are approximately 0.5 to 2% [38-40]. For example, assuming a current incidence density of 0.5 cases per 100 person years, and allowing for a 10% decline in transmission rate per year in the absence of the intervention (due to concurrent prevention activities), the incidence density method would suggest a five year cumulative incidence of approximately 2%. Figure 1 shows the effect size we are powered to detect under the less conservative assumption that the control proportion is 2%.

We further assumed a matched pair coefficient of variation (km) of no greater than 0.4. We note that, while ideally external data would be available to inform choice of km, 1) km values depend (among other things) on which covariates are matched on, how close a match is achieved, and the strength of association between these covariates and the outcome, limiting generalizability between studies; and 2) recent work has demonstrated the instability of estimates of km based on empirical data [32]. We note that prior studies performed in similar settings have assumed a km of closer to 0.25 (Project ACCEPT, Mwanza Trial as discussed in Hayes and Moulton 1999 [31]); in the case that this more optimistic km holds we will be powered to detect a smaller (approximately 30%) reduction in cumulative incidence. Figure 1 shows a graph of the percent reduction we will be powered at 80% to detect under a range of deviations from the assumptions above, including variation in the number of individuals per community who are HIV negative at baseline and have known HIV status at year 5 (t=6), a range of five year cumulative incidence values, and a range of kmvalues (for 16 matched pairs, and correcting for the loss of degrees of freedom when using a paired t-test, page 115 [31]).

11.5 Secondary Analyses

11.5.1. Secondary Health Outcomes

a. <u>Overview.</u>

In addition to estimating the impact of the treatment on expected 3 and 5 year cumulative incidence of HIV among adults, we will also estimate the treatment effect at 3 and 5 years follow up for the set of secondary outcomes detailed in section 2.2 for which data are available. Key secondary outcomes include: vertical transmission; adult, maternal and pediatric mortality; plasma HIV RNA levels; antiretroviral resistance; AIDS; tuberculosis and opportunistic infections; and, linkage, time to ART initiation, retention in care for HIV-infected subjects. Given a community level estimate for each of these

secondary outcomes, statistical analysis to evaluate the intervention's effect on each of these outcomes will follow the general approach described for evaluation of the primary outcome, based on unadjusted and adjusted comparison of treatment and control communities. In the following subsections we outline the data that will be collected to estimate each secondary outcome.

b. Mortality

Deaths and births within each study community will be ascertained using a combination of data from the CHC, post-CHC tracking, local death registries and partnerships between staff and government sponsored village health teams or their equivalent. We will estimate all-cause mortality among adults, children < 1 year of age (infant mortality), children < 5 years of age (pediatric mortality), and women who are pregnant or within 42 days of termination of pregnancy (pregnancy-related mortality).

c. Mother to Child Transmission of HIV

We will evaluate the effect of the intervention on the proportion of live births still alive and HIV uninfected at two years, among all births and among births to HIV-infected mothers. We focus on the outcome among infants two years after birth to capture the interventions effect on transmission prenatally, during birth, and during breastfeeding. Evaluating HIV-free survival among all births, and not only among HIV-infected mothers will allow us to capture the effect of the intervention on vertical transmission rates due to its effect on decreasing the prevalence of HIV infected mothers as well as any effect due to reducing the probability of a mother who is HIV infected transmitting the virus to her baby.

Data from implementing partners on the HIV status of children born to HIV+ women at health facilities will be assessed throughout the study. In addition, estimation of 2 year HIV free survival rates for each community will be performed based on CHCs, combined with tracking of non-attendees. This will provide us with a birth cohort that is representative of the entire community (and not only of those mothers who engage with antenatal care). Specifically, an infant will enter the cohort when his or her mother is seen at the CHC or tracked and the birth reported.

d. Plasma HIV RNA levels, CD4 Cell Count, and Antiretroviral Resistance

Quantitative HIV-1 RNA PCR testing will be used for HIV RNA level metrics, including geometric and arithmetic mean and median HIV RNA level and proportion with HIV RNA level below the limit of detection among all HIV-infected individuals. In addition, HIV RNA will be measured from all HIV+ members of the household socioeconomic survey, providing annual data from both control and intervention communities.

Drug resistance among HIV-infected individuals will be measured by assaying dried blood spots collected during the CHC, HSE and at tracking for the mutations K103N, M184V, and K65R. We will estimate proportion of treatment naive individuals with each

and with any of these three mutations as a marker of transmitted resistance in each community. As markers of acquired resistance, we will also estimate proportion of HIV infected individuals with resistance mutations among those individuals who initiated treatment.

Finally, point of care CD4 cell count testing at the CHC and among tracked subjects will allow us to estimate CD4 cell count recovery rates annually in the intervention arm and will provide population based data after 3 and 5 years of follow up in both arms.

Importantly, the use of the CHC plus tracking will provide us with estimates of each of these metrics among all HIV-infected individuals, regardless of whether they are retained in care. In addition to comparing these community level metrics between treatment and control communities, we will also assess how these outcomes vary as a function of CD4 at antiretroviral initiation, including estimating these metrics in the subpopulation of subjects who initiate therapy at CD4 >350 cells/uL. Supplemental data on HIV+ patients in care will also be obtained from clinic records.

e. Linkage, Retention, and Time to ART Initiation

Use of the CHC combined with tracking of a random sample of non-returnees (irrespective of HIV status), and linkage of resulting data to clinic records will allow us to generate estimates of linkage and retention rates among all HIV infected individuals. Specifically, we will estimate for each community over time the proportion of newly diagnosed HIV infected individuals who successfully link to care (defined as any visit to clinic), as well as the proportion retained in care (defined as at least two visits in the past 12 months). In addition, we will estimate the average time from first HIV diagnosis to ART initiation for each community.

f. Internally Derived HIV Infections

Viral consensus sequences will be used to estimate phylogenetic relationships and genetic distances between HIV viruses sampled during the study. These data, together with additional reference sequences, will be used to classify incident HIV infections among community cohort members as linked or not linked to previously documented infections among community members [41].

Internally derived incident HIV infection will be defined as an incident HIV infection in a study participant classified, based on sequence analysis, as linked to a virus previously measured from a member of the same community. Externally derived incident HIV infection will be defined as infection with a virus classified as unlinked to a previously measured virus in a member of the same community.

The community specific outcome for this secondary analysis will be the probability of becoming infected over the course of the study by an internally derived virus.

g. Additional Health Outcomes

Measurement of AIDS-defining events, TB, and treatment-associated toxicities and adverse events will include passive surveillance systems and secondary data sources, as described in section 6.3.2 and 7.4, with analytic methods used whenever possible to reduce bias in estimates of the underlying population parameters.

Confirmed active TB cases will be identified using existing registries. HIV status of confirmed cases will be based on a) HIV status as recorded in the registry and b) linkage with SEARCH study based on name and demographic information (following an initial feasibility study).

AIDS-defining events among HIV-infected individuals will be measured by obtaining WHO Stage IV diagnoses recorded in clinic. Other information may be obtained from community health campaigns, tracking or hospital records. Note that measurement at the clinic will rely on linkage and retention of HIV infected patient in care. The resulting outcome data will thus be subject to both selection bias and potentially informative interval censoring under a non-monotone missingness pattern (i.e. patient will be seen at clinic intermittently, some not for long intervals, and detection of these outcomes will only be possible when they are seen).

11.5.2 Supplementary Analyses

a. Analysis of Process Outcomes

For each step of the care cascade (testing update, linkage, and retention) we will report basic descriptive statistics, including unadjusted and adjusted associations between individual level characteristics and retention in the cascade.

b. Effect Modification and Mediation

A modification of the two stage approach described for the primary and secondary outcomes above will also be applied to investigate how individual level characteristics modify the effect of the intervention, and the extent to which the intervention effect is mediated by update of specific intervention components. Secondary analyses may also include pooled individual level analyses.

11.5.3 Economic and Education Evaluations

The objective of our analyses will be to determine the causal effect of early ART initiation on several socio-economic and education outcomes. The outcomes will have a different data structure than the health outcomes described above, with annual longitudinal data being obtained for a sample of baseline CHC participants and baseline non-participants and their households. For the entire sample of household socio-economic (HSE) survey participants and for the baseline CHC and non-CHC samples our analysis will assess whether changes in socio-economic outcomes differ between intervention and comparison communities. The analysis will also examine the relationship between socio-economic status and HIV status of respondents.

For the sample of HIV-positive study participants we will analyze changes in socio-economic status as a function of changes in CD4 cell count and viral load. Analyses will be performed using STATA 11.0 statistical software.

Sample Size

A total of 200 participants and their household will be recruited for the HSE in each of the study communities. This will include 100 HIV-infected individuals and their households and 100 HIV-uninfected individuals and their households. The sample will consist of individuals who did and did not participate in the CHC.

Estimation Strategy

The study objectives will be met by comparing changes in the main outcomes between intervention and comparison communities. The following outcome variables will be studied: adults' on- and off-farm employment; children's on- and off-farm employment (child labor); children's time allocation to schooling and household activities; asset holdings (durable good and livestock); agricultural output; cash and in-kind transfers.

For each outcome, a mixed effects regression model will be estimated in order to determine whether there are significant differences between intervention and control communities over time. Standard errors will be clustered at the community level in regressions that include individual- or household-level observations. A limited set of household-level characteristics will be included as covariates in the model. Differences between intervention and control communities will be examined at year 5 and at each of the follow-up periods during which the HSE is conducted in order to identify short- and long-term effects of ART. Analyses will be conducted separately for baseline CHC participants and non-participants. For children's education and labour supply outcomes, the analyses will test for different effects on young and old children due to variation in the ways in which households adjust time allocation of household members. Effects of ART on the labour supply of adults will also be allowed to vary for men and women. In the models that are estimated, trends in the outcome variable that are not due to ART will be identified by including controls for the month during which the HSE was conducted.

11.5.4 Health Care Costing Evaluations

Costs

Costs will be assessed both from the health care system analytic perspective, and from the patient's perspective. During the five-years of cost data collection, costs will be measured using empirical data as described in section 10.3 above. However, because important health effects of ART and the treatment of other chronic disease extends beyond this period, we will model the consequences of early versus later ART initiation using the best available data on disease progression and the health states and associated medical care costs.

Unit Cost Measures

We will calculate several measures of the cost per programmatic goal achieved, from proximate to distal. The proximate measures will be cost per HIV+ person identified, linked to care, and started on ART. The intermediate measure will be cost per ART-month (person on ART for a month). The distal efficiency measures will focus on surrogate biological markers of ART success: cost per CD4 level recovered and viral load suppressed.

Health Status

We will translate observed and projected health events into a standard metric of disease burden, Disability Adjusted Life Years (DALYs). The calculated DALYs occurring will reflect health benefits (e.g., added years of life from ART) estimated from the morbidity and mortality measured during the study, plus future health effects of HIV incidence measured during the trial, using our published methods to project future health burden of HIV adjusted for ART access.

Cost-Effectiveness

Finally we will estimate incremental cost-effectiveness. This is the net added cost per health outcome, e.g., per DALY averted. Both the numerator and the denominator represent the difference between study arms. Thus, the **numerator** will reflect differences in the cost of ART use and in savings from averted disease. (Both arms have a community testing campaign.). The **denominator** will represent the difference in DALYs due to the clinical benefits of ART, HIV infections averted, and any other observed disease effects. The **ratio** is the ICER (incremental cost-effectiveness ratio), in dollars per DALY averted. If the intervention saves money and improves health ("dominant" in cost-effectiveness parlance), no ICER will be calculated (since there is no cost-health tradeoff); results will be expressed as economic savings and health gains.

Sensitivity Analyses

To estimate the impact of uncertainty in inputs, we will conduct extensive one-way and two-way sensitivity analyses. We will also using Monte Carlo multi-variable simulations to estimate the confidence intervals associated with the base-case incremental cost-effectiveness ratios.

12. DATA COLLECTION AND MONITORING

12.1 Data and Safety Monitoring Plan

The SEARCH project will employ a multi-tiered approach to monitoring the progress of the trial for ethics, safety, efficacy, and futility. Monitoring will take place at the levels of the community, the host country, and study-wide through defined groups and processes (see Table 6).

Table 7: SEARCH Trial Monitoring Information Sources and Responsibilities

Information Tier	Organization Unit	Responsibilities
Community	Community Advisory Boards (CAB)	Experiences and concerns of community members of the study communities and agencies.
Host Country	Local Advisory Boards (LAB)	Ethical and policy issues and developments potentially impacting the conduct and rationale of the trial within the host country.
Science & Ethics	Scientific Advisory Board (SAB)	Scientific and ethical issues and potentially impacting the conduct and rationale of the trial.
Study Data	Data Safety Monitoring Board (DSMB)	Study progress including incidence of significant adverse events, interim efficacy and futility analyses, and issues from community and scientific advisory boards.

Information on the conduct and acceptance of the study will be obtained at the community level through the local Community Advisory Boards who are charged with representing the experiences and concerns of community members of the study communities. Issues and concerns about the conduct and impact of the trial on the community will be communicated in writing from local CAB to study investigators and presented in summaries to the study Data Safety Monitoring Board (DSMB). Likewise, scientific and policy issues and developments potentially impacting the conduct and rationale of the trial at the host country level will be assessed by the study-wide and host-country site Scientific Advisory Boards and communicated in writing to study investigators and presented in summaries to the study DSMB. Finally, study progress including incidence of significant adverse events and interim analyses will be presented to the study DSMB and study statisticians in written form and in person at annual or ad-hoc DSMB meetings.

12.1.1 Data and Safety Monitoring Board

Pursuant to the NIH policy for Data and Safety Monitoring: a Data Safety and Monitoring Board will be convened to provide oversight of the SEARCH trial. The role of the DSMB will be to review implementation and progress of the trial and to review the accumulating data from the study to detect early, significant benefit or harm for communities and persons while the trial is in progress. The DMSB will consist of three main categories of Members: 1) Voting members, 2) Advisors, and 3) Observers. *Voting* Members will consist of 5 individuals, including a Chair, who will be nominated by the protocol Principal Investigators and approved by the Executive Steering Committee for the study. At least one of the voting members will be a national of the host site countries. Voting Members are appointed for the duration of the study and participate in all closed-session meetings and votes. The voting membership will possess expertise in medicine, epidemiology/trials, statistics, and ethics/participant advocacy***.** *Advisor* members will consist of 3-5 individuals nominated by Voting Members who provide & exchange knowledge, context and advice, and are approved by the Executive Steering Committee for the study. Advisors do not participate in DSMB voting activities. Observer members are board members that support operations and functions of the DSMB and its participant members but do not directly participate in discussions as representatives of areas of expertise or outside agencies. The DSMB will convene to review study progress and safety and may be called into ad hoc sessions as the Board sees fit or at the request of the study Principal Investigator. At the meeting, the study Statistician and Principal Investigator will present summaries of issues and concerns from the local and study-wide advisory boards and the trial progress and safety and efficacy data, including the results of any planned interim analyses, to the DSMB for consideration. Following its meetings, the DSMB will act in an advisory capacity to the investigators to monitor study participant safety and data quality and evaluate progress of the study and present its recommendations in writing to NIH, study sponsors and the study Principal Investigator.

12.1.2 Interim Reports and Study Stopping Guidelines

Early in the first year the DSMB shall meet to review the DSMB Charter and its guiding principles and to familiarize itself with the study protocol, the primary statistical analysis plan, and the trial safety stopping rules. The first DSMB data review will occur after all 32 communities have completed their first community health campaign and subsequent tracking and a period of 60 days has elapsed to allow for referral patient linkage-to-care. Over the course of the trial one scheduled interim analysis will be performed when all 32 communities have completed collecting 3 years of incidence data. Interim analysis of HIV incidence and of all secondary outcomes for which data are available will be completed as described in the statistical plan (Section 11). At the time of the interim analysis a meeting of the DSMB will be convened and the study team will present information on study progress and the results of interim analyses. Should event triggers such as an unanticipated serious adverse event, series of unanticipated adverse events, or significant developments in the field indicate to the DSMB Chair and the Principal Investigator that the DSMB should meet, an ad hoc review will be scheduled as soon as possible.

DSMB reports will contain information on community and advisory board issues and concerns and on study progress and data quality (including community health campaign testing, ART

initiation and distribution) and safety data (serious adverse events and deaths). For stopping guidelines, the protocol team recommends that an exceptional difference (in either direction) in deaths between the study arms could justify early termination of the study. For the purposes of this study, an exceptional difference in death rates among HIV infected persons with a risk ratio of 3 or greater that is statistically significant according to Peto-Haybittle criteria. The protocol team does not recommend stopping the trial for early indications of intervention efficacy without full consideration of the treatment and policy landscape. . A rationale for continuation in the setting of early significant evidence of efficacy is the value in evaluating the magnitude and durability of the intervention over the full study period. Another rationale is the need for complete data on the economic impact of the intervention (work productivity, reduced health care expenditures for serious HIV illnesses) and the beneficial effect on the other health conditions and children's education. On the other hand, the benefits to continuing the study in its current form may be outweighed by the benefits (to control communities, policy makers, the larger region, or the global community) of the making study results public or modifying the study design at year three. Because the scientific, treatment and policy landscape is evolving rapidly, the protocol team feels that the DSMB will be better positioned to weigh these tradeoffs immediately prior to disclosure of the interim analysis. Prior to any presentation of pre-specified study analyses, the DSMB will meet and consider the full scientific, treatment, and policy landscape at the time of the interim analysis. In consultation with advisors, the DSMB will then issue a formal recommendation regarding criteria for stopping, modifying, or un-blinding the study based on results of the interim analysis. On balance the protocol team believes continuing to evaluate the full effect of the intervention could be ethical and warranted, but the understanding that the board should consider all important contexts in its recommendations.

12.2 Baseline Household Community Level Census

Household Census data will be collected by teams using hand-held computers (tablets). Prior to conducting the census, the census questionnaire will be programmed into the hand-held computers. Programming will include range checks, structure checks and internal consistency checks. Before leaving the household, the completed questionnaire will be checked for mistakes and completeness, ensuring each household has a unique identifier. Data from these devices will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

Each household location will be mapped using a hand-held GPS receiver. Readings will be taken from the door of the household, if possible, or from a point that is most representative of the household. The GPS coordinates for each household will also be recorded in the tablet computer at the time of administering the census questionnaire. GPS data will be synchronized from the GPS to a Microsoft Access database daily and then transferred via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

A digital biometric identifier based on an electronic fingerprint of each household member will be captured in an electronic database on the hand-held computer and linked to the household member name. A portable fingerprint reader will be connected to the tablet computer via a USB port and the biometric identifier will be saved into the electronic database on the tablet. The

database will be transferred daily via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.3 Community Health Campaign

12.3.1 Welcome Station

The first stop for participants during most Community Health Campaign will be the Welcome Station. There will be an electronic database of all the biometric identifiers collected during the Census Survey available at the Welcome Station. Staff members will verify participant's fingerprint biometric identifier against the database to ensure they have a biometric identifier in the system. If a participant did not have a biometric identifier taken during the Census Survey, a biometric identifier based on his or her digital fingerprint will be taken at the Welcome Station and added to the database. Once the participant's biometric identifier is verified, the participant will be given a bracelet with a unique identifier on it. The unique identifier will be added to the biometric identifier database and linked to the participant's biometric identifier. The participant will then be tracked through the Community Health Campaign with the unique identifier on the bracelet.

12.3.2 Health and Socioeconomic Interview Station

During most campaigns, health and socio-economic data will be collected by trained staff members electronically using tablet computers. Prior to conducting the Health and Socioeconomic Interview, the interview will be programmed into the tablet computers. Programming will include range checks, structure checks and internal consistency checks. The unique identifier on the participant's bracelet will be used to link the participant to their interview data. Data from the tablet computers will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

12.3.3 Other CHC Stations

During the campaign, all information recorded at each of the stations will be recorded in Log Books by staff members. The unique identifier on the participant's bracelet will be used to link the participant to their data in the Log Books. Afterwards, the Log Books will be entered directly into an electronic database. Data Integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. All data will be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.3.4 Tracking CHC Non-Participants

Apart from the verbal autopsy questionnaire, data collected during evaluation of non-participants will be collected using hand-held computers (tablets). Prior to conducting the evaluation, the questionnaire will be programmed into the hand-held computers. Programming will include range checks, structure checks and internal consistency checks. Data from these devices will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

12.3.5 Morbidity/Disease Surveillance

Study staff will regularly collect information available from routine encounters at local health centers and, where needed, hospitals within the community. This information will be available in the clinic's standard visit forms and recorded by staff for data entry.

Afterwards, the surveillance forms will be entered directly into an electronic database. Data Integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. All data will be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.4 ART Intervention

All data will be obtained from encounter forms at local health centers and recorded onto standardized case record forms by study staff. Afterwards, the forms will be entered directly into an electronic database. Data Integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. All data will be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

12.5 Grade 3 and 4 Adverse Event and Serious Adverse Event Monitoring

Grade 3 and 4 adverse events (AEs) and serious adverse events (SAEs) will be monitored in all sentinel cohorts. We will utilize the DAIDS Toxicity Table for Adults and Children grading scale (Appendix A) for reported symptoms and laboratory monitoring. The sentinel cohorts will be composed of persons in the intervention arm with CD4 >350 cells. These individuals will be matched on CD4 to individuals not receiving ART and evaluated semi-annually through chart review supplemented by tracking visits.

The following definitions for serious or unexpected adverse events will be followed:

A Serious Adverse Event (SAE) is any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event occurring in a gene therapy study
- Event that changes the risk/benefit ratio of the study.

An Unexpected Adverse Event is defined as being unexpected if the event exceeds the nature, severity, or frequency described in the protocol, consent form and investigator brochure (when applicable). An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the study protocol

Adverse events in sentinel sites will be reported to individual IRBs according to the table below:

Table 8: Adverse Events

Institution	Type of Adverse Events	When to Report
UCSF-CHR	• External [off-site] adverse event that UCSF PI determines changes the study risks or benefits, OR necessitates modification to the CHR-approved consent document(s) and/or the CHR-approved application/protocol	• Within 10-working days of PI's awareness
SOMREC	• All Serious or Unexpected events irrespective of relationship	• Fatal or life-threatening events within 3 working days of awareness • All other SAEs within 7 calendar days
NDA	• All serious and Unexpected events irrespective of relationship	• Within 7-calendar days of awareness
KEMRI SERU	• All Serious or Unexpected events irrespective of relationship	• Study-related events within 24 hours of awareness • Unrelated events within 10 working days of awareness
Gilead Sciences	• Definitely, Probably, or Possibly related to Gilead-supplied Truvada **AND** Serious or Unexpected	• Within 15-calendar days of awareness

12.6 Household Socio-Economic Survey

Household Socio-Economic Survey data will be collected by teams using hand-held computers (tablets). Prior to conducting the survey, the questionnaire will be programmed into the hand-held computers. Programming will include range checks, structure checks and internal consistency checks. Before leaving the household, the completed questionnaire will be checked for mistakes and completeness, ensuring each household has a unique identifier. Data from these devices will be transferred daily via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

12.7 Health Care Costing Evaluations

Each health facility will be identified using a code. Health facility time in motion data will be recorded on paper and transferred to a database by study staff. Cost data will be collected in Microsoft Excel and imported to a database (Microsoft Access or FileMaker) for storage and manipulation. Although there is no confidential patient information in the cost data, it will be integrated with standard secure methods used for other data in the study. The data files will be regularly backed up on secure servers

12.8 Data Security and Integrity

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 GPS devices.
- 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 on a daily basis.
- 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.
- All Log Books and CRF's will be locked in a secure room each night.

13. HUMAN SUBJECTS

13.1 Ethical Considerations

13.1.1 ART Intervention

In this study, ART will be initiated at CD4+ thresholds higher than the national guidelines defining standard of care. We must therefore consider the potential benefits and risks of ART at higher CD4 counts to ensure that the key intervention of this study (ART initiation) meets the strictest ethical guidelines. We submit that initiation of ART at all CD4 thresholds meets and exceeds ethical standards by several criteria:

1) ART is routinely initiated in all HIV-positive patients throughout many countries.

2) ART initiation for all CD4 thresholds is now recommended by many professional HIV medicine societies. For example, ARTs are now formally recommended by the United States Department of Health and Human Services for all patients.

3) Accumulating evidence indicates that there may be substantial clinical benefit to initiating ART as soon as a person is HIV infected. This benefit may accrue from reductions in immune activation and systemic inflammation, as well as limitation of the size of the latent reservoir of HIV. These pathophysiologic discoveries have been partially responsible for the changes in clinical practice guidelines detailed above.

4) The additional amount of time a patient will take ART if initiated at any CD4 threshold vs. country-specific guidelines is relatively small. Accumulated data on the speed of HIV progression (i.e., the time taken for CD4 to decline to 350 cells/uL from the time of infection) indicates that this may take, on average, 2-3 years in most patients. This time is even shorter for countries when policies change to starting at a threshold below 500 cells/uL. This study, therefore, will bridge this length of treatment administration, after which point participants will be allowed to continue ART provided by the local government's country-specific guidelines.

13.2 Institutional Review Board (IRB) and Informed Consent

13.2.1 Obtaining Consent

This protocol, all procedures and consent forms, and any subsequent modifications must 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 Uganda National Drug Authority (NDA), and the Kenya Medical Research Institute (KEMRI) Scientific and Ethics Review Unit.

The Kenya Pharmacy and Poisons Board (PPB) will be notified of any modifications to the protocol and consent forms as well.

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 or their parents 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 or their parents/guardians 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.

Verbal consent will be obtained from adults to participate in the Baseline Household Community Level Census and, for those not available during the Census, at the initial Community Health Campaign. Consent will obtained for adults and their children, by reading the approved consent script and documenting agreement by recording their fingerprint biometric on portable, password-protected computers. Verbal consent will also be obtained for adults participating in the Targeted HIV Testing/Key Population Testing procedures. Written consent will be obtained from adults to participate in the Household Socio-Economic Survey, focus groups, in-depth qualitative interviews and surveys on stigma and new infections, and for the ART Intervention activities. In addition, children 13 years or older will provide consent to participate in ART Intervention, with parental co-signature; written assent will be obtained from children 8 to 12 years old, with parental co-signature; and parental written consent will be obtained for children less than 8 years old. In addition, a letter of commitment will be obtained from community leaders for their site's participation in the study. Consent to take photographs or film adults and their children during Community Health Campaign activities, and for de-identified photographs for dermatologic evaluations, will also be obtained from participants. See Appendix B for further details.

14. PUBLICATION OF RESEARCH FINDINGS

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 NIAID, UCSF, UNCST, KEMRI and Makerere University guidelines.

REFERENCES

1. UNAIDS Report on the global AIDS epidemic 2010. 2010, UNAIDS.

2. Hogan, M.C., et al., Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet, 2010. 375(9726): p. 1609-23.

3. Beegle, K., J. De Weerdt, and S. Dercon, The intergenerational impact of the African orphans crisis: a cohort study from an HIV/AIDS affected area. Int J Epidemiol, 2009. 38(2): p. 561-8.

4. Kublin, J.G., et al., Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet, 2005. 365(9455): p. 233-40.

5. Havlir, D.V., et al., Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. Jama, 2008. 300(4): p. 423-30.

6. Lawn, S.D. and A.D. Harries, Reducing tuberculosis-associated early mortality in antiretroviral treatment programmes in sub-Saharan Africa. Aids, 2011. 25(12): p. 1554-5; author reply 1556.

7. Cohen, M.S., et al., Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med, 2011. 365(6): p. 493-505.

8. Granich, R.M., et al., Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet, 2009. 373(9657): p. 48-57.

9. Wagner, B. and S. Blower, Costs of eliminating HIV in South Africa have been underestimated. Lancet, 2010. 376(9745): p. 953-4.

10. Wagner, B.G., J.S. Kahn, and S. Blower, Should we try to eliminate HIV epidemics by using a 'Test and Treat' strategy? Aids, 2010. 24(5): p. 775-6.

11. Dieffenbach, C.W. and A.S. Fauci, Thirty years of HIV and AIDS: future challenges and opportunities. Ann Intern Med, 2011. 154(11): p. 766-71.

12. Weber, J., R. Tatoud, and S. Fidler, Postexposure prophylaxis, preexposure prophylaxis or universal test and treat: the strategic use of antiretroviral drugs to prevent HIV acquisition and transmission. Aids, 2010. 24 Suppl 4: p. S27-39.

13. Dodd, P.J., G.P. Garnett, and T.B. Hallett, Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. Aids, 2010. 24(5): p. 729-35.

14. Wawer, M.J., et al., Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet, 2009. 374(9685): p. 229-37.

15. Rosen, S. and M.P. Fox, Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med, 2011. 8(7): p. e1001056.

16. Middelkoop, K., et al., Antiretroviral therapy and TB notification rates in a high HIV prevalence South African community. J Acquir Immune Defic Syndr, 2011. 56(3): p. 263-9.

17. Zachariah, R., et al., Reduced tuberculosis case notification associated with scaling up antiretroviral treatment in rural Malawi. Int J Tuberc Lung Dis, 2011. 15(7): p. 933-7.

18. Flateau, C., G. Le Loup, and G. Pialoux, Consequences of HIV infection on malaria and therapeutic implications: a systematic review. Lancet Infect Dis, 2011. 11(7): p. 541-56.

19. Fowler, M.G., et al., Perinatal HIV and its prevention: progress toward an HIV-free generation. Clin Perinatol, 2010. 37(4): p. 699-719, vii.

20. Schouten, E.J., et al., Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. Lancet, 2011. 378(9787): p. 282-4.

21. Donnell, D., et al., Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet, 2010. 375(9731): p. 2092-8.

22. Thirumurthy H, Goldstein M, and Graff Zivin J, The economic impact of AIDS treatment: labor supply in western Kenya. Journal of Human Resources, 2008. 43(June 20): p. 511-552.

23. Habyarimana, J., B. Mbakile, and C. Pop-Eleches, The Impact of HIV/AIDS and ARV Treatment on Worker Absenteeism: Implications for African Firms J. Human Resources, 2010. 45(September 21): p. 809-839.

24. Rosen, S., et al., Economic outcomes of patients receiving antiretroviral therapy for HIV/AIDS in South Africa are sustained through three years on treatment. PLoS One, 2010. 5(9): p. e12731.

25. Thirumurthy, H., et al., Two-year impacts on employment and income among adults receiving antiretroviral therapy in Tamil Nadu, India: a cohort study. Aids, 2011. 25(2): p. 239-46.

26. Graff Zivin, J., H. Thirumurthy, and M. Goldstein, AIDS treatment and intrahousehold resource allocation: Children's nutrition and schooling in Kenya. Journal of Public Economics, 2009. 93(7-8): p. 1008-1015.

27. Integrated National Guidelines on Antiretroviral Therapy, Prevention of Mother to Child Transmission of HIV and on Infant & Young Child Feeding. 2011, Ministry of Health, Republic of Uganda.

28. Guidelines for Antiretroviral Therapy in Kenya, 4th edition 2011. 2011, Ministry of Medical Sciences, Republic of Kenya.

29. Muennig, P.A. and K. Khan, Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults. Clin Infect Dis, 2001. 33(11): p. 1879-85.

30. Marseille, E.A., et al., Case management to improve adherence for HIV-infected patients receiving antiretroviral therapy in Ethiopia: a micro-costing study. Cost Eff Resour Alloc, 2011. 9: p. 18.

31. Hayes, R.J. and L.H. Moulton, Cluster Randomized Trials 2009: Chapman and Hall.

32. Pagel, C., et al., Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomized controlled trials in low and middle-income countries; results and methodological implications. Trials, 2011. 12: p. 151.

33. Chingono, A., et al., Balancing science and community concerns in resource-limited settings: Project Accept in rural Zimbabwe. Clin Trials, 2008. 5(3): p. 273-6.

34. Laan, M.J.v.d. and S. Rose, Targeted Learning: Causal Inference for Observational and Experimental Data. 2011, Berlin Heidelberg New York: Springer.

35. van der Laan, M., L. Balzer, and M. Petersen, Adaptive Matching in Randomized trials and Observational Studies. Journal of Statistical Research, 2012 46(2): p. 113-156.

36. Balzer, L., M.L. Petersen, and M.J. Van der Laan, Adaptive pair-matching in the SEARCH trial and estimation of the intervention effect. U.C. Berkeley Division of Biostatistics Working Paper Series, 2014(320).

37. Hayes, R.J. and S. Bennett, Simple sample size calculation for cluster-randomized trials. Int J Epidemiol, 1999. Apr; 28(2): p. 319-26.

38. Guwatudde, D., et al., Relatively Low HIV Infection Rates in Rural Uganda, but with High Potential for a Rise: A Cohort Study in Kayunga District, Uganda. PloS One, 2009. 4(1): p. e4145.

39. Shafer, L.A., et al., HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989-2005. AIDS, 2008. 22: p. 1641-49.

40. Gray, R.H., et al., Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet, 2007. 369: p. 657-66.

41. Campbell, M.S., et al., Viral linkage in HIV-1 seroconverters and their partners in an HIV-1 prevention clinical trial. PLoS One, 2011. 6(3): p. e16986.

Appendix A Guidelines for Adverse Event Grading – DAIDS Toxicity Table for Adults and Children

Selected portion of the of Division of AIDS [DAIDS] Table for Grading the Severity of Adult and Pediatric Adverse Events, version Dec. 2004.

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
SKIN – DERMATOLOGICAL				
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
RESPIRATORY				
Dyspnea or respiratory distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute neutrophil count (ANC)	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Hemoglobin (Hgb) **Adult and Pediatric ≥ 57 days** (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bilirubin (Total)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*

Appendix B Table of Study and Consent and Commitment Procedures

Study component	No. of participants in Mbarara district, Uganda	No. of participants in Tororo district, Uganda	No. of participants in Kenya	Procedures	Timeline	Consent or commitment process
Community Leader	10	10	12	Meet with local community leaders representing each of the 32 selected communities	Prior to the first Household Census and Community Health Campaign in each selected community	Obtain letter of commitment from leader of each selected community
Baseline Household Community Level Census	All individuals in selected communities	All individuals in selected communities	All individuals in selected communities	Census of all community members to collect identifier and location information	Prior to first Community Health Campaign in each selected community; also at Campaign for those not previously consented	Verbal consent of head of household for themselves and other household members; fingerprint biometric will be recorded as consent documentation
Community Health Campaign	All individuals in selected communities	All individuals in selected communities	All individuals in selected communities	• Tests and measurements including rapid HIV testing, malaria testing on children and other health evaluations • Education and referral to local health services • Distribution of anti-malaria medications and vitamin A in children, and male condoms	Prior to first Community Health Campaign in each selected community; also at Campaign for those not previously consented	Verbal adult consent for themselves and their children to participate in Campaign; fingerprint biometric will be recorded as consent documentation
Targeted/Key Population Testing	Any individuals in selected key population groups	Any individuals in selected key population groups	Any individuals in selected key population groups	• Rapid HIV testing • CD4 testing, if HIV-positive • An optional survey on background and sexual history	Any time after initial Community Health Campaign in each selected community	Verbal consent of participating adult, age ≥15 years
Household Socio-Economic Survey	200 x 10 communities, 100 HIV+ & 100 HIV- (n = 2,000)	200 x 10 communities, 100 HIV+ & 100 HIV- (n = 2,000)	200 x 12 communities, 100 HIV+ & 100 HIV- (n = 2,400)	A survey to collect demographic, health and education information of household members	2-4 weeks after each Campaign	Written consent, adults, conducted at Community Health Campaign
Photography/filming at Community Health Campaigns	Any participants at selected Community Health Campaigns	Any participants at selected Community Health Campaigns	Any participants at selected Community Health Campaigns	Taking photographs or filming participants at selected Campaigns	At selected Community Health Campaigns	Written consent of adults and their children at Campaigns
Photography for dermatologic	Eligible participants in selected	Eligible participants in selected	Eligible participants in selected	De-identified photography of skin conditions at	At selected Community Health Campaigns	Verbal consent of adults at Campaigns

evaluations	communities	communities	communities	selected Campaigns		
ART Intervention	All HIV+ individuals who do not meet in-country treatment guidelines	All HIV+ individuals who do not meet in-country treatment guidelines	All HIV+ individuals who do not meet in-country treatment guidelines	Distribution of ART and routine testing in a streamlined model of care	144 weeks from ART initiation for each participant	• Written consent, adults • Parental written consent, children <8 years • Written assent, children 8-12 years, with parental written consent • Written consent, children ≥13 years, parental co-sign
Qualitative evaluation	a.) 2-4 Community leaders in 2 communities b.) 24-30 Community Health Campaign participants in communities conducting CHCs c.) 10 randomly selected service providers in 2 communities (5 per community) d.) Sub-sample of Household Socio-Economic Survey in 2 communities: 14 x 2 communities, 9 HIV+ & 5 HIV- (n = 28)	a.) 2-4 Community leaders in 2 communities b.) 24-30 Community Health Campaign participants in communities conducting CHCs c.) 10 randomly selected service providers in 2 communities (5 per community) d.) Sub-sample of Household Socio-Economic Survey in 2 communities: 14 x 2 communities, 9 HIV+ & 5 HIV- (n = 28)	a.) 22-4 Community leaders in 4 communities b.) 24-30 Community Health Campaign participants in communities conducting CHCs c.) 10 randomly selected service providers in 4 communities (5 per community) d.) Sub-sample of Household Socio-Economic Survey in 4 communities: 14 x 4 communities, 9 HIV+ & 5 HIV- (n = 56)	a.) In-depth semi-structured interviews b.) Focus group discussions (1 for women, 1 for men, and 1 mixed gender group per community; 8-10 individuals in each group) c.) In-depth semi-structured interviews d.) In-depth semi-structured interviews	a.) 1-2 weeks after each Community Health Campaign b.) Within 1-2 weeks after each Community Health Campaign c.) 2-4 weeks after each Household Socio-Economic Survey d.) 2-4 weeks after each Household Socio-Economic Survey	For all research activities related to qualitative evaluation of SEARCH: Written consent, adults
New infection qualitative cohort	A subset of participants enrolled in the ART Intervention arm in selected communities	A subset of participants enrolled in the ART Intervention arm in selected communities	A subset of participants enrolled in the ART Intervention arm in selected communities	A survey on experiences related to new HIV infection	Within 6 months of enrollment in ART Delivery arm	Written consent, adults
Stigma questionnaire	A random subset of HIV- and HIV+ community members	A random subset of HIV- and HIV+ community members	A random subset of HIV- and HIV+ community members	A questionnaire on stigma issues related to HIV	Any time at CHCs, participant homes or work places, or at health clinics in selected communities	Written consent, adults

Appendix C Uganda Antiretroviral Therapy Guidelines, in place until 2014

Selected portion of The Integrated National Guidelines on Antiretroviral Therapy, Prevention of Mother to Child Transmission of HIV and Infant & Young Child Feeding, Ministry of Health, Uganda.

ART Initiation in Adults

The current MoH guidelines are as summarized in a table bellow

Including HIV positive Partner in a discordant relationship irrespective of CD4 count

Category	Recommendation	First line treatment	
All children <15years	Start ART irrespective of CD4 count	<3yrs	ABC/3TC/NVP
		3-9.9yrs	ABC/3TC/EFV
		10-14.9	<35kg ABC/3TC/EFV
			>35KG TDF/3TC/EFV
		15>	TDF/3TC/EFV
Pregnant women	Start ART irrespective of CD4	OptionB+ TDF/3TC/EFV	
Adults	With CD4 less ≤ than 500 Stage 3and 4, TB , Hep B, HepC , TB co-infection irrespective of CD4	TDF/3TC/EFV	
Most at risk populations (fisher folks, truckers, CSWs)	Start ART irrespective of CD4	TDF/3TC/EFV	

Eligibility criteria for initiating art in infants and children

Three parameters guide the decision making process for initiation of ART in infants and children; these are the age, immunological status and WHO clinical Staging. However ART can also be started in children under 18 months of age presumptively (*as will be described in the next section.*)

Appendix D Kenya Antiretroviral Therapy Guidelines

Selected portion of the Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, Rapid Advice, June 2014.

When to Initiate Antiretroviral Therapy in Adolescents and Adults

The following are the recommendations/indications for initiating ART in HIV-infected adolescents and adults with documented HIV infection.

Table D.1: Criteria for Initiation of ART in Adults and Adolescents

Population	Recommendations
When to start ART in adolescents ≥15 years and adults	• All HIV-infected adolescents and adults with CD4 count ≤500 cells/mm3 irrespective of WHO stage • All HIV-infected pregnant women irrespective of CD4 count, WHO stage or gestation age • All HIV-infected breastfeeding women irrespective of CD4 count, WHO stage • All HIV-infected spouses and sexual partners in sero-discordant relationships irrespective of their WHO stage or CD4 cell count • All HIV-infected adolescents and adults with WHO stage 3 and 4 disease irrespective of CD4 count • All Hepatitis B Virus/HIV co-infected persons irrespective of CD4 count • All TB/HIV co-infected persons irrespective of CD4 count

When to start antiretroviral therapy in children less than 15 years

The following are the recommendations/indications for initiating ART in HIV-infected children less than 15 years.

Table D.2: Criteria for Initiation of ART in Children less than 15 years

Population	Recommendations
When to start ART in children less than 15 years	• ART should be initiated in all HIV-infected children **aged 10 years and below**, regardless of WHO stage or CD4 count/%. • ART should be initiated in all HIV infected children **above 10 years of age** with CD4 cell count ≤500 cells/mm3, regardless of WHO stage • All HIV-infected children above 10 years with WHO stage 3 and 4 disease, Hepatitis B Virus/HIV, TB/HIV co-infection should be initiated on ART irrespective of CD4 count • In circumstances where DNA PCR testing is not readily available ART should be initiated in any child younger than 18 months of age who meets criteria for presumptive diagnosis of severe HIV disease, **confirmatory DNA PCR testing should be done as soon as possible**

<u>Use of antiretroviral drugs for treating HIV-positive pregnant and breastfeeding women</u>

The Ministry of Health recommends immediate initiation of life-long ART for pregnant and breastfeeding women upon HIV diagnosis. The use of ART in pregnant and breastfeeding women markedly reduces the transmission of HIV infection from mother to child. Continuing ART for life for the mother provides additional benefit of keeping mothers healthy and alive, and may also offer benefits for preventing sexual transmission of HIV in sero-discordant relationships.

Appendix E Sample Pediatric ART Dosing Chart

		3 - 5.9 kg	6 - 9.9 kg	10 - 13.9 kg	14 - 19.9 kg	20 - 20.9 kg	25 - 25.9 kg
Tablets/Capsules	EFV 200 - 100 - 50mg	NR	NR	200mg daily	300mg daily	300mg daily	400mg daily
	ABC 300mg	NR	NR	NR	0.5 BID	1 AM/0.5 PM	1 BID
	ABC 60mg	1 BID	1.5 BID	2 BID	2.5 BID	3 BID	Use adult
	3TC 150mg	NR	NR	NR	0.5 BID	1 AM/0.5 PM	1 BID
	LPV/r 100/25mg	NR	NR	2 AM/1 PM	2 BID	2 BID	3 BID
	LPV/r 200/50mg	NR	NR	NR	1 BID	1 BID	2 AM/1PM
	AZT 300mg	NR	NR	NR	0.5 BID	1 AM/0.5 PM	1 BID
	NVP 200mg	NR	NR	NR	1 AM/0.5 PM	1 AM/0.5 PM	1 BID
	NVP 50mg	1 BID	1.5 BID	2 BID	2.5 BID	3 BID	Use adult
Oral Solutions	ABC 20mg/ml	3ml BID	4ml BID	6ml BID	NR	NR	NR
	3TC 10mg/ml	3ml BID	4ML BID	6ml BID	NR	NR	NR
	LPV/r 80/20 mg/ml	3-3.9kg: 1ml BID 4-5.9kg: 1.5ml BID	1.5ml BID	2ml BID	2.5ml BID	3ml BID	3.5ml BID
	AZT 10mg/ml	6ml BID	9ml BID	12ml BID	NR	NR	NR
	NVP 10mg/ml	5ml BID	8ml BID	10ml BID	NR	NR	NR

SEARCH Protocol Summary of Changes, versions 2.0 to 6.0

Protocol version	Summary of significant changes
Version 1.0; July 12, 2012	*Initial protocol version, subsequently modified in response to IRB comments and never implemented*
Version 2.0; November 30, 2012	*First protocol version approved by all IRBs and implemented by study*
Version 3.1; August 29, 2013	• Same day ART initiation upon linkage in intervention communities
	• Streamlined safety testing in ART intervention arm
	• First-line ART regimen for pregnant women includes efavirenz
	• Addition of 2 study investigators
	• Additional secondary health objectives including 3-year incidence of HIV infections, evaluation of attitudes of patients and providers, and evaluation of non-HIV disease care implementation
	• HIV DNA testing by dried blood spot on infants at community health campaigns
	• Additional consent forms for CHC focus group discussion, community leader interview, community qualitative cohort, provider quality cohort, and photography and filming
Version 4.0; December 19, 2013	• Lamivudine added among allowed first-line ART regimens for adults and adolescents
	• Clarification that tenofovir/emtricitabine formulations are not limited to Truvada
Version 5.1; June 5, 2014	• Community health campaign schedules updated to reflect baseline and annual campaigns in intervention communities and follow up years 3 and 5 only in control communities
	• Additional Cost and Cost-Effectiveness secondary objective to evaluate streamlined care
	• Teri Liegler, UCSF, included as the protocol virologist
	• Country treatment guidelines updated to reflect expanded access to ART for persons with CD4 ≤500, pregnant women, HIV serodiscordant couples, and others
	• ART initiation may be included at community health campaigns for some participants
	• Diagnostic services at campaigns may include optional malaria and TB screening
	• Added procedures that may be included at the time of the household socio-economic survey, including HIV RNA, CD4 testing and anthropomorphic measurements
Version 6.0; October 1, 2015	• Additional services individual CHCs could include is provided, such as an urgent care station or men's health services
	• Addition of research-only testing to confirm HIV infection in follow up years 3 and 5 and in a subset of communities in follow up year 2
	• Added description of specialized counseling procedures for seroconverters
	• Updated description of HIV field testing and definition of the HIV Uninfected Community Cohort in the Primary Outcome Measurement
	• Updated adverse event reporting requirements for UCSF-CHR and Uganda's UNCST

Sustainable East Africa Research in Community Health: Analysis Plan for the Primary Outcome

January 21, 2015

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1 Overview

The Sustainable East Africa Research in Community Health (SEARCH) Study is a pair-matched cluster randomized trial, conducted in Kenya and Uganda and designed to evaluate the impact of immediate antiretroviral therapy (ART) delivered using a population-based intervention to optimize uptake at each step of the cascade, compared to ART delivered according to country guidelines, on the five-year cumulative incidence of HIV and a range of health, economic and education outcomes.

This document provides the analytic plan for the primary study outcome: the cumulative incidence of HIV at year five. Primary outcome analyses will be conducted after all SEARCH communities have completed five full years of follow-up. Inclusion and exclusion criteria as well as definition of the control and intervention arms of the trial are reviewed. Section (2) provides a detailed analytic plan for measurement and estimation of five-year cumulative incidence of HIV for each community. Section (3) provides a detailed analytic plan for estimation of and inference for the effect of the randomized intervention on this outcome. Section (4) provides corresponding power calculations under a range of scenarios. Section (5) provides an overview of the analytic plan for additional health outcomes.

1.1 Community selection and pair-matching

Fifty-four candidate communities meeting the following inclusion and exclusion criteria were initially selected in Kenya and Uganda:

Inclusion Criteria:

- Most recent census population between 9,000 and 11,000 individuals.
- Served by a government health center, already providing ART or a highly functioning health center at one organizational level below those generally providing ART.
- Community leaders consent to ethnographic mapping.
- Accessibility to health center via a maintained transportation route.
- Community location with sufficient distance from other potential study communities to limit contamination of intervention or control conditions (i.e. a buffer zone).

Exclusion Criteria:

- Presence of ongoing community-based ART intervention strategies that provide treatment outside of the current in-country treatment guidelines.
- An urban setting, defined as a city with a population of 100,000 or more inhabitants.
- National government not willing or opposed to support commodities needed for Community-based Health Campaign (CHC), if provided by an outside organization.

Data on these communities were gathered with ethnographic mapping. Of the 54 communities, the best 16 matched pairs (5 pairs in Western Uganda, 5 pairs in Eastern Uganda, and 6 pairs in Western Kenya) were selected. Communities were matched based on region, population density, occupational mix, trading centers, and migration.

1.2 Overview: Study arms

One community in each matched pair was randomly assigned to "Control" and one to "Intervention".

Control:

- Baseline household enumeration.
- Community-based Health Campaigns (CHC) with multi-disease prevention and treatment services, including HIV testing and referral at baseline (Year 0), Year 3, and Year 5.
- Home-based testing for all CHC non-attendees who are members of the HIV Incidence Cohort (defined below) at baseline (Year 0), Year 3, and Year 5.
- ART according to in-country guidelines.

Intervention:

- Baseline household enumeration.
- Annual Community-based Health Campaigns (CHC) with multi-disease prevention and treatment services including HIV testing and referral.
- Annual home-based testing for all enumerated CHC non-attendees (irrespective of inclusion in the HIV Incidence Cohort).
- Interim supplemental targeted testing for key populations.
- Streamlined HIV Care:
  - Immediate ART eligibility for all HIV+
  - Supported linkage
  - Rapid ART start
  - ART care 2.0
  - Enhanced retention
- Preplanned HIV cascade optimization.

The core intervention components and the cascade optimization strategy are detailed in the SEARCH Intervention document.

2 Stage I: Identification and Estimation of Community-Specific Five-year Cumulative HIV Incidence

2.1 Overview

In the first stage, we will estimate five-year cumulative incidence of HIV for each community, accounting for incomplete follow-up. The five-year community-specific cumulative incidence of HIV is the probability that a member of the HIV Incidence Cohort becomes HIV-infected within five years of exposure to the intervention or control arm of the study. The HIV Incidence Cohort will consist of all enumerated stable community residents who are ≥ 15 years of age (adults) and HIV-uninfected at baseline. The HIV Incidence Cohort for each community will be generated through (i) enumeration of community residents in a baseline household census; (ii) a baseline (year 0) CHC at which HIV status and other variables are measured; (iii) tracking and evaluation, including home-based HIV testing, of all enumerated stable adult residents who do not attend the baseline CHC. The procedure for determining stable residency is described below. Subjects migrating into the community over the course of the study may attend the CHC and will be both offered equivalent testing and treatment services, but will not be considered part of the HIV Incidence Cohort.

In each cohort, incident HIV cases will be identified by repeat HIV testing using a hybrid model of CHCs followed by home-based testing for non-attendees. HIV status at year 5 will not be observed for all subjects in the Incidence Cohort due to incomplete post-baseline CHC attendance with inevitable partial success tracking non-attendees and due to right-censoring at time of death or outmigration (defined below). Population-based testing will be performed annually in the intervention communities and at years 0, 3 and 5 in the control communities. In the control arm there is thus an increased potential for informative missingness due to the longer intervals between serial testing. To address the potential bias resulting from differential measurement of HIV serostatus between the study arms, we will use data from baseline, year 3, and year 5 for estimation of the five-year cumulative incidence in both study arms. By using equivalent data in intervention and control communities, this approach reduces bias and in simulations results in good confidence interval coverage and type I error control under most plausible scenarios. In secondary analyses, we will consider a mixed approach that makes full use of the annual data available in the intervention communities.

In the primary analysis death will be treated as a right-censoring event. In secondary analyses, we will implement the following alternatives: (i) death treated as a competing risk, and (ii) HIV-free survival as a composite outcome. The decision not to treat death as a competing risk in the primary analysis is based on the desire to define a community-level outcome that is not a function of underlying mortality patterns, which may vary across communities and over time. The decision not to use HIV-free survival for our primary analysis is based on the expectation that the majority of mortality in our HIV Incidence Cohort will not be related to HIV nor will it be strongly affected by the intervention.

In the primary analysis, outmigration will be also be treated as a right-censoring event. We take this approach because subjects who migrate out of an intervention community may be exposed to a higher risk of HIV acquisition than exists within the community and thereby would dilute the effect of the intervention. Further, this dilution would be less likely to occur if a comparable strategy were rolled out region-wide, diminishing generalizability to the future context of interest. In secondary analyses we will (i) censor only at death and (ii) evaluate the impact of the intervention on internally-derived HIV infections, as determined through viral genotyping and phylogenetic analysis.

In the following subsections we define the individual-level data that will be measured in each community at years 0, 3 and 5. We formally define the Stage I target parameter (community-specific five-year cumulative HIV incidence) that we aim to estimate using these data, and provide an overview of assumptions used to identify this parameter. Finally, we describe our estimator of the community-specific cumulative

incidence, which incorporates incomplete CHC attendance, tracking, and right-censoring.

2.2 Longitudinal individual-level data for a given study community

Let J^* denote the number of enumerated, stable, adult residents in a given study community. Residents within the geographic boundaries of each community are either enumerated at the census or linked to an enumerated household at the time of the baseline CHC. A resident is classified as stable if at the time of census he or she reports (or is reported by a key informant as) living outside the parish/sublocation for $\leq$ 6 months of the preceding 12 months. A resident is classified as adult if he or she is $\geq$ 15 years of age at time of the baseline CHC.

We measure individual-level data at time of the census, including age, sex, occupation, location of residence and marital status. For individuals attending a CHC, we measure HIV status, individual-specific covariates including changes in any of the baseline enumeration variables (residence, occupation, marital status), and secondary outcomes as specified in the protocol. For subjects who are tracked, we ascertain vital status and migration status, and if alive and not outmigrated, we measure HIV status and the individual-specific variables measured at the CHC.

For our primary outcome measurement, our priority is to determine HIV serostatus (at CHC or subsequent tracking) for the following groups:

1. At year 0 (baseline): All enumerated stable community residents, $\geq$ 15 years of age (in order to establish a maximally representative incidence cohort).
2. At year 3: All members of the HIV Incidence Cohort who are not censored by death or outmigration by year 3.
3. At year 5: All members of the HIV Incidence Cohort who tested HIV-negative at year 3 and are not censored by death or outmigration by year 5.

More formally, we will measure the following individual-level data at times $t \in \{0, 3, 5\}$:

- $C(t)$ is an indicator of right-censoring by time t, with right-censoring time defined as the minimum of the time of death or outmigration. Outmigration is defined formally below. We assume close to complete ascertainment of outmigration and death through tracking and use of key informants, as detailed in the protocol.
- $\Delta(t)$ is indicator of having HIV serostatus (and other covariates) observed at either the CHC or through home-based tracking at time t.
- $W(t)$ are covariates, other than HIV status, measured at the CHC or on tracking at time t, as described in the protocol.
- $Y(t)$ is HIV status at time t.

Baseline variables B are also measured at the time of census on all enumerated subjects and include age, sex, marital status, occupation, and GPS coordinates.

The non-intervention time-dependent covariates are then $L(t) = (W(t), Y(t))$. We define variables deterministically equal to their last value after either censoring or HIV infection have been observed. Thus, $\Delta(5)$ is deterministically 1 and $C(5)$ is deterministically 0 (HIV status in the absence of censoring is known) for any individual for whom $\Delta(3)Y(3) = 1$ (tested positive at year 3). The observed data structure for individual j is thus

$$O_j = (B_j, C_j(t), \Delta_j(t), \Delta_j(t)L_j(t) : t \in \{0, 3, 5\}) \tag{1}$$

We also observe community-level covariates E and the randomly assigned community treatment A. Because E and A are constant across a community and thus will not impact estimation of the community-level

outcome, we omit these variables from our specification of the individual-level longitudinal data structure within a community. In a given community, we observe J^* copies of

$$O_j \sim P_0$$

where J^* can vary across communities.

2.2.1 Outmigration

When defining outmigration, we would ideally distinguish between migration patterns, resulting in potential exposures to HIV infection primarily within the SEARCH community (which more accurately reflect the risk were an intervention rolled out more broadly) from migration patterns, resulting in potential exposures to HIV infection primarily outside the SEARCH community (which provide less relevant information about the counterfactual exposure level of interest). Such an ideal definition is unknown, likely to vary across communities, and likely to depend on information, difficult to measure in practice. Therefore, we use a definition of outmigration that has low sensitivity and high specificity in place of this unobserved ideal. In other words, we attempt to avoid censoring individuals, whose primary exposure continues to occur within the community, and accept that as a result we may fail to censor people, whose primary exposure is outside the community.

An individual will be defined as outmigrated at year 3 if he or she (or a key informant) reports either of the following.

1. Spending > 6 months of the preceding year outside of the community.
2. Within the preceding 3 years, spending >12 contiguous months outside of the community.

Similarly, an individual will be defined as outmigrated at year 5 if he or she (or a key informant) reports either of the following.

1. Spending > 6 months of the preceding year outside of the community.
2. Within the preceding 2 years, spending >12 contiguous months outside of the community.

2.3 Target parameter: Community-specific cumulative incidence

For Stage I, we aim to estimate the probability that a stable adult resident of the community who is uninfected with HIV at baseline becomes infected with HIV during five years of follow up, in the absence of right-censoring. More specifically, in our primary analysis we define the HIV Incidence Cohort to be enumerated stable adult residents of the community who remain alive and resident in the community at the time of baseline CHC/tracking ($C(0) = 0$) and who have documented HIV-negative serostatus by the close of baseline tracking ($\Delta(0) = 1, Y(0) = 0$). Our stage I community-specific target parameter is the probability of seroconversion to HIV by year five among members of the HIV Incidence Cohort, were right censoring prevented:

$$P\big(Y^{\bar{c}=0}(5) = 1 \big| C(0) = 0, Y(0) = 0, \Delta(0) = 1\big),$$

where $Y^{\bar{c}=0}(5)$ denotes the HIV infection status at year 5 under a hypothetical intervention to prevent right-censoring and where overbars denote the history of right-censoring: $\bar{C} = (C(3), C(5))$. Conditioning on known HIV serostatus at baseline avoids an additional identifiability assumption on factors determining baseline tracking success and corresponding additional complexity in our Stage I estimator. However, it introduces the possibility that the HIV Incidence Cohort is not fully representative. Our design attempts to mitigate this risk to the extent possible by using a prioritized tracking system. After completion of initial baseline tracking, any age-sex strata in which < 80% of enumerated adult stable residents have known serostatus are targeted for additional tracking. To investigate the representativeness of our baseline

cohort, we will report descriptive statistics comparing the age, sex and geospatial distribution of subjects seen at the baseline CHC or tracked to those enumerated in the baseline population.

In addition, the time between the start of the baseline CHC (at which the intervention is first introduced) and the conclusion of baseline tracking (which is the latest date that $Y(0)$ can be measured) introduces the possibility that $Y(0)$ no longer reflects "baseline" HIV status. Specifically, the intervention might reduce the probability of seroconverting between the start of the baseline CHC and the conclusion of tracking. This potentially results in bias by differentially depleting higher risk individuals from the Incidence Cohorts in the control versus intervention communities. To investigate this possibility, we will report the total number of individuals in each community (if any) with $Y(0) = 1$ for whom HIV serostatus determination occurred more than 3 months after the start of the CHC, both over all and stratified by CD4 at time of testing (with three months was chosen as the earliest plausible time at which the intervention might impact incidence, accounting for time from diagnosis to ART start and suppression). We note that individuals testing late and with $Y(0) = 0$ are known to have been HIV-uninfected at baseline. We will also conduct secondary analyses in which we treat $Y(0)$ as missing (ie. set $\Delta(0) = 0$) if $Y(0) = 1$ and testing occurred more than 3 months after the baseline CHC.

In the following, we suppress explicit statement of the conditioning set $\big(C(0) = 0, Y(0) = 0, \Delta(0) = 1,)$ and simply define our target parameter as the five-year cumulative incidence among members of the HIV Incidence Cohort in the absence of right-censoring $\mathbb{E}[Y^{\bar{c}=0}(5)]$. In the next section, our goal is to write this causal parameter as a function of the observed data distribution P_0. For identifiability, we further modify our causal parameter to be the five-year cumulative incidence (among the HIV Incidence Cohort) under a hypothetical intervention to prevent right-censoring and to ensure knowledge of HIV status at years 3 and 5:

$$\mathbb{E}[Y^{\bar{c}=0,\bar{\delta}=1}(5)]$$

where we denote the measurent history as $\bar{\Delta} = (\Delta(3), \Delta(5))$. This quantity will equal the five-year cumulative HIV incidence under a hypothetical intervention only on right-censoring $\mathbb{E}[Y^{\bar{c}=0}(5)]$ if the measurement process does not affect HIV infection and otherwise may deviate slightly. An alternate approach would require knowledge of HIV status only at time 5. This, however, increases the potential for bias if underlying HIV status affects either death, migration, or measurement at time 5. Further, in simulations this alternate approach was shown inn simulations under a range of plausible scenarios to result in higher bias and lower power than the approach adopted here.

2.4 Identifying assumptions and the statistical estimand

Recall the observed data for an individual consist of baseline covariates B, censoring indicators $C(t)$, measurement indicators $\Delta(t)$ and time-dependent covariates $L(t) = \big(W(t), Y(t)\big)$ for $t = \{0, 3, 5\}$. (See Eq. 1). In this subsection, we express our target causal parameter as a function of the observed data distribution P_0, while making any needed assumptions explicit and evaluating their plausibility.

Our causal parameter $\mathbb{E}[Y^{\bar{c}=0,\bar{\delta}=1}(5)]$ can be identified under the sequential randomization assumption:

$$Y^{\bar{c}=0,\bar{\delta}=1}(5) \perp\!\!\!\perp C(3), \Delta(3) \big| B, L(0)$$
$$Y^{\bar{c}=0,\bar{\delta}=1}(5) \perp\!\!\!\perp C(5), \Delta(5) \big| B, L(0), C(3) = 0, \Delta(3) = 1, L(3)$$

These assumptions allow censoring (by death or outmigration) and measurement (CHC attendance and tracking success) to depend prior measured covariates. They will fail, however, if unmeasured covariates, including unmeasured HIV status, affect either censoring or the measurement process.These assumptions would also entail the use of a full adjustment set (i.e. all prior measured covariates) during estimation. This would result in substantially more complex estimators and have unpredictable impacts on bias for the

intervention effect (Stage II parameter) if certain covariates strongly predict censoring and measurement but have a minimal impact on the outcome. We thus reserve this approach for secondary analysis.

In the primary analysis we instead rely on the following stronger identifiability assumptions:

$$Y^{\bar{c}=0,\bar{\delta}=1}(5) \perp\!\!\!\perp C(3), \Delta(3)$$
$$Y^{\bar{c}=0,\bar{\delta}=1}(5) \perp\!\!\!\perp C(5), \Delta(5) \big| C(3) = 0, \Delta(3) = 1, Y(3)$$

Our target statistical estimand is then

$$\mathbb{E}\left[\frac{\mathbb{I}(\bar{C} = 0, \bar{\Delta} = 1)}{P(C(3) = 0, \Delta(3) = 1)P(C(5) = 0, \Delta(5) = 1|C(3) = 0, \Delta(3) = 1, Y(3))} Y(5)\right] \tag{2}$$

where $\mathbb{I}(\cdot)$ is the indicator function. This approach allows censoring and measurement at year 5 to depend on underlying HIV status at year 3. While HIV infection between baseline (year 0) and year 3 or between year 3 and year 5 could plausibly affect subsequent censoring or measurement (resulting in a violation of these assumptions), we minimize the extent to which this bias is likely to be differential in treatment and control arms and thereby bias our estimate of the intervention effect by relying on the equivalent measurement structures in both arms. Under most plausible deviations from these identifiability assumptions, the direction of the bias in estimates of community-specific cumulative incidence should be similar in both control and intervention arms and result in some degree of cancellation for estimates of the intervention effect. Simulations, under a range of both plausible and extreme informative measurement and censoring processes, verify this prediction and show good confidence interval coverage and type I error control for effect estimates based on this approach.

2.5 Estimation of the community-specific cumulative incidence

The statistical parameter (Eq. 2) will be estimated with a non-parametric maximum likelihood estimator (NPMLE), expressed here in inverse probability form:

$$\hat{\psi}_{NPMLE} = \frac{1}{J}\sum_{j=1}^{J} \frac{\mathbb{I}(\bar{C}_j = 0, \bar{\Delta}_j = 1)}{\hat{P}(C_j(3) = 0, \Delta_j(3) = 1)\hat{P}(C_j(5) = 0, \Delta_j(5) = 1|C_j(3) = 0, \Delta_j(3) = 1, Y_j(3))} Y_j(5),$$

where each probability in the denominator can be estimated with its empirical proportion and where J denotes the number of individuals in the HIV Incidence Cohort. This NPMLE relies on the following "reduced" data on individual j:

$$O_{j,reduced} = (C_j(3), \Delta_j(3), \Delta_j(3)Y_j(3), C_j(5), \Delta_j(5), \Delta_j(5)Y_j(5))$$

When implementing secondary analyses with a full adjustment set (including $(B, L(0), L(3))$, a simple non-parametric maximum likelihood estimator will not be defined. For these analyses, we will implement a longitudinal targeted maximum likelihood estimator (TMLE), based on iterated conditional expectations and using super learning to estimate the nuisance parameters [1, 2].

3 Stage II - Identification and Estimation of the Intervention Effect

3.1 Overview

This section is focused on obtaining a point estimate and inference for the intervention effect. We first describe the community-level data and implications of the pair-matched design. Then we specify the target

parameter for Stage II as the average difference in the five-year cumulative incidence of HIV under the intervention and under the control for the study communities. Next we discuss identifiability and two estimation strategies - unadjusted and adjusted. Our primary analysis will adjust for one baseline variable, which will be data-adaptively selected from a set of candidate variables.

3.2 Community-level data and adaptive pair-matching

Given estimates of the community-specific cumulative HIV incidence generated in Stage I, the observed data can be simplified to the cluster-level. Let E represent the baseline community-level covariates, including measures from the ethnographic mapping (e.g. region, proximity to trucking routes, occupational mix), the census (e.g. age distribution, sex ratio, community size), and the baseline CHC with tracking (e.g. community-level summaries of population baseline HIV RNA level). The exposure variable A equals 1 if the community was randomized to the intervention arm and equals 0 if the community was randomized to the control arm. The outcome Y is the estimated community-specific five-year cumulative incidence of HIV (obtained from Stage I). Thereby, the observed data for SEARCH community i can be denoted

$$O_i = (E_i, A_i, Y_i)$$

for $i = 1, \ldots, 32$.

As described in Section 1.1, candidate communities were pair-matched within region and on baseline predictors of HIV transmission and health care delivery. Recall that $N = 54$ candidate communities that satisfied the study's inclusion/exclusion criteria were identified from rural Uganda and Kenya as potential study sites. From these 54 communities, the $n/2 = 16$ pairs (5 in Western Uganda, 5 in Eastern Uganda, and 6 in Kenya) that were best matched on baseline covariates were selected. We consider this pair-matching scheme to be adaptive, because the partitioning of the study communities into matched pairs was a function of the baseline covariates of all candidates. This adaptive design has important implications for estimation and inference [3, 4]. In contrast to other pair-matching schemes, we cannot represent the data as $n/2$ independent, identically distributed (i.i.d.) copies of some paired random variable. Instead, the observed data consist of n dependent copies of $O = (E, A, Y)$.

Nonetheless, there is substantial conditional independence in the data. Given the covariates of all candidate communities $E^N = (E_1, \ldots, E_N)$, the observed data can be represented as $n/2$ conditionally independent random variables:

$$\bar{O}_k = \big(O_{k1}, O_{k2}\big) = \big((E_{k1}, A_{k1}, Y_{k1}), (E_{k2}, A_{k2}, Y_{k2})\big)$$

where the index $k = 1, \ldots, n/2$ denotes the partitioning of the candidates $\{1, \ldots, N\}$ into matched pairs according to similarity on their baseline covariates E^N. Throughout subscripts $k1$ and $k2$ denote the first and second communities within matched pair k. We place no assumptions on the joint distribution of covariates $P_0(E^N)$. The treatment mechanism is known; with probability 0.5, the first unit is randomized to the intervention and the second the control:

$$P_0(A_{k1} = 1, A_{k2} = 0|E^N) = P_0(A_{k1} = 0, A_{k2} = 1|E^N) = 0.5$$

Throughout we assume that the baseline covariates and the intervention assignment in one community do not affect the outcome of another study community. In other words, we assume the study communities are causally independent (i.e. no contamination or spill over effects). Under this assumption, the conditional

distribution of the observed data, given the baseline covariates of the candidate units, factorizes as

$$
\begin{aligned}
P_0(O_1, \ldots, O_n | E_1, \ldots, E_N) &= \prod_{k=1}^{n/2} \Big\{ P_0\big(A_{k1}, A_{k2} | E^N\big) P_0\big(Y_{k1} | A_{k1}, E_{k1}\big) P_0\big(Y_{k2} | A_{k2}, E_{k2}\big) \Big\} \\
&= 0.5 \prod_{k=1}^{n/2} \Big\{ P_0\big(Y_{k1} | A_{k1}, E_{k1}\big) P_0\big(Y_{k2} | A_{k2}, E_{k2}\big) \Big\} \\
&= P_0(O_1, \ldots, O_n | E_1, \ldots, E_n) = P_0^n(O^n | E^n)
\end{aligned}
$$

Throughout, P_0^n denotes the true conditional distribution of the observed data, given the baseline covariates of the n study units $E^n = (E_1, \ldots, E_n)$. There are no other restrictions on the set of possible observed data distributions, and the resulting statistical model $\mathcal{M}$ is semiparametric.

3.3 Target parameter: Intervention effect

Our goal in the primary analysis is to estimate the effect of the SEARCH Intervention on five-year cumulative HIV incidence for our study communities. Our target of inference is the sample average treatment effect (SATE):

$$\Psi^F = \frac{1}{n} \sum_{i=1}^{n} Y_i^1 - Y_i^0$$

where Y_i^a denotes the counterfactual cumulative incidence under intervention level $A = a$ for community i. This parameter is the average of the community-specific causal effects for the study units. This is a data-adaptive parameter in the sense that its value depends on the units included in the study. As discussed in the following sections, estimation and inference for the SATE are analogous to that for the population average treatment effect $\mathbb{E}[Y^1] - \mathbb{E}[Y^0]$ or its relative counterpart $\mathbb{E}[Y^1]/\mathbb{E}[Y^0]$. The differences lie in interpretation and inference, with estimators of the sample parameter often being less variable (more precise) than those of the population parameter [5–8].

3.4 The statistical estimand

Let us rewrite the SATE in terms of the conditional average treatment effect (CATE):

$$\Psi^F = \frac{1}{n} \sum_{i=1}^{n} \mathbb{E}\big[Y_i^1 - Y_i^0 | E_i^*\big]$$

where E_i^* represents all pre-intervention covariates impacting the outcome [8]. To be clear, E^* represents both baseline measured factors (e.g. region, population HIV RNA levels) and baseline unmeasured factors (e.g. stigma) that influence HIV incidence. In words, Ψ^F is the expected difference in the counterfactual outcomes for unit i under the intervention and under the control, given the vector of covariates E_i^*. If we had access the set of covariates E^*, then we could apply the results for estimation and inference for the CATE, as detailed in [4]. In reality, we only measure a subset of these covariates, E, and only this subset is available for estimation and inference. As discussed in [8], a point estimator enveloped for the CATE will nonetheless be consistent and asymptotically linear for the SATE, and the corresponding variance estimator for the CATE will be asymptotically conservative.

Thereby, our statistical estimand for Stage II is the average difference in the expected outcomes, under the intervention and control, for the n study communities:

$$\begin{aligned}\Psi(P_0^n) &= \frac{1}{n}\sum_{i=1}^{n} \mathbb{E}_0(Y_i|A_i = 1, E_i) - \mathbb{E}_0(Y_i|A_i = 0, E_i) \\ &= \frac{1}{n}\sum_{i=1}^{n} \bar{Q}_0(1, E_i) - \bar{Q}_0(0, E_i)\end{aligned}$$

where $\bar{Q}_0(A, E)$ denotes the conditional mean outcome, given the intervention A and measured covariates E. Therefore, this estimand is still random through the vector of covariates $E^n = (E_1, \ldots, E_n)$. The true value ψ_0 depends on the set of n units.

3.5 Estimation of the intervention effect

An intuitive estimator of ψ_0 is the average difference in outcomes within matched pairs:

$$\hat{\psi}_{unadj} = \frac{1}{n/2}\sum_{k=1}^{n/2} \left(Y_{k1} - Y_{k2}\right)$$

where the observations within pair k have been ordered such that the first corresponds to the intervention, $A_{k1} = 1$, and the second to the control, $A_{k2} = 0$, or equivalently, the difference between the average outcomes among intervention units $\bar{Q}_n(1) = \mathbb{E}_n(Y|A = 1)$ and the average outcomes among control units $\bar{Q}_n(0) = \mathbb{E}_n(Y|A = 0)$. When the measured covariates are predictive of the outcome, this simple difference-in-means estimator is often *inefficient* as it fails to adjust for measured covariates. Irrespective of how well matching is performed, there is likely to be some residual imbalance on pre-intervention determinants of the outcome within matched pairs. Furthermore, there are additional baseline covariates, such as baseline HIV prevalence and population HIV RNA levels, that are predictive of the outcome but were unavailable during the matching process. In general, adjusting for baseline covariates during the analysis can reduce variance without bias, even in small trials (e.g. [9, 10]).

Therefore, for the primary analysis we will use targeted minimum loss-based estimation (TMLE) to provide an unbiased and more efficient estimate of the intervention effect. For comparison, in secondary analysis we will also implement the unadjusted estimator. The TMLE for $\Psi(P_0^n)$ is given by the following substitution estimator:

$$\hat{\psi}_{adj} = \frac{1}{n}\sum_{i=1}^{n} \left[\bar{Q}_n(1, E_i) - \bar{Q}_n(0, E_i)\right]$$

where $\bar{Q}_n(A, E)$ denotes a targeted estimate of the conditional mean function $\bar{Q}_0(A, E) = \mathbb{E}_0(Y|A, E)$. In general, this targeting step is used to achieve the optimal bias-variance trade-off for the parameter of interest and to solve the efficient score equation [11]. In an adaptive pair-matched trial, the TMLE for $\Psi(P_0^n)$ can be implemented as follows. We first obtain an estimate of the conditional mean outcome $\bar{Q}_0(A, E)$ by running main terms regression of the outcome on the exposure and covariates. In other words, we use maximum likelihood to estimate the coefficients in the following regression model:

$$\bar{Q}_0(A, E) = \beta_0 + \beta_1 A + \beta_2 E \tag{3}$$

Because the intervention is randomized and the regression model used for adjustment contains an intercept and a main term for the intervention, no additional targeting in necessary [10]. Our point estimate of the intervention effect is the average of the difference in the expected outcomes under the intervention and control for the study units and thus equal to the estimated value of β_1.

With only 16 (conditionally) independent units, we are limited as to the size of the adjustment set (i.e. variables included as main terms in the regression model). Adjusting for too many covariates can result in over-fitting. Therefore, we will use leave-one-out cross-validation to select from a library of candidate regressions. Specifically, the library will consist of regression models for the pairwise difference in outcomes $(Y_{j1} - Y_{j2})$ on each covariate difference $(E_{k1} - E_{k2})$, where observations within matched pairs have been ordered such that the first corresponds to the intervention $(A_{k1} = 1)$ and the second to the control $(A_{k2} = 0)$. Targeting the pairwise difference and using the L2 loss function as the measure of performance will minimize the empirical variance of the estimated influence curve and the maximize empirical efficiency [12]. Treating the pair as the independent unit, we will select the candidate regression (i.e. adjustment variable), resulting in the lowest cross-validated risk estimate. We will then estimate the intervention effect by using the complete data to fit the regression model for the outcome Y on the exposure and selected covariate (Eq. 3).

For candidate adjustment variables, we will consider the following community-level variables, measured at baseline: HIV prevalence, male circumcision prevalence, proportion with plasma HIV RNA ¡400 copies/ml, and median and mean log_{10} copies/ml plasma HIV RNA levels. As a secondary analysis, we will use logistic (as opposed to linear) regression in the cross-validation selector and in the TMLE. Logistic regression can provide stability in the context of rare outcome [4].

3.6 Inference

As established in [4, 8], both the unadjusted estimator and the TMLE are asymptotically linear and normally distributed. Thus, the limit distribution of the standardized estimator is normal with mean 0 and variance given by the variance of its influence curve. Asymptotically conservative approximations of the influence curves for the unadjusted estimator and the TMLE are given by the difference in the residuals within matched pairs:

$$\hat{IC}_{unadj}(\bar{O}_k) = \big(Y_{k1} - \bar{Q}_n(1)\big) - \big(Y_{k2} - \bar{Q}_n(0)\big)$$
$$\hat{IC}_{adj}(\bar{O}_k) = \big(Y_{k1} - \bar{Q}_n(1, E_{k1})\big) - \big(Y_{k2} - \bar{Q}_n(0, E_{k2})\big)$$

where observations within matched pairs are ordered such that the first receives the intervention and the second the control. An asymptotically conservative variance estimator is then given by the sample variance of the estimated influence curve, divided by $n/2$. For $\hat{\psi}_{unadj}$, this is equivalent to the sample variance of the within pair differences, divided by $n/2$, and is commonly recommended for pair-matched randomized trials [13] even though it is known to be conservative [4–6, 14, 15]. Our approach to reduce the true variance of the estimator and obtain a less conservative variance estimate is through adjustment with TMLE.

Inference for the intervention effect will be based on the estimated influence curve and the Student's t-distribution with 15 degrees of freedom. To account for data-adaptive adjustment in finite samples, we will use a cross-validated estimate of the influence curve for the TMLE. Confidence intervals and two-sided hypothesis testing will be conducted at a 5% significance level. Finite sample simulations suggest that under plausible scenarios the adjusted estimator provides modest to substantial efficiency gains and corresponding power improvements, while retaining good type I error control and 95% confidence interval coverage. For either estimator, there is no variance contribution from the covariate distribution, which is considered fixed.

4 Power Calculations and Simulation Results

4.1 Overview

We first present standard power calculations for cluster randomized trials under a range of plausible and conservative assumptions. We then provide results on the impact of regional heterogeneity, such as anticipated in SEARCH, on attained power. Finally, in the Section 4.3, we present full simulations evaluating the performance of our proposed two-stage estimator. We report the attained power under a range of scenarios for changes in the guidelines for ART initiation in the control arm and achieved ART coverage. We also demonstrate conservative confidence interval coverage and type I error control.

4.2 Classical power calculations

Our initial power calculations were based on the standard sample size formulas for an unadjusted comparison of proportions in a pair-matched cluster randomized trial with two arms [16]. Using a two-sided test at a 5% level of significance, these calculations indicated that 16 matched pairs would provide at least 80% power to detect a 40% reduction in the five-year HIV cumulative incidence under a conservative value for the matched pair coefficient of variation (k_m) and to detect smaller effect sizes under more plausible k_m values. Figure 1 shows a graph of the percent reduction detectable with 80% power under a range of deviations from the following assumptions.

- We assumed a stable adult resident size of 5,000, a baseline HIV prevalence of 10%, measurement of HIV status at baseline among 80% of residents, and measurement of HIV status at the final year on 75% of those HIV-negative at baseline. This yields approximately 2700 residents in each community who are in the HIV Incidence Cohort and have their serostatus known at year 5. The exact cohort size will vary, however, if the actual sample size per community is at least 2700 individuals, then these calculations can be considered conservative. We further note that moderate deviations from this number of individuals are not expected to have strong impacts on power.
- We assumed that the five-year cumulative HIV incidence was 1% in control communities. This estimate was considered conservative given the available literature, which suggested that HIV transmission rates are approximately 0.5% to 2% [17–19]. For example, assuming a current incidence density of 0.5 cases per 100 person-years, and allowing for a 10% decline in transmission rate per year in the absence of the intervention (due to concurrent prevention activities and expansion of ART), the incidence density method would suggest a five-year cumulative incidence of approximately 2%. If the five-year cumulative incidence is 2% in control communities, then these calculations can be considered conservative.
- We assumed a matched pair coefficient of variation k_m of no greater than 0.4. While ideally external data would be available to the inform its selection, the generalizability of k_m values across studies is limited. Specifically, k_m depends (among other things) on which covariates are used for matching, how close a match is achieved, and the strength of association between these covariates and the outcome. Furthermore, recent work has demonstrated the instability of estimates of k_m based on empirical data [20]. Prior studies, performed in similar settings, have assumed a k_m closer to 0.25 (e.g. Project ACCEPT [personal communication] and the Mwanza Trial [21]). With the above assumptions, these calculations indicated that would be powered to detect a 40% reduction with $k_m = 0.4$, a 33% reduction with $k_m = 0.3$, and a 30% reduction with $k_m = 0.25$.

We also expect that these calculations are conservative because of the precision gained through covariate adjustment during the analysis. Adjustment with TMLE should improve power by reducing the variability of the estimator and resulting in a less conservative variance estimator. On the other hand, as discussed in

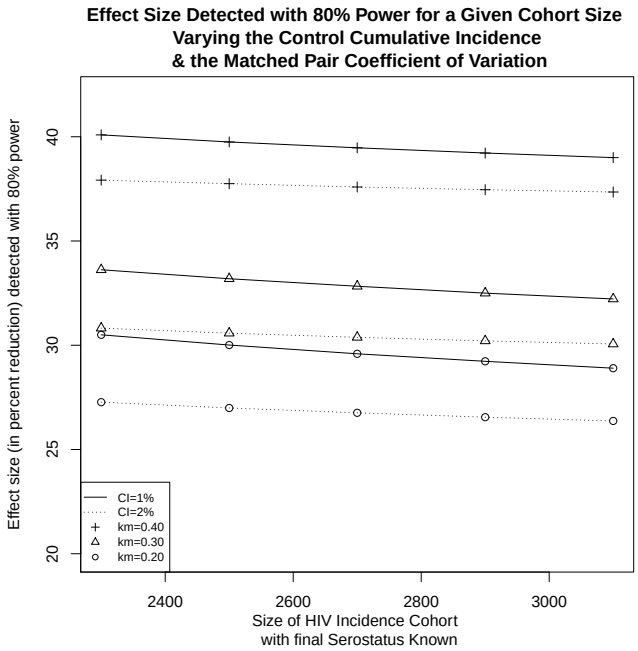

Figure 1: Effect size (in percent reduction) that we are powered to detect at 80% while varying the control cumulative incidence (CI), the matched pair coefficient of variation k_m, and the number of individuals in the HIV Incidence Cohort, who have their status known at the final time point. The calculations were based on the standard sample size formulas for an unadjusted comparison of proportions in a pair-matched cluster randomized trial with two arms [16].

the following subsection, these calculations may be anti-conservative if there is substantial heterogeneity in HIV incidence across the study regions, although use of an adjusted estimator reduces this impact.

4.2.1 Impact of heterogeneity on power

The SEARCH trial involves 5 matched pairs in Eastern Uganda, 5 matched pairs in South Western Uganda, and 6 matched pairs in the Lake Victoria region of Kenya. Prior studies suggested that baseline HIV prevalence and HIV incidence are expected to vary considerably across the 3 regions. To understand the impact of heterogeneity on study power, we conducted a theoretical investigation as well as a simulation study under extreme conditions. We elaborate on the latter here and in the following section evaluate implications of heterogeneity as informed by a more realistic mathematical model. Consider the following table depicting *hypothetical* control cumulative incidences across the three regions:

Control Cumulative Incidence by Region

Scenario	Region 1	Region 2	Region 3
A	2.0%	2.0%	2.0%
B	0.8%	2.0%	5.0%
C	1.1%	2.0%	6.5%
D	1.0%	2.0%	8.0%
E	1.0%	2.0%	10.0%

For example, in Scenario A, there was no heterogeneity and a constant 2% cumulative incidence of HIV was observed across the study sites in the absence of the intervention. Scenario E, in contrast, represented extreme heterogeneity, where the control cumulative incidence was 1% in the Region 1, 2% in Region 2

and 10% in Region 3. Throughout, we assumed there was a constant relative effect size of 35% within each region. Communities were pair-matched on baseline covariates within region, and estimation was based on the TMLE, adjusting for a single covariate, as well as the unadjusted estimator. Inference was based estimated influence curve and the Student's t-distribution with 15 degrees of freedom.

The simulation results are given in Figure 2, showing the power if the estimator's variance were known (not possible in practice) and the attained power using our conservative variance estimator. In more detail, the former refers to the variance of our point estimates across the 2500 simulated trials, and the latter refers to our conservative influence curve-based variance estimator. The x-axis is the absolute effect size in percent and the y-axis power. The following become apparent.

1. Heterogeneity in outcomes across the regions does impact the power despite matching perfectly on region. Power decreased with increasing heterogeneity (Scenarios A $\rightarrow$ E), even though the absolute effect size was increased.
2. Adjusting for a single covariate has substantial potential to improve power. Consider, for example, scenario A, where the outcomes were homogenous across the regions. The power was about 80% with the unadjusted estimator and about 95% with the TMLE.
3. With increasing heterogeneity, the variance estimator for the unadjusted algorithm becomes increasingly conservative as evidenced by the increasing deviation between the power if the variance were known (red letters) and the attained power using the conservative variance estimate (red diamonds). This loss in power was substantially attenuated with use of the TMLE.

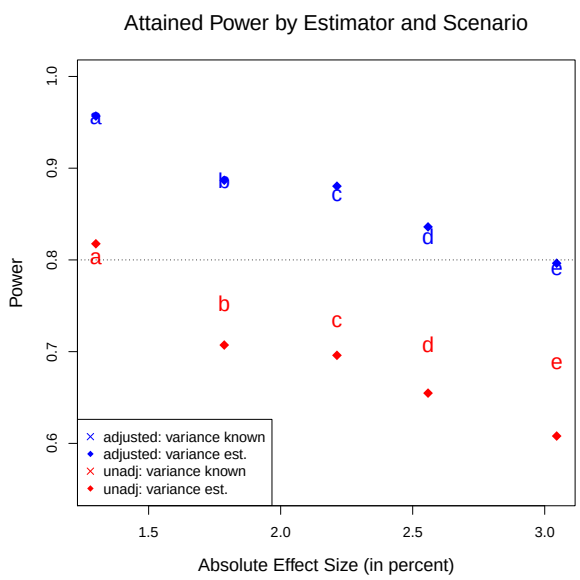

Figure 2: The impact of heterogeneity on estimation of the intervention effect: The scenarios A-E are described in the accompanying table. The letters denote the power if we knew the variance of our estimator and the diamonds denote the attained power using our conservative variance estimator. Blue corresponds to the TMLE, adjusting for 1 baseline community-level covariate, and the red to the unadjusted estimator.

4.3 Simulations and mathematical modeling

We used simulations to examine the performance of our proposed two-stage effect estimator under plausible scenarios. We first used a mathematical model to generate plausible country-specific incidence curves

under a range of assumptions regarding scale-up of ART. These incidence curves were the basis for full hierarchical simulations that incorporated a number of the challenges faced by our primary outcome analysis, including: (i) differential measurement processes in the intervention and control arms, (ii) possibly differential informative right-censoring (due to death and outmigration) by intervention arm and individual HIV status, (iii) possibly differential informative measurement (through CHC attendance and tracking success) by intervention arm and individual HIV status, (iv) the inability to match on all measured baseline covariates predictive of the outcome, (v) few conditionally independent units, and (vi) rare outcomes.

4.3.1 Simulation setup

The following describes the data generating experiment for each of the 32 communities in the simulated study. Throughout, subscript i will be used to denote the community and subscript j to denote an individual within a community. We first describe the generation of the community-level data and then the individual-level data.

For community i, nine baseline community-level covariates were generated by drawing from a multivariate normal. The correlation between the first three covariates $\{E1_i, E2_i, E3_i\}$ and between the second three covariates $\{E4_i, E5_i, E6_i\}$ was approximately 0.65, while the correlation between the last three $\{E7_i, E8_i, E9_i\}$ was 0. Region R_i was set to reflect the study design with 10 communities from Eastern Uganda, 10 communities from South Western Uganda, and 12 communities from Kenya. Baseline HIV prevalence Z_i was generated as a function of region R_i, covariates $\{E1_i, E4_i, E7_i\}$, and random noise U_{Z_i}. The community-specific hazard of HIV infection under study arm a at time t, denoted $h_i(a,t)$, was generated as a function of the projected incidence rate[1], community covariates $\{E2_i, E5_i, E8_i\}$, prevalence Z_i and error $U_{h_i(t)}$, which was correlated within a community over time. The number of stable, adult residents was drawn from a uniform with minimum 4,500 and maximum 6,500. The baseline coverage of HIV testing (via the baseline CHC and tracking) was drawn from a uniform with minimum of 80% and maximum of 90%.

To reflect the underlying processes, including differential measurement between study arms, we simulated the complete data $t = \{0, 1, 2, 3, 4, 5\}$ for all individuals in each community. As previously discussed, our estimators only use data measured at $t = \{0, 3, 5\}$ in both arms. The generation of the individual-level data is represented in Figure 3 for the first three years of the trial. For individual j in community i, baseline HIV status $Y_{i,j}(0)$ was generated as a function the baseline community-level prevalence Z_i and random noise $U_{Y_{i,j}(0)}$, which was correlated within an individual over time. Baseline measurement (CHC attendance or post-CHC tracking) $\Delta_{i,j}(0)$ was generated as a function of the baseline coverage probability for that community and random noise $U_{\Delta_{i,j}(0)}$, which was correlated within an individual over time. The resulting HIV Incidence Cohort was then defined as all community members who were HIV-negative and observed at baseline: $Y_{i,j}(0) = 0$ & $\Delta_{i,j}(0) = 1$. (All community members were assumed to be living, stable residents at baseline: $C_{i,j}(0) = 0$ for all j.)

For the remaining years of the trial $t > 0$, HIV status $Y_{i,j}(t)$ was generated as a function the community-specific hazard $h_i(a,t)$, and random noise $U_{Y_{i,j}(t)}$. Censoring, representing both death and outmigration, was generated as a function of the study arm A, underlying HIV status $Y_{i,j}(t)$, and random noise $U_{C_{i,j}(t)}$, which was correlated within an individual over time. For simplicity, we assumed that past observation status $\bar{\Delta}_{i,j}(t-1) = \big(\Delta_{i,j}(0), \ldots, \Delta_{i,j}(t-1)\big)$ did not affect censoring at t. We explored a variety of censoring mechanisms, ranging from non-differential to quite differential by study arm and underlying HIV status. We also explored a "mixture" scenario, where each community was randomly and independently assigned a censoring scenario with equal probability. The mixture scenario reflects that censoring might be operating in different ways in different communities.

[1]The incidence rate of HIV under exposure-level $A = a$ at time t was informed by Goals module from the Spectrum System of Futures Institute, as detailed in Section 4.3.3.

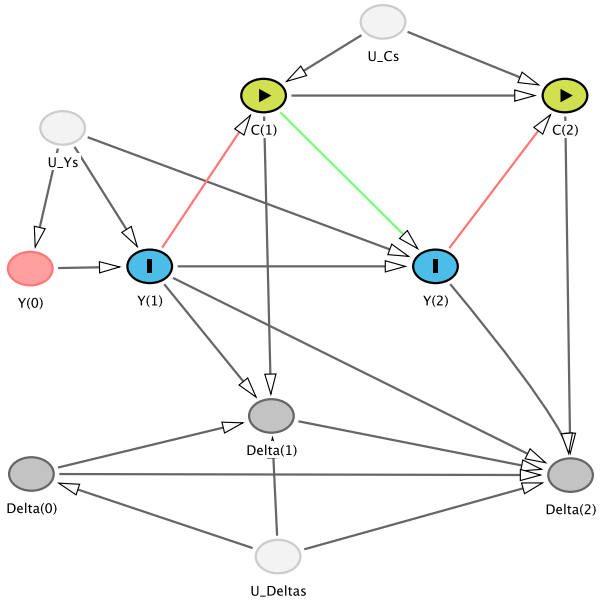

Figure 3: Directed Acyclic Graph (DAG) representing an individual's data generating process for the first 3 years of the SEARCH trial. We denote HIV status at time t as $Y(t)$, censoring status at time t as $C(t)$ and measurement (CHC or tracking) at time t as $\Delta(t)$. The unmeasured factors contributing to HIV status, censoring and measurement are denoted U_Y, U_C and U_Δ, respectively. For estimation, we condition on being in the HIV Incidence Cohort: $Y(0) = 0$ and $\Delta(0) = 1$. For simplicity, we have suppressed the subscripts, assumed everyone was living, stable residents at baseline $C(0) = 0$, omitted the community-level variables and only shown 3 time points.

We also explored two measurement (CHC attendance and tracking) mechanisms. In the first, the observation status after baseline $\Delta_{i,j}(t)$ was generated as function of the study arm A, underlying HIV status $Y_{i,j}(t)$, censoring $C_{i,j}(t)$, and random error $U_{\Delta_{i,j}(t)}$. In the second, the observation status $\Delta_{i,j}(t)$ was generated as a function of the study arm A, known HIV+ status, censoring $C_{i,j}(t)$, and random error $U_{\Delta_{i,j}(t)}$. Here, HIV+ status was "known" if an individual tested positive at a prior CHC or subsequent tracking. For each type of measurement mechanism (i.e. dependent on underlying HIV status or "known" HIV status), we explored a variety of scenarios, ranging from non-informative to quite informative by HIV status and treatment arm. As before, we generated a "mixture" scenario, where each community was randomly and independently assigned a measurement scenario with equal probability. By definition, the observation probability was 0 for control community members at $t = \{1, 2, 4\}$.

Given simulated data under both study arms, we calculated as the true value of our target parameter, the sample average treatment effect:

$$\Psi^F = \frac{1}{n}\sum_{i=1}^{n}\left[Y_i^1 - Y_i^0\right]$$

$$\text{with } Y_i^a = \frac{1}{J_i}\sum_{j=1}^{J_i} Y_{i,j}^{\bar{c}=0,\bar{\delta}=1,a}(5)$$

where $Y_{i,j}^{\bar{c}=0,\bar{\delta}=1,a}(5)$ denotes the counterfactual HIV status at year 5 for individual j in community i under interventions to prevent right-censoring, ensure measurement and set the community-level exposure. (Recall that overbars denote the history of a variable with $\bar{C} = (C(3), C(5))$ and $\bar{\Delta} = (\Delta(3), \Delta(5))$). Here j indexes the individuals in HIV Incidence Cohort (consisting of HIV-negative, living stable residents, who are seen at baseline) and J_i denotes the number of individuals in this cohort for community i. Then Y_i^a is the counterfactual proportion of seroconversions among the HIV Incidence Cohort in community i.

4.3.2 Adaptive pair-matching, intervention randomization and estimation

Using the non-bipartite matching algorithm `npbMatch` [22], we pair-matched communities within region R on baseline covariates E. We explored two matching sets. In the first, communities were matched within region on predictors of baseline prevalence and incidence $\{E1, E4, E5, E9\}$. In the second, communities were matched within region on only measured predictors of incidence $\{E2, E5, E8\}$. Table 1 depicts the relationships between the baseline variables and the community-specific hazard at time t as well as the pair-matching schemes. The intervention A was randomized within the matched pairs.

For Stage I estimation of the community-specific cumulative incidence of HIV, we implemented the non-parametric maximum likelihood estimator (NPMLE). For Stage II estimation of the intervention effect, we implemented both the unadjusted estimator as well as the TMLE with data-adaptive selection of the adjustment variable. For the latter, we used leave-one-out cross-validation, treating the pair as the independent unit, to select from a library of possible algorithms. As candidate adjustment variables we considered $\{R, E2, E5, E8, Z\}$. (Use of the full library, consisting of 11 possible regressions, resulted in similar performance.) For the unadjusted estimator, inference was based on the estimated influence curve, and for the TMLE, inference was based on a cross-validated estimate of the influence curve. For confidence interval construction and two-sided hypothesis testing, we used Student's t-distribution with 15 degrees of freedom and a 5% significance level. These estimation procedures were previously detailed in Sections 2 and 3.

	R	$E1$	$E2$	$E3$	$E4$	$E5$	$E6$	$E7$	$E8$	$E9$	Z
Parents of prevalence Z	✓	✓			✓			✓			
Parents of the hazard at t	✓		✓			✓			✓		✓
Adaptive matching set 1	✓	✓			✓	✓				✓	
Adaptive matching set 2	✓		✓			✓			✓		

Table 1: Table depicting the relationships between baseline covariates and the adaptive pair-matching schemes. Throughout, R denotes region, E denotes the set of baseline community-level covariates, and Z denotes baseline prevalence.

4.3.3 Mathematical modeling

The Goals module from the Spectrum System of Futures Institute was used to provide country-specific projections of the prevalence and incidence of HIV under the SEARCH intervention and under the control (`http://www.futuresinstitute.org/spectrum.aspx`). The software was originally developed by the Futures Group, in collaboration with Family Health International, and is supported by UNAIDS and the Gates Foundation, among others [23–25].

The mathematical model was parameterized with published data from national and regional surveys in Uganda and Kenya on HIV prevalence and coverage of male circumcision (Nyanza region of Kenya) [18, 26–30]. At baseline, we assumed 75% of eligible populations in Uganda and 66% in Kenya were on ART and virally suppressed. The model was also parameterized to reflect post-baseline changes in ART eligibility as well as scale-up of ART coverage. Specifically, the inputs for the control arm reflected in-country implementation of the guidelines to change CD4-based eligibility from ≤ 350 cells/μL to ≤ 500 cells/μL starting in 2014, and universal eligibility for key populations, including pregnant women, tuberculosis/HIV co-infected and discordant couples, starting in 2015. We generated incidence curves in the control arm under these guidelines and a range ART coverage trajectories (control scenarios A-C), in which 62-70% of eligible populations under expanded guidelines were on ART and virally suppressed by year 3 of the study. These were then contrasted with the projected incidence curves under the SEARCH intervention, assuming 73% of all HIV+ were on ART and suppressed by 18 months after baseline (Figure 4).

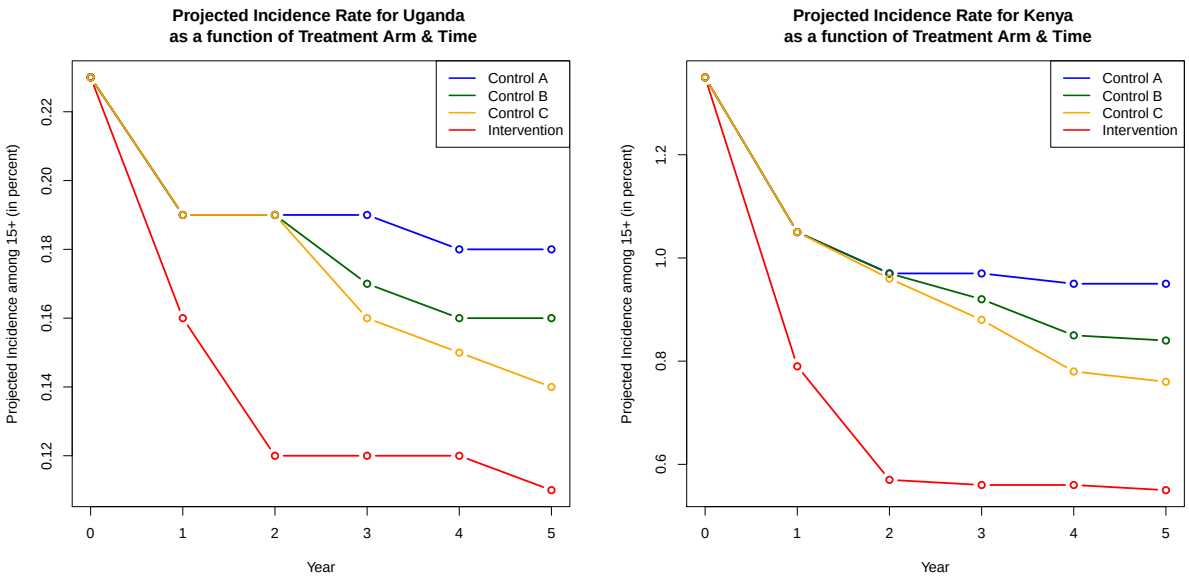

Figure 4: Projected incidence of HIV for Uganda and for Kenya as informed by the Goals module in the Spectrum System of Futures Institute [23–25]. The projected incidence rates (in percent) under the control scenario A (less conservative), control scenario B, control scenario C (more conservative) and the intervention are given by the blue, green, orange and red lines, respectively.

4.3.4 Results

Recall the true value of the statistical estimand depends on the $n = 32$ communities in the sample. Over the 500 simulated data sets, Table 2 shows the mean value of ψ_0 as the sample average difference in the five-year cumulative HIV incidence under the intervention and control. The table also gives the corresponding averages for the exposure-specific outcomes. The variance of ψ_0 and the average matched pair of coefficient of variation k_m are also given. The scenarios explored are described in Figure 4, and the matching schemes are described in Table 1.

	$\psi_0(1)$	$\psi_0(0)$	ψ_0	$Var[\psi_0]$	k_m-set1	k_m-set2
Scenario A	0.57%	0.93%	-0.36%	2.91E-8	0.31	0.25
Scenario B	0.57%	0.88%	-0.31%	2.42E-8	0.32	0.26
Scenario C	0.57%	0.84%	-0.26%	2.07E-8	0.34	0.27

Table 2: Average values and variance across 500 repetitions of the data generating experiment. $\psi_0(1)$ refers to the average risk (five-year cumulative incidence of HIV) under the intervention; $\psi_0(0)$ refers to the average risk under the control; ψ_0 is the average value of the target parameter as the sample average treatment effect. Recall this parameter changes with each sample, and $Var[\psi_0]$ gives the variability of ψ_0 across the 500 runs. Finally k_m is the average value of the estimated matched pair coefficient of variation.

Table 3 illustrates the performance of the estimators over 500 simulated data sets when there was non-differential censoring and non-informative missingess. Specifically, we compare the unadjusted estimator and the TMLE, using cross-validation with the L2 loss function to select from a set of baseline adjustment variables. Both estimators were unbiased. As expected, there was an efficiency gain with improved matching (set 1 vs. set 2). There was also an efficiency gain from adjustment. The attained power ranged from 93-77% (least to most conservative scenarios) when we match moderately ($k_m \approx 0.32$) and from 95-81% (least to most conservative) when we matched well ($k_m \approx 0.26$). Throughout, there was conservative con-

fidence interval coverage and type I error control (Table 4). Simulation results under differential censoring and informative missingness are given in the Appendix.

	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	power	bias	std. err.	tstat	cover	power
Scenario A: set 1	-2.91E-5	1.20E-3	-3.19	0.99	0.85	-2.12E-5	1.11E-3	-3.44	0.98	0.93
Scenario B: set 1	-2.60E-5	1.15E-3	-2.80	0.99	0.73	-2.52E-5	1.04E-3	-3.08	0.99	0.85
Scenario C: set 1	-2.91E-5	1.12E-3	-2.50	0.99	0.61	-2.10E-5	9.98E-4	-2.78	0.99	0.77
Scenario A: set 2	1.64E-5	1.07E-3	-3.57	1.00	0.93	-1.29E-5	1.06E-3	-3.62	0.99	0.95
Scenario B: set 2	1.64E-5	1.01E-3	-3.17	1.00	0.86	-8.20E-6	9.95E-4	-3.25	0.99	0.90
Scenario C: set 2	1.87E-5	9.66E-4	-2.86	0.99	0.76	-3.53E-6	9.43E-4	-2.96	0.99	0.81

Table 3: The bias (average deviation between the point estimate and sample-specific true value), average standard error (estimated with the influence curve), average value of the test statistic (point estimate divided by standard error estimate), confidence interval coverage (proportion of intervals containing the true parameter value) and attained power (proportion of studies correctly rejecting the false null hypothesis) of the unadjusted estimator and the TMLE over 500 simulated trials when there was non-differential censoring and non-informative missingness.

	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	α	bias	std. err.	tstat	cover	α
Scenario A: set 1	-2.55E-5	1.10E-3	-0.03	0.95	0.05	-2.35E-5	9.45E-4	-0.04	0.96	0.04
Scenario B: set 1	-1.72E-5	1.08E-3	-0.01	0.97	0.03	-3.57E-5	9.09E-4	-0.04	0.96	0.04
Scenario C: set 1	-2.15E-5	1.05E-3	-0.01	0.93	0.07	-9.39E-7	8.80E-4	-0.02	0.96	0.04
Scenario A: set 2	5.83E-5	9.40E-4	0.05	0.95	0.05	-6.52E-6	8.81E-4	-0.02	0.97	0.03
Scenario B: set 2	-1.73E-5	8.98E-4	0.00	0.95	0.05	-9.24E-6	8.39E-4	0.01	0.97	0.03
Scenario C: set 2	-2.53E-5	8.71E-4	-0.02	0.97	0.03	1.51E-5	8.15E-4	0.02	0.96	0.04

Table 4: Under the null scenario, the bias, average standard error estimate, average value of the test statistic, confidence interval coverage, and type I error rate (proportion of studies falsely rejecting the true null hypothesis) of the unadjusted estimator and the TMLE over 500 simulated trials when there was non-differential censoring and non-informative missingness. The null scenario was simulated by generating incidence as if the intervention had 0 impact (i.e. the hazard of HIV infection under the intervention equaled that of the control).

5 Secondary Health Outcomes

5.1 Overview

In addition to estimating the impact of the intervention on expected five-year cumulative incidence of HIV among adults, we will also estimate the intervention effect for the set of secondary outcomes. The secondary study health objectives are reviewed below. In this section we focus on the data sources and analyses for key secondary health outcomes, which include : vertical transmission; adult, maternal and pediatric mortality; plasma HIV RNA levels; antiretroviral resistance; AIDS; tuberculosis and opportunistic infections; as well as linkage, time to ART initiation, and retention in care for HIV-infected subjects. Given a community-level estimate for each of these secondary outcomes, statistical analyses to evaluate the intervention's effect will follow the general Stage II approach, described in Sections 3.5 and 3.6 with both adjusted and unadjusted comparisons. In the following subsection, we outline the sources of data that will be collected for each secondary outcome.

Secondary study objectives for health outcomes include

- To compare the time from diagnosis to AIDS between the 2 study arms.
- To compare the incidence of AIDS-defining events between the 2 study arms.
- To compare the proportion of total tuberculosis (TB) and incident TB cases associated with HIV between the 2 study arms.
- To compare mortality between the 2 study arms.
- To compare maternal and child mortality between the 2 study arms.
- To compare mother to child transmission between the 2 study arms.
- To compare population HIV RNA metrics between the 2 study arms.
- To determine the association between population HIV RNA metrics and HIV incidence.
- To compare the prevalence of transmitted HIV drug-resistance mutations and pharmacologic measures of ART between the 2 study arms.
- To compare rates of linkage to and retention in care for HIV-infected persons between the 2 study arms.
- To compare the time to ART-initiation between the 2 study arms.
- To characterize treatment outcomes in high CD4 count individuals (CD4>350) including: (i) CD4 cell count recovery, (ii) rate of virologic suppression, (iii) treatment-associated toxicities and grade 3 and 4 adverse events, and (iv) HIV drug resistant mutations after 1 and 2 years of treatment.
- To compare the five-year cumulative incidence of internally derived HIV infections (infections genetically linked to a prior infection among members of the same community) between the 2 study arms.
- To compare the three year cumulative incidence of HIV infections between the 2 study arms.
- To evaluate implementation of other disease care cascades (hypertension, diabetes, women and children health services) including testing, linkage and retention to care.

5.2 Data sources for the secondary health outcomes

5.2.1 Mortality

Deaths and births within each study community will be ascertained using a combination of data from the CHC, post-CHC tracking, local death registries and partnerships between staff and government-sponsored village health teams or their equivalent. We will estimate all-cause mortality among adults, children < 1 year of age (infant mortality), children < 5 years of age (pediatric mortality), and women who are pregnant or within 42 days of termination of pregnancy (pregnancy-related mortality).

5.2.2 Mother to Child Transmission of HIV

We will evaluate the effect of the intervention on the proportion of live births still alive and HIV-uninfected at 2 years, among all births and among births to HIV-infected mothers. We focus on the outcome among infants 2 years after birth to capture the intervention's effect on transmission prenatally, during birth and during breastfeeding. Evaluating HIV-free survival among all births (and not only among HIV-infected mothers) will allow us to capture the intervention's effect on vertical transmission rates due to its effect on decreasing the prevalence of HIV-infected mothers as well as any effect due to reducing the probability of a HIV-infected mother transmitting the virus to her baby.

Throughout the study, we will assess data from implementing partners on the HIV status of children born to HIV-infected women at health facilities. In addition, we will estimate the two-year HIV-free survival rates for each community with data from CHCs and post-CHC tracking of non-attendees. This will provide us with a birth cohort that is representative of the entire community (and not only of those mothers, who engage with antenatal care). Specifically, an infant will enter the cohort when his or her mother is seen at the CHC or tracked and the birth reported.

5.2.3 Plasma HIV RNA levels, CD4 cell count, and antiretroviral resistance

Dried blood spots from CHCs and post-CHC tracking will provide data to estimate HIV RNA level metrics: the geometric mean, the arithmetic mean, the median and the proportion with HIV RNA level below the limit of detection among all HIV-infected individuals. In addition, HIV RNA will be collected from all HIV-infected members of the household socioeconomic survey, providing annual data in both control and intervention communities.

Point of care CD4 cell count testing at the CHCs and among tracked subjects will allow us to estimate CD4 cell count recovery rates annually in the intervention arm and will provide population-based data after 3 and 5 years of follow-up in both arms.

Drug resistance among HIV-infected individuals will be measured by assaying dried blood spots, collected during the CHC and at tracking, for the mutations K103N, M184V, and K65R. As markers of transmitted resistance, we will estimate the proportion of treatment-naïve individuals with each and with any of these three mutations. As markers of acquired resistance, we will also estimate the proportion with resistant mutations among HIV-infected individuals, who initiated treatment one and two years prior.

Importantly, the data from the CHC with tracking will provide us with estimates of each of these metrics among all HIV-infected individuals, regardless of whether they are retained in care. In addition to comparing these community-level metrics between intervention and control communities, we will also assess how these outcomes vary as a function of CD4 at antiretroviral initiation. In particular, we will estimate these metrics in the subpopulation of subjects, initiating therapy at CD4 >350 cells/uL. Supplemental data on HIV-infected patients in care will also be obtained from clinic records.

5.2.4 Linkage, retention, and time to ART Initiation

Estimates of linkage and retention rates among all HIV-infected individuals will be generated by combining data from the CHC and tracking with clinic records. Specifically, we will estimate for each community over time the proportion of newly diagnosed HIV-infected individuals, who successfully link to care (defined as any visit to clinic), as well as the proportion retained in care (defined as at least two visits in the past 12 months). In addition, we will estimate the average time from first HIV diagnosis to ART initiation for each community.

5.2.5 Internally-derived HIV infections

Viral consensus sequences will used to estimate phylogenetic relationships and genetic distances between HIV viruses sampled during the study. These data, together with additional reference sequences, will be used to classify incident HIV infections among community cohort members as linked or not linked to previously documented infections among community members [31].

An *internally-derived* incident HIV infection will be defined as an incident HIV infection in a study participant classified, based on sequence analysis, as linked to a previously measured virus from a member of the same community. An *externally-derived* incident HIV infection will be defined as an incident HIV infection in a study participant classified as unlinked to a previously measured virus in a member of the

same community. The community-specific outcome for this secondary analysis will be the probability of becoming infected over the course of the study by an internally-derived virus.

5.2.6 Additional health outcomes

Measurement of TB, AIDS-defining events, treatment-associated toxicities and adverse events will be through passive surveillance systems and secondary data sources. Analytic methods will be used whenever possible to reduce bias.

TB cases will be identified using existing TB registries. The HIV status of TB cases will be based on (i) HIV status as recorded in the registry and (ii) linkage with SEARCH study based on name and demographic information (following an initial feasibility study).

AIDS-defining events among HIV-infected individuals will be measured by obtaining WHO Stage IV diagnoses recorded in clinic. Other information may be obtained from CHCs, tracking or hospital records. Note that measurement at the clinic will rely on linkage and retention of HIV-infected patients. The resulting outcome data will thus be subject to both selection bias and potentially informative interval censoring under a non-monotone missingness pattern (i.e. a patient will be seen at the clinic intermittently and detection of these outcomes will only be possible when he or she is seen).

5.3 Effect modification and mediation

A modification of the two-stage approach, described for the primary and secondary outcomes above, will also be applied to investigate how individual-level characteristics modify the intervention effect and the extent to which the intervention effect is mediated by update of specific intervention components. Secondary analyses may also include pooled individual-level analyses.

6 Appendix - Additional Simulation Results

6.1 Differential censoring with non-informative measurement processes

The following simulations examine the impact of differential censoring on estimator performance. (For simplicity we assume individual-level measurement process is non-informative.) As detailed in Section 2.4, Stage I estimation of the community-specific incidence of HIV relies on potentially strong identifiability assumptions. Mainly, we will incur bias if censoring (due to death or outmigration) depends strongly on underlying/unmeasured HIV status. To understand the extent of the bias in threatening our inference, we explored the following censoring mechanisms:

Censoring	HIV-		HIV+		
Scenario	txt	control	txt	control	Description
A	10%	10%	10%	10%	Non-differential
B	10%	10%	12%	14%	More likely among HIV+ & most likely among HIV+ in the control
C	10%	10%	10%	14%	HIV status only predictive in the control
D	10%	10%	14%	12%	More likely among HIV+ & most likely among HIV+ in the intervention
E	10%	10%	14%	10%	HIV status only predictive in the intervention
F	10%	10%	7%	10%	HIV+ are less likely to be censored under the intervention
G	10%	10%	7%	14%	Operating in different directions for HIV+ under the intervention and control
H	10%	10%	12%	12%	Differential by HIV status only
I	10%	12%	12%	14%	More likely among HIV+ than HIV- & among control than intervention
J	12%	10%	14%	12%	More likely among HIV+ than HIV- & among intervention than control
M	Mixed - each community was independently assigned a censoring scenario with equal probability				

The resulting estimator performance is given in Table 5 for the null scenario. In the majority of the scenarios (A, B, D, F, H, I, J, M-mixed), we achieved good confidence interval coverage and type I error control. In scenario C, we achieved reasonable type I error control, but began to see the repercussions of lack of identifiability of our Stage I estimand. In scenarios E and G, we saw the full impact of bias due to censoring by unmeasured HIV status on estimator performance. In scenario G, for example, censoring was operating in different directions among HIV+ in the two treatment arms. While the corresponding type I error rates were unacceptably high, we believe this represented an extreme and unlikely situation.

	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	α	bias	std. err.	tstat	cover	α
Censoring A	5.83E-5	9.40E-4	0.05	0.95	0.05	-6.52E-6	8.81E-4	-0.02	0.97	0.03
Censoring B	3.21E-4	9.14E-4	0.36	0.94	0.06	2.63E-4	8.56E-4	0.32	0.95	0.05
Censoring C	5.72E-4	9.27E-4	0.64	0.92	0.08	5.14E-4	8.67E-4	0.62	0.93	0.07
Censoring D	-1.91E-4	9.13E-4	-0.24	0.95	0.05	-2.49E-4	8.57E-4	-0.32	0.95	0.05
Censoring E	-4.50E-4	9.25E-4	-0.53	0.92	0.08	-5.10E-4	8.69E-4	-0.62	0.92	0.08
Censoring F	4.43E-4	9.58E-4	0.47	0.93	0.07	3.79E-4	8.94E-4	0.44	0.95	0.05
Censoring G	9.56E-4	9.50E-4	1.05	0.85	0.15	9.00E-4	8.90E-4	1.06	0.86	0.14
Censoring H	6.65E-5	9.21E-4	0.06	0.95	0.05	6.41E-6	8.62E-4	-0.00	0.96	0.04
Censoring I	6.62E-5	9.30E-4	0.06	0.94	0.06	1.25E-5	8.74E-4	0.01	0.96	0.04
Censoring J	6.01E-5	9.28E-4	0.05	0.94	0.06	3.52E-9	8.72E-4	-0.01	0.95	0.05
Censoring M	2.06E-4	9.37E-4	0.22	0.95	0.05	1.49E-4	8.77E-4	0.17	0.97	0.03

*Table 5: Under the **null** scenario, estimator performance with non-informative observation (80% for all groups), but where our identifiability assumptions for Stage I estimation are violated. Specifically, censoring depends on underlying HIV status. The censoring scenarios are described in the previous table.*

6.2 Informative measurement process with non-differential censoring

The following simulations examine the impact of informative measurement on estimator performance. (For simplicity we assume censoring is non-differential.) Now whether or not an individual is observed (i.e. attends the CHC or is tracked) may depend on his/her underlying HIV status and the study arm. For example, HIV+ individuals may be more likely to attend the health campaigns in intervention communities. Alternatively, whether or not an individual is observed may depend on his/her known HIV+ status and the study arm. For example, if an individual previously tested positive at a CHC or during tracking, then he/she may be less likely to attend the health campaign in subsequent years.

The measurement scenarios explored are given in following table. For the second measurement mechanism ("known" HIV status), community members, who are HIV- or unknown HIV+, have the same observations probabilities, as given by the first two columns. The resulting estimator performance, under the null, is given in Table 6 for informative measurement by underlying HIV status and by known HIV status. For all scenarios explored, we see good confidence interval coverage and type I error control.

Measurement	HIV-		HIV+		
Scenario	txt	control	txt	control	Description
A	80%	80%	80%	80%	Non-differential
B	80%	80%	75%	75%	Differential by HIV status
C	80%	75%	80%	75%	Differential by treatment arm
D	85%	80%	80%	75%	Differential by HIV status and treatment arm
E	75%	72.5%	70%	67.5%	Differential by HIV status and treatment arm
M	Mixed - each community was randomly assigned an observation scenario with equal probability				

Observation depends on underlying HIV status & study arm										
	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	α	bias	std. err.	tstat	cover	α
Measurement A	5.83E-5	9.40E-4	0.05	0.95	0.05	-6.52E-6	8.81E-4	-0.02	0.97	0.03
Measurement B	5.69E-5	9.09E-4	0.06	0.95	0.05	-4.81E-6	8.54E-4	-0.01	0.97	0.03
Measurement C	5.78E-5	9.49E-4	0.05	0.95	0.05	-5.94E-6	8.88E-4	-0.01	0.97	0.03
Measurement D	1.05E-4	9.03E-4	0.11	0.96	0.04	4.60E-5	8.44E-4	0.05	0.96	0.04
Measurement E	8.26E-5	9.28E-4	0.09	0.94	0.06	1.85E-5	8.77E-4	0.02	0.96	0.04
Measurement M	6.98E-5	9.30E-4	0.07	0.95	0.05	-3.74E-6	8.76E-4	-0.01	0.97	0.03
Observation depends on known HIV status & study arm										
	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	α	bias	std. err.	tstat	cover	α
Measurement A	5.83E-5	9.40E-4	0.05	0.95	0.05	-6.52E-6	8.81E-4	-0.02	0.97	0.03
Measurement B	-1.61E-4	9.32E-4	-0.20	0.94	0.06	-2.32E-4	8.75E-4	-0.29	0.95	0.05
Measurement C	5.78E-5	9.49E-4	0.05	0.95	0.05	-5.94E-6	8.88E-4	-0.01	0.97	0.03
Measurement D	-1.48E-4	9.25E-4	-0.18	0.94	0.06	-2.14E-4	8.65E-4	-0.27	0.96	0.04
Measurement E	-1.75E-4	9.55E-4	-0.20	0.94	0.06	-2.38E-4	8.99E-4	-0.28	0.96	0.04
Measurement M	-7.67E-5	9.42E-4	-0.10	0.95	0.05	-1.47E-4	8.84E-4	-0.18	0.96	0.04

*Table 6: Under the **null** scenario, estimator performance with non-differential censoring (10% for all groups), but where the probability of being observed depends on underlying HIV status or depends on known HIV status. The measurement scenarios are described in the previous table.*

6.3 Power under a mixture of differential censoring and informative missingness

Table 7 illustrates estimator performance and attained power when there was a mixture of differential censoring mechanisms and informative measurement mechanisms across communities within each simulated study. (See Appendix 6.1 and 6.2 for the scenarios explored and further discussion.) As expected, the bias (average deviation between the point estimate and sample-specific true value) was higher, but did not meaningfully harm estimator performance. Again, the attained power was improved with better matching and with data-adaptive adjustment. The confidence interval coverage was conservative for both estimators.

	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	power	bias	std. err.	tstat	cover	power
Scenario A: set 1	2.27E-4	1.15E-3	-3.07	0.97	0.84	2.04E-4	1.07E-3	-3.32	0.98	0.89
Scenario B: set 1	2.07E-4	1.10E-3	-2.68	0.97	0.69	1.86E-4	1.01E-3	-2.95	0.97	0.81
Scenario C: set 1	1.95E-4	1.06E-3	-2.38	0.96	0.58	1.68E-4	9.60E-4	-2.67	0.97	0.72
Scenario A: set 2	1.53E-4	1.03E-3	-3.51	0.98	0.93	1.41E-4	1.03E-3	-3.56	0.97	0.94
Scenario B: set 2	1.39E-4	9.75E-4	-3.11	0.98	0.85	1.31E-4	9.59E-4	-3.19	0.97	0.87
Scenario C: set 2	1.30E-4	9.32E-4	-2.80	0.98	0.76	1.18E-4	9.10E-4	-2.90	0.98	0.79

*Table 7: The bias, average standard error estimate, average value of the test statistic, confidence interval coverage and attained power of the unadjusted estimator and the TMLE, when there were a **mixture** of censoring and measurement mechanisms across communities within each simulated 500 trials.*

References

[1] M.L. Petersen, J. Schwab, S. Gruber, N. Blaser, M. Schomaker, and M. van der Laan. Targeted maximum likelihood estimation for dynamic and static marginal structural working models. *Journal of Causal Inference*, 2(2):DOI: 10.1515/jci–2013–0007, 2014.

[2] E.C. Polley and M.J. van der Laan. Super learner in prediction. Technical Report 266, Division of Biostatistics, University of California, Berkeley, 2010. Available at `http://www.bepress.com/ucbbiostat/paper266/`.

[3] M.J. van der Laan, L.B. Balzer, and M.L. Petersen. Adaptive Matching in Randomized Trials and Observational Studies. *Journal of Statistical Research*, 46(2):113–156, 2012.

[4] L.B. Balzer, M.L. Petersen, M.J. van der Laan, and the SEARCH Consortium. Adaptive pair-matching in the SEARCH trial and estimation of the intervention effect. *Statistics in Medicine*, In press, 2014. doi: 10.1002/sim.6380.

[5] Donald B. Rubin. Comment: Neyman (1923) and causal inference in experiments and observational studies. *Stat Sci*, 5(4):472–480, 1990.

[6] G.W. Imbens. Nonparametric estimation of average treatment effects under exogeneity: a review. *Review of Economics and Statistics*, 86(1):4–29, 2004. doi: 10.1162/003465304323023651.

[7] K. Imai. Variance identification and efficiency analysis in randomized experiments under the matched-pair design. *Statistics in Medicine*, 27(24):4857–4873, 2008. doi: 10.1002/sim.3337.

[8] L. Balzer, M. Petersen, and M.J. van der Laan. Estimation and inference of the sample average treatment effect. *In Progress*, 2014.

[9] K.L. Moore and M.J. van der Laan. Covariate adjustment in randomized trials with binary outcomes: Targeted maximum likelihood estimation. *Statistics in Medicine*, 28(1):39–64, 2009. doi: 10.1002/sim.3445.

[10] M. Rosenblum and M.J. van der Laan. Optimizing randomized trial designs to distinguish which subpopulations benefit from treatment. *Biometrika*, 98(4):845–860, 2011. PMCID: PMC3413180.

[11] M.J. van der Laan and D.B. Rubin. Targeted maximum likelihood learning. *The International Journal of Biostatistics*, 2(1):Article 11, 2006. doi: 10.2202/1557-4679.1043.

[12] Daniel B. Rubin and M.J. van der Laan. Empirical efficiency maximization: improved locally efficient covariate adjustment in randomized experiments and survival analysis. *The International Journal of Biostatistics*, 4(1):Article 5, 2008. doi: 10.2202/1557-4679.1084.

[13] R.J. Hayes and L.H. Moulton. *Cluster Randomized Trials*. Chapman & Hall/CRC, Boca Raton, 2009.

[14] A. Abadie and G. Imbens. Simple and bias-corrected matching estimators for average treatment effects. Technical Report 283, NBER technical working paper, 2002.

[15] A. Abadie and G.W. Imbens. Estimation of the conditional variance in paired experiments. *Annales d'Economie et de Statistique*, (91/92):175–187, 2008.

[16] R.J. Hayes and L.H. Moulton. *Cluster Randomised Trials*. Chapman & Hall/CRC, Boca Raton, 2009.

[17] D. Guwatudde, F. Wabwire-Mangen, L.A. Eller, M. Eller, F. McCutchan, H. Kibuuka, M. Millard, N. Sewankambo, D. Serwadda, N. Michael, M. Robb, and the Kayunga Cohort Research Team. Relatively Low HIV Infection Rates in Rural Uganda, but with High Potential for a Rise: A Cohort Study in Kayunga District, Uganda. *PLoS ONE*, 4(1):e4145, 2009.

[18] L.A. Shafer, S. Biraro, J. Nakiyingi-Miiro, A. Kamali, D. Ssematimba, J. Ouma, A. Ojwiya, P. Hughes, L. Van der Paal, J. Whitworth, A. Opio, and H. Grosskurth. HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989-2005. *AIDS*, 22 (13):1641–1649, 2008.

[19] R.H. Gray, G. Kigozi, D. Serwadda, F. Makumbi, S. Watya, F. Nalugoda, N. Kiwanuka, L.H. Moulton, M.A. Chaudhary, M.Z. Chen, N.K. Sewankambo, F. Wabwire-Mangen, M.C. Bacon, C.F. Williams, P. Opendi, S.J. Reynolds, O. Laeyendecker, T.C. Quinn, and M.J. Wawer. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*, 369(9562):657–666, 2007.

[20] C. Pagel, A. Prost, S. Lewycka, S. Das, T. Colbourn, R. Mahapatra, K. Azad, A. Costello, and D. Osrin. Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomised controlled trials in low and middle-income countries: results and methodological implications. *Trials*, 12(1):151, 2011.

[21] R. Hayes, F. Mosha, A. Nicoll, H. Grosskurth, J. Newell, J. Killewo, J. Rugemalila, and D. Mabey. A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 1. design. *AIDS*, 9(8):919–926, 1995.

[22] B. Lu, R. Greevy, and C. Beck. *nbpMatching: functions for non-bipartite optimal matching*, 2012. URL `http://CRAN.R-project.org/package=nbpMatching`. R package version 1.3.6.

[23] Futures Institute. *Spectrum manual: Spectrum system of policy manuals*, 2014.

[24] Futures Institute. *Goal Manual - A model for estimating the effects of interventions and resource allocation on HIV infections and deaths*, 2011.

[25] Futures Institute. *AIM: A Computer Program for Making HIV/AIDS Projections and Examining the Demographic and Social Impacts of AIDS*, 2014.

[26] Uganda Ministry of Health and ORC Macro. Uganda HIV/AIDS sero-behavioural survey 2004-2005. Calverton, Maryland, USA, 2006.

[27] Uganda Ministry of Health and ICF Internatial. 2011 Uganda AIDS indicator survey: Key findings, Calverton, Maryland, USA 2012.

[28] UNAIDS. HIV estimates with uncertainty bounds 1990-2012, 2013. Avaliable at `http://www.unaids.org/en/resources/campaigns/globalreport2013/globalreport/`.

[29] National AIDS and STI Control Programme (NASCOP). Kenya AIDS indicator survey 2012: Final report. Nairobi, NASCOP, 2014.

[30] D.O. Kimanga and et al. Prevalence and incidence of HIV infection, trends, and risk factors among persons aged 15-64 years in Kenya: results from a nationally representative study. *J Acquir Immune Defic Syndr*, 66(Suppl 1):S13–26, 2014.

[31] Mary S. Campbell, James I. Mullins, James P. Hughes, Connie Celum, Kim G. Wong, Dana N. Raugi, Stefanie Sorensen, Julia N. Stoddard, Hong Zhao, Wenjie Deng, Erin Kahle, Dana Panteleeff, Jared M. Baeten, Francine E. McCutchan, Jan Albert, Thomas Leitner, Anna Wald, Lawrence Corey, Jairam R. Lingappa, and for the Partners in Prevention HSV/HIV Transmission Study Team. Viral linkage in hiv-1 seroconverters and their partners in an hiv-1 prevention clinical trial. *PLoS ONE*, 6(3):e16986, 03 2011. doi: 10.1371/journal.pone.0016986. URL `http://dx.doi.org/10.1371%2Fjournal.pone.0016986`.

Sustainable East Africa Research in Community Health (SEARCH): a community cluster randomized study of HIV "test and treat" using multi-disease approach in rural Uganda and Kenya

Statistical Analysis Plan for Phase I: Health Outcomes among Adults

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November 27, 2017
Version 3.0

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1 Overview

The Sustainable East Africa Research in Community Health (SEARCH) Study is a two-phase pair-matched cluster randomized trial, conducted in rural Kenya and Uganda. The first phase is designed to evaluate the impact of i) annual HIV and non-communicable disease (hypertension and diabetes) population-level testing, ii) immediate antiretroviral (ART) eligibility for all HIV-positive persons, and iii) ART, hypertension (HT) and diabetes (DM) care delivered using a streamlined patient-centered model, compared to an active control consisting of i) baseline population-level HIV and HT/DM testing, and ii) ART and HT/DM care delivered according to national guidelines. Inclusion and exclusion criteria as well as definition of the control and intervention arms for Phase I are reviewed below.

This document provides the analytic plan for evaluating adult HIV incidence, health, and implementation outcomes for the first phase of the SEARCH Study, including:

- Incident HIV infection
- HIV testing uptake and coverage
- ART initiation and coverage
- Plasma HIV RNA suppression
- Mortality
- Tuberculosis
- Hypertension and diabetes control

Primary outcome analyses will be conducted after all SEARCH communities have completed three full years of follow-up.

For all comparisons between intervention and control arms, we take a two-stage approach to our analysis. In Stage I, we estimate the community-level outcomes defined below. In Stage II, we compare average the community-level outcomes between intervention and control communities, accounting for the pair-matched study design and with pre-specified adjustment for baseline factors. Primary effect estimates will be reported on a relative scale (relative risk or rate), with variance estimates based on the estimated influence curve, accounting for the pair-matched design, and inference based on the t-distribution with 15 degrees of freedom [1–3]. Key analytic decisions for each outcome include the choice of candidate adjustment variables and the weights given to each community [4]; below, we pre-specify these decisions for each outcome considered. An additional analytic option in Stage II is to "break the match" and treat the community as the unit of independence; we implement this as a sensitivity analysis for each outcome considered.

Additional explanatory and descriptive analyses are also detailed below. We will provide descriptive statistics of the baseline characteristics of study participants, stratified by region, and (among those with baseline HIV status measured) baseline HIV status. Characteristics reported will include sex, age, marital status (single, married, widowed, divorced/separated), education (no school, primary, secondary, post-secondary), occupation, household wealth index (based on principal components analysis of baseline household socioeconomic survey, as described in protocol), self-reported alcohol and contraceptive use, self-reported prior HIV testing history, stable residence ($\leq$6 months of past year outside of the community), and mobility ($\geq$1 month of past year outside of the community).

For each study outcome compared between arms, we will report formal consort diagrams as well as participant flow diagrams enumerating inclusions and exclusions for all individuals contributing to the analysis.

The document is organized as follows. Section (2) provides an analytic plan for measurement and estimation of three-year cumulative incidence of HIV for each community (Stage I). Section (3) provides an analytic plan for estimation of and inference for the effect of the randomized intervention on this outcome (Stage II). Section (4) provides corresponding power calculations under a range of scenarios. Section (5) provides additional analyses of the HIV incidence outcome, including evaluation of the change in annual HIV incidence over time. Section (6) provides analyses describing contextual factors potentially contributing to observed HIV incidence patterns and investigating community-level drivers of HIV transmission. Section (7) describes analyses of intervention uptake, including the HIV care cascade and plasma HIV RNA suppression. Section (8) describes analyses of mortality, tuberculosis, and non-communicable disease outcomes, as well as ART-associated toxicities and antiretroviral resistance. Full analysis plans for (i) evaluating child and maternal HIV and health outcomes, (ii) supplemental analyses to investiage HIV transmission patterns and drivers, and (iii) evaluating economic, educational, qualitative and costing outcomes, are provided in separate documents.

1.1 Community selection and pair-matching

Fifty-four candidate communities meeting the following inclusion and exclusion criteria were initially selected in Kenya and Uganda:

Inclusion criteria:

- Most recent census population between 9,000 and 11,000 individuals.
- Served by a government health center, already providing ART or a highly functioning health center at one organizational level below those generally providing ART.
- Community leaders' consent to ethnographic mapping.
- Accessibility to health center via a maintained transportation route.
- Community location with sufficient distance from other potential study communities to limit contamination of intervention or control conditions (i.e. a buffer zone).

Exclusion criteria:

- Presence of ongoing community-based ART intervention strategies that provide treatment outside of the current in-country treatment guidelines.
- An urban setting, defined as a city with a population of 100,000 or more inhabitants.
- National government not willing or opposed to support commodities needed for Community-based Health Campaign (CHC), if provided by an outside organization.

Data on these communities were gathered with ethnographic mapping. Of the 54 communities, the best 16 matched pairs (5 pairs in Western Uganda, 5 pairs in Eastern Uganda, and 6 pairs in Western Kenya) were selected. Communities were matched based on region, population density, occupational mix, trading centers, and migration.

1.2 Phase I study arms

One community in each matched pair was randomly assigned to "Control" and one to "Intervention".

Control:

- Baseline household enumeration
- At baseline (Year 0) and Year 3, Community-based Health Campaigns (CHCs) with multi-disease prevention and treatment services, including testing and referral for HIV, hypertension (HT), and diabetes (DM)
- At baseline and Year 3, home-based or in-community testing for all CHC non-attendees

- ART and HT/DM care according to national guidelines

Intervention:

- Baseline household enumeration
- Annual CHCs with multi-disease prevention and treatment services, including testing and referral for HIV, HT, and DM
- Annual home-based or in-community testing for all CHC non-attendees
- Streamlined HIV Care:
  - Immediate ART eligibility for all HIV+
  - Supported linkage
  - Rapid ART start
  - Patient-centered care
  - Enhanced retention
- Preplanned HIV cascade optimization
- HT/DM care delivered using streamlined model

The core intervention components and the cascade optimization strategy are detailed in a separate document.

2 Stage I: Estimation of three-year cumulative HIV incidence in each community

This section is focused on estimating the three-year cumulative HIV incidence in each community. We first define the primary cohort for measurement. Then we formally define the Stage I target parameter (community-specific three-year cumulative HIV incidence) and provide an overview of assumptions used to identify this parameter. Finally, we describe our estimator of the community-specific cumulative incidence, which incorporates incomplete CHC attendance, tracking coverage, and right-censoring due to death or out-migration.

2.1 Defining the HIV Incidence Cohort

In each community, we seek to identify a cohort of baseline HIV-negative, adult residents on whom we will measure the primary outcome of HIV seroconversion. This cohort is generated through

1. Enumeration of community residents during the baseline household census
2. Measuring HIV status and other variable at the baseline CHC
3. Tracking and evaluation, including home-based HIV testing, of residents who do not attend the baseline CHC

We define *enumerated residents* as those who report (or are reported by a key informant) during the census as living in a household within the community-specific geographic boundaries or those who link to an enumerated household at the time of the baseline CHC. A resident is classified as *stable* if at the time of census he or she reports (or is reported by a key informant) as living outside the parish/sublocation for ≤ 6 months of the preceding 12 months. A resident is classified as an *adult* if he or she is ≥ 15 years of age at baseline.

We define the **HIV Incidence Cohort** as all enumerated, stable community residents who are $\geq$ 15 years of age at baseline (adults), and who have documented HIV-negative serostatus by the close of baseline tracking. We exclude individuals who have moved out of the community before the close of baseline

tracking, as well as individuals who have a Ministry of Health clinic or laboratory record indicating HIV care prior to their baseline HIV rapid antibody test.

2.2 Individual-level data

During the census, we measure individual-level data, including age, sex, occupation, location of residence and marital status. For individuals attending a CHC or non-attendees who are successfully tracked, we measure vital status, out-migration status, HIV status, individual-specific covariates including changes in baseline enumeration variables and health outcomes as specified in the protocol. This population-based testing (via the CHC with tracking) occurs annually in the intervention communities and at years 0 and 3 in the control communities.

To simplify notation and presentation, we define the following individual-level data for members of the HIV Incidence Cohort:

- W: covariates measured during the baseline census and at the baseline CHC/tracking (e.g. age, sex, marital status, occupation, education)
- C: an indicator of death or out-migration (defined below) by year 3
- Δ: an indicator of having HIV serostatus (and other covariates) observed at either the CHC or through tracking at year 3
- I: an indicator of having a confirmed HIV-positive diagnosis at year 3 testing (CHC or post-CHC tracking).

The observed data structure for individual i is thus

$$O_i = (W_i, C_i, \Delta_i, \Delta_i I_i)\,. \tag{1}$$

We also observe community-level covariates E (including the size of the incidence cohort in each community) and the randomly assigned community treatment arm A. Because E and A are constant across a community and thus will not impact estimation of the community-level outcome, we omit these variables from our specification of the individual-level longitudinal data structure within a community.

2.2.1 Out-migration

When defining out-migration, we would ideally distinguish between migration patterns resulting in potential exposures to HIV infection primarily within the SEARCH community (which more accurately reflect the risk were an intervention rolled out more broadly) from migration patterns resulting in potential exposures to HIV infection primarily outside the SEARCH community (which provide less relevant information about the counterfactual exposure-level of interest). Such an ideal definition is unknown, likely to vary across communities, and likely to depend on information difficult to measure in practice. Therefore, in the primary analysis we use a definition of out-migration that attempts to avoid censoring individuals whose primary exposure continues to occur within the community, and accept that as a result we may fail to censor people whose primary exposure is outside the community.

An individual will be defined as out-migrated at year 3 if he or she (or a key informant if personal report is not available) reports either of the following.

1. Spending > 6 months of the preceding year outside of the community.
2. Within the preceding 3 years, spending >12 contiguous months outside of the community.

Because less mobile individuals may also represent a selected subset of the population, we will conduct a secondary analyses in which we do not censor at out-migration, as detailed below.

2.3 Target parameter: Community-specific cumulative incidence

In each community-specific cohort, incident HIV cases are identified by repeat testing at year 3 (i.e. three years after the baseline testing campaign), as described above and detailed in the protocol. HIV status at year 3 will not be observed for all members of the Incidence Cohort due to death, out-migration, and incomplete CHC attendance with incomplete success at tracking non-attendees. Let $I(c, \delta)$ denote the counterfactual HIV infection status at year 3 under a hypothetical intervention to set censoring $C = c$ and measurement $\Delta = \delta$. We define our Stage I target causal parameter as the probability that a member of the HIV Incidence Cohort becomes infected with HIV during three years of follow-up under a hypothetical intervention to prevent right-censoring and ensure knowledge of HIV status at year 3:

$$\mathbb{E}[I(0,1)] = \mathbb{P}[I(0,1) = 1]$$

In the primary analysis, death will be treated as a right-censoring event. In secondary analyses, we will use HIV-free survival as a composite outcome. The decision not to treat death as a competing risk in the primary analysis is based on the desire to define a community-level outcome that is not a function of underlying mortality patterns. The decision not to use HIV-free survival for our primary analysis is based on the expectation that the majority of mortality in our HIV Incidence Cohort will not be related to HIV nor will it be strongly affected by the intervention.

In the primary analysis, out-migration will also be treated as a right-censoring event. We take this approach because subjects who migrate out of an intervention community may be exposed to a higher risk of HIV acquisition than exists within the community and thereby would dilute the effect of the intervention. Further, this dilution would be less likely to occur if a comparable strategy were rolled out region-wide, diminishing generalizability to the future context of interest. In secondary analyses we will (i) censor only at death and (ii) evaluate the impact of the intervention on internally-derived HIV infections, as determined through phylogenetic analysis and through self-reported suspected infection source among seroconversions.

We note that defining the community-specific outcome conditional on being a member of the HIV Incidence Cohort avoids additional assumptions on factors determining baseline testing success and corresponding complexity during estimation. However, it introduces the possibility that the HIV Incidence Cohort is not fully representative of the underlying community. Our design attempts to mitigate this risk to the extent possible by using a prioritized tracking system at baseline. After completion of initial tracking, any age-sex strata in which $< 80\%$ of enumerated, stable, adult residents have known serostatus are targeted for additional tracking. To investigate the representativeness of our baseline cohort, we will report descriptive statistics comparing the age, sex and geospatial distribution of subjects seen at the baseline CHC or tracked to those enumerated in the baseline census.

2.4 Identification and estimation

The community-specific cumulative incidence $\mathbb{E}[I(0,1)] = \mathbb{P}[I(0,1) = 1]$ can be expressed as function of the observed data distribution if the randomization assumption holds [5]:

$$I(0,1) \perp\!\!\!\perp C, \Delta \mid W$$

This assumption allows censoring (by death or out-migration) and measurement (CHC attendance and tracking success at year 3) to depend on the measured baseline covariates. It fails, however, if an individual's probability of either censoring or measurement depends on his or her interim HIV status. Reliance on this identifying assumption would also imply the use of a full adjustment set (i.e. all baseline covariates) during estimation of the Stage I target parameter. This would result in more complex estimators with unclear benefit to overall estimator performance (bias, mean squared error, confidence interval coverage, and Type I error control) when evaluating the impact of the intervention (Stage II target parameter). (For example,

use of a full adjustment set might reduce performance if bias occurs in the same direction in intervention and control arms and/or if certain covariates strongly predict censoring and measurement but have a minimal impact on the outcome.)

In the primary analysis, we therefore rely on the following stronger identifiability assumption:

$$I(0,1) \perp\!\!\!\perp C, \Delta.$$

While HIV infection between baseline and year 3 could plausibly affect subsequent censoring or measurement (resulting in a violation of these assumptions), we minimize the extent to which this bias is likely to be differential in treatment and control arms by relying on the equivalent measurement structures in both arms. (In other words, we only use data from baseline and year 3 for estimation of the three-year cumulative incidence in both study arms.) Further, under a range of plausible scenarios, the direction of the bias in estimates of community-specific cumulative incidence is likely to be the same in control and intervention arms, and thus result in some degree of bias cancellation for estimates of the intervention effect. Simulations, under a range of both plausible and extreme informative measurement and censoring processes, verify this prediction and show good confidence interval coverage and type I error control for effect estimates based on this approach.

In the primary analysis, our target statistical estimand is then

$$\mathbb{E}\left[I \middle| C=0, \Delta=1\right] = \mathbb{P}\left[I=1 \middle| C=0, \Delta=1\right]. \tag{2}$$

Community-specific HIV cumulative incidence will be estimated as the corresponding simple empirical proportion of Incidence Cohort members who remain alive and resident in the community at year 3 with HIV status measured at year 3 testing who are confirmed to be HIV-positive at year 3 testing.

In sensitivity analyses, we will use baseline covariates W to adjust for potentially informative censoring and missingness. When implementing these secondary analyses with a full adjustment set, we will use targeted maximum likelihood estimation (TMLE) to estimate

$$\mathbb{E}_W \mathbb{E}\left[I \middle| C=0, \Delta=1, W)\right], \tag{3}$$

with Super Learning for estimation of the outcome regression $\mathbb{E}\left[I \middle| C=0, \Delta=1, W\right]$ and propensity score $\mathbb{P}[C=0, \Delta=1|W]$ [6–8]. We will also conduct additional sensitivity analyses in which we use an analogous approach to further adjust for known interim HIV diagnosis (acknowledging that our measurement of interim diagnosis is expected to be greater in the intervention arm). Finally, while by design we expect very similar follow-up times in intervention and control communities, in further sensitivity analyses we will estimate community-specific HIV incidence rates over the three year follow-up period (using analogous data structures in intervention versus control arms and assuming incident infections occur at the midpoint between the baseline negative HIV test and confirmed seroconversion at year 3).

Additional secondary analyses will use the annual data available in the intervention communities to investigate HIV incidence over time and factors contributing to ongoing transmission (as detailed further below and in the supplementary analysis plan focused on drivers of transmission). In addition, we will report estimates of the three-year cumulative HIV incidence for each community, and compare characteristics of cohort members with HIV status known versus missing at follow-up year 3.

3 Stage II: Estimation of the intervention effect on HIV incidence

This section is focused on obtaining a point estimate and inference for the relative difference in 3 year HIV cumulative incidence between intervention and control arms. We first describe the community-level data and implications of the pair-matched design. Then we specify the target parameter for Stage II as the

expected HIV incidence under the intervention relative to the expected HIV incidence under the control for the study communities. Primary analysis weights each community equally; sensitivity analyses will weight individuals equally.

Next we discuss two estimation strategies - unadjusted and adjusted. Our primary analysis will be adjusted.

3.1 Community-level data and adaptive pair-matching

Given estimates of the community-specific cumulative HIV incidence generated in Stage I, the observed data can be simplified to the cluster-level. Let E represent the baseline community-level covariates, including measures from the ethnographic mapping (e.g. region, proximity to trucking routes, occupational mix), the census (e.g. age distribution, sex ratio, community size), and the baseline CHC with tracking (e.g. HIV prevalence). The exposure variable A equals 1 if the community was randomized to the intervention arm and equals 0 if the community was randomized to the control arm. The outcome Y is the estimated community-specific three-year cumulative incidence of HIV (obtained from Stage I). Thereby, the observed data for SEARCH community j can be denoted

$$O_j = (E_j, A_j, Y_j)$$

for $j = \{1, \ldots, 32\}$. We use J to denote the total number of communities in the study ($J = 32$).

As described in Section 1.1, fifty-four communities were identified from rural Uganda and Kenya as potential study sites. From these candidate communities, the $J/2 = 16$ pairs (5 in Western Uganda, 5 in Eastern Uganda, and 6 in Kenya) that were best matched on baseline covariates were selected. We consider this pair-matching scheme to be adaptive, because the partitioning of the study communities into matched pairs was a function of the baseline covariates of all candidates. This adaptive design has important implications for estimation and inference [1, 2, 9]. Given the covariates of all candidate communities, the observed data can be represented as $J/2$ conditionally independent random variables:

$$\bar{O}_k = \big(O_{k1}, O_{k2}\big) = \big((E_{k1}, A_{k1}, Y_{k1}), (E_{k2}, A_{k2}, Y_{k2})\big)$$

where the index $k = \{1, \ldots, 16\}$ denotes the partitioning of the candidates into matched pairs according to similarity on their baseline covariates. Throughout, subscripts $k1$ and $k2$ denote the first and second communities within matched pair k. The treatment mechanism is known; with probability 0.5, the first unit is randomized to the intervention and the second to the control. Throughout we assume that the baseline covariates and the intervention assignment in one community do not affect the outcome of another study community. In other words, we assume the study communities are causally independent. Self-reported residence location of suspected infection source among seroconversions, as well as linkage of nominated social network contacts across communities, will be used to evaluate the extent of possible spill-over across communities.

3.2 Target parameter: Incidence ratio

Our goal in the primary analysis is to estimate the effect of the SEARCH intervention on three-year cumulative HIV incidence for our study communities. Let $Y_j(a)$ denote the counterfactual cumulative HIV incidence under intervention level $A = a$ for community j, and let

$$\psi(a) = \frac{1}{J} \sum_{j=1}^{J} Y_j(a)$$

be the empirical mean for the study communities. Then our target of inference is the sample cumulative incidence ratio

$$\frac{\psi(1)}{\psi(0)} = \frac{\frac{1}{J}\sum_{j=1}^{J} Y_j(1)}{\frac{1}{J}\sum_{j=1}^{J} Y_j(0)}$$

This parameter is the average incidence under the intervention for the 32 study communities divided by the average incidence under the control for the 32 study communities. As discussed in the following sections, estimation and inference for the sample parameter ($\frac{1}{J}\sum_{j=1}^{J} Y_j(a)$) are identical to estimation and inference for the conditional parameter ($1/J\sum_j \mathbb{E}\left[Y_j(a) \mid E_j\right]$) and analogous to the population parameter $\mathbb{E}[Y(a)]$. The distinction lies in interpretation and inference, with estimators of the sample parameter often being less variable (more precise) than those of the population parameter [2, 10–12].

3.3 Estimation of the intervention effect

An intuitive estimator is the average outcome among intervention units divided by the average outcome among the control units:

$$Unadj. = \frac{\hat{\psi}(1)}{\hat{\psi}(0)} = \frac{\hat{\mathbb{E}}(Y|A=1)}{\hat{\mathbb{E}}(Y|A=0)}.$$

When the measured covariates are predictive of the outcome, this simple estimator is often *inefficient* as it fails to adjust for measured covariates (e.g [13–18]). Irrespective of how well matching is performed, there is likely to be some residual imbalance on pre-intervention determinants of the outcome within matched pairs. Furthermore, there are additional baseline covariates, such as baseline HIV prevalence, that are predictive of the outcome but were unavailable during the matching process. In general, adjusting for baseline covariates during the analysis can reduce variance without bias, even in small trials (e.g. [17, 18]).

Therefore, for the primary analysis we will use targeted minimum loss-based estimation (TMLE) to provide an unbiased and more efficient estimate of the intervention effect [2, 6]. For comparison, in secondary analyses we will also implement the unadjusted estimator. The TMLE for the sample incidence ratio is given by the following substitution estimator:

$$TMLE = \frac{\hat{\psi}^*(1)}{\hat{\psi}^*(0)} = \frac{\frac{1}{J}\sum_{j=1}^{J} \hat{\mathbb{E}}^*(Y_j|A_j=1, E_j)}{\frac{1}{J}\sum_{j=1}^{J} \hat{\mathbb{E}}^*(Y_j|A_j=0, E_j)}$$

where $\hat{\mathbb{E}}^*(Y|A,E)$ denotes a targeted estimate of the conditional mean function $\mathbb{E}(Y|A,E)$. In general, this targeting step is used to achieve the optimal bias-variance trade-off for the parameter of interest and to solve the efficient score equation [6, 19]. Informally, this targeting step incorporates information in the known or estimated exposure mechanism $\mathbb{P}(A|E)$. The algorithm is detailed in [6].

Our *a priori*-specified library of candidate estimators of the expected outcome given intervention arm and covariates, $\mathbb{E}(Y|A,E)$, consists of community-level logistic regressions, each with an intercept, a main term for the exposure, and either one additional covariate (baseline HIV prevalence or baseline male circumcision coverage), or no additional variable (unadjusted estimator). Our *a priori*-specified library of candidate estimators of the known exposure mechanism $\mathbb{P}(A|E) = 0.5$ is defined by logistic regression models with an intercept and a main term for one remaining covariate. For example, if baseline prevalence is selected as the adjustment variable in $\mathbb{E}(Y|A,E)$, the corresponding logistic regression is removed from the set of candidate adjustment variables for the exposure mechanism $\mathbb{P}(A|E)$. To further reduce the library size, we restrict the candidates such that if the unadjusted estimator is selected for estimation of $\mathbb{E}(Y|A,E)$, we will also not adjust when estimating the known exposure mechanism. We will use leave-one-pair-out cross-validation to select the candidate TMLE, with candidate selected to minimize the estimated variance (described in the following section). The procedure is detailed in [4].

In anticipation that certain communities may be poorly matched on baseline drivers of incidence, a challenge only partially addressed by covariate adjustment, we will also conduct two pre-specified secondary analyses: excluding the matched pair with the highest discrepancy on baseline prevalence and excluding the matched pair with the highest discrepancy on baseline male circumcision coverage. Standard power calculations suggest that the reduction in matched pair coefficient of variation k_m offsets the loss in the number of independent units and thus degrees of freedom (Figure 2) [3]. Finally, as a sensitivity analysis, we will "break the match", treating the community as the independent unit and including region in the pre-specified candidate adjustment variables.

3.4 Inference

As established in [2], both the unadjusted estimator and TMLE are asymptotically linear and normally distributed estimators of treatment-specific mean: $\psi(a) = \frac{1}{J}\sum_{j=1}^{J} Y_j(a)$. Thus, the limit distribution of the standardized estimator is normal with mean 0 and variance given by the variance of its influence curve. Under pair-matching, an asymptotically conservative approximation of the influence curve for the TMLE is given by

$$\hat{IC}(a;\bar{O}_k) = \frac{1}{2}\left[\hat{IC}(a;O_{k1}) + \hat{IC}(a;O_{k2})\right]$$
$$\text{with } \hat{IC}(a;O_j) = \frac{\mathbb{I}(A_j = a)}{\hat{\mathbb{P}}(A_j = a|E_j)}\left(Y_j - \hat{\mathbb{E}}^*(Y_j|A_j = a, E_j)\right)$$

For the sample incidence ratio $\psi(1)/\psi(0)$, we apply the Delta method to test the null hypothesis and create 95% confidence intervals on the log-scale:

$$log[\psi(1)/\psi(0)] = log[\psi(1)] - log[\psi(0)]$$

The influence curve for the log(TMLE) $=log[\hat{\psi}^*(1)/\hat{\psi}^*(0)]$ for matched pair k is given by

$$\hat{IC}_{tmle}(\bar{O}_k) = \frac{1}{\hat{\psi}^*(1)}\hat{IC}(1;\bar{O}_k) - \frac{1}{\hat{\psi}^*(0)}\hat{IC}(0;\bar{O}_k)$$

The unadjusted estimator is a specific case of TMLE, where we replace the targeted $\hat{\mathbb{E}}^*(Y|a,E)$ with the empirical $\hat{\mathbb{E}}(Y|a)$ and the estimated exposure mechanism $\hat{\mathbb{P}}(a|E)$ with empirical $\hat{\mathbb{P}}(a) = 0.5$.

Inference for the intervention effect will be based on the estimated influence curve and the Student's t-distribution with 15 degrees of freedom. Specifically, on the log-scale we will estimate the variance by taking the sample variance of the estimated influence curve divided by $J/2$, construct Wald-Type confidence intervals, and test the null hypothesis of no average effect. Confidence intervals and two-sided hypothesis testing will be conducted at a 5% significance level. Finally, the (log) point estimate and confidence intervals will be exponentiated to be on the original scale. While a single hypothesis test will be conducted on the relative scale, effect measures and corresponding confidence intervals will also be reported for the absolute scale ($\psi(1) - \psi(0)$) to facilitate alternative uses. Finite sample simulations suggest that under plausible scenarios the adjusted estimator provides modest to substantial efficiency gains and corresponding power improvements, while retaining good type I error control and 95% confidence interval coverage.

4 Power Calculations and Simulation Results for Primary Outcome

We first present standard power calculations for cluster randomized trials under a range of plausible and conservative assumptions. Then in Section 4.2, we present full simulations evaluating the performance of

our proposed two-stage estimator. We report the attained power under a range of scenarios for changes in the guidelines for ART initiation in the control arm and achieved ART coverage. We also demonstrate good confidence interval coverage and type I error control.

4.1 Classical power calculations

Our initial power calculations were based on the standard sample size formulas for an unadjusted comparison of proportions in a pair-matched cluster randomized trial with two arms [3]. Using a two-sided test at a 5% level of significance, these calculations indicated that 16 matched pairs would provide at least 80% power to detect a 40% reduction in the three-year HIV cumulative incidence under a conservative value for the matched pair coefficient of variation (k_m) and to detect smaller effect sizes under more plausible k_m values. Figure 1 shows a graph of the percent reduction detectable with 80% power under a range of deviations from the following assumptions.

- We assumed a stable adult resident size of 5,000, a baseline HIV prevalence of 10%, measurement of HIV status at baseline among 80% of residents, and measurement of HIV status at the final year on 75% of those HIV-negative at baseline. This yields approximately 2700 residents in each community who are in the HIV Incidence Cohort and have their serostatus known at year 3. While the exact cohort size will vary, if the actual sample size per community is at least 2700 individuals, then these calculations can be considered conservative. We further note that moderate deviations from this number of individuals are not expected to have strong impacts on power.

- We assumed that the three-year cumulative HIV incidence was 1% in control communities. This estimate was considered conservative given the available literature, which suggested that HIV transmission rates are approximately 0.5% to 2% [20–22]. For example, assuming a current incidence density of 0.5 cases per 100 person-years and allowing for a 10% decline in transmission rate per year in the absence of the intervention (due to concurrent prevention activities and expansion of ART) would suggest a three-year cumulative incidence of approximately 1.34%. If the three-year cumulative incidence is 1.34% in control communities, then these calculations can be considered conservative.

- We assumed a matched pair coefficient of variation k_m of no greater than 0.4. While ideally external data would be available to the inform its selection, the generalizability of k_m values across studies is limited. Specifically, k_m depends (among other things) on which covariates are used for matching, how close a match is achieved, and the strength of association between these covariates and the outcome. Furthermore, recent work has demonstrated the instability of estimates of k_m based on empirical data [23]. Prior studies, performed in similar settings, have assumed a k_m closer to 0.25 (e.g. Project ACCEPT [personal communication] and the Mwanza Trial [24]). With the above assumptions, these calculations indicated that would be powered to detect a 40% reduction with $k_m = 0.4$, a 33% reduction with $k_m = 0.3$, and a 27% reduction with $k_m = 0.2$.

We also expect that these calculations are conservative because of the precision gained through covariate adjustment during the analysis. Adjustment with TMLE should improve power by reducing the variability of the estimator and resulting in a less conservative variance estimator [2]. On the other hand, these calculations may be anti-conservative if there is substantial heterogeneity in HIV incidence within study regions and we match poorly on those sources of variability within region.

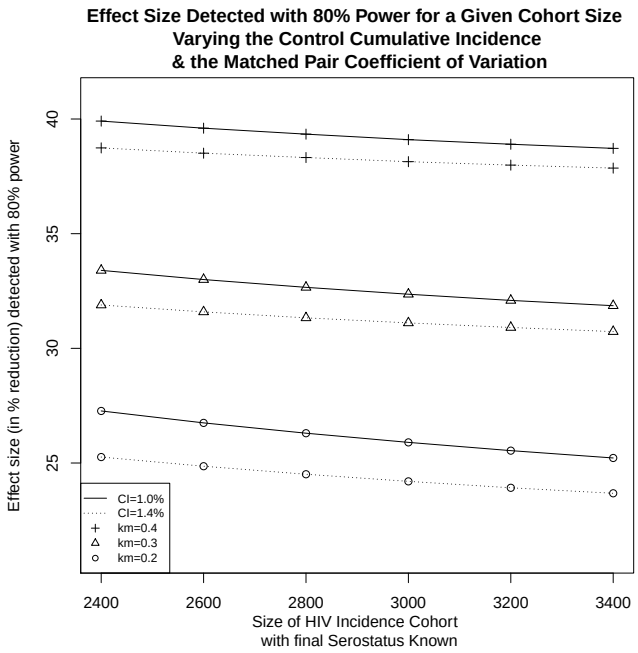

Figure 1: Effect size (in percent reduction) that we are powered to detect at 80%, while varying the control cumulative incidence (CI), the matched pair coefficient of variation k_m, and the number of individuals in the HIV Incidence Cohort, who have their status known at year 3. The calculations were based on the standard sample size formulas for an unadjusted comparison of proportions in a pair-matched cluster randomized trial with 32 communities total [3].

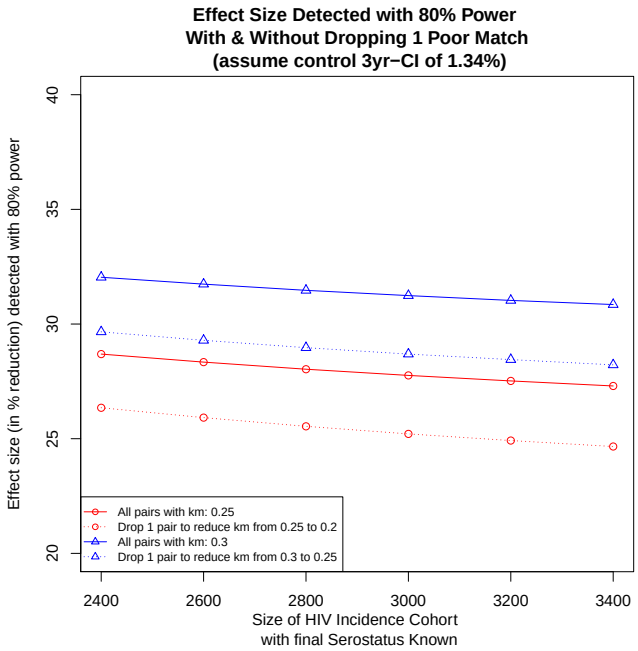

Figure 2: Effect size (in percent reduction) that we are powered to detect at 80% using all 16 matched pairs or dropping 1 poorly-matched pair resulting in a 0.05 reduction in the matched pair coefficient of variation k_m. The calculations were based on the standard sample size formulas for an unadjusted comparison of proportions in a pair-matched cluster randomized trial with two arms [3].

4.2 Simulations and mathematical modeling

We used simulations to examine the performance of our proposed two-stage effect estimator. We first used a mathematical model to generate plausible country-specific incidence curves under a range of assumptions regarding scale-up of ART. These incidence curves were the basis for full hierarchical simulations that incorporated a number of the challenges faced by our primary outcome analysis, including: (i) differential HIV testing processes in the intervention and control arms, (ii) possibly differential informative right-censoring (due to death and out-migration) by intervention arm and individual HIV status, (iii) possibly differential informative measurement (through CHC attendance and tracking success) by intervention arm and individual HIV status, (iv) the inability to match on all measured baseline covariates predictive of the outcome, (v) few conditionally independent units, and (vi) rare outcomes.

4.2.1 Simulation setup

The following describes the data generating experiment for each of the 32 communities in the simulated study. To reflect the underlying processes, including differential HIV testing between study arms, we simulated the complete data at $t = \{0, 1, 2, 3\}$ for all individuals in each community. As previously discussed, our estimators only use data measured at $t = \{0, 3\}$ in both arms. We first describe the generation of the community-level data and then the individual-level data. Throughout, we use i to denote individuals in community j at time t.

For community j, nine baseline community-level covariates were generated by drawing from a multivariate normal. The correlation between the first three covariates $\{E1_j, E2_j, E3_j\}$ and between the second three covariates $\{E4_j, E5_j, E6_j\}$ was approximately 0.25, while the correlation between the last three $\{E7_j, E8_j, E9_j\}$ was 0. Region R_j was set to reflect the study design with 10 communities from Eastern Uganda, 10 communities from South Western Uganda, and 12 communities from Kenya. Pre-intervention HIV prevalence Z_j was generated to reflect baseline study data and as a function of region R_j, covariates $\{E1_j, E4_j, E7_j\}$, and random noise U_{Z_j}. Baseline coverage of male circumcision $Z2_j$ was also generated to reflect baseline study data.

The community-specific hazard of HIV infection under study arm a at time t, denoted $h_{jt}(a)$, was generated as a function of the projected incidence rate[1], community covariates $\{E2_j, E5_j, E8_j\}$, prevalence Z_j, circumcision coverage $Z2_j$, and random noise that was correlated within a community over time. The number of stable, adult residents was drawn from a uniform with minimum 4,000 and maximum 6,000 for Ugandan communities and with minimum 3,500 and maximum 5,480 for Kenyan communities. The baseline coverage of HIV testing (via the baseline CHC and tracking) was drawn from a uniform with minimum of 80% and maximum of 90%.

For individual i in community j at time $t = 0$, baseline HIV status Y_{ij0} was generated as a function the baseline community-level prevalence Z_j and random noise that was correlated within an individual over time $U_{Y_{ijt}}$. Baseline measurement (CHC attendance or post-CHC tracking) Δ_{ij0} was generated as a function of the community-specific coverage probability at baseline and random noise that was correlated within an individual over time $U_{\Delta_{ijt}}$. The resulting HIV Incidence Cohort was then defined as all community members who were HIV-negative and observed at baseline: $Y_{ij0} = 0$ & $\Delta_{ij0} = 1$. (All community members were assumed to be living, stable residents at baseline: $C_{ij0} = 0$ for all i and j.)

For the remaining years of the trial $t > 0$, HIV status Y_{ijt} was generated as a function the community-specific hazard $h_{jt}(a)$, individual-level covariates of age, sex, and circumcision (among males), and random noise $U_{Y_{ijt}}$. (The individual-level covariates were also generated to reflect baseline data.) Censoring, representing both death and out-migration, was generated as a function of the study arm A, underlying

[1] The incidence rate of HIV under exposure-level $A = a$ at time t was informed by Goals module from the Spectrum System of Futures Institute, as detailed in Section 4.2.3.

HIV status Y_{ijt}, and random noise that was correlated within an individual over time $U_{C_{ijt}}$. For simplicity, we assumed that past measurement did not affect censoring at t. We explored a variety of censoring mechanisms, ranging from non-differential to quite differential by study arm and underlying HIV status. We also explored a "mixture" scenario, where each community was randomly and independently assigned a censoring scenario with equal probability. The mixture scenario reflects that censoring might be operating in different ways in different communities.

We also explored two measurement (CHC attendance and tracking) mechanisms. In the first, the observation status after baseline Δ_{ijt} (for $t > 0$) was generated as function of the study arm A, underlying HIV status Y_{ijt}, censoring C_{ijt}, and random noise $U_{\Delta_{ijt}}$. In the second, the observation status Δ_{ijt} was generated as a function of the study arm A, known HIV+ status, censoring C_{ijt}, and random noise $U_{\Delta_{ijt}}$. Here, HIV+ status was "known" if an individual tested positive at a prior CHC or subsequent tracking. For each type of measurement mechanism (i.e. dependent on underlying HIV status or "known" HIV status), we explored a variety of scenarios, ranging from non-informative to quite informative by HIV status and treatment arm. As before, we generated a "mixture" scenario, where each community was randomly and independently assigned a measurement scenario with equal probability. By definition, the observation probability was 0 for control community members at $t = \{1, 2\}$.

Given simulated data under both study arms, we calculated as the true value of our target parameter, the sample incidence ratio:

$$\frac{\psi(1)}{\psi(0)} = \frac{\frac{1}{J}\sum_{j=1}^{J} Y_j(1)}{\frac{1}{J}\sum_{j=1}^{J} Y_j(0)}$$

where $Y_j(a)$ denotes the three-year cumulative HIV incidence for community j under the exposure-level ($A = a$) and under a hypothetical intervention to prevent censoring and ensure final knowledge of HIV status among all members of the community-specific HIV Incidence Cohort.

4.2.2 Adaptive pair-matching, intervention randomization, and estimation

Using the non-bipartite matching algorithm `npbMatch` [25], we pair-matched communities within region R on predictors of baseline prevalence $\{E4, E7\}$. The intervention A was randomized within the matched pairs. For Stage I estimation of the community-specific cumulative incidence of HIV, we implemented the unadjusted estimator based on a simple empirical mean. For Stage II estimation of the intervention effect, we implemented both the unadjusted estimator as well as the pre-specified data-adaptive procedure, described in Section 3.3. Inference was based on the estimated influence curve. For confidence interval construction and two-sided hypothesis testing, we used Student's t-distribution with 15 degrees of freedom and a 5% significance level. These estimation procedures were previously detailed in Sections 2 and 3.

4.2.3 Mathematical modeling

The Goals module from the Spectrum System of Futures Institute was used to provide country-specific projections of the prevalence and incidence of HIV under the SEARCH intervention and under the control (`http://www.futuresinstitute.org/spectrum.aspx`). The software was originally developed by the Futures Group, in collaboration with Family Health International, and is supported by UNAIDS and the Gates Foundation, among others [26–28].

The mathematical model was parameterized with published data from national and regional surveys in Uganda and Kenya on HIV prevalence and coverage of male circumcision (Nyanza region of Kenya) [21, 29–33]. At baseline, we assumed 75% of eligible populations in Uganda and 66% in Kenya were on ART and virally suppressed. The model was also parameterized to reflect post-baseline changes in ART eligibility as well as scale-up of ART coverage. Specifically, the inputs for the control arm reflected in-country

implementation of the guidelines to change CD4-based eligibility from ≤ 350 cells/μL to ≤ 500 cells/μL starting in 2014; universal eligibility for key populations, including pregnant women, tuberculosis/HIV co-infected and discordant couples, starting in 2015; and universal eligibility for all HIV+ starting in 2016. We generated incidence curves in the control arm under these guidelines and a range ART coverage trajectories (control scenarios A-B), in which 62-67% of eligible populations under expanded guidelines were on ART and virally suppressed by year 3 of the study. These were then contrasted with the projected incidence curves under the SEARCH intervention, assuming 73% of all HIV+ were on ART and suppressed by 18 months after baseline (Figure 3).

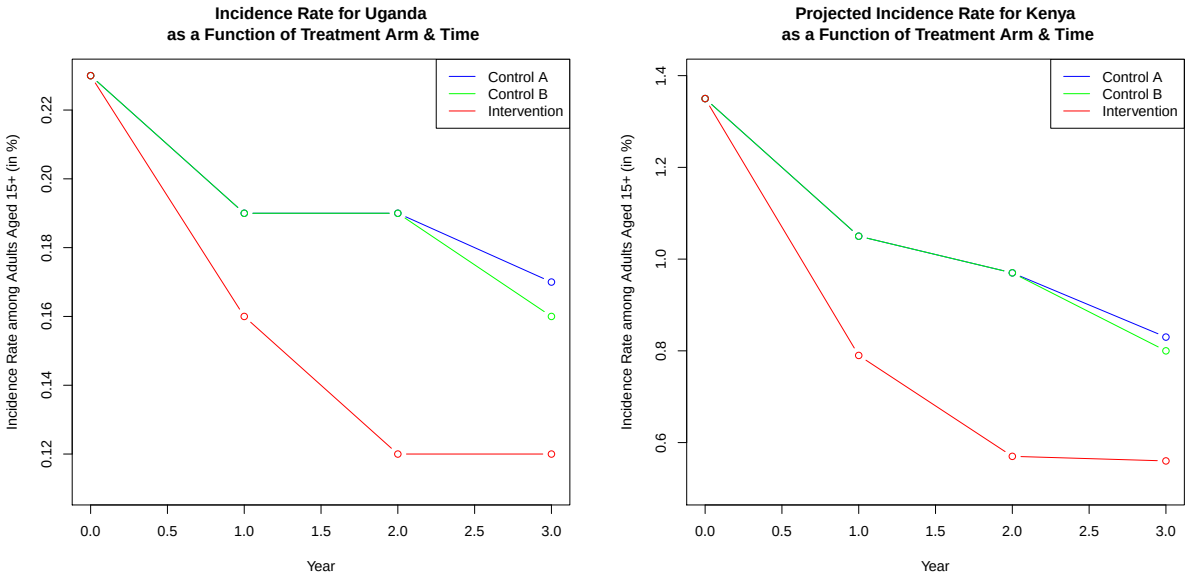

Figure 3: Projected incidence of HIV for Uganda and for Kenya in percent (%) as informed by the Goals module in the Spectrum System of Futures Institute [26–28]. The projected incidence rates (in percent) under the control scenario A (less conservative), control scenario B (more conservative) and the intervention arm are given by blue, green and red lines, respectively.

4.2.4 Results

The true value of the sample effects depends on the $n = 32$ communities in the study. Over the 500 simulated data sets, Table 1 shows the average value of the sample incidence ratio: $\psi(1)/\psi(0)$. The variance of the effect and the average matched pair of coefficient of variation k_m are also given. The scenarios explored are described in Figure 3.

	$\psi(1)/\psi(0)$	$Var[\psi(1)/\psi(0)]$	k_m
Scenario A	0.695	7.04E-5	0.372
Scenario B	0.704	7.55E-5	0.366

Table 1: The average values and variance of the causal parameter across 500 repetitions of the data generating experiment. $\psi(1)$ refers to the average risk (three-year cumulative incidence of HIV) under the intervention, and $\psi(0)$ refers to the average risk under the control. Recall this parameter changes with each sample, and $Var[\psi(1)/\psi(0)]$ gives the variability of the effect across the 500 runs. Finally k_m is the average value of the estimated matched pair coefficient of variation.

Table 2 illustrates the performance of the estimators over 500 simulated data sets. Specifically, we compare the unadjusted estimator and the TMLE. Both estimators were unbiased. As expected, there was

an efficiency gain with adjustment through TMLE. The attained power ranged from 81 to 83% with the unadjusted and from 88 to 91% with the TMLE. Throughout, there was nominal to conservative confidence interval coverage and type I error control (Table 2). Simulation results under alternative matching schemes, differential censoring, and informative missingness are available elsewhere.

	Unadjusted Estimator					*TMLE*				
	bias	std. err.	tstat	cover	power	bias	std. err.	tstat	cover	power
Scenario A	1.46E-3	1.34E-2	-3.31	0.98	0.83	2.45E-4	9.85E-3	-3.91	0.95	0.91
Scenario B	2.10E-3	1.34E-2	-3.18	0.97	0.81	1.28E-3	1.01E-2	-3.73	0.95	0.88
	bias	std. err.	tstat	cover	α	bias	std. err.	tstat	cover	α
Null	5.60E-3	1.31E-2	-0.00	0.97	0.03	5.06E-3	9.30E-3	-0.00	0.95	0.05

Table 2: The bias (average deviation between the point estimate and sample-specific true value), average standard error (estimated with the influence curve), average value of the test statistic (point estimate divided by standard error estimate), confidence interval coverage (proportion of intervals containing the true parameter value), attained power (proportion of studies correctly rejecting the false null hypothesis), and type I error rate α (proportion of studies falsely rejecting the true null hypothesis) of the unadjusted estimator and the TMLE over 500 simulated trials. The null scenario was simulated by generating incidence as if the intervention had 0 impact (i.e. the hazard of HIV infection under the intervention equaled that of the control).

5 Additional analyses of incident HIV infection

5.1 Subgroup analyses for the primary outcome

For the following baseline subgroups, we will report estimates of the three-year cumulative HIV incidence by treatment arm (conducted as for Stage I of the primary analysis) and estimate the effect of the randomized intervention on this outcome, including a formal hypothesis test of no intervention effect (conducted as for Stage II of the primary analysis): sex, age (15-24 years and > 24 years), marital status (ever vs. never married), non-mobile populations (< 1month of past year spent away from the community), and uncircumcised men. We will further compare intervention versus control incidence for each region separately; Stage II analyses for region-specific comparisons will be unadjusted due to the small number of communities.

In addition, for the following baseline strata, we will report estimates of the three-year cumulative HIV incidence by treatment arm: adolescents (15-24 years; overall and by sex), adults aged 15-49 years, adults aged 15-59 years, mobile populations (≥1month of past year away from the community), non-stable residents (>6month of past year away from the community), circumcised men, students, and fishermen.

5.2 Change in HIV incidence over time

To understand the changes in HIV incidence over time, we will estimate the annual incidence of HIV in the intervention arm, making use of community-based testing results from annual CHC and tracking to construct three annual incidence cohorts. Specifically, for testing years $t \in \{0, 1, 2\}$ (where $t = 0$ denotes study baseline), among an open cohort of adult (aged ≥ 15 years at year t) residents (including inmigrants identified through the follow-up year 3 re-census) who test HIV-negative at year t, we will estimate HIV incidence during the subsequent year of study follow-up (infection by testing round $t + 1$). Estimates will be reported overall, and further stratified by region, gender, age (≤ 24, > 24), and circumcision status, as well as reported for each community.

Primary analyses will report estimates of annual HIV incidence rate among individuals with measured HIV status at year $t+1$, assuming incident infections occur at the mid-point between negative and positive tests, excluding individuals who have out-migrated during the year. Sensitivity analyses will (i) not censor

at outmigration; (ii) restrict to baseline stable residents (acknowledging the potential depletion of high risk individuals, even after adjustment for measured differences); (iii) calculate annual risks vs. rates using a 95-day annual testing window; and (iv) adjust for potentially informative incomplete ascertainment of HIV status (including due to censoring by death or outmigration in the interim year).

The primary analysis to evaluate the change in annual HIV incidence rate over time will use Poisson regression with generalized estimating equations, and with standard errors estimated using an robust sandwich estimator based on an an exchangeable working covariance matrix. We will estimate change over time both with and without adjustment for changes in the characteristics of the measured incidence cohort.

We will further estimate the change in annual risk of HIV acquisition using a pooled individual interval-level TMLE, with the exposure of interest defined as the time interval, and influence curve-based estimation of the standard error, respecting the community as the independent unit (i.e. allowing for dependence of observations within a community conditional on the covariates included in the adjustment set), and using the t-distribution as the basis for statistical inference.

5.3 Individual-level predictors of HIV seroconversion

We will provide descriptive statistics of members of the HIV Incidence Cohort who seroconverted by year 3, including the distributions of age, sex, and other baseline characteristics, stratified by arm and by region. For each of the following baseline predictor variables, we will report unadjusted associations and adjusted variable importance measures on the relative scale (statistical analogs of the causal risk ratio), treating each baseline predictor in turn as the intervention variable, and the remainder (together with region) as the adjustment set. Baseline predictors to be considered will include sex, age, marital status, education, occupation, household wealth index, mobility, circumcision (among men), self-reported alcohol use, self-reported contraceptive use, relationship to head of household, polygamy, self-reported prior HIV testing, and baseline testing location (CHC vs. tracking).

Variable importance measures will be estimated with pooled individual-level TMLE with the community treated as the independent unit for influence curve-based variance estimation and with inference based on the Student's t-distribution. Secondary analyses will treat individuals as the independent unit and include community as a fixed effect. Variable importance measures will be calculated with and without adjustment for potentially informative censoring and measured HIV status, and will be reported overall and stratified by arm, region and sex.

5.4 Potential sources of HIV seroconversions and internally-derived HIV infections

5.4.1 Discordant spouses

We will provide descriptive statistics of known discordant couples at baseline. For the overall pooled HIV Incidence Cohort (pooled over all communities and arms) and each arm-specific HIV Incidence Cohort (pooled over all communities within each arm), we will report the number and proportion of seroconversions that occurred among baseline discordant couples.

5.4.2 Seroconversion interviews

Based on qualitative interviews of participants who seroconverted, we will create descriptive tables of the self-reported suspected source of HIV infection. Using self-reported residence of suspected infection source, we will classify seroconversions as internal or external to the seroconverter's community of residence (or "unable to classify"). We will estimate an alternative community-level HIV incidence outcome, defined as the probability of becoming infected over the 3 years of the study by a suspected source resident in the same community ("internally derived" by self-report). We will conduct analyses analogous to those

performed for the primary outcome to compare the probability of becoming infected by an internally derived virus (with and without including seroconversions with unknown source) across treatment arms and among subgroups.

5.4.3 Phylogenetic analyses

Viral consensus sequences will be used to estimate phylogenetic relationships and genetic distances between HIV viruses sampled during the study. These data, together with additional reference sequences, will be used to classify incident HIV infections among community cohort members as linked or not linked to previously documented infections among community members [34].

An internally-derived infection will be defined as a seroconversion classified, based on sequence analysis, as linked to a previously measured virus from a member of the same community. An externally-derived infection will be defined as a seroconversion classified as unlinked to a previously measured virus from a member of the same community. We will estimate an alternative community-level HIV incidence outcome, defined as the probability of an HIV Incidence Cohort member becoming infected over the 3 years of the study by an internally-derived virus. We will conduct analyses analogous to those performed for the primary outcome to compare the probability of becoming infected by an internally derived virus across treatment arms and among subgroups. We will also provide descriptive statistics and evaluate predictors of internally-derived infection.

In addition, characteristics of transmission clusters detected using phylogenetic data will be reported, including age, sex, occupation, mobility, discordant spouses, shared household membership, and geospatial proximity. Information from seroconversion interviews will further be used to identify possible transmission links and shared risks between cluster members.

6 Community-level descriptive and explanatory analyses

At baseline and year 3, stratified by intervention arm, we will estimate the following potentially important drivers of HIV incidence: HIV prevalence, male circumcision coverage (traditional, medical, and overall), HIV RNA suppression, and migration status. Sexual behavior and mixing patterns will be further investigated in a complimentary nested study that will provide more detailed measurement and analysis of mobility.

6.1 Community-level drivers of HIV incidence

6.1.1 HIV prevalence

We will report HIV prevalence at baseline and year 3 among all adult residents. We will estimate prevalence by community, region, treatment arm, age-sex strata (here and throughout this section, using as age categories 15-24, 25-34, 35-44, 45-54, and >55 years), and baseline mobility (here and throughout this section, using as primary mobility categories those reporting <1mo away vs. ≥1mo away from the community in past year). We will compute both unadjusted prevalence estimates based on the empirical proportion of HIV-positive individuals among those tested, and adjusted estimates, accounting for incomplete coverage of HIV testing. For the latter, we will use TMLE to adjust for ways in which individuals tested for HIV are different from those not tested [35, 36]. Among individuals who test HIV-positive at baseline, we will report the proportion in the following CD4 strata: <50 cells/μl, 50-200 cells/μl, 201-349 cells/μl, 350-500 cells/μl, and >500 cells/μl.

6.1.2 Male circumcision coverage

At baseline and year 3, we will report the proportion of adult male residents who are circumcised (overall and by medical vs. traditional means). We will also report coverage by community, region, treatment arm, age strata, and baseline mobility. Estimates will be based on the unadjusted empirical proportion of circumcised adult males among those seen at the CHC/tracking and adjusted estimates, accounting for incomplete measurement with TMLE to adjust for ways in which individuals seen are different from those not [35, 36].

6.1.3 Plasma HIV RNA ≥500 copies/ml

Among individuals known to be HIV-positive at baseline, we will report the proportion in the following baseline plasma HIV RNA strata: <500 cps/ml, 500-999 cps/ml, 1,000-9,999 cps/ml, 10,000-99,999 cps/ml, ≥100,000 cps/ml).

We will estimate the proportion of the total adult population, and of the HIV-positive adult population, with plasma HIV RNA ≥500 copies/ml at baseline and at year 3, adjusting for incomplete measures of HIV status and HIV RNA levels among HIV-positive individuals, as detailed in Section 7 ("Population-level HIV RNA metrics"); sensitivity analyses will consider a threshold of 1000 copies/ml. Estimates will be reported by community, region, treatment arm, age-sex strata, and baseline mobility. We will further use adjusted variable importance measures, estimated using a pooled individual-level TMLE with community included as a fixed effect, to evaluate predictors of having plasma HIV RNA level ≥500 copies/ml at year 3.

In addition, to investigate relationships between community-level HIV viral replication and HIV incidence, we will estimate the proportion of cumulative person time (of adult person time in the community contributed by all residents, not only those who are HIV-positive) with unsuppressed HIV viral replication (plasma HIV RNA >500 copies/ml) within each community. Estimation of such a metric is complicated by different measurement structures in the intervention and the control arms. Specifically, HIV status, plasma HIV RNA levels, and in-migration to the study communities are measured at only two time points in the control communities. In contrast, in the intervention communities, HIV status is measured annually at CHC/tracking; HIV RNA is measured both at annual CHC/tracking and during interim clinic visits, and in-migrants to the community are (partially) ascertained annually. Further, a linear extrapolation between community-specific proportions unsuppressed at baseline and year 3 will fail to detect any change in the shape of the suppression curve over time, as might be expected to result from the intervention (for example, due to expanded ART eligibility at baseline and facilitated linkage with streamlined ART delivery post-baseline in the intervention communities).

We will therefore estimate the total unsuppressed person-time for each community with an algorithm that relies on baseline and year 3 measures of HIV status, HIV RNA level, and migration status only (to ensure comparability between arms), but also incorporates interim data on ART initiation date (ascertained in both arms).

For these analyses, adult person-time in a community will begin at the first of the start of the community-specific baseline CHC (for baseline residents aged ≥ 15 years at baseline) or first date at which an individual is a resident (including in-migration) and is aged 15 years old or more. Adult person-time in the community will end at the first of (i) date of death, (ii) date of out-migration (if any), and (iii) end of year 3 tracking. Within this person-time, we will estimate the total person-time with unsuppressed HIV RNA levels in the population using the following algorithm.

1. Estimate total unsuppressed time between baseline and year 3 contributed by adult residents diagnosed with HIV at or before study baseline.

- Assume baseline HIV-positive residents who are suppressed at baseline and suppressed at year 3 are never unsuppressed.
- Assume baseline HIV-positive residents who are unsuppressed at baseline and suppressed at year 3 are unsuppressed until minimum of 6 months after ART initiation date or year 3.
- Assume baseline HIV-positive residents who are unsuppressed at baseline and unsuppressed at year 3 are always unsuppressed.
- Among individuals in each of the categories above who are classified as outmigrants at year 3, censor person-time at date of out-migration.

2. Estimate total unsuppressed time between baseline and year 3 contributed by incident HIV infections (tested HIV-negative at baseline and HIV-positive at year 3) among baseline residents

   - Among incident infections that are unsuppressed at year 3, assume that infection occurred midway between baseline and year 3, and the individual was never suppressed.
   - Among incident infections that are suppressed at year 3, assume that the infection occurred midway between baseline and ART initiation date, and that the individual was unsuppressed from time of infection until the minimum of 6 months after ART initiation date or year 3.
   - Among individuals in each of the categories above who are classified as outmigrants at year 3, censor person-time at date of out-migration.

3. Estimate total unsuppressed time between baseline and year 3 contributed by HIV-infected in-migrants (tested HIV-positive at year 3 and are not baseline enumerated residents).

   - Among HIV-positive in-migrants who are unsuppressed at year 3, assume that the individual was HIV-positive at date of in-migration, and that the individual was never suppressed.
   - Among HIV-positive in-migrants who are suppressed at year 3, assume that the individual was HIV-positive at date of in-migration, and that the individual was unsuppressed from time of in-migration until the minimum of 6 months after ART initiation date or year 3.

4. Estimate total unsuppressed time between baseline and year 3 contributed by baseline enumerated residents who are missing baseline HIV status and who are HIV+ at year 3.

   - Among individuals who are missing baseline status and tested HIV-positive at year 3 (this includes both incident infections and baseline prevalent HIV-positive), assume that individual was baseline prevalent HIV-positive. If suppressed at year 3, assume always suppressed. If unsuppressed at year 3, assume never suppressed. If classified as out-migrants at year 3, censor person-time at date of out-migration.

For analyses including the intervention arm only, we will construct analogous estimates of total non-suppressed time, incorporating all available interim data on migration, HIV status, and HIV RNA levels.

6.1.4 Migration & Mobility

Mobility may impact health outcomes and HIV transmission risk in a number of ways. First, mobile HIV-positive individuals may be less likely to be diagnosed, treated, and virally suppressed. Thereby, mobile HIV-positive individuals may be at risk of poor health outcomes and of transmitting HIV. Second, individuals who migrate into the community during the study will not have benefited from the intervention prior to moving into the community. Such individuals further are not systematically ascertained during interim years, and as a result will not be tracked if they do not attend an annual campaign and may fail to fully benefit from the intervention. Third, individuals who migrate out of the community, as well as those

who remain official residents but spend substantial time in other locations, may have greater challenges accessing testing, treatment and care services, while nonetheless continuing sexual contact with community residents. Finally, mobility may also be associated with additional factors that place individuals at risk of HIV transmission and acquisition (such as occupations that involve transactional sex). Mobile individuals may also have more sexual contacts with residents of communities not served by the SEARCH intervention and thereby sexual contacts who are less likely to be virally suppressed if HIV-positive.

We will, therefore, conduct analyses to quantify migration, to investigate HIV care cascade outcomes among mobile individuals, and investigate the role mobile individuals play in ongoing transmission. First, we will report descriptive statistics on the following metrics, stratified by treatment arm, by community, and within treatment arm by region, sex, and age.

- Baseline mobility: Among baseline adult residents, we will provide descriptive statistics on months spent outside community in the past year, an indicator of moving main residence within the past year, and nights spent at the main residence in the past month.
- Follow-up year 3 mobility: Among adult residents at year 3, we will provide descriptive statistics on time at current residency (less than 1 year, 1-2 years, 2+ years), months spent outside the community in the past year, an indicator of moving main residence within the past year, nights spent at the main residence in the past month, indicator of spending more than 6 contiguous months away from main residence in the last year, an indicator of spending more than 12 contiguous months away outside of the community in the last 3 years, and an indicator of living in the community for the past 5 years. In this population, we will further report the number and proportion who are classified as in-migrants, defined as an individual resident in the community at year three, but not at baseline enumeration. We will provide basic descriptive statistics of the in-migrants' characteristics (e.g. sex, age, occupation, relation to head of household), their reason for moving into the household, and their reported time spent living in the community.

We will also evaluate the following metrics quantifying HIV status and HIV RNA suppression status among mobile populations.

- HIV prevalence among in-migrants
- The proportion of HIV-positive adult residents at year 3 who are in-migrants
- The proportion of all HIV-positive adult residents with (i) HIV RNA$\geq$500 copies/ml and (ii) HIV RNA >100,000 copies/ml at year 3 who are in-migrants
- Among HIV-positive adult residents at year 3 who are in-migrants, the proportion with (i) HIV RNA$\geq$500 copies/ml and (ii) HIV RNA >100,000 copies/ml at year 3
- The proportion of baseline HIV-positive adults who out-migrate by year 3
- Among all adults who are known to be HIV-positive at year 3, are classified as out-migrants, and have measured HIV RNA, the proportion with (i) HIV RNA<500 copies/ml at year 3, (ii) HIV RNA >100,000 copies/ml at year 3 - overall and stratified by FUY3 testing location.

6.2 Descriptive and community-level explanatory analyses

The community-specific cumulative incidence (as estimated for the primary outcome) and the community-specific incidence rates (incident cases per 100 person-years at risk) over the three year period will be reported. In estimating incidence rates, person-years at risk for individuals who test HIV-negative at both

baseline and year 3 will be calculated from date of baseline negative test to date of year 3 negative test; person-years at risk for incident HIV infections will be calculated from date of baseline negative test to midway between date of baseline HIV-negative test and year 3 HIV-positive test.

We will consider the following independent explanatory variables, estimated as specified in the prior section:

- HIV prevalence (at baseline and using the average of baseline and year 3).
- HIV RNA metrics: total unsuppressed person-time/total adult person-time; proportion of HIV-positive adults with HIV RNA> 500 copies/ml and with >100,000 copies/ml, at baseline and using the average of baseline and year 3; and proportion of total adult population with HIV RNA> 500 copies/ml and with >100,000 copies/ml, at baseline and using the average of baseline and year 3.
- Male circumcision coverage, using the average coverage at baseline and year 3.
- Mobility: proportion of the adult population who are in-migrants at year 3, proportion of the baseline population who have out-migrated by year 3, proportion of all adults and HIV-positive adults who are unsuppressed in-migrants.

We will conduct these analyses overall, and stratified by sex. In sex-stratified analyses, we will consider as additional predictors corresponding to metrics among the opposite sex.

Unadjusted and adjusted associations between each explanatory variable and HIV incidence will be evaluated. Community-level Poisson regression of the community-specific HIV incidence on the community-level explanatory variables, in turn and jointly, will be used to estimate the unadjusted and adjusted (conditional) relative risks and rates. We will also conduct analyses under the additional assumption that individual outcomes are independent given the explanatory variables and additional individual-level covariates included in the adjustment set (listed below). Individual-level Poisson regression will be used to estimate the relative risk/rate of incident HIV infection per unit change in each explanatory variable, adjusted for the remaining explanatory variables, region, and additional individual-level risk factors measured at study baseline (listed below). Inference will employ robust standard error estimates based on an exchangeable working covariance matrix. In addition to the explanatory variables above and region, these individual-level analyses will adjust for the following baseline individual-level covariates: sex, age, marital status, education, occupation, household wealth index, mobility, alcohol use, contraceptive use, polygamy, and self-reported prior HIV testing.

7 Intervention uptake: Testing, HIV care cascade, and population-level HIV RNA metrics

The study intervention aims to achieve high annual levels of HIV testing coverage, rapidly initiate ART among all HIV+ individuals, and retain these individuals in care with HIV viral suppression (plasma HIV RNA<500 copies/ml). The control arm of the study also aims to achieve high levels of HIV testing coverage at study baseline, and provides a clinical officer to support adherence to ART guidelines, which evolved over the course of the study. To evaluate intervention uptake in both study arms over time, with implications for understanding both health of HIV-positive individuals and HIV transmission potential, we will conduct the following analyses. Throughout, we will define prior HIV diagnosis and ART initiation (i) using Ministry of Health records only, and (ii) incorporating self-report.

7.1 Testing uptake in intervention and control arms

We will provide descriptive statistics to characterize testing coverage and other services by treatment arm, by community, and over time among the open cohort of adult ($\geq$15 years at year t, $t \in \{0, 1, 2, 3\}$) community residents. Community residence in a given year will be determined by the baseline enumeration combined with the re-census of the adult population at year 3. An individual will be considered resident in the community at year t if he or she was resident at baseline and is not known to have died or out-migrated by year t, or if he or she was not a resident at baseline and is reported to have in-migrated by year t. In this open cohort of adult residents, we will report for each year t: (i) the proportion of the population with known HIV status at the close of year t testing, and (ii) the proportion of the population ever tested for HIV by the close of year t testing. Known HIV status at year t will be defined as either having a prior HIV diagnosis or having no prior HIV diagnosis and a positive or negative HIV test result at year t testing. Ever testing for HIV by year t will be defined as having a prior HIV diagnosis or any prior HIV rapid test result by close of year t testing. Pre-baseline and secondary analyses will also incorporate self-report of prior HIV testing and self-reported prior test results.

For each year, by arm and by region, we will report the portion of the eligible population (i) attending the CHC, (ii) seen at tracking, and (iii) contacted at either CHC or tracking. We will further report the proportion of the eligible population receiving specific screening and testing services. These include HIV testing (among those not already known to be HIV-positive), plasma HIV RNA level testing (among HIV-positive individuals), and hypertension and diabetes screening. We will characterize predictors of not attending the CHC and of not being contacted at either the CHC or tracking. We will also report the extent and components of community mobilization carried out prior to testing campaigns.

We will describe clinic-specific timing of the uptake of each of the components of streamlined HIV care: rapid ART start, appointment reminders, viral load counseling, and tiered tracking for missed visits. We will also provide clinic-specific timing of the implementation of evolving national ART guidelines in the control arm. Further analyses of linkage, retention, and suppression over time in intervention and control communities are described in detail below.

7.2 Cross-sectional cascade coverage in open cohort of HIV-positive individuals

At baseline and year 3 ($t = \{0, 3\}$), we will estimate the proportion of all HIV+ adults who are previously diagnosed, the proportion of previously diagnosed adults who have ever initiated treatment, the proportion of those ever on ART who are currently suppressed, and overall population-level suppression (the proportion of all HIV+ who are currently suppressed). This analysis will be based on the open cohort of individuals who are aged $\geq$15 years and are community residents at t, as defined above. Primary analyses will include baseline residents (regardless of stability) and in-migrants identified at follow-up year 3; secondary analyses will restrict to baseline stable residents. We will also report simple descriptive analyses of HIV status and suppression among non-residents with measured HIV RNA levels. We will use TMLE to adjust for potentially differential measurement of HIV status and viral loads, using methods detailed in [35, 36]; unadjusted numbers and proportions will also be reported. We will conduct sensitivity analyses to incorporate self-report of prior diagnoses and ART use and to adjust for potentially differential measure of prior diagnoses and ART use.

We will report cascade and suppression estimates by community, by treatment arm, and for the following strata: region, sex, age (15-24 years; 25+ years), mobility ($<$ 1mo away; $\geq$1mo away), students, and fishermen. We will also generate annual estimates in the intervention arm.

We will estimate the effect of the randomized intervention on population-level suppression at year 3 and test the null hypothesis that population-level viral suppression at year 3 is the same between the intervention and control arms. To test this null hypothesis, we will use methods analogous to those used for

the primary study endpoint. Specifically, we will estimate a community-specific outcome (population-level viral suppression at year 3) and then estimate the effect with a community-level TMLE using data-adaptive selection of adjustment variables from a pre-specified set. For this outcome, the pre-specified candidate adjustment variables are the proportion of the baseline HIV-positive population with HIV RNA$<$ 500 copies/ml, and the proportion of baseline HIV-positive adult population below the age of 25. Our primary analysis will give equal weight to individuals (weight communities relative to the size of their HIV-positive population); secondary analysis will give equal weight to communities. Subgroup analyses will include region (using an unadjusted stage II estimator), sex, age, mobility, and circumcision status.

Within each treatment arm, we will also estimate the change in population-level suppression between baseline and year 3 and test the null hypothesis that population-level viral suppression remained constant between baseline and year 3. First, we will estimate change in population-level suppression between baseline and year 3, adjusting for missing HIV serostatus and HIV RNA measures, but without adjusting for changes in the HIV-positive population over time. This estimate will be based on a comparison of the time point-specific TMLE-based population suppression estimates described above. Second, we will estimate the change in population-level suppression over time adjusted for any changes in the distribution of individual-level characteristics among those with known HIV and viral suppression status over time. This parameter, in addition to accounting for changes in measurement patterns, adjusts for any changes in the distribution of the HIV-positive population over time. Estimation will be based on a TMLE that pools over individuals and years, with time as the exposure of interest. Standard errors will be estimated based on the estimated influence curve, treating the individuals as independent within communities. In both approaches, community will be adjusted for as a fixed effect. Outcome and propensity score models will be fit data-adaptively using Super Learning. Adjustment variables will include age, sex, occupation, education, mobility, wealth, marital status, and testing location.

For the same primary and secondary populations, we will use analogous methods to estimate the proportion of all HIV-positive adults in the following viral load strata at baseline and year 3: $<$1000 cps/ml, 1000-100,000 cps/ml, and $>$100,000 cps/ml. We will estimate the effect of the randomized intervention on (i) the population-level proportion with viral loads $>$100,000 cps/ml, and (ii) the population-level proportion with viral loads $\geq$1000 cps/ml. Using methods analogous to those used for suppression, we will estimate the ratio of the mean of these community-level outcomes between treatment and control arms and the change in their mean between baseline and year 3, and test the corresponding null hypotheses.

7.3 Longitudinal HIV RNA levels in the closed cohort of baseline HIV-positive individuals

For the subgroup of adult (aged $\geq$15) baseline residents diagnosed with HIV at or before baseline, we will estimate the proportion virally suppressed at year 3 by treatment arm. We will censor at death and out-migration, using TMLE to adjust for potentially non-differential measurement of viral loads and for censoring, as detailed in [35, 36]; unadjusted proportions will be reported as secondary analyses. The primary analysis will include all baseline residents; secondary analyses will restrict to baseline stable residents.

We will report suppression estimates by region, by community, by treatment arm, and for the following baseline strata: cascade subgroup (no prior HIV care, prior care but no prior ART initiation, prior ART but not suppressed, and suppressed), CD4+ T cell count ($<$350 cells/μl, 350-500 cells/μl, $>$500 cells/μl) region, sex, age (15-24 years; 25+ years), mobility ($<$ 1mo away; $\geq$1mo away), students, and fisherman. Within the intervention arm, we will report analogous estimate for years 1 and 2.

We will estimate the effect of the randomized intervention on the proportion of the baseline HIV-positive population who are suppressed at year 3 and test the null hypothesis of no difference in proportion suppressed between intervention and control, using the same approach as for the open cohort of HIV-

positive adults (Section 7.2).

Using analogous methods, we will estimate the proportion of baseline HIV-positive individuals in the following viral load strata at year 3: <1000 cps/ml, 1000-100,000 cps/ml, and >100,000 cps/ml. We will estimate the effect of the randomized intervention on the proportion of baseline HIV-positive individuals with viral loads >100,000 cps/ml and test the corresponding null hypothesis.

In a complimentary analysis of the closed cohort of baseline HIV-positive individuals, we will report the probability of being in each of the following mutually exclusive and exhaustive states at baseline and follow-up year 3: died, migrated out of the community, newly diagnosed, previously diagnosed but never on ART, had initiated ART but are unsuppressed, and currently suppressed. This analysis will adjust for informative viral load measurement, using methods described in [35, 36]; unadjusted estimates will also be reported.

We will evaluate baseline predictors of (i) having a plasma HIV RNA level >500 copies/ml at year 3, and (ii) having a plasma HIV RNA >100,000 copies/ml at year 3. Specifically, we will report unadjusted associations and adjusted variable importance measures on the relative scale (statistical analogs of the causal risk ratio), treating each baseline predictor in turn as the intervention variable, and the remainder as the adjustment set. Variable importance measures will be estimated with pooled individual-level TMLE, adjusted for community as a fixed effect, and treating the household as the independent unit for variance estimation. Using methods described in [35, 36], we will further adjust for potentially informative censoring and missing viral load measures. Baseline predictors considered will include region, sex, age, marital status, education, occupation, household wealth index, mobility, alcohol use, and testing location.

7.4 Time to linkage and ART initiation

For the subgroup of adult residents diagnosed with HIV but not yet on ART at baseline, we will conduct longitudinal analyses to estimate the probability of initiating ART. Specifically, among adult residents testing HIV-positive at either the baseline CHC or tracking, and not currently in care, we will evaluate the probability of ART initiation over time. Time-zero will be the date of the baseline campaign or home-based contact. Primary analysis will right-censor at the time of death, out-migration, or close of community-specific follow-up year 3 testing. Secondary analyses will (i) not censor at out-migration, and (ii) censor at out-migration, but treat death before ART initiation as a failure to initiate. The primary analysis will include all baseline residents; secondary analyses will restrict to baseline stable residents.

In estimating longitudinal probabilities of ART initiation, we will use Kaplan-Meier analyses, and will plot the corresponding survival curves by treatment arm and by region. Using a two stage approach, we will estimate the effect of the randomized intervention on probability of initiating ART by 6, 12, and 24 months. We will test the corresponding null hypotheses of no intervention effect, using a community-level TMLE analogous to that used to compare viral suppression between arms, weighting individuals equally and as candidate adjustment variables the proportion of adult residents known to be HIV-positive at baseline but not yet on ART at baseline who are (i) aged 15-24 years, and (ii) new HIV diagnoses.

We will report estimates by treatment arm, by region, by community, and for the following baseline strata: no prior HIV care at at baseline, prior HIV care without a record of prior ART at baseline, CD4 count (<350, 350-500, ≥500), sex, age (15-24 years; 25+ years), and baseline mobility (<1mo away; ≥1mo away). Among individuals who initiate ART in the control communities, we will document reason for ART start. We will provide descriptive statistics of the following variables at the time of ART initiation: CD4 count, sex, age, occupation, and mobility (< 1mo away; ≥1mo away) by treatment arm and by community.

We will evaluate baseline predictors of not initiating ART within 12 months. Specifically, we will report unadjusted associations and adjusted variable importance measures on the relative scale (statistical analogs of the causal risk ratio), treating each baseline predictor in turn as the intervention variable, and the remainder as the adjustment set. Variable importance measures will be estimated with pooled individual-

level TMLE, adjusted for community as a fixed effect, and treating the individual as the independent unit for variance estimation. Baseline predictors considered will include region, sex, age, marital status, education, occupation, household wealth index, mobility, alcohol use, and testing location, and CD4 count.

7.4.1 Time to Linkage

Time to ART initiation is a function of both time to linkage and time from linkage to ART start, and both may be differentially impacted by the study intervention. To further disaggregate these steps in the care cascade, we will conduct analyses analogous to the above, among individuals who are not currently in HIV care at baseline (either newly diagnosed with HIV at baseline, or previously diagnosed but not currently in HIV care), using the alternative outcome of linkage to care, defined as the first recorded visit to an HIV clinic following baseline.

7.5 Retention in HIV Care

Among HIV-positive adult residents who initiate ART during study follow-up (between the start of baseline community-specific CHC and start of follow-up year 3 community-specific testing), we will conduct longitudinal analyses to estimate the probability of being retained in HIV care over time. Retention failure is defined as more than 90 days late to a scheduled 12-month follow-up [37]. Retention failures include those living in the community but not engaged in care, those who move out of the community without a documented transfer, and those otherwise lost to follow-up. Time-zero will be the date of ART initiation. The primary analysis will right-censor at time of death, documented transfer to a non-SEARCH clinic, or close of community-specific follow-up year 3 testing. Secondary analyses will also censor at date of outmigration (even if no transfer documented). The primary analysis will include all baseline residents; secondary analyses will restrict to baseline stable residents.

In estimating longitudinal probabilities of retention over time, we will conduct both unadjusted (Kaplan-Meier) analyses and corresponding analyses adjusted for potentially informative censoring using TMLE. We will plot the resulting survival curves by treatment arm and by region. We will estimate the effect of the randomized intervention on the probability of being retained in care 12 months after ART initiation and test the corresponding null hypothesis of no intervention effect, using a community-level TMLE analogous to that used to compare time to ART initiation between arms - weighting individuals equally and with candidate adjustment variables consisting of the proportion of adults newly diagnosed with HIV at baseline who are aged <25 years and the proportion of adults newly diagnosed with HIV at baseline who are mobile (≥ 1 month of past year spent outside the community).

Any differences observed in retention between treatment arms may be attributable in part to differences in the population initiating ART (the population of ART initiators evaluated may differ by study arm in terms of how challenging they are to retain in care). We will, therefore, conduct complimentary analyses to estimate the probability of having initiated ART and remaining retained in HIV care.This outcome captures the total intervention effect on both ART start and subsequent retention among starters.

We will report estimates by treatment arm, by region, by community, and for the following strata: no prior HIV care at baseline, prior HIV care without a record of prior ART at baseline, study year of ART initiation, CD4 <500 versus ≥ 500 at time of ART initiation, and ≤ 30 days versus >30 days between date of first HIV-positive test during SEARCH follow-up and ART initiation.

We will provide descriptive statistics as well as evaluate unadjusted and adjusted associations between baseline individual-level characteristics and non-retention. Specifically, we will report unadjusted associations and adjusted variable importance measures on the relative scale (statistical analogs of the causal risk ratio), treating each baseline predictor in turn as the intervention variable, and the remainder as the adjustment set. Variable importance measures will be estimated with pooled individual-level TMLE,

adjusted for community as a fixed effect, and treating the individual as the independent unit for variance estimation. Baseline predictors considered will include region, sex, age, marital status, education, occupation, household wealth index, mobility, alcohol use, testing location, CD4 count at ART start (<500; $\geq$ 500), and time from diagnosis to ART start ($\leq$ 30 days; > 30days).

We will implement analogous analyses to evaluate retention among individuals with a prior history of ART use at study baseline who have at least one documented clinic visit post-baseline. For this subgroup, time-zero is the date of first post-baseline clinic visit, and the primary outcome is, as above, retention 12 months after this date.

7.6 Analysis of interim testing

To further understand the impact of annual population-based testing, for communities in the intervention arm we will report the following descriptive statistics, overall and by region:

- Number of newly diagnosed HIV-positive individuals seen during population-based testing at time t; their demographics (sex, age (15-24 years; 25+ years), and baseline mobility (< 1mo away; ≥1mo away)), CD4+ T cell count, HIV RNA level, prior SEARCH testing history, and residence status (baseline stable resident, baseline non-stable resident, in-migrant, non-resident); and the proportion of all HIV-positive individuals seen at time t who are newly diagnosed, overall and stratified by prior HIV testing history.

- Number of previously diagnosed HIV-positive individuals with no history of ART seen during population-based testing at time t; their demographics (sex, age (15-24 years; 25+ years), and baseline mobility (< 1mo away; ≥1mo away)), CD4 count, HIV RNA level, prior SEARCH testing history, and residence status (baseline stable resident, baseline non-stable resident, in-migrant, non-resident); and the proportion of all HIV-positive individuals seen at time t who are previously diagnosed but with no prior history of ART.

- Among new diagnoses, time to linkage, time to ART initiation, and the proportion suppressed one (for new diagnoses at year 1 and year 2) and two years following diagnosis (for new diagnoses at year 1) (Noting that analysis of these outcomes among individuals testing baseline HIV-positive at baseline are described above).

Analogous analyses will be conducted restricting to incident HIV infections identified at interim campaigns (i.e. restricting new diagnoses to those with a prior negative HIV test). To quantify background (non-SEARCH) diagnosis and linkage rates, we will further report in both arms the number and proportion of new diagnoses and of incident infections during the three years of study follow-up using the earliest record of HIV-positive status recorded in Ministry of Health clinical records or linkage to the tuberculosis registry rather than SEARCH annual population-based testing.

8 Community adult health outcomes

A primary aim of the SEARCH Study is to understand the intervention's effect on the health of the overall community as well as the health of people living with HIV. This section describes evaluation of the adult health outcomes of mortality, tuberculosis (TB), and non-communicable diseases (NCDs), specifically diabetes (DM) and hypertension (HTN). Descriptive analyses of ART toxicity and resistance are also given.

8.1 Mortality

The SEARCH intervention may reduce mortality by enabling earlier diagnosis, earlier ART initiation, and improved ART retention and suppression outcomes among HIV-positive individuals, as well as, to a lesser degree, reducing exposure to infectious outcomes like TB. In addition, the comprehensive mortality data collected as part of SEARCH provides an opportunity to accurately quantify overall mortality in this rural East Africa setting in the context of universal test and treat, as well as community-wide HIV testing and linkage to care at study baseline (the active control arm of the trial). In this section, we specify analyses to compare mortality among baseline HIV-positive individuals and among the overall adult population between intervention and control arms, as well as additional descriptive and explanatory analyses.

8.1.1 Mortality among HIV-positive adults

Mortality among HIV-positive adults will be compared between arms using a two-stage approach analogous to that employed for the HIV incidence, ART initiation, and plasma HIV RNA suppression outcomes. The first stage will estimate community-specific mortality risk among adults known to be HIV-positive at or before study baseline, both overall and restricted to those with no record of ART use prior to baseline. Kaplan-Meier estimators will be used to estimate post-baseline survival in each community. In primary analyses, failure will be defined as death due to illness, and follow-up time will be censored at death to other causes or out-migration from the community; in secondary analyses, failure will be defined as death due to any cause. Primary analyses will estimate survival among baseline stable adult residents; sensitivity analyses will include baseline non-stable residents. In the second stage, risk of mortality by three years (or, if less than three years, by the minimum Phase 1 follow-up time across communities) will be compared between arms, weighting individuals equally, and with candidate adjustment variables consisting of the proportions of the analytic population with baseline CD4+ T cell count $\leq$50 cells/μl and with baseline CD4+ T cell count $\leq$350 cells/μl, as well as for analyses of all baseline HIV-positive adults (including those on ART at baseline) the proportion of the analytic population with baseline plasma HIV RNA level $<$500 copies/ml.

To distinguish between the impact of streamlined linkage and ART delivery in the intervention arm from the impact due to differences in CD4+ T cell count eligibility threshold for ART initiation at study baseline, we will further conduct subgroup analyses testing the null hypothesis of no difference in mortality risk between arms within subgroups defined by baseline CD4+ T cell count: $\leq$350 cells/μl and $>$350 cells/μl. The intervention effect will be estimated using a two stage approach identical to the primary analysis described above, with the exception of the following modification to the candidate CD4-based adjustment variables used in Stage 2:

- For the subgroup of baseline CD4+ T cell count $\leq$350 cells/μ: the proportion with CD4+ T cell count $\leq$100 cells/μl
- For the subgroup of baseline CD4+ T cell count $>$350 cells/μ: the proportion with CD4+ T cell count 350-500 cells/μl

We will also report the following descriptive analyses of mortality among baseline HIV-positive individuals:

- Kaplan-Meier-based survival estimates, stratified by baseline cascade status (no prior HIV care, prior HIV care but no prior ART, prior ART but with plasma HIV RNA level $\geq$500 copies/ml at baseline, and plasma HIV RNA level $<$500 copies/ml at baseline)
- Estimated mortality rates (per 100,000 person years) with person-time at risk beginning at the start of Phase I and ending at death, out-migration, or end of phase 1. Mortality rates will be reported among all baseline HIV-positive individuals, and among baseline HIV-positive adults aged 15-59.

Primary analyses will be based on baseline stable residents; secondary analyses will include non-stable residents.

We will further estimate unadjusted and adjusted predictors of death among the baseline HIV-positive population. A pooled individual-level TMLE including community as a fixed effect will be used to estimate adjusted and unadjusted variable importance measures (on the relative scale) for the following covariates: sex, age, marital status (including widow as a separate category if sufficient data support exists), education, occupation, household wealth index, mobility, having a baseline HIV+ adult (other than the current individual) in the same household, baseline CD4+ T cell count, and baseline plasma HIV RNA level <500 copies/ml.

Finally, we will estimate the mortality rate due to illness, and due to any cause, following ART initiation. Person-time at risk will begin at the time of ART initiation and end at the first of death, out-migration or end of Phase 1. We will compare this rate between arms, using a two stage TMLE, weighting person-time equally and with candidate adjustment variables consisting of the proportions of baseline HIV-positive individuals not on ART at baseline with CD4+ T cell count $\leq$50 cells/μl and CD4+ T cell count $\leq$350 cells/μl at baseline. In interpreting this cross arm comparison, we note that any difference between arms will be a function of both any intervention effect on the underlying mortality risk of individuals initiating ART (i.e. via intervention effects on time to ART initiation overall and within subgroups), as well as any effect of the intervention on survival post-ART initiation. In descriptive analyses, Kaplan-Meier-based survival following ART initiation will also be estimated.

8.1.2 Mortality among all adults

Mortality rate (all-cause, and due to illness) will be estimated among all baseline stable residents (primary) and among all baseline residents (regardless of stability; secondary). Person-time at risk will begin at the first of the start of Phase 1, or age $\geq$15 years, and will end at the first of death, out-migration, or the end of Phase 1. We will compare this rate between arms, using a two stage TMLE weighting person-time equally, with candidate adjustment variables consisting of baseline HIV prevalence and the proportion of adult residents falling in lowest quintile of household socioeconomic index.

Additional descriptive analyses of mortality in the adult population will include:

- A description of the distribution of causes of death (illness, childbirth, homicide, accident, suicide) among adult deaths, stratified by arm.
- Age-adjusted mortality rates, using direct standardization to the WHO standard age distribution, and stratified by arm and by baseline HIV status.
- Unadjusted and adjusted predictors of mortality, analogous to the variable importance measures estimated for the baseline HIV-positive population.

8.1.3 Comparison of mortality between HIV-positive and HIV-negative adults

We will compare mortality rates between the adult baseline HIV-positive and baseline HIV-negative populations, over all communities, and stratified by region and treatment arm. Mortality rates will be standardized to the pooled age-sex distribution of the populations being compared. We will compare survival curves over time between the adult baseline HIV-positive and HIV-negative populations, using both unadjusted Kaplan-Meier estimators, and TMLE of baseline HIV-status-specific survival curves, adjusted for baseline predictors of mortality including age, and including community as a fixed effect.

8.2 Tuberculosis (TB)

More rapid initiation and effective ART delivery as a result of streamlined care may reduce the incidence of TB disease and death among HIV-positive individuals by reducing susceptibility to TB disease among HIV-positive persons, and by reducing death due to HIV-associated TB. In this section we describe analyses to compare the composite outcome of HIV-TB and death between treatment arms, as well as additional descriptive analyses of incident active TB and TB-associated morbidity.

8.2.1 Incident Active HIV-associated Tuberculosis

Our primary HIV-TB outcome for comparison between intervention and control arms will be estimated among baseline stable adult residents who either test HIV-positive at baseline or who have a missing baseline HIV test. Our motivation for including individuals with a missing baseline HIV test is that individuals who are harder to access for HIV testing may be those individuals at higher risk of HIV-TB. In sensitivity analyses we will (i) include non-stable residents; and (ii) restrict to individuals known to be HIV-positive at baseline. The population will exclude individuals with an active TB diagnosis within 6 months prior to the start of Phase 1. In this population, we will estimate risk of the composite outcome of (i) death due to illness or (ii) incident active TB disease with an HIV diagnosis recorded at or prior to date of TB diagnosis. The primary HIV-TB analysis is focused on this composite outcome based on evidence that a substantial portion of death due to illness among HIV-positive persons is due to undiagnosed TB.

Comparison of HIV-TB outcomes between arms will be based on a two stage analysis. In the first stage, community-specific Kaplan-Meier estimators will be used to estimate the risk of the composite outcome by three years (or the minimal time for which all communities have follow-up), censoring at death due to other causes or out-migration. In the second stage, these community-level risk estimates will be compared between arms using TMLE, weighting individuals equally, and with a candidate adjustment set consisting of (i) baseline HIV prevalence among adults, and (ii) the number of TB cases diagnosed in year prior to baseline divided by the number of baseline adult residents.

In secondary analyses, we will evaluate the non-composite outcome of HIV-associated TB (censoring at outmigration or death due to any cause) among the full adult population (irrespective of baseline HIV status). Comparison of these secondary outcomes between arms will be implemented analogously to the primary TB outcome, using community-specific Kaplan Meier estimators to estimate risks, and comparing estimated risks between arms using TMLE, weighting individuals equally, and with the same candidate adjustment set as for the primary TB outcome.

The above analyses will also be implemented stratifying on region (unadjusted Stage 2 estimator only) and for the following subgroups: (i) baseline HIV-positive adults with baseline CD4+ T cell count $\leq$500 cells/μl; (ii) baseline HIV-positive adults with baseline CD4+ T cell count >500 cells/μl; (iii) baseline HIV-positive adults with baseline plasma HIV RNA level $\geq$500 copies/ml; and (iv) men and women.

8.2.2 Additional TB analyses

We will implement the following additional secondary analyses to characterize incident active TB by HIV status, to determine the predictors of HIV-associated active TB, and to compare the clinical outcomes of participants with active TB in intervention vs. control communities. The overall goal of these secondary analyses is to better understand potential changes in the epidemiology of HIV-associated TB, including how the SEARCH intervention might impact the risk of developing active TB and clinical outcomes.

- We will report Kaplan-Meier survival curves for the time-to-event outcomes corresponding to the primary and secondary HIV-TB outcomes, by region and arm, and within the following subgroups: baseline HIV-positive adults with CD4+ T cell count $\leq$500 and >500 cells/μl at baseline; baseline

HIV-positive adults with plasma HIV RNA level ≥500 and <500 copies/ml at baseline; men and women; youth (aged 15-24 years) and older individuals (aged ≥ 25 years).

- We will use Kaplan-Meier estimators to evaluate the risk over time for developing (i) TB, and (ii) HIV-TB among (i) the baseline HIV-negative population, and (ii) the baseline HIV-positive population, censoring at death or outmigration. We will report the corresponding survival curves.
- We will estimate annualized TB and HIV-TB incidence rates in an open cohort of adult residents, overall and stratified by baseline HIV status. Person-time at risk will begin at the first date at which the individual is a community resident (either a baseline resident, or has in-migrated, using in-migration date ascertained at year 3) and aged ≥15 years, and will end at the first of diagnosis of active TB, death, outmigration, or end of Phase 1. Annual TB incidence rates will be reported by community and by treatment arm (overall and within region).

8.2.3 Predictors of incident TB

We will report unadjusted associations and adjusted variable importance measures on the relative scale (statistical analogs of the causal risk ratio), treating each baseline predictor in turn as the intervention variable, and the remainder as the adjustment set. Variable importance measures will be estimated with pooled individual-level TMLE, using the community as the independent unit when estimating variance, and with inference based on the t-distribution. The population, outcome, and right-censoring variables will be defined as for the primary outcome; analogous to predictors of HIV seroconversion, secondary analysis will consider community as a fixed effect. Baseline predictors considered will include: sex, age, education, household wealth, mobility, alcohol use, and among baseline HIV+, baseline CD4+ T cell count and plasma HIV RNA level. Predictors will be evaluated overall and stratified by baseline HIV status.

8.2.4 Characterization of active TB cases by HIV status

We will conduct the following analyses to evaluate how individuals diagnosed with active TB and the clinical presentation of active TB varies over time and by HIV status. Specifically, we will describe demographic and clinical characteristics of incident active TB cases diagnosed during Phase 1, overall and stratified by (i) HIV status, (ii) intervention vs. control arm, and (iii) by study year. We will provide descriptive statistics of the following characteristics of TB cases: demographics (age, sex, wealth index, education); mobility; TB disease site (pulmonary, extra-pulmonary); AFB smear; TB disease type (new, re-treatment, failure, default); and, among HIV-positive individuals, CD4+ T cell count and plasma HIV RNA level at time of TB treatment start.

We will also calculate the empirical proportion of incident TB cases that are HIV-associated (defined, as for the primary outcome, as having an HIV diagnosis at or prior to TB diagnosis date), stratified by intervention arm and by year. We will compare this proportion between intervention and control arms using the two stage approach used for the primary TB outcome.

8.2.5 Clinical Outcomes among HIV-associated TB cases

We hypothesize that TB clinical outcomes following TB treatment start will be positively impacted by the SEARCH intervention due to earlier diagnosis of HIV, universal access to ART, and streamlined HIV care delivery. These impacts may include reduced mortality during TB treatment, reduced risk of IRIS (defined as CD4<100 at TB treatment start), and more rapid time to ART start (if not on ART at TB diagnosis) in intervention communities compared to control.

Among individuals diagnosed with HIV-associated, incident active TB disease in Phase 1, we will estimate the mortality rate due to illness during TB treatment, with person-time at risk beginning on date

of TB treatment initiation and ending on first of out-migration, death due to other causes, TB treatment end date, or end of Phase 1. We will compare this rate between intervention arms with a two-stage approach analogous to the approach used for the primary TB outcome, weighting person-time equally, and with candidate adjustment variables consisting of proportion of baseline HIV-positive individuals with CD4+ T cell count$\leq$350 cells/μl, and proportion of baseline HIV-positive individuals with HIV RNA level <500 copies/ml. As with mortality rates following ART initiation, we note any intervention effect may be mediated in part by impacts on the characteristics of TB treatment initiators at time of TB treatment start.

We will also report the following descriptive analyses:

- The proportion of incident active TB cases among HIV-positive individuals with CD4+ T cell count <200 cells/μl that develop IRIS
- The proportion of incident active TB cases with prior ART use at time of TB diagnosis
- Time to ART initiation following incident active TB diagnosis among individuals who are HIV-positive and not on ART at the time of TB diagnosis

8.3 Non-Communicable Diseases

At baseline, all communities received population-based hypertension (HT) screening and referral for treatment according to national guidelines. Intervention communities further received annual population-based HT screening, with HT treatment for HIV-positive and HIV-negative individuals delivered using an integrated streamlined-care delivery model. Screening and care for diabetes (DM) was delivered analogously in the intervention and control arms, with the exception that DM screening at baseline was limited to Ugandan communities. The SEARCH intervention may thus improve HT and DM control through earlier diagnosis and through more effective treatment delivery. As with HIV RNA suppression and HIV incidence, baseline population-based testing in the control arm may also improve HT/DM control over time. In this section, we describe analyses to evaluate these hypotheses among adults aged $\geq$ 30 years at follow-up year 3. As throughout, to ensure comparable data structures, analyses comparing intervention and control arms only make use of data collected at population-based testing at baseline and at follow-up year 3.

We define HT control as having at least one systolic blood pressure (BP) measurement <140 mmHg and at least one diastolic BP measurement <90 mmHg. In other words, uncontrolled HT is defined as all systolic BP measures $\geq$140 mmHg or all diastolic BP measures $\geq$ 90 mmHg (requiring that at least one BP measure was recorded). We define prevalent HT as current or previous (i) self-report of a prior diagnosis, or (ii) uncontrolled blood pressure. For HIV-positive and HTN prevalent persons, dual-control is defined as joint control of HT and suppressed viral replication (<500 copies/ml). The metrics for DM are defined analogously, with DM control defined as a finger-prick blood glucose $\leq$11 mmol/L and prevalent DM defined as previous or current (i) self-report of a prior diagnosis, or (ii) uncontrolled blood glucose.

8.3.1 Hypertension (HT) control among individuals with prevalent HT at year 3

HT control among adults aged $\geq$ 30 years and with prevalent HT at year 3 will be compared between arms using the two-stage approach, detailed above. The first stage will estimate the community-specific proportion of adults with prevalent HT at year 3 who have their HT controlled at follow-up year 3, both overall and among those known to be HIV-positive at year 3. Using an approach analogous to that used to estimate population-level viral suppression, these population-level proportions will be estimated for each community using an individual-level TMLE, adjusting for incomplete measures of both HT disease status at year 3 and incomplete measures of disease control at year 3. Secondary analyses will restrict to individuals known to have HT at year 3, adjusting for incomplete measures of disease control. Among adults with prevalent HT and HIV at year 3, we will also estimate the community-specific proportion with dual-control

(both controlled HT and plasma HIV RNA level <500 copies/ml) at follow-up year 3, adjusting for missing measures of both HT control and plasma HIV RNA at year 3.

Primary analyses will be restricted to baseline stable residents; sensitivity analyses will include baseline non-stable residents and in-migrants identified in year 3 testing. Primary analyses will condition on being alive and resident in the community at follow-up year 3; secondary analyses will further adjust for censoring by death and out-migration. Sensitivity analyses will be based on unadjusted empirical proportions.

In the second stage, community-specific estimates of control at follow-up year 3 will be compared between arms, weighting individuals equally, and with the following candidate adjustment variables:

- baseline CHC testing coverage and baseline prevalence of having a body mass index (BMI) > 24 when estimating the effect on HT control at follow-up year 3
- baseline CHC testing coverage and baseline dual-control when estimating the effect on dual-control at follow-up year 3

We will also test the null hypothesis of no intervention effect stratifying on region (for each population) in unadjusted analyses. Using the analogous two-stage approach, we will also report estimates of HT control and HIV-HT dual-control stratified by community, by intervention arm, and within intervention by region, sex, and age (30-44 years, 45-59 years, 60+ years).

8.3.2 HT control among individuals with prevalent HT at baseline

HT control among adults (≥30 years) known to have HT at baseline (via self-report or elevated blood pressure at baseline) will be compared between arms using the two-stage approach, detailed above. The first stage will estimate the community-specific proportions of adults known to have HT at baseline who have their HT controlled at follow-up year 3, overall and among those also known to be HIV-positive at baseline (with and without a further restriction on uncontrolled viral replication at baseline). For the baseline HIV-HT prevalent population, we will also estimate the community-specific proportions with dual-control at follow-up year 3. These proportions will be estimated with TMLE, adjusting for incomplete measures of control at year 3 (including HIV RNA levels for the dual-control outcome); secondary analyses will be unadjusted. Primary analyses will be restricted to baseline stable residents; sensitivity analyses will include baseline non-stable residents. Primary analyses will condition on being alive and resident in the community at follow-up year 3; secondary analyses will further adjust for censoring by death and out-migration.

In the second stage, estimates of control at follow-up year 3 will be compared between arms, weighting individuals equally, and with candidate adjustment variables:

- baseline CHC testing coverage and baseline control when estimating the effect on HT control at follow-up year 3
- baseline CHC testing coverage and baseline dual-control when estimating the effect on dual-control at follow-up year 3

We will also test the null hypothesis of no intervention effect stratifying on region (for each population) in unadjusted analyses. We will report estimates of HT control and HT-HIV dual-control stratified by community, by intervention arm, and within intervention by region, sex, and age (30-44 years, 45-59 years, 60+ years).

8.3.3 Predictors of uncontrolled HT

We will conduct the following analyses to evaluate individual-level predictors of uncontrolled HT at follow-up year 3. We will report unadjusted associations and adjusted variable importance measures on the relative

scale (statistical analogs of the causal risk ratio), treating each baseline predictor in turn as the intervention variable, and the remainder as the adjustment set. Variable importance measures will be estimated with a pooled individual-level TMLE, adjusted for community as a fixed effect and adjusting for potentially differential missingness of HT control measures. These descriptive statistics and predictor analyses will be reported for the following populations: all adults, HT-prevalent at follow-up year 3, HIV-positive at follow-up year 3, and HIV-HT prevalent at follow-up year 3. For the HIV-HT prevalent population, we will also evaluate predictors of lack of dual-control. Baseline predictors considered will include region, sex, age (30-44 years, 45-49 years, and 60+ years), marital status, education, occupation, household wealth index, mobility, alcohol use, and body mass index (BMI). Additional predictors for HIV-positive populations include evidence of prior HIV diagnosis and previous treatment with ART.

8.3.4 NCD (hypertension and diabetes) control and predictors of uncontrolled NCD

We will conduct the following analyses to examine the intervention impact on both HT and diabetes (DM) control, as well as predictors of uncontrolled NCD at follow-up year 3. We consider an individual to be NCD prevalent if he or she is HT prevalent and/or DM prevalent at a given time-point. NCD control is defined as current control of all prevalent NCDs. Dual HIV-NCD control is defined as current control of all of prevalent NCDs and plasma HIV RNA level <500 copies/ml.

The analyses described in Sections 8.3.1 and 8.3.2 will be repeated to estimate NCD control and dual HIV-NCD control at follow-up year 3. Specifically, we will estimate the intervention effect on

- NCD control at follow-up year 3 in the overall population of adults with prevalent NCD at follow-up year 3, in the population of adults who are HIV-NCD prevalent at follow-up year 3, and in the subgroups specified above
- Dual HIV-NCD control at follow-up year 3 in the population of adults who are HIV-NCD prevalent at follow-up year 3, and within the subgroups specified above
- NCD control at follow-up year 3 in the overall population of Ugandan adults with prevalent NCD at baseline, in the population of Ugandan adults who are HIV-NCD prevalent at baseline, and within the subgroups specified above
- Dual HIV-NCD control at follow-up year 3 in the population of Ugandan adults who are HIV-NCD prevalent at baseline and within the subgroups specified above

(Recall screening for DM occurred only in Uganda communities at baseline.) We will also conduct a sensitivity analysis where all individuals are considered to have blood glucose $\leq$11 mmol/L unless there is evidence otherwise.

The analyses specified in Section 8.3.3 will be repeated to evaluate predictors of uncontrolled NCD at follow-up year 3.

8.3.5 HT and NCD care cascades

Analogously to the HIV care cascade (Section 7.2), we will estimate the following population-level metrics at baseline and year 3 ($t = \{0, 3\}$): prevalence among adult residents (aged $\geq$ 30 years), the proportion of all prevalent adults who are previously diagnosed, the proportion of previously diagnosed who have ever initiated treatment, the proportion of treatment initiators who are currently controlled, and the overall population-level control (the proportion of all prevalent adults who are currently controlled). These analyses will be performed for the overall population as well as the HIV-positive population at time t.

Primary analyses will use TMLE to adjust for potentially differential measurement of both disease status and control; unadjusted numbers and proportions will also be reported. Primary analyses will include baseline residents (regardless of stability) and in-migrants identified at follow-up year 3; secondary

analyses will restrict to baseline stable residents. Primary analyses will condition on being alive and resident in the community at time t; secondary analyses will further adjust for censoring by death and out-migration. For both HT (only) and NCD (HT and/or DM), these metrics will be estimated overall, and stratified by community, by intervention arm, and within intervention by region, sex, and age (30-44 years, 45-59 years, 60+ years). We will generate analogous estimates of dual-control for the HIV-NCD prevalent population. Annual estimates of cascade coverage will also be reported in the intervention arm.

To further understand the impact of the intervention on the HTN and the NCD care cascades, we will conduct the following analyses.

- Using analogous methods to those described in Section 7.2, we will estimate in each arm the change in cascade coverage from baseline to follow-up year 3.
- Using analogous methods to those described in Section 7.3, we will estimate HT and NCD care cascade outcomes at year 3 in a longitudinal closed cohort of adults with baseline prevalent disease (overall and among baseline HIV-positive). We will characterize this cohort by baseline status (prior diagnosis, treatment and control) as well as evaluate individual-level risk factors for lack of control at follow-up year 3. Within the intervention arm, we will report analogous estimates for years 1 and 2.

8.4 Antiretroviral Treatment Associated Toxicities

We will report number and incidence of grade 3 and grade 4 adverse events and treatment limiting toxicity among individuals initiated on ART outside country guidelines.

8.5 Antiretroviral resistance among HIV-positive individuals

Drug resistance among HIV-infected individuals will be assessed based on the presence of NRTI, PI, and NNRTI mutations. Transmitted resistance will be assessed at year 3 based on the prevalence of resistance mutations at year 3 among individuals with HIV-seroconversion during the course of the study who remain ART naïve at year 3. Transmitted resistance at time of first HIV diagnosis will also be reported among interim seroconversions in the intervention arm of the study. Acquired resistance will be assessed at baseline and year 3 based on the prevalence of resistance mutations among HIV-positive individuals with a history of prior ART initiation, stratified by current ART use at baseline and year 3. Resistance will be reported stratified by community, treatment arm, and within treatment arm by region. The demographic characteristics (sex, age (15-24 years; 25+ years), and baseline mobility ($<$ 1mo away; $\geq$1mo away)) of individuals with resistance will be summarized.

References

[1] L.B. Balzer, M.L. Petersen, M.J. van der Laan, and the SEARCH Consortium. Adaptive pair-matching in randomized trials with unbiased and efficient effect estimation. *Statistics in Medicine*, 34(6):999–1011, 2015. doi: 10.1002/sim.6380.

[2] L.B. Balzer, M.L. Petersen, and M.J. van der Laan. Targeted estimation and inference of the sample average treatment effect in trials with and without pair-matching. *Statistics in Medicine*, 35(21): 3717–3732, 2016. doi: 10.1002/sim.6965.

[3] R.J. Hayes and L.H. Moulton. *Cluster Randomised Trials.* Chapman & Hall/CRC, Boca Raton, 2009.

[4] L. Balzer, M. van der Laan, M. Petersen, and the SEARCH Collaboration. Adaptive pre-specification in randomized trials with and without pair-matching. *Statistics in Medicine*, 35(10):4528–4545, 2016. doi: 10.1002/sim.7023.

[5] J.M. Robins. A new approach to causal inference in mortality studies with sustained exposure periods–application to control of the healthy worker survivor effect. *Mathematical Modelling*, 7:1393–1512, 1986. doi: 10.1016/0270-0255(86)90088-6.

[6] M. van der Laan and S. Rose. *Targeted Learning: Causal Inference for Observational and Experimental Data*. Springer, New York Dordrecht Heidelberg London, 2011.

[7] M.J. van der Laan, E.C. Polley, and A.E. Hubbard. Super learner. *Statistical Applications in Genetics and Molecular Biology*, 6(1):25, 2007. doi: 10.2202/1544-6115.1309.

[8] M.L. Petersen, J. Schwab, S. Gruber, N. Blaser, M. Schomaker, and M. van der Laan. Targeted maximum likelihood estimation for dynamic and static marginal structural working models. *Journal of Causal Inference*, 2(2):DOI: 10.1515/jci–2013–0007, 2014.

[9] M.J. van der Laan, L.B. Balzer, and M.L. Petersen. Adaptive Matching in Randomized Trials and Observational Studies. *Journal of Statistical Research*, 46(2):113–156, 2012.

[10] Donald B. Rubin. Comment: Neyman (1923) and causal inference in experiments and observational studies. *Statistical Science*, 5(4):472–480, 1990.

[11] G.W. Imbens. Nonparametric estimation of average treatment effects under exogeneity: a review. *Review of Economics and Statistics*, 86(1):4–29, 2004. doi: 10.1162/003465304323023651.

[12] K. Imai. Variance identification and efficiency analysis in randomized experiments under the matched-pair design. *Statistics in Medicine*, 27(24):4857–4873, 2008. doi: 10.1002/sim.3337.

[13] R.A. Fisher. *Statistical methods for research workers*. Oliver and Boyd Ltd., Edinburgh, 4th edition, 1932.

[14] W.G. Cochran. Analysis of covariance: its nature and uses. *Biometrics*, 13:261–281, 1957. doi: 10.2307/2527916.

[15] D.R. Cox and P. McCullagh. Some aspects of analysis of covariance. *Biometrics*, 38(3):541–561, 1982. doi: 10.2307/2530040.

[16] A.A. Tsiatis, M. Davidian, M. Zhang, and X. Lu. Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: A principled yet flexible approach. *Statistics in Medicine*, 27(23):4658–4677, 2008. doi: 10.1002/sim.3113.

[17] K.L. Moore and M.J. van der Laan. Covariate adjustment in randomized trials with binary outcomes: Targeted maximum likelihood estimation. *Statistics in Medicine*, 28(1):39–64, 2009. doi: 10.1002/sim.3445.

[18] M. Rosenblum and M.J. van der Laan. Simple, efficient estimators of treatment effects in randomized trials using generalized linear models to leverage baseline variables. *The International Journal of Biostatistics*, 6(1):Article 13, 2010. doi: 10.2202/1557-4679.1138.

[19] M.J. van der Laan and D.B. Rubin. Targeted maximum likelihood learning. *The International Journal of Biostatistics*, 2(1):Article 11, 2006. doi: 10.2202/1557-4679.1043.

[20] D. Guwatudde, F. Wabwire-Mangen, L.A. Eller, M. Eller, F. McCutchan, H. Kibuuka, M. Millard, N. Sewankambo, D. Serwadda, N. Michael, M. Robb, and the Kayunga Cohort Research Team. Relatively Low HIV Infection Rates in Rural Uganda, but with High Potential for a Rise: A Cohort Study in Kayunga District, Uganda. *PLoS ONE*, 4(1):e4145, 2009.

[21] L.A. Shafer, S. Biraro, J. Nakiyingi-Miiro, A. Kamali, D. Ssematimba, J. Ouma, A. Ojwiya, P. Hughes, L. Van der Paal, J. Whitworth, A. Opio, and H. Grosskurth. HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989-2005. *AIDS*, 22 (13):1641–1649, 2008.

[22] R.H. Gray, G. Kigozi, D. Serwadda, F. Makumbi, S. Watya, F. Nalugoda, N. Kiwanuka, L.H. Moulton, M.A. Chaudhary, M.Z. Chen, N.K. Sewankambo, F. Wabwire-Mangen, M.C. Bacon, C.F. Williams, P. Opendi, S.J. Reynolds, O. Laeyendecker, T.C. Quinn, and M.J. Wawer. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*, 369(9562):657–666, 2007.

[23] C. Pagel, A. Prost, S. Lewycka, S. Das, T. Colbourn, R. Mahapatra, K. Azad, A. Costello, and D. Osrin. Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomised controlled trials in low and middle-income countries: results and methodological implications. *Trials*, 12(1):151, 2011.

[24] R. Hayes, F. Mosha, A. Nicoll, H. Grosskurth, J. Newell, J. Killewo, J. Rugemalila, and D. Mabey. A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 1. design. *AIDS*, 9(8):919–926, 1995.

[25] C. Beck, B. Lu, and R. Greevy. *nbpMatching: functions for optimal non-bipartite optimal matching*, 2016. URL `https://CRAN.R-project.org/package=nbpMatching`. R package version 1.5.0.

[26] Futures Institute. *Spectrum manual: Spectrum system of policy manuals*, 2014.

[27] Futures Institute. *Goal Manual - A model for estimating the effects of interventions and resource allocation on HIV infections and deaths*, 2011.

[28] Futures Institute. *AIM: A Computer Program for Making HIV/AIDS Projections and Examining the Demographic and Social Impacts of AIDS*, 2014.

[29] Uganda Ministry of Health and ORC Macro. Uganda HIV/AIDS sero-behavioural survey 2004-2005. Calverton, Maryland, USA, 2006.

[30] Uganda Ministry of Health and ICF International. 2011 Uganda AIDS indicator survey: Key findings, Calverton, Maryland, USA 2012.

[31] UNAIDS. HIV estimates with uncertainty bounds 1990-2012, 2013. Avaliable at `http://www.unaids.org/en/resources/campaigns/globalreport2013/globalreport/`.

[32] National AIDS and STI Control Programme (NASCOP). Kenya AIDS indicator survey 2012: Final report. Nairobi, NASCOP, 2014.

[33] D.O. Kimanga and et al. Prevalence and incidence of HIV infection, trends, and risk factors among persons aged 15-64 years in Kenya: results from a nationally representative study. *J Acquir Immune Defic Syndr*, 66(Suppl 1):S13–26, 2014.

[34] Mary S. Campbell, James I. Mullins, James P. Hughes, Connie Celum, Kim G. Wong, Dana N. Raugi, Stefanie Sorensen, Julia N. Stoddard, Hong Zhao, Wenjie Deng, Erin Kahle, Dana Panteleeff, Jared M. Baeten, Francine E. McCutchan, Jan Albert, Thomas Leitner, Anna Wald, Lawrence Corey, Jairam R. Lingappa, and for the Partners in Prevention HSV/HIV Transmission Study Team. Viral linkage in hiv-1 seroconverters and their partners in an hiv-1 prevention clinical trial. *PLoS ONE*, 6(3):e16986, 03 2011. doi: 10.1371/journal.pone.0016986. URL `http://dx.doi.org/10.1371%2Fjournal.pone.0016986`.

[35] M. Petersen, L. Balzer, D. Kwarsiima, N. Sang, et al. Association of implementation of a universal testing and treatment intervention with HIV diagnosis, receipt of antiretroviral therapy, and viral suppression among adults in East Africa. *JAMA*, 317(21):2196–2206, 2017. doi: 10.1001/jama.2017.5705.

[36] L.B. Balzer, J. Schwab, M.J. van der Laan, and M.L. Petersen. Evaluation of progress towards the UNAIDS 90-90-90 HIV care cascade: A description of statistical methods used in an interim analysis of the intervention communities in the SEARCH study. Technical Report 357, University of California at Berkeley, 2017. URL `http://biostats.bepress.com/ucbbiostat/paper357/`.

[37] L.B. Brown, D.V. Havlir, J. Ayieko, F. Mwangwa, A. Owaraganise, et al. High levels of retention in care with streamlined care and universal test and treat in East Africa. *AIDS*, 30:2855–2964, 2016.

Statistical Analysis Plan for SEARCH Study
Summary of Changes: v1.0, January 21, 2015 to v3.0, November 27, 2017

1. In April 2016, the SEARCH Trial was converted to a two-phase study and the primary endpoint for Phase I was modified from five to three year cumulative incidence of HIV, with no interim population-based testing in the control arm. The analysis plan was updated throughout to reflect this design change.
2. The pre-specified adjustment procedure used in stage II (cluster-level comparisons between arms) for point estimation and inference was clarified. In particular, estimation of the treatment mechanism was added in order to improve precision, and the relative risk was specified as the primary measure of effect to be reported.
3. In September 2015, the WHO modified its treatment guidelines to recommend antiretroviral therapy (ART) for all HIV+ individuals, irrespective of CD4+ T cell count. Simulations and power calculations for the primary study outcome were updated to reflect this modification to ART eligibility guidelines and the above modifications to study design.
4. Additional secondary and sensitivity analyses for the primary HIV-incidence outcome were specified. These included:
    a. Methods to be used for adjustment for potentially informative missingness and censoring used in stage I (incidence estimation within each cluster)
    b. Use of seroconversion interviews to classify incident HIV infections as externally-derived
    c. Analyses dropping the worst matched pair (according to pre-specified baseline characteristics: HIV prevalence and male circumcision) and "breaking the match"
    d. Pre-planned subgroup analyses
5. Additional detail was added for each of the secondary adult health outcomes, including:
    a. Detailed implementation of stage I outcome estimation within each cluster
    b. Detailed implementation of stage II between-cluster comparisons, including candidate adjustment variables and the decision to weight individuals versus communities equally in the primary analysis for each secondary outcome.
    c. Planned secondary and sensitivity analyses.
6. New health-related secondary outcomes to examine hypertension and diabetes control were added.
7. Additional detail was added regarding explanatory and descriptive analyses for HIV incidence, health outcomes, and intervention uptake (implementation). This included:
    a. Methods to evaluate predictors of primary and secondary outcomes
    b. Methods to evaluate change in HIV incidence over time

    c. Descriptive and explanatory analyses for HIV incidence outcomes
    d. Methods for HIV care cascade estimates
8. Maternal and pediatric health outcomes were moved to a separate analysis plan