High-yield HIV testing, facilitated linkage to care, and prevention for female youth in Kenya (GIRLS Study)

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1.

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September 9, 2016

2. STATEMENT OF COMPLIANCE

We, the principal investigators agree to conduct this study in compliance with this IRB approved protocol as it is described. We agree to comply with the ethical principles for the protection of human subjects as described in International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) and applicable ethical guidelines and regulatory requirements (outlined below). We, the principal investigators will assure no deviation from, or changes to, the protocol will occur without prior agreement from the sponsor and documented approval from the IRB (Kenyan and US), except where necessary to eliminate immediate hazard(s) to the participants. We, the principal investigators will promptly report to the IRB and the sponsor any changes in research activity and all unanticipated issues involving risks to human subjects.

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

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5. LIST OF ABBREVIATIONS

ACASI	Audio Computer Assisted Self-interviews
AE	Adverse Event/Adverse Experience
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
CAB	Community Advisory Board
CAPI	Computer Assisted Personal Interview
CCC	Comprehensive Care Center
CCT	Conditional Cash Transfer
CDC	U.S. Centers for Disease Control and Prevention
CRF	Case Report Form
DAIDS	Division of AIDS
DBS	Dried blood spots
ERC	Ethics and Research Committee
GCP	Good Clinical Practice
HAPI	HIV and Pregnancy Intention
HIV	Human Immunodeficiency Virus
HTS	HIV Testing Services
HPTN	HIV Prevention Trials Network
IC	Informed Consent
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
IRDO	Impact Research and Development Organization
KNH	Kenyatta National Hospital
MOH	Ministry of Health
MP3	Methods for Prevention Packages Program
N	Number (typically refers to participants)
NASCOP	National AIDS and STI Control Programme
NGO	Non-Governmental Organization
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
OF HIVST	Oral Fluid HIV Self-testing
OHRP	Office for Human Research Protections
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Principal Investigator
PITC	Provider-initiated Testing and Counseling
PIMA Analyzer	Pima CD4 test delivers an absolute count of T-helper cells from either a finger stick or venous whole blood sample within 20 minutes

PMTCT	Prevention of mother–to-child transmission
POC	Point of Care
PrEP	Pre-Exposure Prophylaxis
PSRC	Prevention Science Review Committee
PSRT	Protocol Safety Review Team
PTID	Participant Identification Number
RA	Research Assistant
RE	Regulatory Entity
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SES	Socioeconomic status
SMC	Safety Monitoring Committee
SMS	Short Message Service
SOP	Standard Operating Procedure
SSA	sub-Saharan Africa
SSP	Study-Specific Procedures (manual)
STIs	Sexually Transmitted Infections
UCT	Unconditional Cash Transfer
UN	United Nations
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNICEF	The United Nations International Children's Emergency Fund
UoN	University of Nairobi
USSD	Unstructured Supplementary Service Data
VCT	Voluntary counseling and testing
VL	Viral Load
VMMC	Voluntary Medical Male Circumcision
WHO	World Health Organization

6. PROTOCOL SUMMARY

Full Title	High-yield HIV testing, facilitated linkage to care, and prevention for female youth in Kenya
Short Title	GIRLS Study
Principal Investigator(s)	Ann Kurth, PhD, CNM, MPH, FAAN Irene Inwani, MD, MPH Kawango Agot, PhD, MPH
Sample Size	(N=1200). HIV positive cohort: (N≈108)[a]; Subset of HIV negatives (N≈185) [a] note that the positive cohort is an estimate based on expected HIV prevalence
Study Population	Female youth (aged 15-24) from Homa Bay County, Nyanza region, western Kenya
Study Design	The GIRLS study will rigorously compare two 'seek' recruitment strategies, three 'test' strategies, and two enhancements to an adaptive (SMART trial design) 'linkage' to care intervention, among young at-risk women, 15-24 years old, in Homa Bay County, western Kenya. Additionally, we will evaluate a scalable primary prevention messaging intervention to support identified HIV-negative young women in reducing HIV risk and adhering to HIV re-testing recommendations. This study design will allow us to follow participants along both the prevention and care continua.
Study Sites	The study will take place in Homa Bay County, Nyanza region, Kenya. • Homa Bay municipality • Mbita sub-county • Ndhiwa sub-county
Study Duration	Anticipated 12 months of accrual with 12 months of follow-up.
Study Intervention Description	The following will be offered to <u>all female youth</u> (N=1200): (1) HIV Testing Services (HTS) via home-based or community based recruitment strategies (2) HIV testing approaches that females can choose from include: (a) oral fluid HIV self-testing (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test, OraSure Technologies) at their convenience; (b) staff-aided testing at home/mobile site; and (c) a referral to a health care facility where HIV testing will be done by a health care provider (standard facility-based HTS) (3) Behavioral survey at baseline visit (4) SMS HIV test experience satisfaction survey (5) Staff-administered questionnaire about self-testing for females who choose self-testing option. <u>For all HIV positive females</u>: All HIV positive females will receive the following; (1) Point of care (POC) CD4 cell count at baseline (2) Viral load testing using dried blood spot (DBS) at 0 and 12 months (3) ***Referral for care and treatment; Adaptive linkage to care intervention.*** All HIV positive participants (N≈108) will be randomized to receive standard referral (N≈54) or standard referral plus SMS message (N≈54) to link to HIV care and treatment services; those who do not link to care within 2 weeks will be re-randomized in a ratio of 1:1 to a second SMS message or a one-time economic incentive to link to care.

	We will confirm linkage by self-report via phone call, and verified by medical record review. (4) ART adherence and treatment SMS reminders, combined with health status surveys at 3, 6, 9, and 12 months aligned to school holidays for those in school, when the participants would have access to phones. (5) Face-to-face (or telephone) interview on barriers and facilitators to seeking HIV care services after receiving a positive diagnosis at 12 months. If a phone interview is conducted, participant's identity will be confirmed by asking the participant to provide three names used at enrollment as well as their current age, so that her identity may be ascertained correctly. <u>For HIV negative females</u>: All HIV negative females will receive the following: Risk assessment counseling, condoms, and referral for other prevention services (partner and family testing, PrEP, other family planning (contraception) methods, STI screening and treatment, drug use counseling, mental health services, social and nutritional support, legal services, sexual and gender based violence services and others that might be identified during the interview/risk assessment with participants). A subset of randomly selected high risk (risk score ≥2 as defined by eligibility criteria for high risk) HIV negative females (N≈185) will receive: (1) An SMS text at 6 and 12 months with a health promotion message; (2) SMS survey to collect HIV risk behaviors, condom use, and willingness to retest for HIV at 6 and 12 months; (3) HIV test at 12 months; (4) Face-to-face (or telephone) interview on barriers and facilitators to accessing HIV prevention services at 12 months. If a phone interview is conducted, participant's identity will be confirmed by asking the participant to provide three names used at enrollment as well as their current age, so that her identity may be ascertained correctly.
Primary Objectives	(1) To determine the preferred recruitment venue and testing modality that targets and finds the highest number of HIV infected and at risk female youth aged 15-24 years in Homa Bay County, Nyanza region, western Kenya (Aim 1). • This will be determined by examining the uptake and yield of previously undiagnosed HIV infection of the two (2) 'seek' strategies (community or home-based) and the three (3) 'test' strategies (self-testing, HTS in a home/mobile setting, or facility-based HTS) among female youth; (2) To conduct an economic evaluation, using cost effectiveness analyses to determine the relative utility of each seek, test, link, and prevention intervention (Aim 3).
Secondary Objective	(1) To pilot and evaluate an adaptive intervention to link newly diagnosed HIV-positive female youth to treatment and care services (Aim 2a); (2) To identify barriers and facilitators to seeking HIV care services after receiving a positive diagnosis (Aim 2b); (3) To identify barriers and facilitators to seeking HIV prevention services for high risk female youth after receiving a negative HIV test result (Aim 2c);

	(4) To provide an HIV prevention intervention to a randomly selected subset of high risk negatives (N≈185) (motivational text message, with referral for combination prevention interventions), and to re-test them at 12 months (Aim 2d).

Primary Endpoint(s)	Primary outcomes of interest for Aim 1 are based on the HIV prevention and treatment continua as outlined below:
	• Recruitment/Seek: Ability to identify and recruit female youth that are high risk for HIV infection using two seek strategies (home-based vs. community-based)
	  ○ The proportion of youth in the community who accept study screening (estimated from total youth approached as the denominator);
	  ○ The proportion of youth who accept study enrollment (estimated from youth screened and eligible as the denominator);
	• Testing:
	  ○ Testing uptake by different testing modalities;
	  ○ Completion of confirmatory testing;
	  ○ Proportion that are positive;
	  ○ Among those who are positive, completion of baseline collection of CD4 and viral load tests.
	
	Outcomes of interest for Aim 3 economic evaluation to determine the comparative cost effectiveness of the seek, test, link, and prevention interventions are:
	• Compute the cost per HIV-infected female youth identified under each 'seek' strategy (home-based vs. community based);
	• Compute the cost per HIV-infected female youth identified under each 'test' strategy (self-testing, staff delivered HTS testing, standard facility-based HTS);
	• Calculate the incremental cost-effectiveness ratio of the adaptive linkage to care intervention among HIV positive female youth;
	• Compute the cost of the SMS prevention intervention among HIV negative female youth.

Secondary Endpoint(s)	Secondary outcomes of interest for Aim 2 are based on the HIV prevention and treatment continua as outlined below:
	
	• Linkage to Care:
	  ○ Percent of females who tested positive that attended a first HIV care appointment at an HIV Comprehensive Care Center (CCC)
	  ○ Time to link to care after positive confirmatory test result.
	• Retention in Care:
	  ○ Completion of viral load testing at 12 months;
	  ○ Reported appointment attendance via SMS and verification by study staff at 3, 6, 9, and 12 months.
	• Primary Prevention (N≈185):
	  ○ Proportion reporting HIV risk behaviors, and condom use, at 6 and 12 months;
	  ○ Proportion who re-tested at 12 months;
	  ○ Proportion who tested positive at 12 months.

7. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

7.1 Introduction

Over three decades into the epidemic, sub-Saharan Africa (SSA) remains the region most heavily affected by HIV with nearly 70% of the 35.3 million people living with HIV globally, residing in the region (UNAIDS, 2013). Youth (15-24) bear the highest burden of new infections and in SSA account for 80% of the 2.3 million new infections each year (UNAIDS, 2013). Young females are twice as likely as their male counterparts to be infected, making females (15-24) in SSA the most at risk group for HIV infection.

Despite this, the literature shows that programs for adolescent girls and young women are often uncoordinated and not evidence based. The incidence of HIV has declined in SSA, indicating efforts for HIV treatment and prevention (primary and secondary) have had an impact on curbing the epidemic. Although this improvement is encouraging, the incidence and prevalence of HIV continues to remain high, suggesting that innovative and effective HIV prevention and treatment is urgently needed. We propose an implementation science framework to address the HIV prevention and treatment continua that will inform best practices on how to identify, test, link, and retain female youth in HIV care, as well as primary HIV prevention in this vulnerable population.

The major aims of the study entitled “High-yield HIV testing, facilitated linkage to care, and prevention for female youth in Kenya (GIRLS Study) are to:

- Identify preferred recruitment venue and testing modality for female youth who are at highest risk for HIV in Homa Bay County, Nyanza region, western Kenya;
- Pilot and evaluate an adaptive intervention to link newly diagnosed HIV-positive female youth to treatment and care services;
- Deliver a primary HIV prevention intervention to high risk negative female youth; and
- Conduct an economic evaluation, using cost effectiveness analyses to determine the relative utility of each seek, test, link, and prevention intervention.

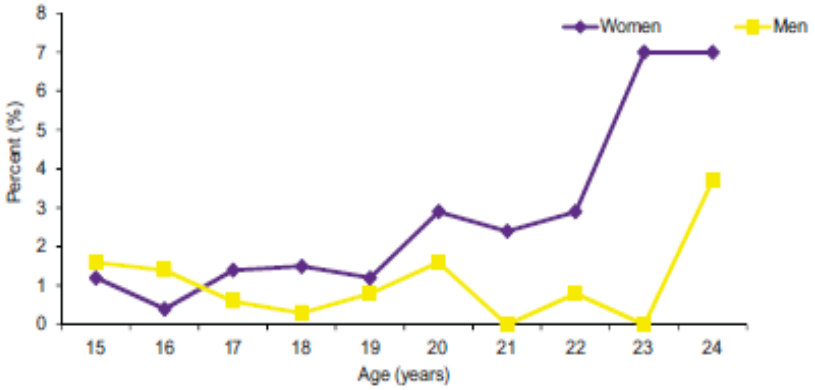
The focus will be to determine the preferred recruitment venue and testing modality that identifies the highest number of HIV infected and at-risk female youth (aged 15-24) in western Kenya. Knowledge of HIV status is a first step towards accessing HIV care, treatment, and prevention services. Particular care will be taken to protect minors who, in addition to their assent, will be required to have written parental or guardian informed consent (IC) in order to participate. This will add greatly to the science of how best to increase young women’s uptake of HIV prevention, testing, and linkage to care services in high-HIV burden settings, in order to optimize engagement in both the HIV prevention and care continua (McNairy & El-Sadr, 2012, 2014). Lessons learned will inform Government of Kenya, and other key policymakers, implementing partners and agencies throughout SSA that are exploring policies about appropriate scale up of these multiple seek, test, link, retain, and prevention strategies to realize the dream of an AIDS-free future for adolescent girls and young women.

7.2 Background

HIV in Kenyan Female Youth

In Kenya, HIV prevalence is 5.9% among individuals aged 15-64 (NASCOP, 2014a), and estimated HIV incidence declined by 34% 2001-2011 (UNAIDS, 2012b). HIV prevalence has dropped since 2007 in most regions of Kenya but not in Nyanza region (NASCOP, 2014a), where this study will take place. The prevalence of HIV varies drastically per region in Kenya, with variations between 2.1-15.1% (NASCOP, 2014a). Children and youth aged 0-24 years form 66% of Kenya's population. Surveillance data indicate that most new HIV infections occur among youth ages 15-24, when many are unaware of HIV status, condom and contraceptive use are low, and gender inequalities, concurrent sexual partnerships, and cultural value of childbearing enhance risk (Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010). The majority of Kenya's population is at high risk for HIV infection and the rest of the population will be affected by reduced productivity, increased medical bills, and strained social support.

Figure 1: Gender-Age Specific HIV Prevalence (KAIS, 2014)



Females between ages 20-24 have a risk of HIV infection three times higher than males of the same age (NASCOP, 2014a). The 2010 Kenya Demographic Health Survey (KDHS) showed that prevalence of HIV among females aged 15-19 is 2.7%, and 20-24 is 6.4%, whereas the prevalence of HIV among males aged 15-19 is 0.7%, and 20-24 is 1.5% (Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010). Young females have a much higher prevalence of HIV. Figure 1 shows HIV prevalence among women is higher than men from age 17 on and increases linearly with age, but for young men, remains lower and stable until age 24. This pattern underscores the need to focus on preventing HIV among 15-24 year old women. The UN and PEPFAR, among others, have emphasized the need to focus on disproportionately affected populations, such as young females, to have greater impact on HIV control (Birx, 2014a, 2014b). Exploration of sociocultural drivers of the HIV epidemic in Kenya highlights the need for age and gender-specific multi-level combination HIV prevention interventions that are delivered in youth-friendly mobile settings in an integrated services approach. Details of the mobile health event are outlined in the procedures section (section 7) and the rationale is in section 7.4.

The Luo are the main cultural group in our study area of Homa Bay County, Nyanza region, the epicenter for HIV in Kenya, with the highest prevalence at 25.7% (NASCOP, 2014b); 23% of Luo females are HIV+. In Nyanza, 18.3% of young women and 27.2% of young men had sex before age 15. By age 18, this is two-thirds of both young women and men. From these data, it is evident that there exists a crucial window between 15 and 18 years of age during which young people should be tested for HIV. PEPFAR lists HIV testing services (HTS) and creation of demand for clinical services, along with voluntary medical male circumcision (VMMC) and condoms, as high

impact interventions that should remain HIV prevention priorities (Birx, 2014a). This is especially important because among those who had their sexual debut before age 15, only 52.9% of young women and 33.7%% of young men used a condom at first sexual intercourse (NASCOP, 2014a). Only 65% of young Kenyan women (15-24 years) know where to find a condom, vs. 85% of young men. Many young Kenyans say they know where to get an HIV test (85.2% of females and 84.2% of males aged 15-19) (KNBS and ICF Macro, 2010). But only 55.6% of young women aged 15-19 tested for HIV (vs. 44.7% of men) in 2012. In contrast, 91.6% and 67.3% of youth aged 20-24 years have ever been tested for HIV (NASCOP, 2014a). These data suggest that barriers exist that are keeping youth including girls from getting HIV tested. Girls 15 to 24 years contribute 21% of all new infections in Kenya, with most at risk being post high school ages 18 to 24 (NASCOP, 2014b). In these areas where high fertility, early coitarche, frequent intergenerational sex and low male circumcision put many young women at increased risk for HIV, it is critical to prioritize access to HIV testing, prevention, and treatment for this population. Highlighting the urgency of increasing knowledge about HIV testing in Kenya is the fact that only 47% of those people living with HIV know that they are HIV positive. Further along the HIV care continua (see Figure 2), only 42% of people living with HIV are enrolled in care, only 34% of people living with HIV receive ART, and adherence to ART, data suggest, is also low, as only 26% of people living with HIV have suppressed viral load (Birx, 2014a; NASCOP, 2014a; UNAIDS, 2012a). Adolescent girls and young women are biologically and socially more susceptible to contracting HIV (more likely to have older sexual partners) and youth less often receive HIV testing (A. E. Kurth, Cleland, Chhun, et al., 2015; UNAIDS, 2012a; UNICEF, 2012).

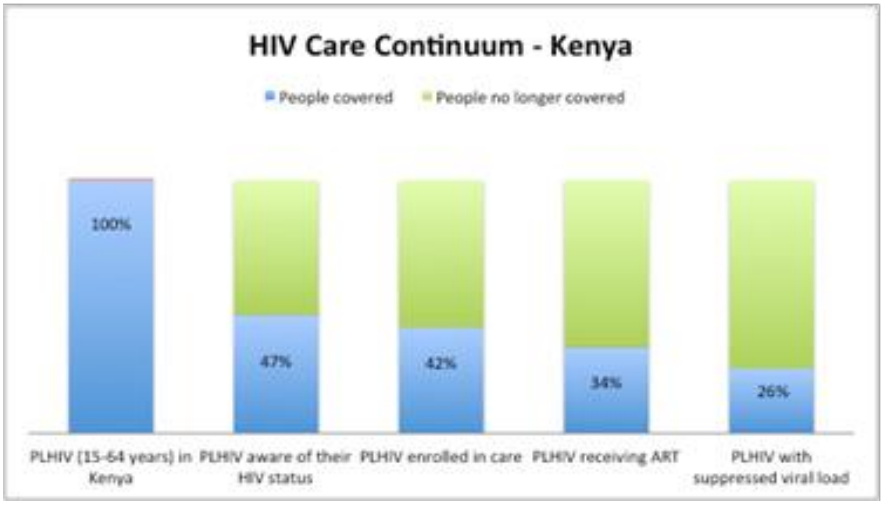


Figure 2: HIV Care Continuum (calculated from KAIS 2012 data)

Female dominant risks

While same-age sex also carries risk, **cross-generational sex (age mixing)** can expose younger women to older men with cumulative probability of HIV infection. KDHS 2003 found that women whose first partner was more than 10 years older had higher HIV (10%) than those whose first partner was less than 10 years older (8%) (CBS, MOH, & ORC Macro, 2003), whereas the KDHS 2010 found that the rates of HIV among these groups converged at 7%. Studies show that HIV risk is greatest among couples where the female is aged 15-19 and the male partner is more than 10 years older (13%). Girls with limited to no education were twice as likely to engage in cross-generational age mixing as those who completed more schooling; age mixing needs to be addressed as an HIV prevention focus (Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010). Mathematical models have suggested that sexual age mixing across age and high and low prevalence groups, as well as concurrent sexual partnerships, may drive the sub-Saharan

African epidemic (Goodreau et al., 2012; Hallett et al., 2010). In Nyanza, there are high levels of **concurrent partnerships:** 21% of marriages are polygynous (being one of ≥3 wives had OR 3.4 for HIV, compared to single-spouse marriages) (K. Johnson & Way, 2006), and high reported concurrency (Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010; Voeten, Egesah, & Habbema, 2004).

HIV serodiscordant couples are at high risk of HIV transmission within the relationship. Nearly half of all people living with HIV in sub-Saharan Africa in a relationship have a partner who is HIV negative (Curran et al., 2012). Of individuals in a discordant couple, half of the HIV negative partners are unaware that their partner is HIV positive (Curran et al., 2012). Among married or cohabiting couples in Kenya, approximately 6% are discordant. Among unmarried non-cohabitating couples, approximately 10% are discordant. In Nyanza, 13% of all couples are discordant (Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010; NASCOP & CDC, 2009). In sub-Saharan Africa, condom use is generally low, HIV testing services is low (particularly couples testing), partner disclosure of HIV positive status is low, and for those who are HIV positive and eligible for antiretroviral therapy (ART), uptake and adherence to antiretroviral medicine (ARV) is poor (Curran et al., 2012; Hughes et al., 2012; A. E. Kurth, Celum, Baeten, Vermund, & Wasserheit, 2011; UNAIDS, 2012b; WHO, 2011). There is a need to tailor HIV prevention strategies to recognize the vulnerability and gender sensitivity of discordant couples.

Pregnancy

Another factor increasing HIV risk among female youth is pregnancy, given the shared precursor of unprotected sex. Pregnancy is in the causal pathway for HIV acquisition and for vertical HIV transmission. Pregnancy itself increases HIV risk (Gray et al., 2005; Mugo et al., 2011) showed in a prospective cohort that pregnancy increases both male to female and female to male HIV risk 2-fold. The fertility rate in Kenya is 4.6 children per woman, a slight decrease since 2003 (Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010). Effective contraceptive use and women's ability to negotiate condom use is low, thus unintended pregnancy rates are high. In Nairobi 95% of all abortions are to women under the age of 25 (Biddlecom, 2008) and are estimated to cause between 25 - 35% of maternal deaths (Hussain, 2012; Lema, Rogo, & Kamau, 1996; Obare, van der Kwaak, & Birungi, 2012; Rogo, 1993; Shah & Áhman, 2010). New legislation passed in Kenya in 2010 permits abortion when "necessary", but the majority of abortions remain unsafe and result in poor sexual and reproductive health outcomes, and death (Hussain, 2012). In Kenya the pressure for childbearing is a rite of passage to adulthood and is seen as necessary for a happy and productive life. These social values around childbearing often outweigh HIV concern, which increases HIV acquisition and vertical transmission in HIV+ pregnant females (Duflo, Dupas, Kremer, & Sinei, 2006; Ujiji, Ekström, Ilako, Indalo, & Rubenson, 2010). **Given the prevalence differential and other risk patterns, this study will focus on the 15-24 year old females as a highly-vulnerable group.**

7.2.1 Preliminary studies; MP3 Youth Study Interventions for HIV Prevention

The GIRLS study builds upon the successes of the previous HIV prevention studies and offer an abridged version of a previous study entitled, "Gender-specific combination HIV prevention for youth in high-burden settings (MP3 Youth): A pilot study." (R01AI094607; DAIDS Protocol

Number 11989; Unpublished data). The focus of the GIRLS study is to find out the best strategies for reaching, recruiting, HIV testing and linking HIV infected female youth to care and treatment, and HIV negatives to prevention services. All services offered in the GIRLS study were partially informed by findings from the MP3 Youth study and were chosen because they were youth-friendly, efficacious, and possible to implement in a mobile (community/venue-or home-based recruitment) setting. These services include HIV testing services (HTS), CD4 POC testing, viral load testing, and condoms. Referrals are made for ART, family planning (contraception), and other health service needs identified at the time of enrollment (e.g., partner and family testing, PrEP, STI screening and treatment, drug use counseling, mental health services, social and nutritional support, legal services, sexual and gender based violence services and others that might be identified during the interview/risk assessment with participants). Below, please see the basis of the interventions that will be offered in the GIRLS study.

Interventions for HIV prevention

There are numerous examples of individual HIV prevention interventions aimed at addressing the drivers of the HIV epidemic among youth. In the MP3 Youth study (data not yet published), we successfully reached 1740, recruited 1093 youth between the ages of 15-24 years old, carried out HIV testing for 1074, linked 69.7% of newly diagnosed HIV positives to care, and enrolled 284 for follow-up (HIV positive cohort: 106; PrEP cohort: 28; CCT cohort: 50, and HIV negatives: 100). From MP3 Youth, we learnt that we can reach and recruit youth in a mobile health care setting. In the GIRLS study, we will learn whether we can reach and recruit female youth in a home-based setting as well. In MP3 Youth we demonstrated that we were able to successfully test youth in a mobile health event setting, but unlike in the GIRLS study, MP3 Youth did not offer alternative options to staff provided rapid HIV testing, such as self-testing or referral to a health facility. In addition, although we successfully linked HIV infected participants in the MP3 Youth study to care and treatment using a one-time economic incentive (i.e., bus fare), the MP3 Youth study did not have SMS reminders as a linkage strategy. We were able to successfully verify school enrollment for the CCT cohort and will use similar procedures in the GIRLS study for linkage verification.

The Government of Kenya recently approved pre-exposure prophylaxis (PrEP) use as a national strategy for HIV prevention among key populations including high-risk females (Mukoma, 2016, NASCOP, 2015). PrEP is an HIV prevention method by which an uninfected individual takes antiretroviral drugs prior to HIV exposure to reduce the risk of infection (Plosker, 2013). Homa Bay is one of the selected counties that will offer PrEP, therefore, referrals will be made to government, private and NGO facilities offering the approved HIV prevention services, which includes PrEP.

7.2.1.1 HIV Testing Services (HTS), CD4 POC Testing, Viral Loads

HIV testing services (HTS) is a gateway for HIV prevention, care, and treatment. Knowledge of HIV status is powerful. For individuals who are HIV negative, it is important to maintain a negative status and continue to practice risk reduction strategies. For those who are positive, HTS is a critical entry point to life-sustaining care for people living with HIV, a key element of which is antiretroviral therapy (ART)/HIV treatment. Successful treatment is essential for prevention of secondary transmission, particularly from mother to child and to sex partners. Offering HTS to

female youth (ages 15-24) is a way of addressing HIV transmission amongst this age group at high risk of HIV infection. The mobile setting increases accessibility to the interventions and reduces stigma by offering it in the context of a health event where other youth-friendly services are also being provided (J. K. B. Matovu et al., 2007; Sweat et al., 2011). In addition, offering HTS in a home-based setting increases knowledge of HIV status for those who would not otherwise come forward for testing due to HIV-testing stigma (Low et al., 2013). In the KAIS 2012 survey, among those who have not been tested for HIV, 36.7% of women aged 15-64 felt they did not need to be tested, and 17.5% of women were never offered an HIV test (NASCOP, 2014a). We will follow the current GoK guidelines for HTS, which includes educational risk reduction methods (NASCOP, 2015).

CD4 testing. We will use a point of care (POC) CD4 cell count assay in order to reduce the time between HIV+ test knowledge and seeking clinical relevant HIV care including ART. An accurate CD4 count is needed for clinical staging, counseling and acceleration of treatment preparation of HIV+ patients.

We will use the PIMA CD4 POC assay, which is being actively and successfully used in Kenya by NASCOP and with which our team has familiarity (TLC-IDU study, NIDA R01DA032080, PIs Kurth, Cherutich; MP3 Youth Study, NIAID R01AI094607, PIs Kurth, Inwani). The Kenya AIDS Indicator Survey (KAIS) used PIMAs for the last round of the survey. The PIMA assay uses a fingerstick specimen to count CD4 cells in 20 minutes, using a portable reader or analyzer. The PIMA analyzer is designed for use in field settings like those we expect in Kenya. The PIMA analyzer has been evaluated against conventional systems including: the Beckman Coulter PLG/CD4 (Glencross, Coetzee, Lawrie, Stevens, & Osih, 2010), the BD FacsCalibur (Mtapuri-Zinyowera et al., 2010), the BD FacsCount and the Guva instruments and compared well with conventional laboratory based CD4 testing in these studies.

The MP3 Youth study measured participant CD4 at baseline and 12 months. However, WHO new Test and START guidelines recommends immediate treatment irrespective of CD4 count (WHO, 2015). There is a priority shift from CD4 monitoring to scale-up of viral load testing as a more efficient indicator of adherence. Kenya is currently moving towards adopting these new recommendations, and we will ensure alignment with GoK national policies and will measure CD4 levels only at baseline for clinical staging and treatment preparation and counseling purposes.

Viral Load Testing. We will also collect specimens using dried blood spot (DBS) for HIV viral load (VL) testing at the mobile event or in the home for those found to be HIV-positive, and will repeat the VL at 12 months We have successfully used a DBS VL approach in the TLC-IDU (A. E. Kurth, Cleland, Des Jarlais, et al., 2015) and MP3 Youth studies in Kenya.

Refer to the HTS section 11.5.1 under the intervention specific procedures section 11 for specific information on how HTS will be conducted.

7.2.1.2 Condoms

Male latex condoms are a barrier device that cover the penis and when used correctly and consistently during sexual intercourse can reduce unwanted/unplanned pregnancy and reduce the risk of contracting sexually transmitted infections (STIs), including HIV. Similarly, female condoms, made from thin, soft plastic called polyurethane (some are also made from latex), are worn inside the vagina, and when used correctly during vaginal sex, also help to protect against unwanted pregnancies and STIs. Condoms and counseling (that includes correct and consistent condom use and other safe sex practices) will be offered to female youth (15-24 years) who are recruited in either the community-based or home-based 'seek' strategies (Holmes, Levine, & Weaver, 2004).

Although referrals will be made for other contraceptive methods for female youth, HTS counselors will also provide education about other available methods of birth control at the time of enrollment. Referrals for family planning will allow female participants to avoid unwanted or mistimed pregnancies, anticipate and attain their desired number of children as well as the spacing and timing of their births. A woman's ability to space and limit her pregnancies has a direct impact on her health and well-being as well as on the outcome of each pregnancy. There is also increased risk for HIV acquisition and transmission during pregnancy (Gray et al., 2005; Mugo et al., 2011).

We will ensure that the study staff is sensitive to lesbian, gay, bisexual, transgender, questioning (LGBTQ) issues in Kenya, which is a sensitive topic (Harper, 2013). We will ensure that counseling during all interventions, primarily HTS and condoms/contraception is both gender, age and sexuality appropriate where possible (Taegtmeyer et al., 2013).

Refer to the condoms section 11.5.2 for specific information on how condoms will be distributed.

7.3 GIRLS Study

This study will inform best practices to increase young women's, recruitment, uptake of HIV prevention, testing, and linkage for HIV to care services in a high-HIV burden African setting. As this study will be conducted within the framework of implementation science, data generated will help determine which study elements can be scaled-up to national level and will directly inform and support Kenya's HIV epidemic control.

7.4 Rationale

Why focus on adolescent girls and young women?
Adolescent girls and young women in sub-Saharan Africa are among the most vulnerable of populations globally. We will evaluate prevention-treatment continua interventions to increase uptake of HIV testing, linkage to care, retention and high-impact prevention among adolescents and young women. Kenya is a leader in developing evidence-based HIV care and prevention programs, and female youth in Nyanza are one of the highest priorities for HIV prevention and effective care (NASCOP & NACC, 2014). In sub-Saharan Africa girls 15-24 are 2-3 times more likely to be HIV+ than same-age males (Glynn et al., 2001; Kenya National Bureau of Statistics (KNBS) and ICF Macro, 2010; WHO, 2006). Girls' education is low, cross-generational sex is

high, condom negotiation is low, and girls are at a social, biomedical, and behavioral risk for HIV infection.

Cross-sectional socio-demographic, HIV prevention, health services access, and other behavioral data will be collected at baseline from all females using a provider administered computer assisted personal interview (CAPI). Audio computer assisted self-interviews (ACASI) and CAPI surveys are being used successfully in Kenya (Osoti et al., 2014). The CAPI data will contribute to better understanding specific behavioral risks, HIV testing, and prevention intervention exposure for youth enrolled in the study. These data will serve as baseline for those subsets of study participants who are followed up in the HIV+ cohort and a subset of the HIV- females. The outcomes of this study will inform policymakers, implementing partners and agencies throughout sub-Saharan Africa that are (1) exploring HIV self-testing as a method for increasing knowledge of HIV status, and (2) wrestling with the urgent need to enhance the HIV prevention and treatment cascade for young women.

Rationale for use of a mobile health delivery format

The Government of Kenya (GoK) with implementing partners, including Impact Research and Development Organization (IRDO), have utilized mobile health teams and useful community engagement lessons have been learned (K. E. Johnson et al., 1989). Mobile health units have been successfully utilized in east Africa for rapid HIV assessment, HIV testing (J. K. Matovu & Makumbi, 2007), VMMC, and care including ART (Babigumira, Sethi, Smyth, & Singer, 2009; Chang et al., 2008) and palliative care (Downing & Kawuma, 2008). Adding mobile HIV testing to VCTs was found to be cost-effective in Kenya (Grabbe et al., 2010). They have been used in other settings for HIV prevention including HIV/STI (Clark, Bowles, Song, & Heffelfinger, 2008; Cojan & Fanello, 2009; Grusky, Roberts, Swanson, Rhoades, & Lam, 2009; Liang et al., 2005; Liebman, Pat Lamberti, & Altice, 2002), screening and treatment (Ellen, Bonu, Arruda, Ward, & Vogel, 2003; Kahn, Moseley, Thilges, Johnson, & Farley, 2003), among youth (Auerswald, Sugano, Ellen, & Klausner, 2006), and syringe/needle exchange (Hebert et al., 2008; Miller et al., 2002). They have been used to deliver contraceptive services to at-risk populations in other low-income settings (Delvaux, Crabbe, Seng, & Laga, 2003; Desai & Tarozzi, 2011), and have been credited with being one of the reasons for high contraceptive use prevalence in Colombia ("Mobile family planning units," 1995). The President's Emergency Plan for AIDS relief (PEPFAR) is implementing the DREAMS intervention in Kenya, focusing on identifying youth at risk for HIV and a mobile outreach strategy will also be used in many counties.

The MP3-Youth study demonstrated that mobile health teams are an acceptable platform for delivery of gender-specific combination HIV prevention (data not yet published). As mentioned previously, the MP3 Youth study (data not yet published), successfully reached 1740, recruited 1093 youth between the ages of 15-24 years old, carried out HIV testing for 1074, linked 69.7% of newly diagnosed HIV positives to care, and enrolled 284 for follow-up (HIV positive cohort: 106; PrEP cohort: 28; CCT cohort: 50, and HIV negatives: 100). Our partner NGO, the IRDO program, has successfully used mobile health teams to deliver HIV testing and VMMC outreach services delivery to >75,000 youth in Nyanza region since 2009. IRDO was able to recruit girls and young women to their health events by including information on life skills, along with reproductive and sexual health talks (Agot & Onyango, 2004). Given this track record, the GIRLS study will utilize

a community-based recruitment strategy to seek female youth who are at highest risk for HIV in Homa Bay County.

Rationale for home-based HIV testing services

Additionally, a home-based strategy will also be utilized in order to assess preferences around recruitment venue, and to ascertain which seek strategy will identify the highest number of HIV positive female youths. Home-based HIV testing services has been provided in Kenya to individuals and families since 2006 and was piloted in Nyanza Province, with a high acceptance rate above 90% (NASCOP, 2008). Home-based testing is efficient and confidential, with high uptake. Over 80% of KAIS 2012 survey participants who had never tested for HIV, accepted home-based testing services; with 81.6% acceptance among female youth aged 15-19 years, and 79.3 % in the 20-24 age group (NASCOP, 2014a). With any home-based approach, community entry procedures will be observed and we will follow home-based testing services protocols and guidelines that have been established by the Government of Kenya. Study team leadership are experienced in home-based HTS delivery in a rural setting (PIs: J. Kiarie, A. Kurth, Co-I: I. Inwani, R01HD058363). The home-based and community-based recruitment strategies used in the study is a departure from the more passive approach to HTS that is conducted in antenatal clinics, health facilities, and research clinic settings. HIV testing services and recruitment for research has traditionally been done in health facilities. Due to financial, health system, cultural, and knowledge barriers experienced by adolescents, young women are unlikely to access standard facility based HTS. Therefore, our study offers HIV testing and recruitment in different settings in order to inform best practices regarding HIV and recruitment strategies targeting this population.

Rationale for self-testing

HIV testing is a critical component in the control of the HIV epidemic and essential as an entryway into HIV treatment and care services. HIV testing has increased in Kenya, with 79.8% of adult women and 62.5% of men reporting in 2012 ever having been tested (NASCOP, 2014a). However, only 55.6% of young women aged 15-19 tested for HIV (vs. 44.7% of men) during this same year. In a study among young people in Uganda, 70% did not get tested because they feared stigmatization (Kitara & Aloyo, 2012). Currently available options for knowledge of HIV status in Kenya include voluntary counseling and testing (VCT), provider-initiated or facility testing (PITC), home-based testing services, and mobile testing campaigns. Self-testing has been studied in a series of studies (Kabiru, Sidze, Egondi, Osok, & Izugbara, 2014; Ann E. Kurth et al., 2014; Ochako, Vu, & Peterson, 2014; Okal, Obare, Tun, & Matheka, 2014; Stankard, LeTouze, & Jones, 2014) overseen by the International Initiative for Impact Evaluation (3ie) organization for the GOK/MOH/NASCOP. Availability of oral fluid HIV self-testing (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test, OraSure Technologies) (A. E. Kurth, Cleland, Chhun, et al., 2015) is one of several options to increase access to testing especially in higher-risk subpopulations that may not access current forms of HIV testing, such as HIV-discordant couples, men who have sex with men (MSM), sex workers (SWs), people who inject drugs (PWID), and high-risk youth.

Data from studies conducted in Malawi, Spain, Singapore, and the US show that self-testing in the general population is feasible, acceptable, and accurate (Napierala Mavedzenge, Baggaley, & Corbett, 2013; Pant Pai et al., 2013). Kenya has been a leader in innovative approaches to HIV prevention and care, and has demonstrated that HIV self-testing among health professionals

(Kalibala et al., 2014) and the general population is feasible and acceptable (A. E. Kurth, Cleland, Chhun, et al., 2015).

Youth are least likely to get HIV testing, and innovative strategies are needed to reach young women. Currently, oral fluid HIV self-tests kits are only available for research purposes and not accessible to the general public in Kenya. The acceptability of self-testing and use of this testing strategy among our target population of adolescent girls and young women have not been well documented. Therefore, this study provides an opportunity to expand the knowledge base of how HIV self-testing may contribute as an additional option for youth to know their status; uptake of HIV testing and hence self-knowledge of HIV status is low in this population (KAIS, 2014a). Offering self-testing as a testing option in this study will answer the question of acceptability and uptake of self-testing among young women. If we find that HIV self-testing is acceptable, with high uptake, this will add to available data that would inform strategies for increasing knowledge of HIV status in this population.

Kenya is the first African country (and one of the first countries globally) to include HIV self-testing in their national guidelines (NASCOP, 2008). HIV self-testing is a confidential testing option that can increase testing uptake, especially for populations that choose not to receive HTS in a facility due to fear or stigma. The 2012 KAIS found that among adults who have ever tested for HIV, only 3.5% of Kenyan adults reported using an HIV self-test kit; with more men (5.2%) than women (2.3%) reporting use. However, the low reported usage of these kits may be due to limited availability of these self-test kits for the general public. Among women aged 15-64 years surveyed on their willingness to use a self-testing kit, 67.3% reported that they were willing to use such a kit if it were available. HIV self-testing has the potential to be scaled-up and widely implemented, with minimal involvement of trained health professionals. HIVST could have an impact on the HIV epidemic in high burden countries, and can complement existing strategies, increase coverage of HIV testing and repeat testing, and provide earlier diagnosis for hard-to reach populations such as adolescents.

Although there have been concerns related to QA/QC measures of HIV self-testing by adolescents, one of the appeals of self-testing is that the individual is empowered to conduct an HIV test to learn their status when they feel ready, in a setting of their choosing. Therefore, whether recruited in the home or in the community, participants who choose to self-test can perform the test at their convenience hence real-time monitoring would not be possible. A study conducted in Malawi found that uptake of self-testing was high, especially among adolescents, notably among young women aged 16-19 years old (Choko et al., 2015). Therefore, given this strong interest in using a self-test kit to learn their status, it seems highly unlikely that study participants would give their self-test kit away for someone else to use. Study staff include trained HTS counselors, and until there is evidence to the contrary, we will operate under the belief that the test kits distributed were used by study participants in which they were assigned. The lessons learned from this component of the study may inform the MoH about some of the challenges of making self-test kits available for the general public. One of these challenges may be ensuring that the kits are stored under optimal storage conditions. The option of HIV self-testing in our study needs to reflect real world use. Therefore, although we can ensure correct storage conditions per manufacture's guidelines (please see section 11.7.1) when the kits are in our care,

once distributed to participants, we cannot know the storage conditions prior to use. However, as previously mentioned, participants will be given information about the best way to store the kits and encouraged to call the study if they have any questions or concerns. In a self-testing study conducted in Kisumu, Kenya, where self-test kits were distributed, there were no reports of any issues related to storage or use of the test kits (Thirumurthy, Masters, Napierala Mavedzenge, Maman, Omanga and Agot, 2016).

Rationale for short message service (SMS) for engagement and retention in care

Offering linkage to care after a positive HIV test is critical – for risk reduction and lifesaving ART initiation. Data show that sexual risk behaviors decrease after a positive test and ART initiation, but over time these risky behaviors may begin all over again (Allen et al., 2003; Bunnell et al., 2006; Colfax et al., 2002). Of Kenyans 15-64 years old self-reported as positive, 79.4% enrolled in care services within 90 days of diagnosis (NASCOP, 2014a). Previous studies in Uganda and South Africa showed 90% uptake of HTS and linkage among adults, but adolescents were not included; effective strategies need to be identified for them as barriers likely differ. Two strategies that were key to linkage were found to be POC CD4 and follow-up with participants (Barnabas et al., 2014). Evidence of SMS effectiveness for supporting linkage to and retention in HIV care exists (Finocchario-Kessler et al., 2014; Lester et al., 2010) for adults and we incorporate SMS elements in our study to assess impact for female youth.

Kenya is developing a new electronic tracking system using SMS messaging to facilitate linkage and retention in care and adherence to ARVs for people living with HIV, and messages for high-risk HIV-negatives. This national platform envisions use of mobile phones via the SMS platform for communication among facilities, health care workers, and patients to track and support linkage, treatment adherence, adherence to prevention interventions, and retention for improved outcomes. Data generated by this research in the use of SMS to engage participants (while maintaining their privacy and confidentiality) will inform this planned national platform and guide improvements of the system.

Rationale for unconditional cash transfer

A novel HIV prevention intervention that has been effective in sub-Saharan Africa is the cash transfer (CT), which can be conditional or unconditional. A conditional cash transfer (CCT) is a program that transfers pre-specified incentives (cash or goods) particularly to low-income households (individuals, caregivers, or schools), on the condition that they make investments in pre-specified conditions (Fiszbein, Schady, & Ferreira, 2009). However, unconditional cash transfers (UCT), which are not tied to any pre-specified behaviors, have also been found to be effective as an HIV prevention strategy (Baird, Garfein, McIntosh, & Özler, 2012).The National Government of Kenya, in collaboration with UNICEF and the World Bank, initiated a program in 2002 called '*the Kenya cash transfer programme for vulnerable children'*. The program transfers $14-$28 USD per month (depending on the number of vulnerable children in the household) to vulnerable youth in Kenya (Alviar & Pearson, 2009). Handa and colleagues evaluated the Kenya CT program and found a 31% reduction in sexual debut among young people (Handa, Halpern, Pettifor, & Thirumurthy, 2014). A randomized controlled cash transfer program examining the role of conditionality among adolescent girls in Malawi, found that although school attendance was lower in the unconditional cash transfer group, pregnancy and marriage rates were also significantly lower when compared to the conditional cash transfer group (Baird et al., 2012).

These findings demonstrate that UCT can improve important outcomes such as delayed marriage and childbearing, but there may be a trade-off, between these desired behaviors and improved educational outcomes. In our study, we offer a one-time unconditional cash transfer for a subset of participants (i.e., those who do not link to care after the first randomization in the adaptive linkage to care pilot) because adolescents who test positive may experience structural barriers (i.e. transportation costs) in linking to care in a timely manner. Linkage is a one-time event and we assume that newly diagnosed HIV positive female youth will link to care within two weeks after the first randomization (standard referral vs. standard referral and SMS). The two-week timeframe for linkage to care is defined by the national government; those identified as HIV infected should be started on treatment during this period. In the study we will track if the participants have linked during this two-week time frame and will analyze time to linkage to HIV care and treatment services. We will also explore the use of the economic incentive for linkage during the face-to-face (or telephone) exit interview which will be conducted at 12 months. If a phone interview is conducted, participant's identity will be confirmed by asking the participant to provide three names used at enrollment as well as their current age, so that her identity may be ascertained correctly.

8. STUDY OBJECTIVES

Primary Objectives

(1) To determine the preferred recruitment venue and testing modality that targets and finds the highest number of HIV infected and at risk female youth aged 15-24 years in Homa Bay County, Nyanza region, western Kenya. This will be determined by examining uptake and yield of previously undiagnosed HIV infection of the two 'seek' strategies (community or home-based) and the three 'test' strategies (self-testing, HTS in a mobile/home setting, or facility-based HTS) among female youth;

(2) To conduct an economic evaluation, using cost effectiveness analyses to determine the relative utility of each seek, test, link, and prevention intervention.

Secondary Objectives

(1) To pilot and evaluate an adaptive intervention to link newly diagnosed HIV-positive female youth to treatment and care services;

(2) To identify barriers and facilitators to seeking HIV care services after receiving a positive diagnosis;

(3) To identify barriers and facilitators to seeking HIV prevention services for high risk female youth after receiving a negative HIV test result;

(4) To provide an HIV prevention intervention to a randomly selected subset of high-risk negatives (motivational text message with referral for combination prevention interventions), and to re-test them at 12 months.

9. STUDY DESIGN

9.1 Description of the Study Design

The GIRLS study will rigorously compare two 'seek' recruitment strategies, three 'test' strategies, and two enhancements to an adaptive (SMART trial design) 'linkage' to care intervention, among young at-risk women, 15-24 years old, in Homa Bay County, western Kenya. Additionally, we will evaluate a scalable primary prevention messaging intervention to support identified high risk HIV-negative young women in reducing HIV risk and adhering to recommended HIV re-testing recommendations. This study design will allow us to follow participants along both the prevention and care continua. Figure 3, summaries the study design.

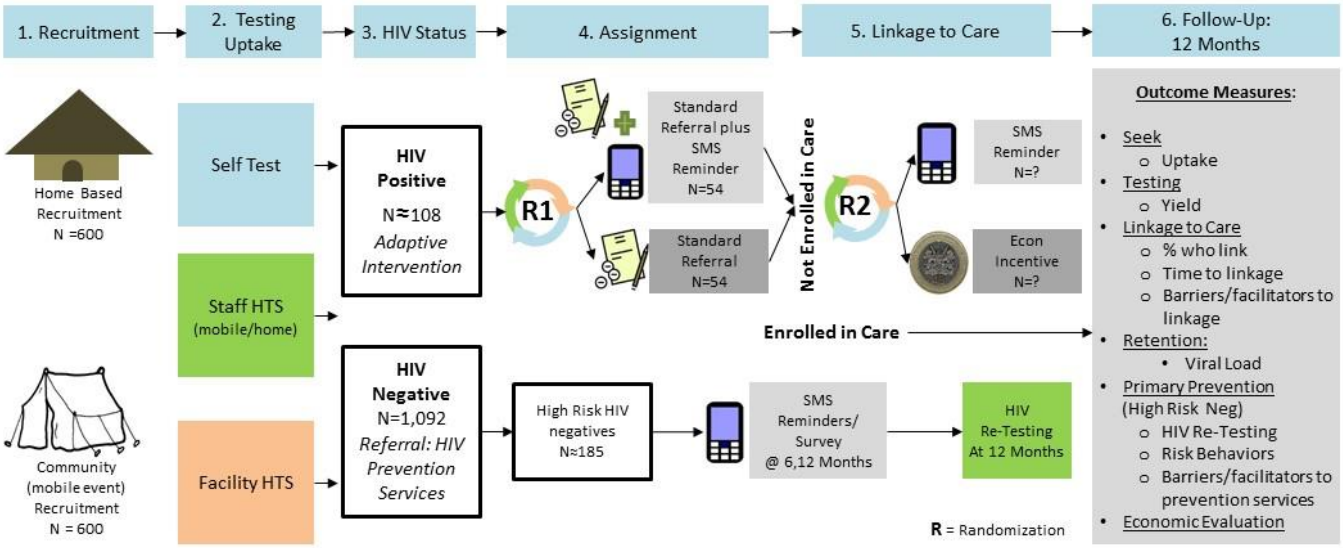


Figure 3: Study Design

10.STUDY POPULATION

10.1 Description of Study Site and Study Population:

The study will be carried out in Homa Bay County, Nyanza region, western Kenya. HIV is a major crisis in Nyanza with ages 15-64 having an HIV prevalence of 15.1% compared to national prevalence of 5.6% (NASCOP, 2014a). Homa Bay County has a total population of 1,053,465 and has the highest prevalence of HIV in Kenya, at 25.7% (NASCOP, 2014b). In addition, prevalence is higher among women (27.4%) than men (23.7%). Despite this high prevalence and the importance of HIV testing for prevention and treatment, 31% of people in Homa Bay still had never tested for HIV by 2009 (NASCOP, 2014b). High fertility, early coitarche, frequent intergenerational sex and low male circumcision put many young women at increased risk for HIV infection. It is therefore critical to prioritize access to HIV testing, prevention, and treatment for this population. This study will be conducted among female youth 15-24 years old (the highest risk age group).

10.2 Target sample size

We project to reach 1,200 female youth over an accrual period of up to 12 months, plus one year of follow-up. Therefore, in order to stay within the estimate 12 months of recruitment, we will put in place adequate field staff during the implementation phase of the project.

Because Aim 1 of this study is not a clinical trial, but rather an exploration of differences in the yield of previously undiagnosed HIV infection across recruitment and testing strategies, we started with this large and feasible sample size and conducted power calculations to determine the size of effects detectable with at least 80% power. By recruiting 1200 female youth between the age of 15-24 years, we will have 80% power to detect an odds ratio of 1.67 when comparing recruitment strategies, on the proportion of previously undiagnosed female youth testing positive for HIV infection. And when comparing testing approaches within a recruitment strategy on that same outcome, an odds ratio of 2.01 can be detected with 80% power. These calculations, which are presented in more detail in section 15.11, show the proposed sample size (N=1200) is capable of detecting modest differences in the yield of previously undiagnosed HIV infection across both recruitment strategies and testing approaches.

We expect large numbers of youth to participate through both venues (IRDO reaches tens of 1000s of youth/year). Based on our experience with MP3 Youth (data not yet published) study (KNH/UON ERC P23/03/2011), which screened N=788 female youth and enrolled N= 690 female youth over a period of 8 months (November 19, 2014 – June 12, 2015) in the same county, we anticipate that we will be able to recruit 1,200 females over a period of 12 months with enhanced recruitment effort. We expect the sample accrual rate to be slower than in MP3 Youth, because we will be recruiting only female youth and mainly those out of school (a large proportion of younger MP3 Youth girls were in school and easier to recruit). In addition, we have two different recruitment strategies, and the home-based strategy may be more labor intensive and time consuming than a community mobile event. We therefore expect a somewhat lower accrual rate.

The sample size for the linkage to care adaptive intervention pilot is an estimate of the number of female youth with previously undiagnosed HIV infection we anticipate reaching. The expected percentage of girls testing positive was based on our MP3 Youth pilot study (data not yet published), and we expect 9% of all tested girls to have HIV infection not previously diagnosed. Thus given a total sample size of 1,200 female youth, we anticipate enrolling about 108 previously undiagnosed HIV positive females in the adaptive intervention pilot to link HIV positive female youth to HIV treatment and care.

Sampling method: We will stratify the sample by conveniently selected sub-counties; Homa Bay municipality, Mbita sub-county and Ndhiwa sub-county. Mapping of catchment areas surrounding health facilities will be used to establish relationships with referral clinics. We select a random starting point that is within walking distance (about 5km) of the catchment area of the health facility. Approximately four hundred (400) participants will be recruited from each stratum and for each stratum it is assumed that 200 participants will be recruited through each recruitment approach. Both recruitment strategies (household and mobile event) will run concurrently until the desired sample size is reached. If needed for sample size attainment, we will expand the sampling area to a 6 - 10 km circumference of the referral clinic.

11. STUDY INTERVENTIONS

11.1 Recruitment

11.1.1 Recruitment strategy

We will work in partnership with the local community in conjunction with IRDO, our implementing partner. IRDO, has already successfully delivered combination HIV prevention services to youth in many counties in Nyanza, and most recently completed an HIV prevention study (MP3 Youth; R01AI094607; DAIDS Protocol Number 11989).

Point of Entry:

Local Mobilizers (Liaisons): Existing community mobilizers (outreach workers), who are affiliated with the implementing partner, will be the project liaisons for community entry. The individuals will facilitate meetings between the project staff and the local authorities (chiefs, community representatives, youth leaders, and health authorities). Community entry will begin by contacting local mobilizers who are well established in the target area through their established HTS efforts.

Community Meetings: The study staff will request the local authorities for permission to participate in *barazas* (community meetings) or other organized community meetings where they will present the objectives of the study using a study-specific IRB-approved recruitment flier in an effort to sensitize the community to the study and to obtain the community's permission to proceed with conducting the study.

Meeting with Local Chief: In cases where there are no local mobilizers, the field site PI, field site coordinator, and study staff will first request a meeting with the respective chiefs of each site. The chiefs will then direct the study staff to the appropriate local partners (community representatives, youth leaders, and health authorities).

Community Advisory Boards: We have identified community stakeholders in each of the study sites to engage as members of community advisory boards (CABs). We will form three CABs, one for each site. The CABs will act as the link between the study and the community/participants. We will train them on the study to enable them to address issues that could arise about the study in the community, or to contact study staff where needed. Given their vast knowledge of the study population and communities, the CAB members will review and give input on our recruitment strategies before we start and on an ongoing basis.

Community Recruitment: The following areas were identified by female youths during the formative research phase of the MP3 Youth study (data not yet published) as venues where they would like to receive HIV testing services: (1) markets, (2) schools, (3) community organizations, non-governmental organizations, (4) community social events, (5) health facilities, and/or (6) churches. Therefore, these venues will serve as the sites for the community-based recruitment, where mobile health tents will be set up. Study staff will identify an appropriate location to set up

the mobile tents that will ensure that study procedures can be conducted while protecting participant confidentiality. Information on other recruitment sites and approaches will be obtained from CAB members and study recruiters hired from the same communities.

Home Based Recruitment: Households will be included if there is a female 15-24 years of age. Participants will be identified in their homes. RAs/Counselors/Study Staff will ensure that any other family members in the home understand the study is focusing on females, but the RA will be trained to make referrals for any other issues that he/she identifies within the home.

Home-based and community-based recruitment will be carried out by GIRLS study staff, who will offer participation to a potential participant by reading them the IRB-approved **recruitment script.** If a potential participant declines to participate, they will be asked to fill out a refusal survey and thanked for their time. If willing to participate, they will be given a flier and if recruited via the community-based strategy will be directed to or taken to the mobile study tent area for IC. If recruited via the home-based strategy, they will undergo IC in a private area in their household. All participants will be informed that they will be contacted in 2 weeks in order to complete an SMS survey about their HIV testing experience.

Offer of Participation

IRB approved fliers will be used to recruit participants. The fliers will be distributed and posted in areas frequented by female youth (15-24), such as (1) markets, (2) schools, (3) community organizations, non-governmental organizations, (4) community social events, (5) health facilities, and/or (6) churches.

All potential participants who are approached will be documented on the participant assessment tracking form. If the individual agrees to participate, then study staff will explain about the study and proceed with IC, eligibility determination, and registration.

Individuals who do not consent/or withdraw consent, or who do not meet the study eligibility criteria will not be enrolled in the study but will receive onsite provision of standard services provided by IRDO program (not study) staff and referrals for whatever other services they request

11.2 Informed Consent (IC)

Participation of Minors & Emancipated Youth

In order to participate in the GIRLS study, participants (18 and older or emancipated minors) must undergo written IC procedures. Consenting will be conducted by trained study staff and research counsellors. Participants under the age of 18 must bring the parent(s) or guardian(s) to give consent on behalf of minors who must also give assent. Emancipated minors (those who are married, have children, sexually active or have formally gone through a legal process of emancipation) can give their own consent. Upon completion, a copy of the informed consent will be provided to the participant. See appendices C-E for sample informed consent forms.

Informed Consent (IC) Process

All female youth enrolled in either the home or the community sites (potential participants) will be consented by RAs/Counselors/Study Staff, who will provide information about the study, explain study procedures, eligibility, and available options.

1. The potential participant's age will be determined as part of the eligibility determination (described in more detail in the next section)

2. If the participant is less than 18 years old, and not an emancipated minor under Kenyan law, and if both youth and parent are present, then parental consent will be obtained and thereafter, participant assent will also be obtained. If the parent is not present, the potential participant will be required to return to the mobile event with a parent and then IC /assent procedures for parents of minors will commence. Both the parent and the youth will append their signature on the IC and assent form (on-site) respectively. Home consenting will not be done if the parent is not present, the study staff will make an appointment to visit the home when the parent/guardian are available. If youth are 18 years of age or older or an emancipated minor (married, has child, legally emancipated), IC procedures will continue.

RAs/Counselors/Study Staff will provide the participant with the approved IC form in the participant's language of choice: English, Dholuo or Kiswahili.

RAs/Counselors/Study Staff will not assume a participant can read. Participants will be given the option of having the script read to them if they cannot read or feel more comfortable with the form being read to them. They will clarify the main points of the IC form with potential participants, to assess comprehension. This information includes: 1) purpose of study, 2) time commitment including follow up visit(s), 3) study procedures, 4) confidentiality, 5) incentive/payment, 6) eligibility assessment, and 7) voluntary nature of the study.

RAs/Counselors/Study Staff will allow time for participants to ask questions about the study. Once all questions are addressed, they will verify that the potential participant is still interested in being in the study. If so, the RA will witness the participant and or parent sign and date the consent/assent form, or place left thumb print if participant/parent cannot write (an additional witnesses signature will be required on the form if this option is used). RAs/Counselors/Study Staff will then sign and date the consent form and provide the participant with a copy of the consent form.

If a potential participant is unable to read (all will be given a small portion of the IC document to read to ascertain their literacy), an independent witness will be brought in to witness the consenting process. To qualify as an independent witness, the person must not be linked to the study in any way and must be over 18 years, literate and understand the language selected by the participant.

- The potential participant will then be screened for eligibility.

11.3 Eligibility Determination (Inclusion/Exclusion) and Enrollment

Participants will be screened for eligibility by Research Assistants or other study staff. Participants must meet all inclusion criteria and may not meet any exclusion criteria in order to be eligible to participate in the study.

Eligibility Requirements:

Inclusion Criteria:

- Female between the ages of 15-24.
- Able to understand spoken English or Kiswahili or Dholuo.
- Resides in Homa Bay County.
- Not previously diagnosed as HIV positive.
- Willing to give informed consent or if younger than 18 years of age and not an emancipated minor, has a parent or guardian willing to provide consent in addition to the minor's assent.

Exclusion Criteria:

- Male.
- Unable to understand spoken English, or Kiswahili or Dholuo.
- Females who are older or younger than the ages of 15-24.
- Resides outside of Homa Bay County.
- HIV positive.
- If under 18 and not an emancipated minor, unable to get parental consent.

Enrollment

After eligibility is assessed/confirmed, participants will be offered enrollment using the approved recruitment script. If she agrees, she will be taken through the following study enrollment procedures: (1) completing registration (to generate a study ID and to ensure single enrollment); and (2) completing the baseline behavioral survey using the tablet computer. Once enrolled, the participant will choose her preferred HIV testing options: (1) oral fluid HIV self-testing at her convenience, (2) HIV testing services (HTS) by study staff at the recruitment location, or (3) a referral to a health care facility for standard HTS. Participants who elect self-testing will be given the self-test kit and will be taken through the self-testing counseling using visual aids (either in the home or in the community). For participants who select staff administered HTS, the test will be conducted by the study staff. For participants who request a referral for HTS at a health facility, they will be given a referral card with the name of a staffer (or other contact to be determined) at the facility. All participants will complete the participant assessment tracking form (this includes locator information for follow-up).

11.4 Two 'seek' recruitment strategies

Participants for this study will be recruited from either their homes or from a community-based venue. The purpose is to identify which recruitment venue gives the highest yield of HIV infected and at risk female youth. The sample will be stratified by the 3 selected sub-counties; Homa Bay municipality, Mbita and Ndhiwa sub-counties. Approximately four hundred (400) participants will

be recruited from each stratum and for each stratum it is assumed that approximately 200 participants will be recruited through each recruitment approach. Both recruitment strategies (household and mobile community-based event) will run concurrently until the desired target of N=1,200 female youths are enrolled in order to identify N≈108 HIV positive females. See Figure 4, Recruitment Strategy (note: numbers are an approximation).

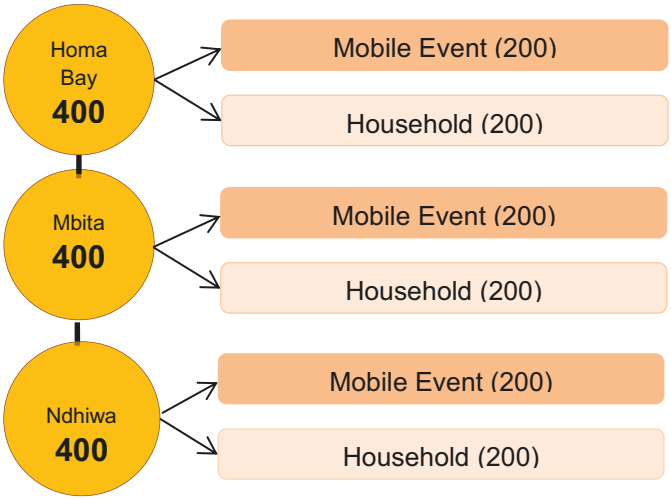
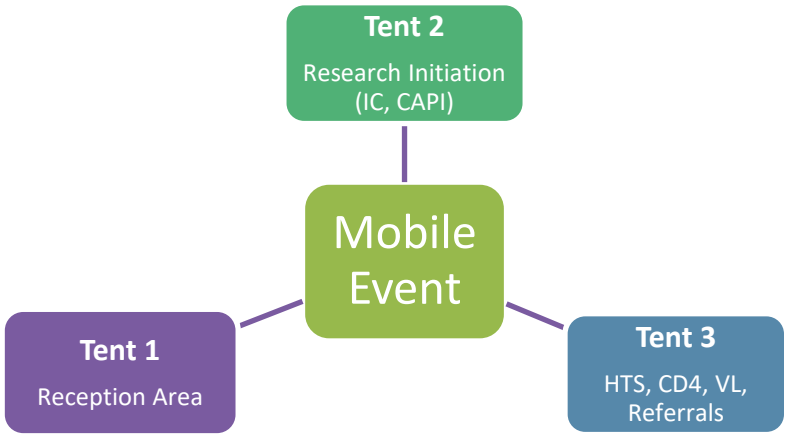


Figure 4: Recruitment Strategy

11.4.1 Community Based Recruitment Strategy

Possible venues for community based recruitment include: (1) markets, (2) schools, (3) community organizations, non-governmental organizations, (4) community social events, (5) near health facilities, and/or (6) churches. Therefore, these venues will serve as the sites for the community-based recruitment, where mobile health tents will be set up (see Figure 5 below), ensuring that study procedures can be conducted while protecting participant confidentiality.

Figure 5: Layout of Tents at Mobile Event



Female youth will be screened and will then flow through the series of GIRLS study tents. Some interventions will require off-site follow-up (i.e., oral HIV self-testing option or referral to standard facility based HTS).

Mobile Recruitment Layout

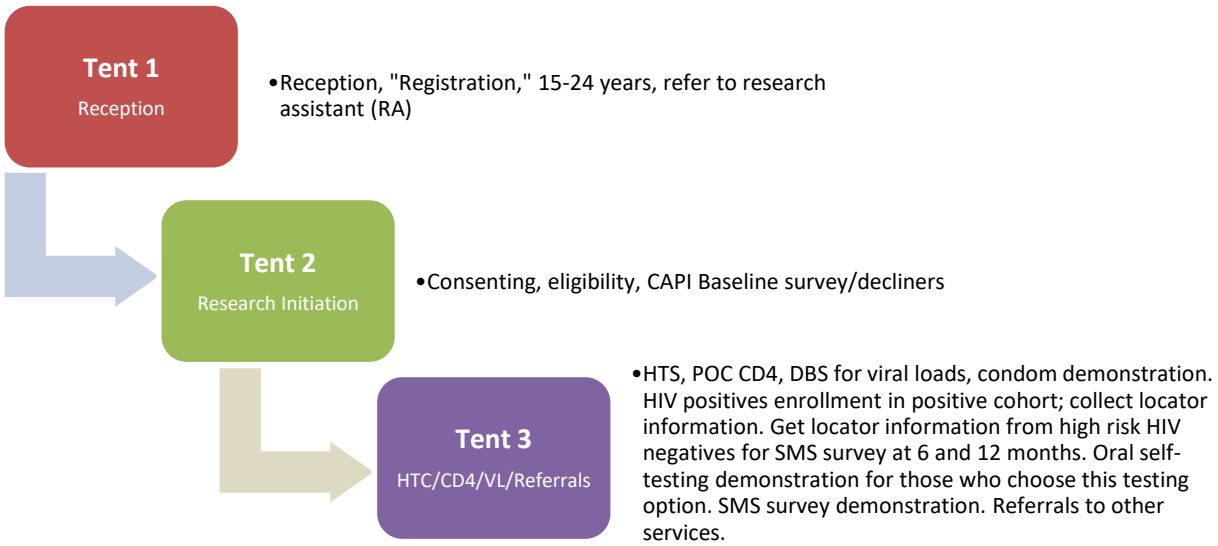
This section describes the anticipated layout of the mobile health community based recruitment. The events will be akin to a health campaign/health event and will have music playing and a series of tents set up where the interventions will be delivered and through which participants will flow. Below is a description of the 3 areas to be set up at the mobile event. (See Figure 6 for details).

Tent 1: Reception area where registration of interested potential female participants (15-24 years) will occur.

Tent 2: Research initiation tent where screening/eligibility, consenting, study ID allocation, and administration of CAPI behavioral questionnaire.

Tent 3: HIV testing services if participant choose to be tested by study staff (per GoK HTS Guidelines, 2015), POC CD4, DBS for VL, condom demonstration. If participant chooses to receive HTS at a health facility, a referral card will be given at this time. For those who choose the self-testing option, she will be counseled on how to use the self-test including a demonstration by staff. She will also be given a pictographic instruction sheet in English, Kiswahili or Dholuo to use as reference. Referrals for other services as needed, such as FP/contraceptives and PMTCT. SMS survey demonstration.

Figure 6: Mobile Event Layout



Participant Flow at Mobile Event

The mobile event receptionist in Tent 1 will register potential participants. The RA in Tent 2 will generate a study ID from the eligible and consented participant. The RA will write the participant's name and date of birth in the link log, alongside the study ID information. Baseline behavioral survey and other data collection described below. The protection of these data is described in the data collection/management procedures (See section 18). Participant flow at the mobile event is described below:

1. The mobile event receptionist will orient the participants to the ongoing study at "Tent 1" area. Receptionist will register participant and confirm age and gender. After registration, participant will be referred to Tent 2.

2. If the participant is interested in the study, they will undergo the process of informed consent in Tent 2. If participant is not interested, they will be asked to fill out a refusal survey. After IC, eligibility is verified, and participant file opened as appropriate. Once enrolled, the interviewer will conduct the baseline interview (CAPI) and then participants will proceed to Tent 3.

3. HIV testing services will take place in Tent 3. If participant chooses staff aided HTS, it will be done at this time. If participant chooses to self-test, she will be counseled on how to use the self-test including a demonstration from staff. If standard facility based HTS is chosen, she will be given a referral card (more details provided in HIV Testing Procedures section below). In addition, referrals to the district hospital or other facilities will be made for services not covered in the GIRLS study (e.g., partner and family testing, PrEP, other family planning (contraception) methods, STI screening and treatment, drug use counseling, mental health services, social and nutritional support, legal services, sexual and gender based violence services and others that might be identified during the interview/risk assessment with participants). Participants eligible for the HIV positive and negative cohorts will have their locator information collected at this time.

11.4.2 Household Recruitment Strategy

On arrival to the household, study staff will introduce him or herself and enquire if there are any females between the ages of 15-24 residing in the household. The research assistant (licensed HTS counselor) will ensure that any other family members in the home understand that the study is focusing on females, but the RA will be trained to make referrals for any other issues that he/she identifies within the home.

If the female youth is not present, then RA will enquire the best time to return to the household. If female youth is present and interested in learning more about the study, RA will identify a private location in the household and explain the purpose of the study in more detail. Enrollment of participants will follow the same process of registration, consent, screening/eligibility, CAPI, HTS options, referrals etc., as participants enrolled via the community-based recruitment strategy as detailed above in Section 11.4.1.

NOTE: Individuals who do not consent/or withdraw consent, or who do not meet the study eligibility criteria will not be enrolled in the study but will receive whatever services/referral to services they require.

11.5 Three 'test' strategies

Enrolled young women will be offered the following testing options 1) oral fluid HIV self-testing (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test, OraSure Technologies), 2) staff-aided testing (HTS) using the recommended rapid HIV testing algorithm and 3) standard provider/facility-based testing. See Figure 7, HIV Testing Options. All participants will be sent a brief SMS satisfaction survey about their HIV test experience 2 weeks post enrollment, and will receive a small incentive (KSh 100) for airtime to fill out the survey. This is to ensure that we do not unintentionally bias an individual to choose a testing modality.

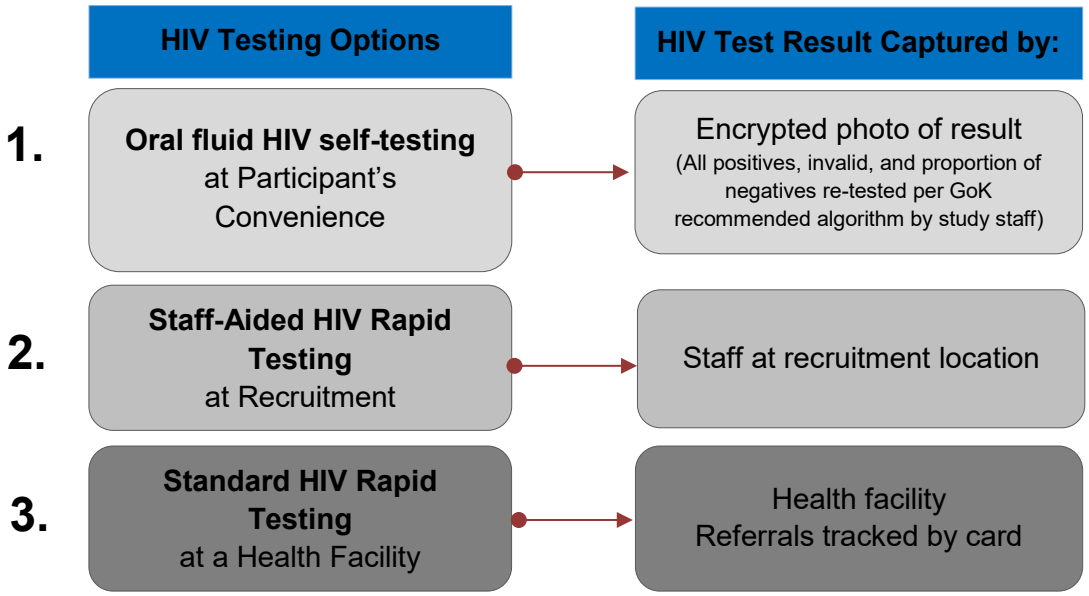


Figure 7: HIV testing options

This section describes the intervention specific procedures that will occur in the GIRLS Study as well as the off-site procedures that will occur for girls who choose the self-testing or standard facility based HTS. The interventions described in this section include: HTS testing options, condoms demonstration and distribution. Referrals will be given for other services, identified at the time of enrollment and not available within the study settings (partner and family testing, PrEP, other family planning (contraception) methods, STI screening and treatment, drug use counseling, mental health services, social and nutritional support, legal services, sexual and gender based violence services and others).

11.5.1 HIV Testing Services, POC CD4 Testing, and Viral Load Testing

- HTS sample target N=1200.

Whether recruited in the home or in the community, after an individual has been consented, screened for eligibility and registered to participate in the GIRLS study, they will be offered three

HIV testing options: staff-aided testing, self-testing, and referral to standard facility based HTS. The current government of Kenya HTS testing guidelines will be followed in all the cases. The government of Kenya has set standards on HIV self-testing (NASCOP, 2015), and we will follow these guidelines.

Staff-aided testing

The participant will receive:

- Pre-test counseling,
- HIV testing per GoK guidelines,
- Post-test counseling,
- PIMA–CD4 POC assay and viral load test (if positive),
- Referral to services if applicable.

This HTS process is based on the Kenyan National guidelines on rapid HIV testing; most recently updated August 2015 (See Appendix G).

- Participants will undertake a screening rapid test. If positive a confirmatory test will be administered. A third rapid tie breaker will be done to confirm discordant results. This testing will be done sequentially by staff in the home or mobile setting.
- Those who test negative will be reported as HIV negative.
- Those who test positive on two rapid tests will be reported as HIV positive.

For an individual who has an HIV positive test result, the CD4 and viral load samples will be taken immediately on site. The CD4 results will be communicated and the printout will be given to the participant. The viral load sample will be done using dried blood spot (DBS) which we have done successfully in our other studies through the CDC Kenya lab (Inzaule et al., 2013). The viral load results will be communicated after 2 weeks when the results are received from the lab. The HTS intervention will last approximately 35-45 minutes depending on the participant's level of knowledge and engagement during the pre and post counseling sessions.

Self-testing

If an individual selects oral self-testing (Hurt & Powers, 2014) she will be counseled on how to use the self-test kit, including a demonstration by staff. In order to reduce false negatives, the demonstration will cover the following topics: (1) best way to store the test kit, and (2) how to collect the sample, stressing the importance of making sure they do not eat or drink anything less than thirty minutes before sample collection. She will also be given a pictographic instruction sheet in English, Kiswahili or Dholuo to use as reference (Appendix F). She can conduct the self-testing at her convenience within 2 weeks, but will be reminded that she can call the study contact number at any time if there are additional questions about how to administer the test. She will be informed that once she completes the test herself, she should take a picture of the result using the phone camera provided by the study (an anonymous barcode will be affixed to each kit and camera so as to confirm that the result links with participant). The participant will be instructed to page the number listed on the self-test kit so that she can immediately be sent the satisfaction survey via SMS and receive her incentive for completing the survey. Also, by paging the number listed, study staff will arrange for collection of the camera and used self-test kit, and conduct a brief interview on her experience with self-testing and interpretation of results.

We will use pre-printed barcode labels, and each label will have a unique barcode number. At the time of kit and camera distribution to participant, study staff will affix one barcode label to the camera and one barcode label to the test kit. Study staffer will then record the barcode numbers on a tracking form to ensure that it links with the participant's study identification number.

If the participant does not page the number within a 2-week period, the RA will contact them by phone. If they still do not respond, we will trace them using the locator information provided at enrollment. For participants with a positive or indeterminate self-test result, the RA will ascertain a convenient location for conducting the confirmatory test in accordance with current government of Kenya HTS rapid testing algorithm. This may include home based or community, in line with the current recruitment strategy, or at a health care facility. Additionally, a randomly selected proportion (10%) of participants with a negative result will also undergo confirmatory testing for QA/QC purposes per current GoK HIV testing guidelines (NASCOP, 2015). Study staff will be trained and enrolled in the proficiency panel testing QA program with the MoH. When a participant requires confirmatory testing, the RA will follow the standard HTS guidelines for rapid HIV testing, which includes conducting two rapid tests and a tie-breaker if the results are discrepant. At this point if the HIV test is positive, CD4 and VL will be collected and the individual will be invited to enroll in the linkage intervention.

Standard facility based HTS

We will be working with Homa Bay County, Ndhiwa and Mbita health facilities. Participants who choose to test via standard facility based HTS will be given a card with the name of a research assistant/contact person at the facility. Additionally, the participant's detailed locator information will be collected to ensure we can follow up with them as needed. HTS procedures will be conducted per Government of Kenya guidelines. If the participant tests positive, they will be invited to enroll in the linkage intervention.

POC CD4 Testing

At a mobile event, in the home, or facility, if a participant is confirmed positive for HIV, a portable PIMA CD4 analyzer (Alere, Inc., Waltham, Massachusetts, USA) will be used for a Point of Care (POC) CD4 count (Mwau et al., 2013). A finger stick specimen will be taken using an aseptic technique and processed in the PIMA analyzer. Results will be given verbally and in writing to the participant. The results will be used in the counseling for HIV-1 positives. Although WHO new Test and START guidelines recommends immediate treatment irrespective of CD4 count (WHO, 2015), we will collect CD4 at baseline for clinical staging, counseling and treatment preparation purposes.

Viral Load Testing

Blood for viral load testing will be collected by finger prick and a DBS prepared for transportation to KEMRI CDC laboratory in Kisumu. The DBS will be stored at 4^{o}C and transported to the laboratory once a week. We have used this method successfully with several studies in Kenya to enhance linkage and earlier ART initiation. The results will be returned to the participants/facilities where the care will be provided. We will use the viral load at baseline and 12 months as an

adherence correlate comparing those suppressed and those with viral loads <1000, complemented by information from the surveys.

Behavioral Baseline Interview (CAPI)

The behavioral survey will be a provider administered computer assisted personal interview (CAPI) for all participants, regardless of recruitment strategy. Study team leadership have successfully administered CAPI surveys in a home-based setting (PIs: J. Kiarie, A. Kurth, Co-I: I. Inwani, R01HD058363). For sensitive questions (which we will identify in the survey), youth will be instructed that they can tap on the answer with the tablet facing away from the interviewer and the answer will not be visible after entry; this will incorporate elements of 'ballot box response' or ACASI approaches while reducing issues around lack of literacy and unfamiliarity with tablet computers (Kelly et al., 2014). The behavioral baseline interview (CAPI) will collect the following types of information:

- Basic demographic information
- HIV risk behaviors
- Sexual risk behaviors
- Attitudes/knowledge about HIV transmission and prevalence
- Knowledge and acceptability of specific HIV prevention interventions
- Knowledge and acceptability of family planning methods

Based on the responses to the key questions in the CAPI survey, we will use an algorithm to determine participants who are considered **at "high risk**", i.e., they are sexually active AND meet **at least one or more of the following: Sexual partner is HIV positive or of unknown HIV status, reports three or more sexual partners in the last month, or reports her sexual partner has multiple sexual partners**. These "high risk" HIV uninfected females will be offered participation in the primary prevention component of the study.

11.5.2 Condoms: Counseling and Distribution

- Intervention delivery target (100%) to those enrolled (N =1200).

Condoms (male and female) and counseling (that includes correct and consistent condom use and other safe sex practices) will be offered to female youth (15-24 years) in the home or at the mobile event. Condoms will be the brand approved for distribution by the government of Kenya.

11.5.3 Referrals

- Intervention delivery target (100%) to those enrolled (N =1200).

Referrals are made for health service needs identified at the time of enrollment not available within the study (this may include referrals for ART, PrEP, family planning (contraception, PMTCT, STI screening, hepatitis, drug use counseling, etc. as per GOK HIV testing Guidelines 2015 page 21-29).

Accessing Services

Whether recruited in the home or in the community, all services will be offered to eligible registered participants on the day of enrollment. These include HIV testing services (HTS), CD4 POC testing, viral load testing, and condoms. Participants will receive referrals for ART, PrEP, family planning (contraception), and other health service needs identified at the time of enrollment. These other health service needs may be partner and family testing, STI screening and treatment, drug use counseling, mental health services, social and nutritional support, legal services, sexual and gender based violence services and others that might be identified during the interview/risk assessment with participants. Referrals will be made to the designated study clinics, Homa Bay County Referral Hospital, Mbita Health Centre, or Ndhiwa Health Centre. PrEP is approved for use among key populations, including high risk females (NASCOP, 2015). Homa Bay is one of the selected counties that will offer PrEP, therefore, referrals will be made for combination prevention interventions through approved government, private and NGO health facilities.

11.6 Screening and cohort enrollment procedures

HIV POSITIVE COHORT

All participants who test HIV positive will be invited to enroll in the SMART design adaptive intervention pilot. Prior to enrollment in the linkage intervention, all participants who test HIV positive will be asked if they are willing to receive cell phone text messages to remind them to link to care, or if they would be willing to respond to cell phone text messages with no more than 15 questions every 3 months for 12 months. If so, they will be given a low-cost cell phone.

All participants who test HIV positive, give consent and are eligible, will be enrolled in the HIV positive cohort.

HIV Positive Cohort Eligibility Requirements:

Inclusion Criteria:

- Meets general eligibility criteria.
- Registered with the GIRLS study and assigned a valid Study ID number.
- Previously signed IC or if younger than 18 years of age (and not an emancipated minor) has a parent or guardian who provided consent in addition to their individual assent.
- Resides in the catchment area.
- HIV positive by two (2) rapid tests.
- Willing to receive SMS texts to link to HIV care and treatment services.

11.6.1 Linkage to Care Intervention

We will use an adaptive intervention/SMART trial design methodology to compare the success of a) short message service (SMS) text messaging and b) economic incentive (transport re-imbursement worth KSh 400) systems in linking to HIV care and treatment services participants who test positive for HIV (expected N≈108) and require augmented linkage support. The initial intervention (first randomization) is that participants who test positive for

HIV gets a standard referral or standard referral plus an SMS message with instructions on where to seek care. Some participants may engage in HIV care after receiving either the referral or referral plus SMS. Subsequently, the intervention will be tailored so those participants who are not linked to care within 2 weeks after the initial intervention, who will be randomized again to receive either follow-up SMS with linkage encouragement, or a one-time economic incentive to seek care (shown to be effective in previous studies (Handa et al., 2014)). All HIV positive participants enrolled for follow up will receive a motivational SMS with adherence to medication and care messages and an SMS survey at intervals of 3 months for 12 months.

At 12 months, we will follow-up with those participants that tested positive and enrolled in care to measure their viral load to determine whether they have been linked, retained in care and are adhering to treatment. We will also conduct an interview at 12 months to determine barriers and facilitators for linkage to care and treatment.

We will be working with Homa Bay County, Ndhiwa and Mbita health facilities. Participants identified as HIV+ will be referred to Government of Kenya HIV Care centers referred to as Comprehensive Care Centers (CCC) for ART initiation. As previously stated, the GoK is moving towards adopting the WHO's recommended Test and START guidelines; therefore, we will test for CD4 at baseline for clinical staging, counseling and treatment preparation purposes and collect sample (DBS) for viral load at the point of recruitment (community mobile event or home based) for those who test HIV-positive so as to enhance the motivation and information for the HIV+ female youth. Any HIV-positive female who self-reports that she is pregnant will be actively referred for PMTCT interventions and follow-up. Those eligible for ART/PMTCT referral but declining linkage intervention will be offered a declined intervention survey to examine reasons and will be referred to a facility of their choice and support group.

Successful linkage to care is defined as date of first appointment at the HIV clinic (registering for care, and being assigned a patient number). We will work with existing structures at IRDO to verify if and when the participant reached the clinic and entered into care.

Figure 8, Adaptive Intervention.

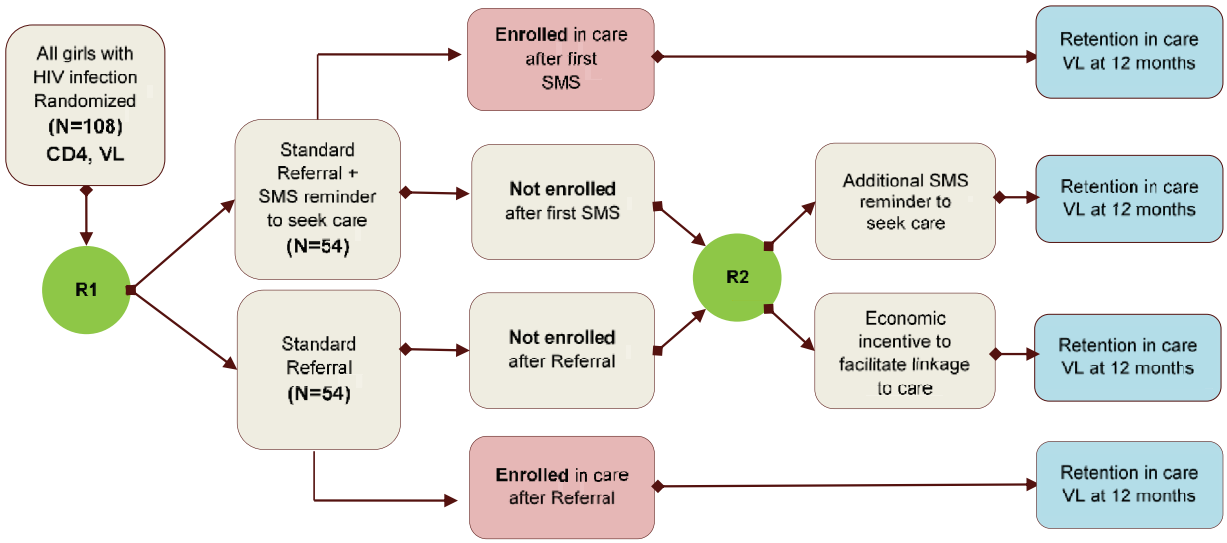


Figure 8: Adaptive Intervention *

* those not enrolled into the HIV positive cohort will be referred for care and treatment at facilities of their choice.

Randomization

Newly diagnosed HIV-positive females identified in our study will be randomized to receive standard referral to link to care or standard referral plus SMS message to link to care. Those that do not successfully link to care will then be re-randomized to receive either a second SMS message or an economic incentive. We will utilize an approach called permuted blocks randomization for participant assignment to the intervention. Permuted block randomization has several advantages, one of which is promoting equal distribution of participants in each group. A list of random allocations will be generated by the study statistician in randomly ordered permuted blocks of either 2, 4, 6, 8 or 12 allocations. The allocation list will be stored in a password protected file which will only be accessible to the study statistician, data manager or project manager.

The field study coordinator will provide a list of study ID numbers of participants needing allocation. The study statistician or data manager will record the unique study identification number and the date of the assignment on the allocation list, and relay the assignment to the field study coordinator. Alternatively, if we find that this is not efficient during implementation of our study, we will pursue other methods, such as using sequentially numbered, sealed envelopes containing participant allocation that may be prepared beforehand (Doig & Simpson, 2005).

We anticipate a total of 108 HIV positive participants to be randomly assigned to either standard referral or standard referral plus SMS at the first randomization. Participants not linked to care after the first randomization will be re-randomized in a 1:1 ratio to receive either another SMS text or an economic incentive.

11.6.2 Retention in Care

- Offered to HIV positives who have successfully linked to HIV care (defined as date of first appointment at the HIV clinic (registering for care, and being assigned a patient number)).

The goal is that at least 85% of young HIV+ women linked to treatment will stay engaged in care. Using the Weltel model (Lester et al., 2010), ART adherence and treatment engagement SMS reminders combined with health status surveys will be sent every 3 months, aligned to school holidays for those in school, when the participants have access to phones. We will get informed consent to look at records in the CCCs to confirm self-report of clinic attendance, though one of the primary outcomes is study collected viral load as a measure of adherence.

HIV NEGATIVE COHORT

A subset of participants who test negative, consent and are eligible will be enrolled in the HIV negative cohort. They will be given a low-cost cell phone.

HIV Negative Cohort Eligibility Requirements:

Inclusion Criteria:

- Meets general eligibility criteria.
- Registered with the GIRLS study and assigned a valid Study ID number.
- Previously signed IC or if younger than 18 years of age (and not an emancipated minor) has a parent or guardian who provided consent in addition to their individual assent.
- Resides in the catchment area.
- HIV negative
- Determined to be “high risk” for HIV, based on key responses to key questions in the baseline CAPI survey (sexually active AND meet at least one or more of the following: Sexual partner is HIV positive or of unknown HIV status, reports three or more sexual partners in the last month, or reports her sexual partner has multiple sexual partners)
- Willing to receive SMS texts to assess HIV risk behaviors, condom use and HIV retesting behaviors and intentions.

We will collect locator information (telephone contacts) from N≈185 randomly-selected youth who test HIV-negative and identified as “high risk”, to participate in a primary prevention messaging intervention to support HIV risk reduction and adherence to HIV re-testing recommendations. They will receive an SMS text at 6 and 12 months with a health promotion message and will also collect HIV risk behaviors, condom use, and assess their HIV retesting behaviors and intentions. At 12 months, we will re-test them for HIV and they will also complete a face-to-face (or telephone) interview on barriers and facilitators to accessing HIV prevention services. If a phone interview is

conducted, participant's identity will be confirmed by asking the participant to provide three names used at enrollment as well as their current age, so that her identity may be ascertained correctly. **Those not enrolled into the cohort will be referred for prevention and other services** (partner and family testing, PrEP, other family planning (contraception) methods, STI screening and treatment, drug use counseling, mental health services, social and nutritional support, legal services, sexual and gender based violence services and others that might be identified during the interview/risk assessment with participants).

Follow Up SMS Surveys

Participants will be educated on how to complete surveys on their phone at the time of enrollment. At this time, their cell phone number will be linked to their study ID. Each participant will be assigned a unique password/PIN code and a memory word. When they are sent the survey, they will need to enter their password to participate. If the participant forgets their password, they will be required to enter their memory word and if this fails, they will be required to visit the study site in person for identity verification and allocation of a new pass word. Once study staff ensures that the phone user is the study subject, (receiving texts is free in Kenya) staff will then wirelessly transfer airtime, so the cohort participant can send surveys using short message service (SMS) texting (Kumar, Chen, Paik, & Subramanian, 2009). In this way we will ensure follow up with the cohort regardless of where they live (if they moved since baseline). The SMS surveys will collect the following types of information, including but not limited to:

- HIV testing option and test experience
- Successful linkage
- Sexual risk behaviors
- Retention in care
- Adherence barriers and facilitators
- Willingness to re-test (for subset of HIV negatives)
- Status disclosure

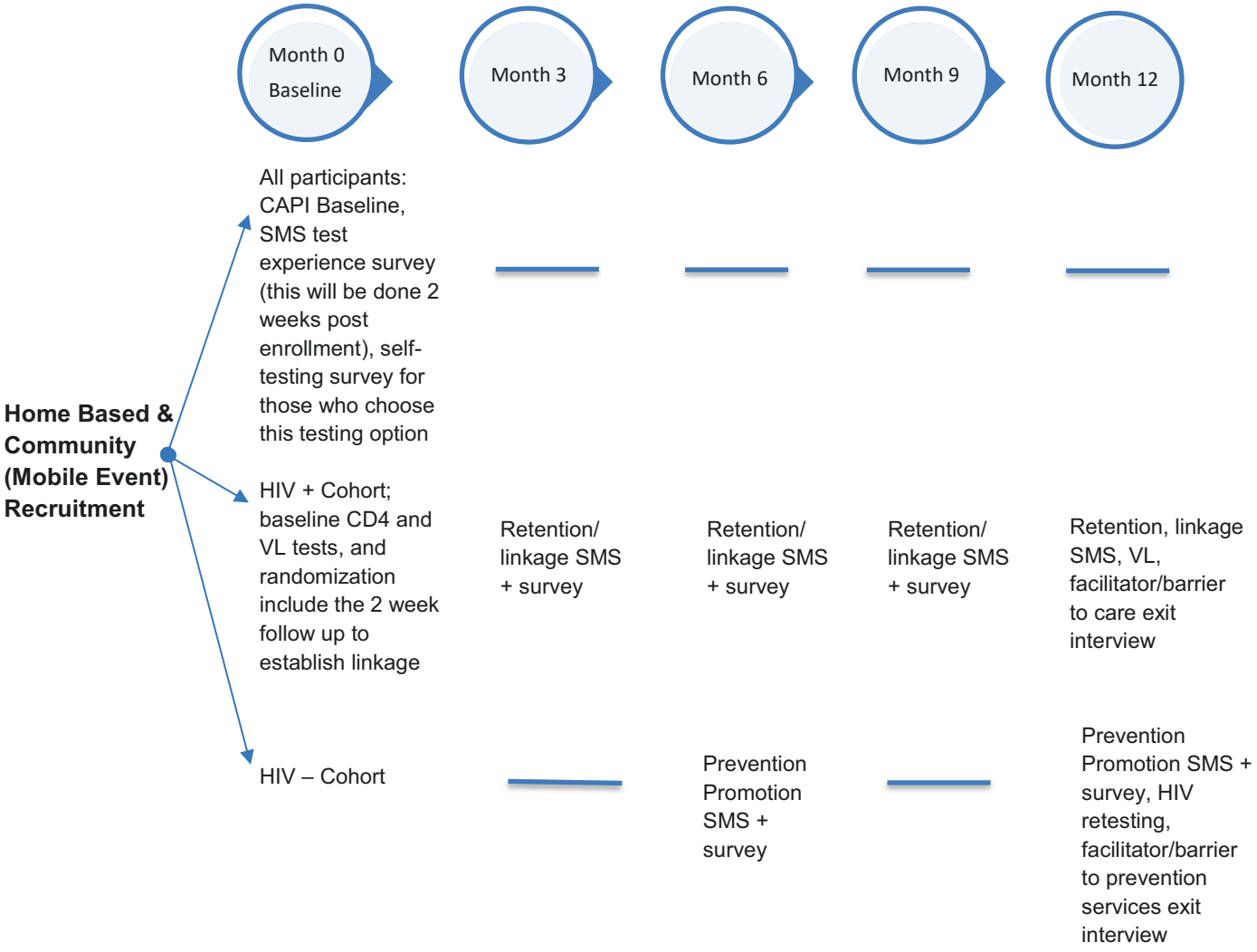
11.6.3 Final Study Visit (for HIV+ and HIV- Cohorts)

The HIV+ cohort enrollees will be asked to come to the study site (Homa Bay County Referral Hospital, Mbita Health Centre, or Ndhiwa Health Centre) to get a repeat viral load specimen collection done. In fulfillment of Aim 2b, which is to identify barriers and facilitators (social demographic, clinical, health system related) to seeking HIV care services after receiving a positive diagnosis, all HIV positive cohort participants will be invited to an exit interview administered by study staff on computer tablets at the study sites. The purpose of the interview is to capture barriers and facilitators to HIV care and treatment services. These data will provide more contextual understanding of care seeking (i.e., different questions being assessed than by SMS) for young HIV+ women. We will interview all participants in the HIV positive cohort so that we are able to capture different linkage, retention, and ART adherence experiences.

The HIV- cohort enrollees will be contacted to arrange for HIV re-testing. At this time, the HIV- cohort participants will be invited to an exit interview administered by study staff on computer tablets. The purpose of the interview is to capture barriers and facilitators to HIV prevention services. The data will be informative for understanding HIV prevention strategies.

The figure below summarizes GIRLS study follow-up timeline and outcome measures after successful linkage to care.

Figure 9: Follow-up and outcome measures after linkage to care



11.7 Study supplies, distribution, and accountability

11.7.1 Study supplies storage.

- **HIV Testing Services:** HIV test kits based on GoK HIV testing algorithm (currently Determine HIV 1/2 for screening, First Response™ HIV Care 1-2.0 for Confirmatory and Unigold™ for the Tie Breaker; OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test for oral fluid HIV self-testing), will be stored between 2 – 27°C, in a dry location, away from direct sunlight and avoiding extremes of hot or cold conditions (as per manufacturer's instructions provided in the kit insert) at study office and in the mobile health secured supply-chest. Kit components are stable until expiration date when stored as directed. We

will collect data on storage conditions (e.g., temperature tracking log), duration of storage, date self-test kit dispensed etc. We will also request that the meteorological department in Homa Bay provide data on average temperatures in the study locations during the study period. This information will not be used for weather prediction but as a proxy for temperature monitoring log for the test kits issued to participants. Meteorological data is part of QA for the test kits and will not be shared with participants.

- **PIMA CD4 cartridge** will be stored at 2–30° temperature range (as per manufacturer's instructions provided in the kit insert).
- **Condoms:** Condoms will be stored at study office and in the mobile health secured supply-chest.

11.7.2 Study Accountability Procedures:

The designated study personnel supported by the field site coordinator will be responsible for tracking study test kits and supplies, and will be responsible for maintaining logs of study supplies/interventions administered to participants.

- **HIV Testing Services (HTS):** Documentation of test kits (including **PIMA CD4s**) administered will be kept in the inventory log by the field study coordinator and in a log by the research assistants/nurses who conduct HTS.
- **Condoms:** Documentation of condoms given will be kept in the inventory log by the field study coordinator/clinical officer and in a log by the research assistants/nurses who distribute condoms.

11.8 Assessment of Participant Compliance with Study Intervention(s)

Compliance with study interventions and recommendations will be assessed in the longitudinal cohorts.

HIV positive Cohort:

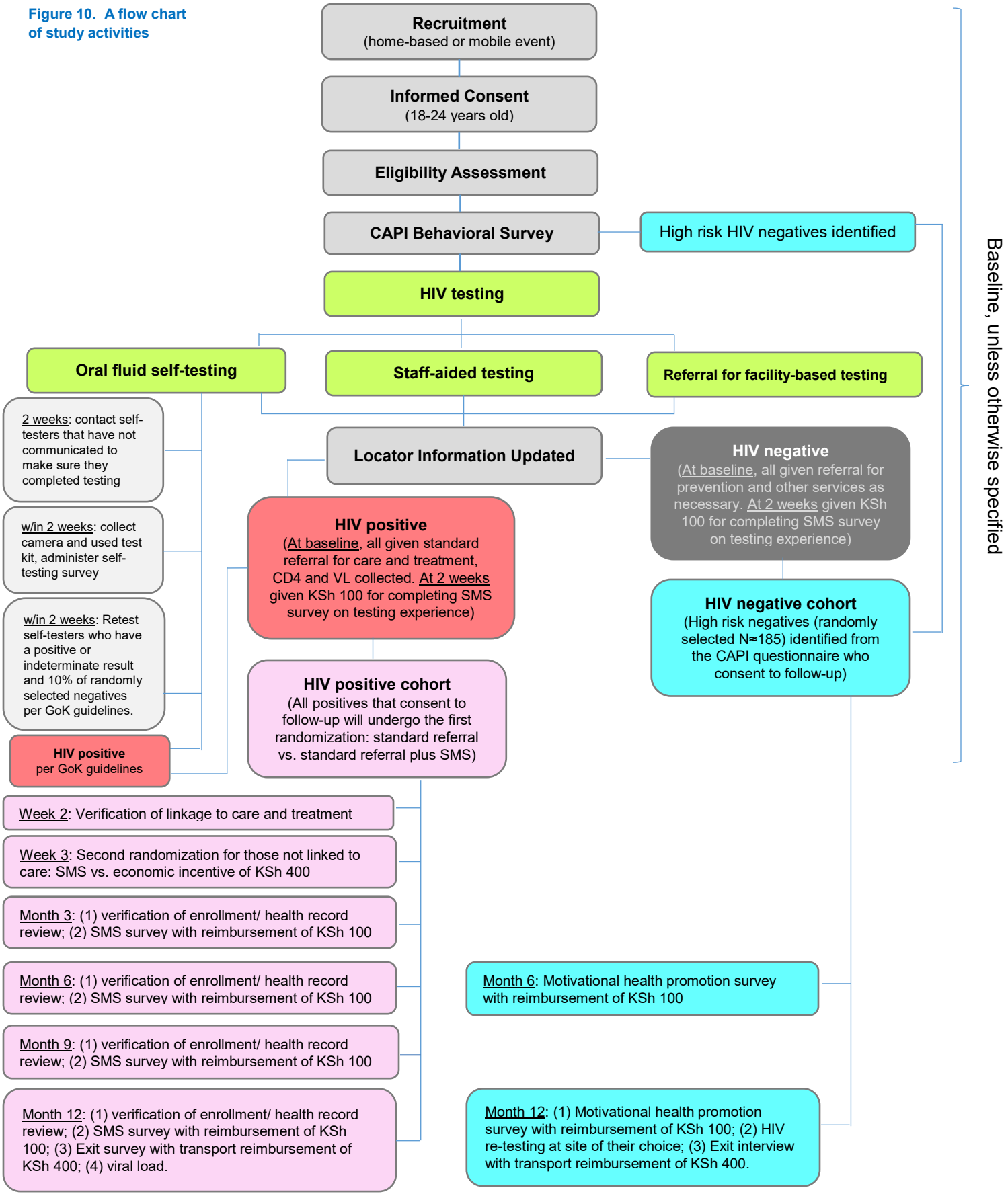
- We will be working with Homa Bay County, Ndhiwa and Mbita health facilities. Participants identified as HIV+ will be referred to Government of Kenya HIV Care centers referred to as Comprehensive Care Centers (CCC) via the intervention described for ART initiation for those who meet treatment criteria (See Figure 8, Adaptive Intervention).
- We will have a database of all participants who tested positive so when a participant goes to the referral clinics (comprehensive care centers (CCCs)) she will be identified using the tracking card. After a girl has received a positive test result she will be given a card with the contact information of our study staff (or other contact to be determined) at the clinic. We will then check with the clinics to see if that participant has visited.
- Among those that have successfully linked to care, adherence to antiretroviral medication and clinic visits will be assessed by self-report via an SMS text survey at 3, 6, 9 and 12 months of follow-up, and a repeat of viral load measure at 12 months. We will also review her medical records at the CCC to confirm her self-report of clinic attendance.
- All HIV positive girls will complete an exit interview at month 12 of follow up that will identify barriers and facilitators to seeking HIV care services after receiving a positive diagnosis. This exit interview will also capture information about the use of economic incentive for linkage.

HIV negative Cohort:

- Response rate to SMS survey at 6 and 12 months to collect HIV risk behaviors, condom use and willingness to retest for HIV among the approximately 185 HIV negative high risk girls on follow up.
- At 12 months, whether or not we were able to re-test the participant for HIV at a site of their choice.
- At 12 months, completion of face-to-face (or telephone) exit interview on barriers and facilitators to accessing HIV prevention services. If a phone interview is conducted, participant's identity will be confirmed by asking the participant to provide three names used at enrollment as well as their current age, so that her identity may be ascertained correctly.

We have included a flow chart below that brings all the interventions together, Figure 10.

Figure 10. A flow chart of study activities



12. OTHER STUDY PROCEDURES

12.1.1 Early Termination

Early termination visit
Participants may voluntarily withdraw from the study for any reason at any time. Field site investigators may withdraw a participant before their scheduled termination visit to protect their safety. Participants may be withdrawn if the study sponsors, government or regulatory authorities, IRBs/ERCs terminate the study prior to its planned end date. Site investigators are required to consult with the principal investigators prior to termination of any study participant. Study staff will record the reasons for all withdrawals in participants' study records. There are no pharmaceutical, surgical or ongoing biomedical interventions; early termination will primarily be behavioral in nature.

Voluntary Withdrawal
If a participant voluntarily withdraws from the study, an exit questionnaire/debrief will be administered to determine reasons for withdrawal and risk behavior assessment as well as VL tests if HIV positive (as would normally be done at end of 12-month cohort).

12.1.2 Pregnancy Visit

Participants who become pregnant will be allowed to continue in the study. **Our study does not include any pharmacological or surgical intervention.**

12.1.3 Unscheduled Visits

Unscheduled visits will occur by sending an invitation SMS text to the participant, calling them, or locating them using their participant locator information (also known as locator tracking form), details can be found in the informed consent procedures section 11.2. Participant initiated unscheduled visits occur when a participant initiates an unscheduled visit by, texting, calling, or stopping by in person.

13. STATISTICAL CONSIDERATIONS

13.1 Overview and Study Objectives

We will rigorously compare two 'seek' recruitment strategies, three 'test' strategies, and two enhancements to an adaptive (SMART trial design) 'linkage to care intervention, among young at-risk women who are 15-24 years old. Additionally, we will evaluate a scalable primary prevention messaging intervention to support identified HIV-negative young women in reducing HIV risk and adhering to recommended HIV re-testing recommendations. This study design will allow us to follow participants along both the prevention and care continua.

Primary Objectives:

1. To determine the preferred recruitment venue and testing modality that targets and finds the highest number of HIV infected and at risk female youth aged 15-24 years in Homa Bay County, Nyanza region, western Kenya. This will be determined by examining the uptake and yield of previously undiagnosed HIV infection of the two 'seek' strategies (community or home-based) and the three 'test' strategies (self-testing, HTS in a home/mobile setting, or facility-based HTS) among female youth;

2. To conduct an economic evaluation, using cost effectiveness analyses to determine the relative utility of each seek, test, link, and prevention intervention.

Secondary Objectives:

1. To pilot and evaluate an adaptive intervention to link newly diagnosed HIV-positive female youth to treatment and care services;

2. To identify barriers and facilitators to seeking HIV care services after receiving a positive diagnosis;

3. To identify barriers and facilitators to seeking HIV prevention services for high risk female youth after receiving a negative HIV test result;

4. To deliver an HIV prevention intervention to a randomly selected subset of high risk negative female youth, and to re-test them at 12 months.

13.2 Description of the Analyses

See Table 1: Evaluation Plan for Data Management and Analysis.

Baseline Data

1. Basic demographic information
2. Sexual risk behaviors
3. HIV risk behaviors
4. Attitudes/knowledge about HIV transmission and prevalence
5. Knowledge and acceptability of specific HIV prevention interventions

6. Knowledge and acceptability of family planning methods

The primary endpoint for comparisons of recruitment and testing strategies is newly diagnosed HIV infection. The key outcomes we detail below are broken out by study aims and based on the HIV prevention and treatment continua, which organizes our outcomes of interest by recruitment strategies, testing, linkage, retention and primary prevention.

Primary Endpoints

Primary outcomes of interest for Aim 1 is based on the HIV prevention and treatment continua as outlined below:

- Recruitment/Seek: Ability to identify and recruit female youths that are high risk for HIV infection using two seek strategies (home-based vs. community-based)
    - The proportion of youth in the community who accept study screening (estimated from total youth approached as the denominator);
    - The proportion of youth who accept study enrollment (estimated from youth screened and eligible as the denominator).
- Testing:
    - Testing uptake by different testing modalities;
    - Completion of confirmatory testing;
    - Proportion that are positive;
    - Among those who are positive, completion of baseline collection of CD4 and viral load tests.

Outcomes of interest for the Aim 3 economic evaluation include:

- Compute the cost per HIV-infected female youth identified under each 'seek' strategy (home-based vs. community based);
- Compute the cost per HIV-infected female youth identified under each 'test' strategy (self-testing, staff delivered HTS testing, standard facility-based HTS);
- Calculate the incremental cost-effectiveness ratio of the adaptive linkage to care intervention among HIV positive female youth;
- Compute the cost of the SMS prevention intervention among HIV negative female youth.

Secondary Endpoints

- Linkage to Care:
    - Percent of females who tested positive that attended a first HIV care appointment at an HIV Comprehensive Care Center (CCC)
    - Time to link to care after positive confirmatory test result
- Retention in Care:
    - Completion of viral load testing at 12 months;
    - Reported appointment attendance via SMS and verification by study staff at 3, 6, 9, and 12 months.
- Primary Prevention (N≈185):
    - Proportion reporting HIV risk behaviors, and condom use, at 6 and 12 months;
    - Proportion who re-tested at 12 months.
    - Proportion with a positive HIV test result for a sub-set of negatives at 12 months.

Statistical Analyses

Recruitment Strategy and Testing Modality: We will determine which HIV testing approaches are most preferred among all female youth and among higher risk female youth. We also will determine which recruitment and HIV testing approaches yield the highest rates of newly diagnosed HIV infection. Multinomial logistic regression (Hosmer & Lemeshow, 2004; Hosmer, Lemeshow, & Sturdivant, 2000) will be used to understand which testing approaches are most preferred/used by female youth. Preference for HIV testing at a health facility will be the reference category for the dependent variable. A model with only an intercept will be used to estimate the proportion of girls preferring each testing approach, and to test for pairwise differences in preferences (e.g., does a higher proportion of girls prefer staff-aided rather than self-testing?). In addition to overall preferences, we will consider age, risk behaviors, and HIV testing history as predictors of preferences by adding participant characteristics to the multinomial logistic regression analysis. Type of testing selected by participants, including refusal to test, will be regressed on predictors to estimate how characteristics of female youth impact HIV testing preferences. Model coefficients will describe the change in odds of preferring other types of testing relative to the reference category (facility-based testing).

Logistic regression analysis will be used to determine which recruitment and HIV testing approaches yield the highest proportion of newly diagnosed HIV infection. HIV testing result (negative vs. positive) will be regressed on variables indicating recruitment strategy (home vs. community) and type of HIV testing (self, staff-aided, facility-based). With facility-based testing following community-based recruitment as a reference category, we will estimate how home-based recruitment and other testing approaches change the odds of a positive test result. The interaction between recruitment strategy and HIV testing approach will be tested to determine whether the yield of each testing approach is conditional on recruitment strategy. If a significant interaction effect is found, simple main effects of testing approach within each recruitment strategy and simple main effects of recruitment strategy within each testing approach will be estimated. In addition to comparing yield by recruitment strategies and testing approaches, we will consider interaction effects with youth characteristics, such as age, risk behaviors, and HIV testing history, and type of testing. Similar logistic regression analyses will examine differences in the odds of completing all confirmatory testing by recruitment strategy and approach to testing.

Home-based and community-based recruitment strategies will also be compared to determine which strategy is more effective in reaching higher risk female youth. Rates of acceptance of screening among potential participants offered screening and rates of enrollment among eligible participants will be compared by recruitment strategy using logistic regression. Risk will be characterized by number and serostatus of sex partners, concurrency, condom use, and patterns of HIV testing by the participant and any sex partners.

A random selection of N≈185 girls with HIV negative tests will be followed-up. We will assess risk behaviors, condom use, additional HIV testing, linkage to prevention and any new HIV diagnoses over the year since study enrollment. Re-testing, prevention service use, and new HIV will be examined in relation to recruitment strategy, testing approach at enrollment, and participant risk behavior and other characteristics.

Adaptive Intervention Pilot: Descriptive statistics and survival plots will be used to characterize occurrence and timing of linkage among girls responding to the initial SMS message and girls in each augmented treatment condition. Survival analysis (Singer & Willett, 2003; Therneau & Grambsch, 2000) will determine which approach to augmenting linkage – continued SMS or economic incentives – is more effective in linking female youth newly diagnosed with HIV to care sooner. Using the Cox Proportional Hazards Model, difference in the likelihood and timing of linkage between treatment conditions will be quantified with an interval estimate of the hazard ratio. Median time to linkage also will be estimated and compared across treatment conditions.

Cost Effective Analysis

In order to determine costs, we will conduct a micro-costing of the cost per HIV-infected person identified under each 'seek' and 'test' strategy. This will be followed by an incremental cost-effectiveness analysis of the linkage to care interventions among HIV-infected, and a cost analysis of the SMS intervention among HIV-uninfected, women. These costs will include all costs required to deliver each intervention (home visits, staff time, supplies, and monitoring). Data will primarily utilize a micro-costing methodology that uses project expenditure and management records, employing structured costing spreadsheets that record each resource, category (e.g., personnel, supplies), quantity (e.g., hours), and unit costs. The cost data for the self-test group will include costs of obtaining a confirmatory test for those with positive self-testing results. The cost data will be stratified by HIV testing venue (home based, community based (mobile), or referral facility). With these cost data, we will calculate and compare the cost per HIV-infected person identified in each HTC strategy. We will also evaluate the costs of the linkage interventions per individual successfully linked to care. The results of the economic evaluation will allow us to identify the most efficient, affordable way to seek high risk young women and test them. For the linkage interventions, we will utilize the cost data as well as the effectiveness results to compute the ICER for the novel linkage intervention that is used. The ICER will reveal whether the costs of achieving the incremental gains from additional linkage intervention(s) suggest whether it is cost-effective or not. These results will provide novel data on the cost-effectiveness of linkage to care interventions for high-risk females in sub-Saharan Africa.

Finally, we will conduct a novel economic evaluation, using a societal perspective, to compare the relative utility of the seeking, testing, and linkage to care strategies. This analysis will take into account the economic gains to individuals and households from early diagnosis of HIV and prompt initiation of ART. We will conduct a cost-benefit analysis that focuses on the societal level economic gains that result from individuals who are successfully linked and retained in HIV care and treatment (H. Thirumurthy et al., 2013). We will comprehensively evaluate and model the costs, morbidity averted, new infections averted, and the societal impact of increased household socioeconomic status (SES) resultant from being linked to care and receiving HIV treatment. Data regarding costs will be collected using methods described above. Impacts on SES as a result of higher linkage to care and retention in care will be imputed from other studies we have conducted in Kenya and Uganda showing association between CD4 cell count and employment, income, and domestic (household) labor. We will also explore the possibility of collecting SES data from HIV-infected young women at the time they are enrolled in the linkage to care study and at 12 months. Building on previous work which included a cost effectiveness analysis of HIV prevention interventions (Alsallaq R, Buttolph J, Cleland C, Hallett T, & A., 2013; A. E. Kurth, Inwani, I., Agot,

K., Hallett, T., Cleland, C.M., Buttolph, J., Alsallaq, R, 2013) as well as economic evaluations of the effect of HIV treatment on the labor supply in Kenya (Harsha Thirumurthy, Zivin, & Goldstein, 2008), we will expand the work to include the effect of different strategies for HIV seeking, testing, and linkage, which will complete the economic evaluation for the entire HIV continua of care.

Other Analysis

Logistic regression will be used to explore predictors of timely linkage to care among girls newly diagnosed with HIV infection. Potential predictors will include behavioral (e.g, number of sex partners), demographic (e.g., age), and clinical (e.g., baseline CD4) variables assessed at baseline. Interactions between these participant characteristics and treatment conditions of the adaptive intervention also will be explored.

14. LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

14.1 Local Laboratory Specimens

HIV infection

- HIV testing
- CD4 cell count
- Viral load (VL) testing

Local laboratory Kenya Medical research, CDC laboratory will perform testing for viral load and quality assurance for CD4 and rapid HIV tests. The CDC research lab in Kisumu has an elaborate internal and External Quality Assurance (EQA) programs.

The study will adhere to standards of good laboratory practice, SSP manual, and local SOPs for proper collection, processing, labeling, transport, and storage of specimens. Specimen collection, testing, and storage at the local Lab will be documented using the **Data Management System (LDMS)** as described in the SSP Manual.

Quality Control and Quality Assurance Procedures

The CDC lab staff will follow up directly with site staff to resolve any QC or quality assurance (QA) problems identified through proficiency testing and/or on-site assessments. Throughout the course of the study, the lab will select a random sample of specimens to test for QA purposes.

QC for HIV diagnostic testing

Algorithms for HIV diagnostic testing are provided in the protocol and the SSP Manual. Participants will be tested for HIV infection status following current GoK guidelines. Participants with a positive or indeterminate result using the oral self-test kit will undergo confirmatory testing by study staff using a rapid blood test. In addition, a proportion of participants with a negative result from the oral self-test will also undergo confirmatory testing per current GoK guidelines for QA/QC purposes. HIV testing using blood samples will be subjected to quality assurance procedures. Proficiency panel testing from a proportion of tested samples will be done for both positive and negative per current GoK testing guidelines. We will follow these guidelines and will train our HTS staff on proficiency testing, i.e., staff conducting the tests will be subjected to testing of blinded panels of blood samples two or three times a year as part of quality assurance.

QC for HIV RNA monitoring

Quantitative HIV RNA (viral load) testing will be performed at Kisumu CDC lab at baseline and at 12 month follow up in any subject with confirmed HIV infection. QA for the VL testing will be done at the CDC lab and will fall under their QA system that has been established.

QC for CD4 cell count determination

For participants who test positive, CD4 cell count testing will be performed at the time when HIV infection is confirmed using PIMA POC machines which have been validated in Kenya and used

for the recent national household KAIS survey. QA will be carried out by CDC lab, every third sample will be sent to the CDC lab for re-testing.

Specimen Preparation, Handling and Shipping

No specimens will be stored long-term. Specimens will be prepared according to the protocol and the WHO guidelines on biosafety. All containers will be clean. All containers will be appropriately labeled. Specimens that need to be transported to the CDC lab will be packaged in the triple packaging system. Specimens will be placed in the primary receptacle, then placed in leak-proof secondary containers, (boxes fitted with racks), and a third layer of outer packaging to protect the secondary container from damage. The box will be regularly decontaminated.

Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the U.S. CDC. All infectious specimens will be transported in leak proof containers.

Sample storage

Study site staff will store all DBS samples collected in this study, at -20ºC or -80ºC, until all protocol-related testing has been completed, including QC testing and other testing performed at the site.

15. SAFETY MONITORING STRUCTURE

15.1 Safety Monitoring

In order to ensure participant safety, a multi-tiered communication network will be established between the study staff, field study coordinator, field site director, project manager, biostatistician, principal investigators, and NIAID project officer and medical officer to monitor participant safety and who will compose the Protocol Safety Review Team (PSRT). The PSRT will be chaired by the PIs. Regular (monthly and if needed more frequent) Skype calls will occur between the principal investigators, field site director, biostatistician, project manager and the field study coordinator and any issues will be communicated to the larger scientific team and brought immediately to the attention of the project officer and medical officer. Any serious adverse events (AEs) will be reported to the IRBs following protocols outlined below. The reports of safety issues will be reviewed by the study scientific team (PIs, biostatistician). Any SAE will be reported to NIAID, MoH, and IRBs as outlined in the next pages. The data manager will compile routine safety reports with the field study coordinator for review by the PSRT. The content, format, and frequency of the safety data reports will be agreed upon by the PSRT in advance of study implementation.

15.2 Level of Severity for Adverse Events (AE)

As with any evaluation involving medical interventions, potential adverse events (AEs) are expected. However, we expect that the risk of an adverse event as a result of study-related activities is minimal, our study does not involve a pharmacological agent. Possible adverse events in this population may include risk of distress and embarrassment during collection of personal data such as sexual risk behaviors. Taking a finger stick blood sample for HIV testing may cause a little pain, but poses minimal risk of infection because we will use sterile equipment and follow infection control and prevention procedures. All AEs reported by or observed in enrolled study participants will be documented regardless of severity and presumed relationship to study procedures.

Adverse events
An AE is any untoward medical occurrence in a participant for which there is a reasonable possibility that the experience may have been caused by the procedure; All AEs will be graded according to their intensity using the most recent DAIDS AE Grading Table available at: http://rsc.tech-res.com/safetyandpharmacovigilance.Serious Adverse Events (SAEs) (described below) will be recorded and reported to the Provincial Director of Health and the regulatory bodies using both DAIDS AE grading table and the implementing partner's AE severity scale (listed below).

Serious Adverse Events (SAE):

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,

- Is a congenital anomaly/birth defect, or
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Adverse Events/Serious Adverse Events Severity Scale

- **Grade 1 (Mild)**: events require minimal or no treatment and do not interfere with the patient's daily activities.

- **Grade 2 (Moderate)**: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Grade 3 (Serious)**: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Serious events are usually incapacitating.

- **Grade 4 (Life threatening)**: any adverse drug experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

- **Grade 5 (Death)**

15.3 Recording/Documentation of AEs

Study staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study procedures. AE severity will be graded per the DAIDS Table for Grading Adverse Events.

If an adverse event is identified the adverse events form will be completed. If a serious adverse event is identified, the serious adverse events form will be completed. Serious Adverse Events (SAEs) will be recorded and reported to the Provincial Director of Health and the DAIDS Medical Officer. All SAEs are being reported to review boards and sponsors per protocol.

15.4 Analysis/Management of AEs

Data will be obtained during the study visit, SMS text questionnaires, and through a study mobile number given to all participants to call for free if they feel that there are any complications due to an intervention they received.

Study participants will be given specific instructions (a phone call card) for contacting the study staff to report any untoward medical occurrences they feel they may experience. In the case of life-threatening events, participants will be instructed to seek immediate emergency care.

Emergency follow-up visit

Participants who reach out, request, or come in for an emergency follow-up visit will be seen as soon as possible.

For all emergencies, the field coordinator/study staff will:

- Ask the participant about the sequence of events since the intervention. Ask about: any problems; how problems developed; and any medication or other treatments obtained.
- Plan treatment of any problems that can be handled on an outpatient basis.
- Refer the participant to a higher level of care for treatment of potentially serious complications.
- Ensure that the means of communicating with and timely transport to a higher level health facility are available
- Note in the participant's research record all problems and actions taken.

15.5 Reporting Procedures of AEs and SAEs

- All adverse events (AEs): will be recorded in the adverse events form and will be reported to:
    - The field study coordinator, who will then communicate the adverse events to the Principal investigators.
    - Relevant Ministry of Health authorities

- Serious adverse events (SAEs): will be recorded on the serious adverse events form and reported to:
    - The field study coordinator, who will then communicate the adverse events to the Principal investigators.
    - The Provincial Director
    - DAIDS Medical Officer and Project Officer (sponsor).
    - Kenyan IRB and Yale IRB.

15.5.1 Specific Serious Adverse Event Requirements

All serious adverse events will be:

- recorded on the appropriate serious adverse event case report form
- followed through resolution by a study physician
- reviewed by a study physician (Kenyan PI)

Expedited Adverse Event Reporting Requirements

N/A. Our study does not involve a pharmacological agent, therefore does not fulfill the requirements, definitions, and methods for expedited adverse event reporting as outlined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at http://rsc.tech-res.com/safetyandpharmacovigilance.

15.6 Type and Duration of the Follow-up of Participants after Adverse Events

Participants who report any adverse event will be followed up weekly via SMS text or phone call until the adverse event is resolved.

15.7 Halting Rules for the Protocol

N/A. **No pharmacologic or surgical interventions.**

15.8 Premature Withdrawal of a Participant

See section 12.1.1.

15.9 Social Harms Monitoring and Reporting

It is possible that participants' involvement in the study could lead to social harms such as stigmatization, discrimination, disruption to social support network, abuse (physical/verbal). Social harms will be monitored closely throughout the study. Information on social harms will be solicited from participants during follow-up visits to examine their experiences. This information will be recorded on case report forms. If a participant reports social harms, study staff will make every effort to provide appropriate counseling, care, and referrals if necessary. Any social harms that are deemed to be serious or unexpected will be reported to the IRBs and reported to DAIDs.

Table 1: Evaluation Plan

Aims 1 and 2: Outcomes evaluated based on HIV prevention and treatment continua	Measures (Sources)	Data Collection Timeline	Data Analysis	N
Recruitment/Seek: Ability to recruit female youths that are high risk for HIV infection using two seek strategies (home-based vs. community-based). The proportion of youth in the community who accept study screening; the proportion of youth who accept enrollment.	CAPI baseline; (youth participants, total approached)	Baseline	Frequencies; differences in proportion by age, and recruitment strategy; which recruitment strategy yielded the highest rates of newly diagnosed HIV infection. Rates of acceptance of screening among potential participants offered screening and rates of enrollment among eligible participants will be compared by recruitment strategy using logistic regression. Risk will be characterized by number and serostatus of sex partners, concurrency, condom use, and patterns of HIV testing by the participant and any sex partners.	N=1200
Testing: Testing uptake; completion of confirmatory testing; proportion who are positive; among those who are positive, completion of baseline collection of CD4 and viral load tests.	GIRLS study project database	Baseline, 2 week SMS Satisfaction Survey.	Frequencies; multiple logistic regression for which testing approach most preferred/used by females. Age, risk behaviors, HIV testing history as predictors of preferences; which testing approach yielded the highest rates of newly diagnosed HIV infection.	N=1200
Linkage to Care: Percent of females who tested positive that attended a first HIV care appointment at a CCC; time to link to care after positive confirmatory result.	GIRLS study project database, medical record review at CCC, exit interviews.	2 weeks after first randomization; 1 week to re-randomize; 2 weeks after second randomization (5 weeks total from start of linkage pilot). Exit interview collected at 12 months.	Descriptive statistics; survival plots for occurrence and timing of linkage. Cox proportional hazards model for differences in likelihood and timing of linkage between the two treatment conditions; median time to linkage. Predictors of successful linkage to care.	N≈108
Retention in Care: Completion of viral load testing one year after positive confirmatory test; self-report of appointment attendance. Review of medical records to confirm self-report of clinic attendance.	SMS surveys, medical record review, exit interviews.	3, 6, 9, 12 months for SMS surveys. Medical record review to confirm clinic attendance self-report. Exit interview collected at 12 months.	Frequencies; assess number retained in care at 12 months. Proportion who complete viral load testing at 12 months.	N≈108
Primary Prevention: HIV risk behaviors, condom use, and HIV re-testing of a sub-sample of high risk HIV negatives	SMS surveys GIRLS study project database	6 and 12 months for SMS surveys. At 12 months, exit interview and re-testing	Descriptive statistics; new HIV diagnosis at 12 months.	N≈185
Aim 3 economic evaluation	**Measures (Sources)**	**Data Collection Timeline**	**Data Analysis**	
Economic evaluation to determine the comparative cost effectiveness of the seek, test, link, and prevention interventions.	GIRLS study project database	Accrual and follow-up period.	Micro-costing of the cost per HIV infected person under each seek and test strategy; incremental cost effectiveness of linkage to care intervention for HIV +; cost analysis of SMS intervention and re-testing for HIV negative females.	

15.10 Appropriate Methods and Timing for Analyzing Outcome Measures.

See Table 1: Evaluation Plan.

15.11 Sample Size Considerations

Baseline sample size calculation

Based on our experience with MP3 Youth (data not yet published), which screened N=788 female youth and enrolled N=690 female youth over a period of eight months (November 19, 2014 – June 12, 2015), we expect we can recruit N=1200 female youth over a period of around twice that time. We expect the sample accrual rate to be slower than in MP3 Youth, because we will be recruiting only female youth and mainly those out of school (a large proportion of younger MP3 Youth girls were in school and easier to recruit). In addition, we have two different recruitment strategies, and the home-based strategy may be more labor intensive and time consuming than a community mobile event. We therefore expect a somewhat lower accrual rate. Therefore, in order to stay within the estimate 12 months of recruitment, we will increase our field staff during the implementation phase of the project. Sample size estimates are also based on IRDO's program data and the estimated number of youth in Homa Bay. We expect large numbers of youth will be successfully recruited from the home and mobile events (IRDO reaches tens of thousands of youth/year) for a total sample size of ≥ 1200 female youth.

Power Analysis

Power calculations for Aim 1 are based on the yield of newly diagnosed HIV across recruitment strategies and testing options offered to female youth. Using version 12 of the PASS program (Hintze, 2013) for logistic regression, we did not approach this power analysis from the perspective of calculating a sample size needed to detect a particular effect size with at least 80% power. Rather, because this part of the study (Aim 1) is not a clinical trial but rather an exploration of preferences and yield of recruitment and participant-selected testing strategies, we started with the large, feasible sample size and determined the size of effects that could be detected with at least 80% power when comparing recruitment strategies and HIV testing approaches.

The expected percentage of girls testing positive is based on our MP3 Youth pilot study. In that study, 55 of 636 female youth not previously diagnosed were found to have HIV infection (data not yet published). Thus, we expect about 9% of all tested females in this study to have HIV infection not previously diagnosed.

With this estimate of the expected percentage of girls with newly diagnosed HIV infection, we asked how small of an increase in the odds of newly diagnosed HIV infection could be detected with 80% power when community-based recruitment is compared to home-based recruitment. With 600 youth recruited by each strategy, power is 80% to detect an odds ratio of 1.67, in other words, a modest increase from 9% to 14% newly diagnosed with HIV infection. When comparing testing approaches, and assuming an equal proportion of girls prefers each approach and testing approach does not interact with recruitment strategy, power is 80% to detect an odds ratio of 1.85. If there is an interaction between recruitment strategy and testing approach, when comparing

testing approaches within a recruitment strategy (i.e., estimating simple main effects), power is 80% to detect an odds ratio of 2.32.

These calculations show the proposed sample size (N=1200) is capable of detecting modest differences in the yield of newly diagnosed HIV infection across both recruitment strategies and testing approaches.

Among the approximately 108 female youth we expect to be newly diagnosed with HIV infection, about 20% are expected to successfully initiate HIV care at a health facility after a single SMS message. The remaining 80% (N=86) who are not linked to care after the initial SMS message will be randomly assigned to either continued SMS messages or to economic incentives. Assuming at least 60% are linked to care at some point during follow-up, survival analysis employing Cox regression will be able to detect a hazard ratio of 2.2 describing the impact of treatment condition (continued SMS vs. economic incentives) on the occurrence and timing of successful linkage to care at a health facility, with 80% power.

15.12 Randomization

Our study is observational in nature, but the Aim 2a adaptive linkage to care intervention does contain a randomization component. Newly diagnosed HIV-positive females identified in our study will be randomized to receive standard referral to link to care or standard referral plus SMS message to link to care. Those that do not successfully link to care will then be re-randomized to receive either an SMS message or an economic incentive. We will utilize an approach called permuted blocks randomization for participant assignment to the intervention. Permuted block randomization has several advantages, one of which is promoting equal distribution of participants in each group. A list of random allocations will be generated by the study statistician in randomly ordered permuted blocks of either 2, 4, 6, 8 or 12 allocations. The allocation list will be stored in a password protected file which will only be accessible to the study statistician, data manager or project manager.

The field study coordinator will provide a list of study ID numbers of participants needing allocation. The study statistician or data manager will record the unique study identification number and the date of the assignment on the allocation list, and relay the assignment to the field study coordinator. Alternatively, if we find that this is not efficient during implementation of our study, we will pursue other methods, such as using sequentially numbered, sealed envelopes containing participant allocation that may be prepared beforehand (Doig & Simpson, 2005).

We anticipate a total of 108 HIV positive participants to be randomly assigned to either standard referral or standard referral plus SMS at the first randomization. Participants not linked to care after the first randomization will be re-randomized in a 1:1 ratio to receive either another SMS text or an economic incentive.

See Section13: Statistical Considerations and Section 18: Data Handling and Record Keeping.

16. QUALITY CONTROL AND QUALITY ASSURANCE

A co-principal investigator who is a Kenyan physician with clinical research experience, the project manager, and IRDO internal research auditor who is a clinician (Clinical Officer) with extensive experience overseeing quality assurance in numerous clinical trials have been identified as the monitors to conduct Quality assurance/Quality control for the study. Following written standard operating procedures as they appear in the study specific operating procedures (SSP) and this protocol, the monitor will verify the study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, IRB, government of Kenya regulations, DAIDS and any other regulatory requirements. Details about data specific QA/QC are provided in the data management SOP. Also the study specific protocols contain built-in QA/QC procedures per intervention.

17. ETHICS/PROTECTION OF HUMAN SUBJECTS

17.1 Institutional Review Board/Ethics Committee

The principal investigators will ensure that this study is conducted in a manner that protects human subjects.

Prior to implementation of this protocol, and any subsequent full version amendments, each site will have the protocol and the protocol informed consent form(s) approved, as appropriate, by the local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received

Following DAIDS approval, the Kenyatta National Hospital and Impact Research and Development Organization submit for review and approval the GIRLS Study protocol to their governing IRB in Kenya, Kenyatta National Hospital/University of Nairobi - Ethics and Research Committee (KNH-ERC). Once approval is granted from the local IRB (KNH-ERC) the approval and protocol are submitted to Yale University's Human Research Protection Program.

17.2 Informed Consent (IC) Process

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RCC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Informed consent is required to participate in the study (See Appendices C, D & E).

All female youth coming to the mobile event site (potential participants) or recruited from the home will be consented by the trained RAs/Counselors/Study Staff who will explain more of the study, eligibility, and study procedures.

1. Potential participant's age will be determined by asking them how old they were at their last birthday.
2. If the participant is less than 18 years old and not an emancipated minor, then parental consent will be obtained and thereafter, participant assent will also be obtained. Both the parent and the youth will append their signature on the respective IC form (on-site).
3. If 18 years of age or older, or an emancipated minor by Kenyan standards, informed participant consent procedures will continue.

RAs/Counselors/Study Staff will provide the participant with the approved IC form in the participant's language of choice; English, Dholuo or Kiswahili. Participants will be given the option of having the script read to them if they cannot read or feel more comfortable with the form being read to them. RAs will not assume a participant can read. They will clarify the main points of the IC form with potential participants, to assess comprehension. This information includes: 1) purpose of study, 2) time commitment including follow up visit(s), 3) study procedures, 4) confidentiality, 5) incentive/payment, 6) eligibility assessment, and 7) voluntary nature of the study.

RAs will allow time for participants to ask questions about the study. Once all questions have been addressed, they will verify that the potential participant is still interested in being in the study. If so, the RA will witness the participant and or parent sign and date the consent/assent form, or place left thumb print if participant/parent cannot write. (An additional witness signature will be required on the form if this option is used). RAs will then sign and date the consent/assent form and provide the participant with a copy of the consent/assent form. The potential participant will then be screened for eligibility. Individuals who do not consent/or withdraw consent, or who do not meet the study eligibility criteria will not be enrolled in the study but will receive referrals for relevant services.

17.2.1 Minor Assent/ Informed Consent (IC) Process

In order to participate in the study, participants (18 and older or emancipated minors) must undergo written IC procedures. Participants under the age of 18 must bring parent(s) or guardian(s) to give consent on behalf of minors who must also give assent. Emancipated minors can give their own consent. Participants will sign the overall study IC document during registration. Upon accessing services, participants will provide the IC form to the provider. Upon completion, a copy of the completed IC form will be provided to the participant.

Participants under the age of 18 who choose staff-aided HTS, will have two options once the parent has consented to the test: (1) the youth can request that parent stays for the youth's test results and post-test counseling or (2) the youth can request that her parent not see the test results, but if she tests positive for HIV, she must designate a guardian to whom she will disclose her results, in order to be able to receive treatment for HIV. However, if the youth is considered an "emancipated minor", that is she is under 18 years old, but is either married, pregnant or has an STI, she is exempt from the need to disclose her status to a parent or guardian.

17.3 Exclusion of Women, Minorities, and Children (Special Populations)

There are no special exclusions other than males as this study is focused on young females who have a higher HIV prevalence and have been identified by the Government of Kenya as being a highly vulnerable group. Innovative strategies across the HIV prevention care continua are needed to reach young women; programs already exist to reach men for voluntary medical male circumcision (VMMC). This underlies the scientific justification for the focus on young women in this study.

17.4 Participant Confidentiality

All study staff will be trained on participant confidentiality. All study staff will hold all aspects of the study (protocol documentation, and all other study related documents) in the strictest confidence. No information concerning the study or data will be released to any unauthorized third party, without written permission from the sponsor and the study participant.

The study monitors (Yale, KNH, IRDO), other local, US, and international regulatory entities, and IRBs/ECs, or other authorized representatives of the sponsor (e.g., monitors, DAIDS, and OHRP) may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) for the participants in this study.

See section 18: Data Handling and Record Keeping for additional information on participant confidentiality.

We will ensure confidentiality with mobile phone usage confirming user identity for SMS messages as well as airtime incentive and digital cash transfers. (See data management responsibilities section).

17.5 Potential Risks and Benefits

17.5.1 Potential Risks

Sensitive Information

Surveys will be conducted on a staff administered computer assisted personal interview (CAPI) designed to collect and protect sensitive information. Computer assisted self-interviews (ACASI) has been found to have mixed results in terms of social desirability bias reporting of sensitive behaviors by Kenyan youth, suggesting a benefit to staff elaboration and support found in the CAPI. Only authorized study staff will have access to the participant's questionnaire responses. SMS text surveys from the cohort will be sent over TCP/IP as encoded data without identifiers.

HIV Testing – Adolescents

HIV testing in adolescents poses special risks particularly for those who are still under the care of parents and guardians because of the fact that HIV can be sexually transmitted. This may result in adolescents refusing to test unless they are assured of confidentiality of the results. Study procedures will therefore ensure that all young people are provided with the opportunity to test in private. HIV testing will be accompanied by age appropriate, individualized HIV prevention messages for all adolescents whether testing HIV negative or positive. Prevention with positives messaging and referrals will be incorporated into the post-test counseling, to include referral to appropriate PMTCT for those girls who test HIV+ and are pregnant. Youth may be embarrassed discussing their sexual history. Youth may become worried, anxious, or upset by learning the result of their HIV test is positive. Taking a finger stick blood sample for HIV testing poses minimal risk of infection because we will use sterile equipment. However, the finger stick may cause a little pain.

Social Harms

It is possible that involvement in the study could lead to stigmatization, discrimination, disruption to social support network, abuse (physical/verbal). We will monitor these and will protect confidentiality to reduce potential social harms.

Stigma

Adolescents who test positive may be particularly vulnerable to isolation, stigma and discrimination and will therefore be proactively linked to youth and other support groups in the community for ongoing psychosocial support. They will also be assisted with getting appointments at the nearest facility offering HIV care and treatment services in their catchment area. HIV labs and medications at these facilities are free, but sometimes transport costs are a barrier. **Therefore, the study's one-time financial incentive linkage arm is justified and not an undue incentive.**

Minimization of Risk

All efforts will be made to minimize risks for participating in this study. Study staff are trained in human subjects' protections. Study data will be collected, stored, and analyzed following strict security procedures.

USSD or SMS text surveys from the cohort will be sent over TCP/IP as encoded data without identifiers. Data will be kept secure and minimal personal identification information will be collected, and will then be anonymized in the study database. Safeguards for protecting confidentially of questionnaires and other data will be strictly enforced.

Physical risk protection

The study staff responsible for obtaining fingerstick capillary blood samples will be trained in infection control and will use disposable gloves, alcohol swabs, sterile gauze, and retractable, disposable lancets so as to eliminate risk of contamination. As part of the informed consent

procedure, all eligible respondents will be told that the supplies that will be used are clean and sterile.

Psychological risk protection

All study staff will undergo training on HIV counseling and testing as per the Kenyan national curriculum and all HIV testing sessions will be conducted according to the Kenya guidelines for HIV testing. Several study members are specially trained clinicians able to handle crises situations due to any difficulties in coping with positive HIV test results.

Protection of Minors

In order to participate in the study, participants (18 and older or emancipated minors) must undergo written informed consent procedures for the study elements. Participants who are age 15-17 and are not emancipated minors must bring parent(s) or guardian(s) to give consent on behalf of these minors who must also give assent. Emancipated minors can give their own consent. Participants will sign the study informed consent documents during enrollment. One copy of the signed informed consent form will be provided to the participant.

17.5.2 Potential Benefits

Although HIV testing has inherent risks, knowledge of HIV status is a powerful tool for behavior change and is an entry point for care and treatment services for the HIV infected. Community-based counseling and testing improves access to testing and is associated with high levels of acceptance and identification of a large proportion of previously undiagnosed HIV. However, the majority of Kenyans who desire to know their status have never had a HIV test. Youth in rural Kenya have limited opportunities to get a HIV test. This study will therefore be an important way of improving access to HIV testing for youth who are at high risk.

All study subjects will benefit by receiving evidence-based HIV prevention services. High risk negative females will receive referral for PrEP, which the GoK has recently endorsed (January 2016) as a national strategy for HIV prevention among key populations, including high-risk females. In addition, all HIV-positive youth identified during the study will be linked with community support groups as well as lifesaving care and treatment services for themselves. Those found pregnant will be supported to access prevention of mother-to-child transmission (PMTCT) services. Information regarding how to prevent infection or transmission of HIV to and from their sexual partners will also be offered.

All participants will receive free HIV counseling and testing, information on the locations and operating times of the nearest HTS centers and other community-based HIV service organizations. Those found to have HIV infection will be properly counseled and referred for appropriate follow-up at HIV care and treatment facilities in the area. Those randomized to additional linkage strategies (SMS, one-time cash transfer) will receive additional support for linking to care. All HIV-negative girls will receive counseling around risk reduction, and those high-risk HIV-negative girls will receive referral for PrEP and SMS messages about the benefits

of recommended re-testing, which may support HIV infection avoidance or early detection of HIV for treatment.

The community will benefit from knowledge gained during interaction with the study staff on young peoples' HIV and reproductive health. Several recent studies in Kenya have documented that the community feels more HIV prevention services for youth are needed in western Kenya (Knopf, 2012; Omanga et al., 2013).

Importance of the Knowledge to be Gained

The information gathered is expected to contribute to the literature by providing some of the first data on high yield seeking strategies combined with uptake of self-testing data, and an SMS based adaptive linkage to care intervention for young women in sub-Saharan Africa, who are among the highest HIV risk age-group globally. As such the lessons learned from the study are expected to be generalizable to the many similar settings where young people are at high risk of HIV acquisition.

17.6 Study Discontinuation

The principal investigators, sponsor, and the IRB/IEC, have the authority to discontinue or suspend the study. The Investigator will promptly inform the participants if the study is discontinued or suspended and will assure appropriate referrals. Furthermore, if the **investigator** discontinues or suspends the study, the institutions, sponsor and IRB will be promptly notified with a detailed written explanation. If the **sponsor** discontinues or suspends the study, the institutions and IRB will be promptly notified with a detailed written explanation. If the **IRB** discontinues or suspends the study, the institutions and sponsor will be promptly notified with a detailed written explanation.

18. DATA HANDLING AND RECORD KEEPING

18.1 Data Management

18.1.1 Screening IDs, Participant ID Numbers (PTIDs), and unique barcodes

Screening IDs will be assigned to all potential study participants who are approached for enrollment.

- Screening IDs are assigned at the participant's first screening visit, regardless of whether or not the potential participant completes screening for the study.
- Participant Identification Numbers (PTIDs) are assigned at Enrollment and are separate from the Screening ID.
- The Nairobi Office will provide both Screening IDs and PTIDs.

Both Screening IDs and PTIDs ideally will be assigned in sequential order; however, it is recognized that deviations from sequential ordering occur from time to time, e.g., when several potential participants are approached for possible screening or enrollment at the same time.

Pre-printed barcode labels will be procured from a vendor. Study staffer will place a pre-printed barcode label (with a unique barcode number) on the camera and on the self-test kit. Study staffer will then record the barcode numbers on a tracking form to ensure that it links with the participant's study identification number.

The Data Manager/Designee is responsible for maintaining the list of screening IDs and PTIDs and assigning screening IDs and PTIDs to potential participants. The Data Manager/Designee will also maintain the list of the unique barcodes affixed on the self-testing kit and the camera that is assigned to each participant who chooses the self-testing option.

- The Data Manager will enter participant details (age, last-name) into the Participant Tracking Access Database after the participant visits and after he/she has reviewed the information for accuracy and completeness.
- The Data Manager will enter the unique barcode number affixed to the test kit and camera into the Participant Tracking Access Database. He/she will ensure that the barcode numbers are linked to the correct participant identification number. Electronic photos from the camera will be uploaded to a study computer and labeled with the unique camera barcode number. No participant name or other identifier will be attached to these images.

Additional information on organization, types of data, and storage of study files can be found in the SSP.

18.1.2 Procedures for Organization of Files

Screening Folders: Each participant who screens for the study will be assigned a Screening Folder.

- Screening folders will contain documents identified by the screening ID, and will not contain any documents with the participant names or identifiers.
- Screening folders will be pre-assembled by the Data Manager, and will contain all forms necessary for the screening visits.
- Hard copy screening folders will be stored in a lockable cabinet in the study office.
- The hard copy and electronic screening folders of participants who do not enroll in the study will be stored separately.
- Electronic screening data will be stored in a password protected database.

Chart Note Binders

- Enrolled participants will each have a chart-note binder.
    1. Participants will be identified only by Screening ID or PTID on documents in these binders.
    2. Forms from screening visits which do not contain participant names or identifiers will be transferred to the Chart Note Binders.

- **Name Charts**
    1. Each participant will be given a Name Chart at the first screening visit, and will keep the same chart if he/she enrolls in the study.
    2. Name charts will be stored in a lockable cabinet in the Study Coordinator's office.
    3. Name charts will be stored in cabinets which are separate from the Link Log, CRF binders, and Chart Note Binders.
    4. Documents in the Name Chart of screening participants will include:
        a) Screening Informed Consent Forms (ICFs)
    5. Documents in the Name Charts of enrolled participants will include the above and:
        a) Enrollment Informed Consent Forms
        b) Locator Forms (names and contact information)
        c) Tracer Forms
    6. As needed:
        a) Locator information updates
        b) Participant tracking forms
        c) Tracer forms (for calls and if no-response, or in person visits)
        d) Any other information about the participant that includes participant name

- **Link Log:** A paper Link Log will link the participant name and Screening ID/PTID.
    1. The link between participant name and PTID will also be stored in a password protected database (Participant Tracking Database).
    2. The paper Link Log will be stored in a lockable drawer in the Study Coordinator's desk with limited access by study coordinator, principle investigators and representatives of the regulatory bodies only.

3. The Participant Tracking Database will be stored on a password protected computer in the Data Manager's office.
4. Only the Data Manager and Data Manager backup/Designee, Study Coordinator, and Principal Investigator will have access to the Participant Tracking Database.
5. The electronic database will be backed up daily and kept on a separate digital storage (e.g., CD, encrypted thumb drive, etc.) in the data room. We will also have a secure web based backup at Yale.
6. A second back up copy will be kept offsite in a lockable drawer in the Principal Investigator's desk. This will be created daily; the digital storage will be transferred weekly to the PI.
7. The Study Coordinator, Data Manager, IT Officer or Driver may transport the offsite back up digital storage in a secure fashion, not leaving it unattended at any time.
8. **Staff who transports the Offsite storage device will receive instruction on its proper transport.**

18.1.3 Data Management Process

18.1.3.1 Quality Assurance (QA)/Quality Control (QC)

1. The SMS survey will be programmed so that it will be impossible to move from one question to the next unless all prior questions have been answered. The Data Manager will at the end of the week distribute a report on the quality and completeness of data received during the week. This information will be used to advise the field staffers on improvements that need to be made.

18.1.3.2 Data Revision:

1. No changes will be made to the Master Database. All revisions, corrections, additions and deletions will be made using a Data Revision Script. The Data Manager will maintain the Data Revision Script, which will work by copying the Master Database then updating existing data, deleting erroneous data, and inserting missing data through standardized queries.
2. In cases where study staff are not sure how to resolve a query, or when repeated attempts to resolve a query do not result in elimination of the query from the QC report, the Data Manager will contact the Database Administrator for guidance.

18.1.3.3 Data Storage Process

- All study data — screening and on-study — will be stored securely as described in this protocol. All study data will be password security-protected. The data collected on the tablet or smartphone using CAPI will be encrypted in the field/within the software such that only password-authorized study staff can access the data. The cohort USSD - SMS text data will be attached only to an anonymous study ID and thus not contain any personally identifying information.

1. All participant study files will be retained for at least five years after study completion unless otherwise specified by the Kenyatta National Hospital Administrative Office.
2. All files will be retained on-site throughout the study period of performance.
3. Arrangements for record storage after the study period of performance will be made in accordance with instructions to be provided by the Kenyatta National Hospital Administrative Office.

- The Master Database and the Data Revision Script will be backed-up on a separate digital device at the end of each day and stored onsite. Weekly back-ups will be transported for offsite storage.

- Information entered and stored in the Participant Tracking Database — which is not considered source data — will be backed-up on a separate digital device at the end of each day.
    1. This copy of the database will be overwritten with a new copy the following day.
    2. A second back up copy will be kept offsite in the Principal Investigator's desk.
    3. The Study Coordinator, Data Manager, IT Officer or Driver may transport the offsite back up in a secure fashion, not leaving the CD unattended at any time.
    4. Staff who transports the Offsite digital device will receive instruction on its proper transport and a tracking log filled.

18.1.4 Confidentiality

- **De-identified data:** Participant study files will be stored as described in the previous sections.
    1. The use of participant names to identify study related documents will be minimized to the extent possible. All documents bearing participant names will be stored apart from documents bearing PTID or Screening ID or barcode numbers. In lieu of names, the study ID will be used so that the names will not appear on study documents.

- **Locked Cabinets:** All files will be stored in locked cabinets in Homa Bay and Nairobi, with access limited to study staff.
    1. During working hours, the data room will be unlocked when the IT Officer is present to allow staff access to phones and other files to conduct participant visits and perform other required data management functions.
    2. If the IT Officer is away from the data room, the key for the data room will be left with the Study Coordinator, or other designated staff member.
    3. At the end of the workday, the IT Officer will lock the data room. The IT Officer will keep the key to the data room. One additional key to the data room will be kept at the study clinic by the Study Coordinator. A set of spare clinic keys, including a data room key, will also be kept in a locked cabinet in the GIRLS Administrative Office.
    4. Only the PI, Study Coordinator, and Study Administrator/Designee will have access to this key.

5. Non staff members who may need to perform tasks in the data room such as carpentry or repairs will be allowed into the data room only when the IT Officer is present and care will be taken to ensure that participant records are not in view.

- **Access to the Participant Tracking Access Database**, which contains names, PTID, Screening ID, barcode numbers and information about each study participant, will be limited to authorized study staff members through the use of password protections.
    1. The Data Manager, who will be responsible for printing out clinic schedules and reports from the database, will never print out reports that bear participant names.

- **No participant identifiers other than the Screening ID or PTID will be recorded on any CRF or other documents not in the name charts.**
    1. Written permission will be obtained from participants prior to the release of any study-related information that personally identifies the participant outside of the study site.

18.2 Data Capture Methods

18.2.1 Data Collection

All participants who are eligible, consented, and registered for the GIRLS study will be required to complete a baseline behavioral CAPI survey and an HIV testing experience satisfaction SMS survey. HIV positive participants who have successfully linked to care will complete SMS surveys every 3 months as described in the study procedures section. A subset of the HIV negative participants will also complete SMS surveys at 6 and 12 months. The HIV positive cohort and the HIV negative cohort will also complete a face-to-face (or telephone) interview at 12 months. If a phone interview is conducted, participant's identity will be confirmed by asking the participant to provide three names used at enrollment as well as their current age, so that her identity may be ascertained correctly.

Administering Computer Assisted Personal Interview (CAPI) Surveys – interviewer assisted.

- **Data Collection Setup**
    1. The CAPI will be staff-administered on a tablet computer.
    2. All survey questions will be pre-programmed in tablet by the IT Officer and the Data Manager who will be responsible for training the field staffers and other study personnel on their use.
    3. The CAPI will be administered by the RAs/Counselors.
    4. Once a participant is enrolled in the study, her screening data will be entered into the main database in the study IT Office.
- **Data Collection Procedures**
    1. Participants are required to complete the baseline survey.
    2. The behavioral CAPI survey will be administered after IC. The survey should be completed in one sitting.

3. For sensitive questions, the participant can input the answer without the interviewer viewing the screen, to reduce discomfort.
4. Once complete, the RA will thank the participant for completing the survey.

- **Data Transfer Process**
    1. All data will be temporarily saved on the hard-drive of the tablet.
    2. The data from the tablets will then be securely uploaded to the IT Office Data Computer and then securely transferred to the Data Manager's office in Nairobi where the GIRLS study database will be housed. This transfer will occur within 12 hours after completion of data collection.
    3. Data will not be deleted from the tablets before it is uploaded onto the IT Officer's Data Computer and has been transmitted to Nairobi Office.
    4. The IT Officer will make a printout of all information on the tablets and file these hard copies in binders filed sequentially according to the Participant Identification Number (PTID) or Screening ID number and will be stored on shelves in lockable cabinets in the IT Office, separate from the Name Charts and Link Log (which will be stored in the Study coordinator's office).
    5. Information in the tablets will be identified only by the Participant Identification Number (PTID) or Screening ID number.
    6. The RA assigned to the tablet will be responsible for it. When not in use, the tablet will be locked in a lock box. At the end of the day, tablets will be stored in lock boxes in the GIRLS study office in Homa Bay.

SMS Survey data collection

Participants in the HIV+ cohort will receive SMS text reminders to link to care and will also receive cell phone surveys regularly for follow-up data collection. The content of the surveys was previously described in section 11. USSD or SMS text surveys from the cohort will be sent over TCP/IP as encoded data without identifiers. Data will be kept secure and minimal personal identification information will be collected, and will then be anonymized in the study database. Safeguards for protecting confidentially of questionnaires and other data will be strictly enforced. Surveys will be automatically sent by the program used to push notifications. The responses will be saved in the GIRLS study database. The management of the SMS data will follow the same process as other forms of data for management and storage.

18.3 Types of Data

Examples of data to be collected include behavioral data, HIV testing modality uptake, HIV status, CD4 count, viral load level, linkage to care, and adverse events. See Table 1: Evaluation Plan, page 61 for detailed types of data collected.

18.4 Source Documents and Access to Source Data/Documents

The implementing partner, IRDO and clinical sites (Homa Bay County Referral hospital, Mbita and Ndhiwa Health centers) will maintain appropriate medical and research records for this study,

in compliance with ICH-GCP, regulatory and institutional requirements for the protection of confidentiality of participants. The data management/analysis team (data managers and biostatistician), field study coordinator, project manager, and principal investigators will have access to the data. Once data are de-identified they can be shared with the rest of the scientific team as appropriate.

The data management site will permit authorized representatives of the sponsor(s), NIAID, and other local, US, and international regulatory entities to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

18.5 Timing/Reports

See section 18 Data Handling and Record Keeping

Data Management.

18.6 Study Records Retention

See section 18 Data Handling and Record Keeping

Data Management.

18.7 Protocol Deviations

All protocol deviations will be immediately reported to the IRBs as well as the study sponsor (see section 16 Quality Control and Quality Assurance). Regular (monthly or more frequently as necessary) communication will provide a consistent and regular forum to examine protocol compliance (see section 15.1 Safety Monitoring).

Intensive trainings on the study specific protocol and intermittent in-service trainings will be scheduled to ensure protocol compliance by all study staff.

19. PUBLICATION POLICY

Publication of the results of this trial will be governed by NIAID publication policies. All publications shall make the following acknowledgement as per the publication policy:

Research reported in this publication was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under **Award Number R01AI122797**. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication.

The study will be registered under ClinicalTrials.gov. We will undertake randomized comparison of interventions in the adaptive linkage to care pilot.

ClinicalTrials.gov Identifier: NCT02735642
Website: https://clinicaltrials.gov/ct2/show/NCT02735642

Appendix A: Schedule of Procedures/Evaluations

Procedures (All Participants)	Baseline	2 weeks	3 weeks	3 months	6 months	9 months	12 months
Recruitment (at home or mobile event)	x						
Signed Consent Form	x						
Eligibility Assessment	x						
CAPI Behavioral Survey	x						
HIV Testing							
Enrollment for follow-up	x						
ART/PMTCT referral	x						
Condoms	x						
Other referrals as appropriate	x						
SMS HIV testing satisfaction survey (KSh 100)		x					
Staff administered survey for participants who chose HIV self-testing		x					
HIV Negative Cohort							
SMS primary prevention survey (KSh 100 each time complete survey)					x		x
HIV re-test							x
Exit interview (KSh 400)							x
HIV Positive Cohort							
HIV test/confirmation	x						
CD4 POC test	x						
VL test	x						x
Adaptive intervention pilot first randomization: standard referral or standard referral and SMS	x						
Adaptive intervention pilot second randomization: SMS or economic incentive of KSh 400			x				
Retention in care survey (KSh 100 each time complete survey)				x	x	x	x
Exit Interview (KSh 400)							x

(X) = as indicated/appropriate

Appendix B: Logic Model

<table>
<tr><th>Study Objectives</th><th>Resources/Inputs
(what we invest)
In order to accomplish our activities we will need the following:</th><th>Activities
(what we do)
In order to address HIV prevention we will conduct the following activities:</th><th>Outcomes (Outputs) for Aims 1 and 2.
We expect that once completed or under way, these activities will produce the following evidence along the HIV prevention and treatment continua:</th><th>Outcomes for Aim 3</th><th>Long-term Outcomes/ Impact
We expect that once completed our study will have the following impact</th></tr>
<tr><td rowspan="3">Aims 1 and 2 Objectives:

(1) To determine the preferred recruitment venue and testing modality that gives the highest number of HIV infected and at risk female youth aged 15-24 years in Homa Bay County, Nyanza region, western Kenya. This will be determined by examining uptake of the two ‘seek’ strategies (community or home-based) and the three ‘test’ strategies (self-testing, HTC in a home/mobile setting, or facility-based HTC) among female youth;

(2) To pilot and evaluate an adaptive intervention to link HIV-positive female youth to treatment and care services; and

(3) To identify barriers and facilitators to seeking HIV care services after receiving a positive diagnosis.</td><td>Funding</td><td>Human Subjects Approval</td><td>Aims 1 and 2 Outcomes:</td><td>Aim 3 Outcomes:</td><td>Increased HIV testing/counseling</td></tr>
<tr><td>Community engagement</td><td>Hire and train field staff</td><td><u>Recruitment/Seek</u>: Ability to identify and recruit female youths that are high risk for HIV infection using two seek strategies (home-based vs. community-based)
-The proportion of youth in the community who accept study screening (estimated from total youth approached as the denominator);
-The proportion of youth who accept study enrollment (estimated from youth screened and eligible as the denominator);</td><td>Conduct comprehensive economic evaluation to determine the comparative cost effectiveness of the seek, test, link, and prevention interventions.</td><td>Increased correct and consistent condom use</td></tr>
<tr><td>Scientific team</td><td>Enroll participants.</td><td><u>Testing</u>:
-Testing uptake by different testing modalities;
-Completion of confirmatory testing;
-Proportion that are positive;
-Among those who are positive, completion of baseline collection of CD4 and viral load tests.</td><td><u>Seek</u>: Compute the cost per HIV-infected female youth identified under each ‘seek’ strategy (home-based vs. community based)</td><td>Increased treatment/ART adherence, reduced HIV</td></tr>
</table>

(4) To deliver an HIV prevention intervention to a randomly selected subset of negatives.					
Aim 3 objectives: To conduct an economic evaluation, using cost effectiveness analyses to determine the relative utility of each seek, test, link, and prevention intervention.	Established local implementing partner	Pilot adaptive linkage intervention.	**Linkage to Care:** -Percent of females who tested positive that attended a first HIV care appointment at an HIV Comprehensive Care Center (CCC) -Time to link to care after positive confirmatory test result.	**Test**: Compute the cost per HIV-infected female youth identified under each 'test' strategy (self-testing, staff delivered HTC testing, standard facility-based HTC);	Increased use and familiarity with oral HIV self-testing kits.
	Protocol	Follow up cohorts	**Retention in Care:** -Completion of viral load testing at 12 months; -Self-report of appointment attendance via SMS at 3, 6, 9, and 12 months. -Medical record review to confirm self-report of clinic attendance.	**Link**: Calculate the incremental cost-effectiveness ratio of the adaptive linkage to care intervention among HIV positive female youth;	
	Training	Disseminate results	**Primary Prevention:** -HIV risk behaviors, and condom use, at 6 and 12 months for a subset of negatives (N≈185); -HIV re-testing for a sub-set of negatives (N≈185) at 12 months; -HIV status for a sub-set of negatives (N≈185) at 12 months.	**Prevention**: Compute the cost of the SMS prevention intervention among HIV negative female youth.	
	Local clinics				

Appendix C: GIRLS Study (18+ and Mature Minors) Sample Informed Consent Form

High-yield HIV testing, facilitated linkage to care, and prevention for female youth in Kenya (GIRLS Study)

Introduction

Hello, my name is ----------. You are invited to take part in a research study. Before you decide whether to participate, you need to understand why the research is being done and what it would involve. Please take the time to read or to listen as I read the following information. You may talk to others about the study if you wish. Please stop me at any time and ask if there is anything that is not clear, or if you would like more information. When all of your questions have been answered and you feel that you understand this study, you will be asked if you wish to participate in the study, and if you decide to join this research study, we will then ask you to give your written consent. Your participation is completely voluntary and you can withdraw your participation at any time with no penalty.

HIV testing services is an important gateway for HIV prevention, care, and treatment. Adolescent girls and young women in sub-Saharan Africa are the most at risk group for HIV infection. This is because of a number of reasons that include high fertility, young age at first sexual encounter, frequent intergenerational sex and low likelihood of partner circumcision. These reasons put many adolescent girls and young women at increased risk for HIV infection. It is therefore important to prioritize HIV testing for this population.

Purpose of the Study and Study Requirements

What is the study about? This study is being carried out by Impact Research and Development Organization in collaboration with Kenyatta National Hospital and Yale University. We are offering services to up to 1,200 female youth between the ages of 15-24 that help youth stay healthy and reduce chances of acquiring or transmitting HIV/AIDS. The study is called the **GIRLS Study**. We would like to know which testing services female youth prefer and if they like receiving services at home, in the community outside the health facilities or in the health facilities. The ultimate goal of this study is to improve the health and well-being of female adolescents and young women like you.

The study offers the following:

- HIV Testing Services
    - For those who will turn out HIV positive, they will be assisted to access care and treatment in a government facility
    - For those who are at risk of HIV infection, they will be assisted to access prevention services

- In addition, about 293 (about 185 negative and 108 positive) girls like you may be requested to be followed for one year.

The testing, referral, and follow-up services will be delivered by health teams, made of nurses and counselors, among others.

In order to participate in the **GIRLS Study,** you must be aged between 15 and 24 years. Because you are 18 years or older or a 'mature minor' (if you are under the age of 18 years old but are married or pregnant or have a child), you must agree to participate voluntarily after getting all the necessary information. You will give your permission to participate in the study in writing. You will sign two copies of this form, and will

be given a copy to take with you if you wish. One copy will remain with the study staff. If you do not wish to take a copy with you, we will give you a piece of paper with information on whom to contact if you have questions about the study or your rights as a participant.

To be a participant, you must also agree to provide information on where/how you can be reached by the study staff if needed.

Why have I been invited to take part? You have been invited to take part because you are a young girl between the ages of 15-24 living in Homa Bay County where the study is taking place.

What will happen if I take part? If you agree to take part in the study today, the following things will happen:

1. You will be asked to agree to HIV counseling and rapid testing using a little blood from your finger or saliva.

   You can choose any of the following HIV testing approaches:

   a) Oral fluid HIV self-testing (OHIVST) at your convenience, where you carry out the test yourself using fluid from your mouth OR
   b) Staff-aided testing, where rapid testing using a little blood from your finger will be carried out either at home or at a mobile health event OR
   c) You go to a health facility where rapid testing using a little blood from your finger will be done by a health provider (standard health facility based testing)

   You will be contacted in 2 weeks via SMS regardless of your testing choice. You will be asked to answer a few questions about your HIV test experience for which you will receive KSh 100 for your airtime and for time you will take to respond to the SMS.

2. Study staff will ask you a few questions about yourself, your behaviors, and your knowledge of health promotion services and HIV prevention services using a questionnaire on a small hand-held computer called a tablet. This interview will be held in private where others cannot hear what you say and will take about 15 minutes.

3. We will collect information of how we can locate/contact you in case we need to follow-up with you during the study (we will not reveal your identity to anyone outside the study).

4. Once you receive the results of the HIV test, you will be told what additional services you may require and you will be offered appropriate referral.

If the HIV test is positive: If the oral fluid self-test, or staff-aided screening test, or facility-based screening test is **positive**, another test must be done to confirm the results. If one result is negative and one is positive, we will refer you to a health facility of your choice for HIV re-testing. If two HIV test results are positive, we will refer you to a local HIV care facility of your choice. We will also take blood (up to 4 mL, less than 1 teaspoon) to see how strong the body's defense system is (test your CD4 count) and how much of the virus is in your blood (HIV viral load level).

If the test is positive and you are also pregnant, we will refer you to a health facility of your choice where you can get care for both the pregnancy and HIV and help prevent the unborn baby from getting HIV.

All HIV infected girls will be invited to participate in a follow up for 12 months. We want to know what is the best way to support you in making sure that you receive the care you need. If you are positive and agree we will provide referral to a health care facility or referral plus SMS message to go for services, and after 2 weeks we will check with you and with the clinic to see if you were able to get services. Among those who will not have gone to the clinic, they will be randomized (have a 50/50 chance) to receive either SMS text reminder to attend the clinic, or provided transport reimbursement. This is to help us understand the best approach to link young girls to HIV care. If you have linked to HIV care, we will send you SMS every three months to find out how you are doing and if you are keeping your appointments. We will confirm your self-report of clinic attendance by reviewing your medical records at the health facility. At 12 months, you will be contacted and invited to have blood taken for a repeat viral load test. At this time, all HIV positive girls will be invited to participate in an exit interview looking at what makes it easy or hard to go for HIV care among young girls.

If the HIV test is negative: If you test HIV negative, you may be asked if you would be willing to provide your phone number. A randomly selected number of girls (≈185) will receive an SMS at 6 and 12 months with a health promotion message and asked to answer a few questions on their behaviors, condom use, and willingness to retest for HIV. At 12 months, they will be retested for HIV and also complete an exit interview on what makes it easy or hard to go for HIV prevention services.

If you select OHIVST: If you choose this approach, you will be counseled/explained to on how to use the self-test and some paper with explanation and pictures on how to do the test given to you. Once you complete the test, you will be asked to take a picture of the result with a study camera (non-identifiable barcode (unique lines) will be placed on each kit and camera so as to confirm that the kit and camera links with your study number). You will be given a number that you can contact once you complete the self-test. You will be sent a few questions about your testing experience via SMS within 2 weeks and will receive KSh 100 for your airtime and for time you will take to respond to the SMS. Also, by sending a message or calling the number listed, study staff will arrange for collection of the camera and used self-test kit. At the time of kit and camera collection, study staff will conduct a brief interview on your experience with self-testing. (Note, you should not discard the test kit or camera, they will be collected by study staff).

For those who have a positive or indeterminate test result with the self-test, and a randomly selected proportion of those who report testing negative, study staff will connect with you at a convenient location to help you get the confirmatory test. This may be at home, somewhere in the community, or at a health facility where you would be comfortable.

Risks

What are the risks of participating in the study? You may feel uncomfortable discussing your behaviors. Taking a finger stick blood sample for HIV testing may cause a little pain and poses minimal risk of infection, however we will use sterile equipment. We will ensure that infection control procedures are followed.

HIV Testing Services: You may become worried, anxious, or upset by learning the result of your HIV test is positive. You will be counseled and referred for care and support.

Social Harms: It is possible that your involvement in the study could lead to stigmatization, discrimination, disruption to social support network, and abuse (physical/verbal). We will monitor these and will protect confidentiality to reduce potential social harms. We will also provide you with information on where you can get support services. In addition, you can call the Study Coordinator on the number provided at the end of this form to report any harm you may experience.

Benefits

What are the benefits of participating in the study?
The direct benefits to you for participating in the study are that you will know your HIV status. If the test is negative, this will help you in making decisions on how to remain negative or live positively, depending on the results. You will also have access to HIV prevention services and health services that have been shown to help reduce HIV risks. You may learn a few things from the discussion that could help you protect yourself or others against HIV and other sexually transmitted infections. Also, the results of this study may contribute to the implementation of future intervention programs to reduce the risk of HIV in female adolescents and youth.

Anyone found to be HIV positive will be linked with community support groups as well as life-saving care and treatment services for themselves. Those found pregnant will be supported to access prevention of mother-to-child transmission (PMTCT) services. Information regarding how to prevent infection or transmission of HIV to and from their sexual partners will also be offered.

Confidentiality

Will my participation in the study be kept confidential? We will take all steps necessary to ensure your privacy and confidentiality. Given that it is a mobile event/ home visit/ clinic visit, your attendance at any of these places may be known to other people. However, we will request all participants/ members of the homestead to keep information that they observe about others during the visit confidential and not to share it with anyone. The services will be offered in a place where other people cannot see you or hear what you say.

You will be assigned a unique number and your name will not appear on any information like your responses on the computer or services accessed. Safeguards for protecting confidentially of questionnaires and other data will be strictly enforced. All data will be kept in a secure location at the Kenyatta National Hospital and Impact Research and Development Organization and destroyed at the end of the study. Each participant will be asked to respect the participation of others and the confidentiality of others they see. This point will be stressed throughout.

Your study records (not your name) may be reviewed only by approved study staff and representatives of:

- Yale University
- Kenyatta National Hospital
- Impact Research and Development Organization
- Yale University Human Investigation Committee
- Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC)
- National Institutes of Health USA

- Office for Human Research Protections (OHRP)
- Division of AIDS (DAIDS)
- Ministry of Health Kenya
- Other local, US, and international regulatory entities

Voluntariness

What are my rights as a research participant/subject? Your participation in this study is completely voluntary. Significant new findings developed during the course of the research which may affect your willingness to continue participation will be provided to you. If you decide not to participate, you will not lose any existing benefits you may receive from **Impact Research and Development Organization or health facility**. If you decide to take part, you are free to refrain from answering any questions and you may end your participation at any time without penalty or loss of existing benefits to which you are entitled.

Involuntary Early Termination of Participation:
The field site investigators may withdraw a participant before their scheduled termination visit to protect their safety. Participants may be withdrawn from the study if the study sponsors, government or regulatory authorities, ethical/institutional review boards stop the study before its planned end date.

Voluntary Early Withdrawal:
If someone voluntarily withdraws from the study, a few brief questions will be asked. We will offer HIV testing for those initially negative, and if HIV positive we will collect a small amount of blood sample to test how much of the virus is in your blood and refer you for services.

Additional Information

What will I receive for participating? You will not be paid for your participation in the study. However, you will receive KSh 100 for your airtime and time taken in completing the SMS questions about your satisfaction with your HIV test experience.

HIV-negative group: If you are HIV negative and selected to complete SMS questions at 6 and 12 months, you will receive KSh 100 for your airtime and time you will take to respond to the SMS. At 12 months, you will receive KSh 400 transport reimbursement when you retest for HIV and complete an exit interview about what made it easy or hard to access prevention services.

HIV-positive group: You will receive KSh 100 for your airtime and time you will take completing SMS surveys. For participating in the exit interview about what made it easy or hard to access care, you will be compensated a total of KSh 400 for your time and travel. A randomly selected number of HIV positive youth will receive KSh 400 for transport to go for HIV care services.

Will it cost me anything to participate? No, it will not cost you anything to participate.

Please note that the U.S. National Institutes of Health (NIH) that is funding this study does not have a mechanism to provide direct compensation for research related injury.

A description of this clinical trial will be available on www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen to the results of the research study? The results of the study will be discussed and presented in a report at team meetings or as a publication. The information may be presented at a conference with other studies that relate to youth health promotion, sexual health and HIV prevention and treatment. Neither the report nor the presentation will show your name.

Who has reviewed the study for ethical issues? This study has been reviewed and approved by the Institutional Review Boards at both the **Kenyatta National Hospital/ University of Nairobi (KNH/UON) and Yale University.**

What if I need more information? For any information about the study, you may contact the Study Coordinator, **Mr. Samwel Rao on 0713-687-399** at any time.

What if there is a problem? Any complaint about the way you have been treated during the study or any possible harm you might suffer will be addressed. **Please contact the Principal Investigator of the study, Dr. Irene Inwani from the Kenyatta National Hospital on 0202-726-300 or Professor Chindia, Secretary to the KNH/UON Ethics and Research Committee on 0202-726-300.**

At this time, I want to make sure you understand the study and see whether you have any additional questions. After we discuss any questions you may have, we can discuss whether you are interested in participating in the study today.

Are you willing to participate in the overall study (which includes HIV testing)? (Select one)

No ☐ **(if no, stop here)**

Yes ☐ **(if yes, continue below)**

SIGNATURE PAGE
GIRLS Study Information and Informed Consent

Participant: If you have read this consent form (or had it read and explained to you), all of your questions have been answered and you agree to take part in this study, please sign this form or make your mark to indicate your willingness to participate.

Study staff who conducted informed consent discussion: I confirm that I have personally explained the nature and extent of the planned research, study procedures, potential risks and benefits, and confidentiality of personal information.

Participant's name (print)	**Participant's signature/thumbprint and date**
Study staff conducting consent discussion (print)	**Study staff signature and date**
Witness's name (print) (if appropriate)	**Witness's signature and date (if appropriate)**

Appendix D: GIRLS Study Parental Sample Informed Consent Form for Minors (15-17)

High-yield HIV testing, facilitated linkage to care, and prevention for female youth in Kenya (GIRLS Study)

Introduction

Hello, my name is ----------. Your child is being invited to take part in a research study. Before you decide whether to allow your child to participate, you need to understand why the research is being done and what it would involve. Please take the time to read or to listen as I read the following information. You may talk to others about the study if you wish. Please stop me at any time and ask if there is anything that is not clear, or if you would like more information. When all of your questions have been answered and you feel that you understand this study, you will be asked if you will allow your child to participate in the study, and if you decide to allow your child to join this research study, we will then ask you to give your written consent. Your child's participation is completely voluntary and you or your child can withdraw her participation at any time with no penalty.

HIV testing services is an important gateway for HIV prevention, care, and treatment. Adolescent girls and young women in sub-Saharan Africa are the most at risk group for HIV infection. This is because of a number of reasons that include high fertility, young age at first sexual encounter, frequent intergenerational sex and low likelihood of partner circumcision. These reasons put many adolescent girls and young women at increased risk for HIV infection. It is therefore important to prioritize HIV testing for this population.

Purpose of the Study and Study Requirements

What is the study about? This study is being carried out by Impact Research and Development Organization in collaboration with Kenyatta National Hospital and Yale University. We are offering services to up to 1,200 female youth between the ages of 15-24 that help youth stay healthy and reduce chances of acquiring and transmitting HIV/AIDS. The study is called the **GIRLS Study**. We would like to know which testing services female youth prefer and if they like receiving services at home, in the community outside the health facilities or in the health facilities. The ultimate goal of this study is to improve the health and well-being of female adolescents and young women like your child.

The study offers the following:

- HIV Testing Services
    - For those who will turn out HIV positive, they will be assisted to access care and treatment in a government facility
    - For those who are at risk of HIV infection, they will be assisted to access prevention services

- In addition, about 293 (about 185 negative and 108 positive) girls like your child may be requested to be followed for one year.

The testing, referral, and follow-up services will be delivered by health teams, made of nurses and counselors, among others.

In order to participate in the **GIRLS Study**, your child, who is under the age of 18 must bring a parent or guardian to give consent on their behalf, but they must also agree (give assent).

You will give your permission for your child to participate in the study in writing. You will sign two copies of this form, and will be given a copy to take with you if you wish. One copy will remain with the study staff. If you do not wish to take a copy with you, we will give you a piece of paper with information on whom to contact if you have questions about the study or your rights as a participant.

You must also agree to provide information on where/how you can be reached by the study staff, if needed.

Why has my child been invited to take part? Your child has been invited to take part because she is a young girl between the ages of 15-17 living in Homa Bay County where the study is taking place.

What will happen if my child takes part? If you allow your child to take part in the study today, the following things will happen:

1. She will be asked to agree to HIV counseling and rapid testing using a little blood from her finger or saliva.

   Your child can choose from the following testing approaches:

   a) Oral fluid HIV self-testing (OHIVST) at her convenience, where she will carry out the test herself using fluid from her mouth OR
   b) Staff-aided testing, where rapid testing using a little blood from her finger will be carried out either at home or at a mobile health event OR
   c) She will go to a health facility where rapid testing using a little blood from her finger will be done by a health provider (standard health facility based testing)

   Your child will be contacted in 2 weeks via SMS regardless of her testing choice. She will be asked a few questions about her HIV test experience for which she will receive KSh 100 for her airtime and for time she will take to respond to the SMS.

2. Study staff will ask your child a few questions about herself, her behaviors, and her knowledge of health promotion services and HIV prevention services using a questionnaire on a small hand-held computer called a tablet. This interview will be held in private where others cannot hear what your child says and will take about 15 minutes.

3. We will collect information of how we can locate/contact your child in case we need to follow-up with your child during the study (we will not reveal your child's identity to anyone outside the study).

4. If your child chooses staff-aided HTS, she may choose to allow you to stay for her HIV test result. Once your child receives the results of the HIV test, she will be told what additional services she may require and she will be offered appropriate referral. If her test result is positive, she must name a parent or guardian to whom she will share her results in order to be able to receive treatment for HIV.

   If the HIV test is positive: If the oral fluid self-test, or staff-aided screening test, or facility-based screening test is **positive**, another test must be done to confirm the results. If one result is negative and one is positive, we will refer your child to a health facility of their choice for HIV re-testing. If two HIV test results are positive, we will refer your child to a local HIV care facility of their choice. We will also take blood (up to 4 mL, less than 1 teaspoon) to see how strong the body defense system is (test her CD4 count) and how much of the virus is in your child's blood (HIV viral load level).

If the test is positive and your child is also pregnant, we will refer your child to a health facility of her choice where they can get care for both the pregnancy and HIV and help prevent the unborn baby from getting HIV.

All HIV infected girls will be invited to participate in a follow up for 12 months. We want to know what is the best way to support your child in making sure that she receives the care she needs. If your child is positive and she agrees, we will provide referral to a health care facility or referral plus SMS message to go for services, and after 2 weeks we will check with her and with the clinic to see if she was able to get services. Among those girls who will not have gone to the clinic, they will be randomized (have a 50/50 chance) to receive either SMS text reminder to attend the clinic, or provided transport reimbursement. This is to help us understand the best approach to link young girls to HIV care. If your child has linked to HIV care, we will send her SMS every three months to find out how she is doing and if she is keeping her appointments. We will confirm her self-report of clinic attendance by reviewing her medical records at the health facility. At 12 months, she will be contacted and invited to have blood taken for a repeat viral load test. At this time, all HIV positive girls will be invited to participate in an exit interview looking at what makes it easy or hard to go for HIV care among young girls.

If the HIV test is negative: If your child tests HIV negative, she may be asked if she would be willing to provide her phone number. A randomly selected number of girls (≈185) will receive an SMS at 6 and 12 months with a health promotion message and asked to answer questions on their behaviors, condom use, and willingness to retest for HIV. At 12 months, they will be retested for HIV and also complete an exit interview on what makes it easy or hard to go for HIV prevention services.

If your child selects OHIVST: If your child chooses this approach, she will be counseled/explained to on how to use the self-test and some paper with explanation and pictures on how to do the test given to her. Once she completes the test, she will be asked to take a picture of the result with a study camera (non-identifiable barcode (unique lines) will be placed on each kit and camera so as to confirm that the kit and camera links with her study number). She will be given a number that she can contact once she completes the self-test. She will be sent a few questions about her testing experience via SMS within 2 weeks and will receive KSh 100 for her airtime and for time she will take to respond to the SMS. Also, by sending a message or calling the number listed, study staff will arrange for collection of the camera and used self-test kit. At the time of kit and camera collection, study staff will conduct a brief interview on your child's experience with self-testing. (Note: she should not discard the test kit or camera, they will be collected by study staff).

If your child has a positive or indeterminate test result with the self-test, the study staff will connect with her at a convenient location to help her get the confirmatory test. Study staff will also administer a confirmatory test to a randomly selected proportion of girls who report testing negative with the self-

test. This may be at home, somewhere in the community, or at a health facility where she would be comfortable.

Risks

What are the risks of participating in the study? Your child may feel uncomfortable discussing her behaviors. Taking a finger stick blood sample for HIV testing may cause a little pain and poses minimal risk of infection, however we will use sterile equipment. We will ensure that infection control procedures are followed.

HIV Testing Services: Your child may become worried, anxious, or upset by learning the result of her HIV test is positive. Your child will be counseled and referred for care and support.

Social Harms: It is possible that your child's involvement in the study could lead to stigmatization, discrimination, disruption to social support network, and abuse (physical/verbal). We will monitor these and will protect confidentiality to reduce potential social harms. We will also provide her with information on where she can get support services. In addition, she can call the Study Coordinator on the number provided at the end of this form to report any harm she may experience.

Benefits

What are the benefits of participating in the study?

The direct benefits to your child for participating in the study are that she will know her HIV status and this will help her in making decisions on how to remain negative or live positively, depending on the results. She will have access to HIV prevention services and health services that have been shown to help reduce HIV risks. You may learn a few things from the discussion that could help your child protect herself or others against HIV and other sexually transmitted infections. Also, the results of this study may contribute to the implementation of future intervention programs to reduce the risk of HIV in female adolescents and youth.

Anyone found to be HIV positive will be linked with community support groups as well as life-saving care and treatment services for themselves. Those found pregnant will be supported to access prevention of mother-to-child transmission (PMTCT) services. Information regarding how to prevent infection or transmission of HIV to and from others will also be offered.

Confidentiality

Will my child's participation in the study be kept confidential? We will take all steps necessary to ensure your child's privacy and confidentiality. Given that it is a mobile event/ home visit/ clinic visit, your child's attendance at any of these places may be known to other people. However, we will request all participants/ members of the homestead to keep information that they observe about others during the visit confidential and not to share it with anyone. The services will be offered in a place where other people cannot see your child or hear what she says.

Your child will be assigned a unique number and her name will not appear on any information like her responses on the computer or services accessed. Safeguards for protecting confidentially of questionnaires and other data will be strictly enforced. All data will be kept in a secure location at the Kenyatta National Hospital and Impact Research and Development Organization and destroyed at the end of the study. Each participant will be asked to respect the participation of others and the confidentiality of others they see. This point will be stressed throughout.

Your child's study records (not her name) may be reviewed only by approved study staff and representatives of:

- Yale University
- Kenyatta National Hospital

- Impact Research and Development Organization
- Yale University Human Investigation Committee
- Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC)
- National Institutes of Health USA
- Office for Human Research Protections (OHRP)
- Division of AIDS (DAIDS)
- Ministry of Health Kenya
- Other local, US, and international regulatory entities

Voluntariness

What are my child's rights as a research participant/subject? Your child's participation in this study is completely voluntary. Significant new findings developed during the course of the research which may affect you and your child's willingness to continue participation will be provided to you and your child. If you decide not to allow her to participate, she will not lose any existing benefits she may receive from **Impact Research and Development Organization or health facility**. If you decide to allow your child to take part, she is free to refrain from answering any questions and she may end her participation at any time without penalty or loss of existing benefits to which she is entitled.

Involuntary Early Termination of Participation:

The field site investigators may withdraw a participant before their scheduled termination visit to protect their safety. Participants may be withdrawn from the study if the study sponsors, government or regulatory authorities, ethical/institutional review boards stop the study before its planned end date.

Voluntary Early Withdrawal:

If someone voluntarily withdraws from the study, a few brief questions will be asked. We will offer HIV testing for those initially negative, and if HIV positive we will collect a small amount of blood sample to test how much of the virus is in your child's blood and refer her for services.

Additional Information

What my child receives for participating? Your child will not be paid for participation in the study. However, she will receive KSh 100 for her airtime and time taken in completing the SMS questions about her HIV test experience.

HIV-negative group: If your child is HIV negative and selected to complete SMS questions at 6 and 12 months, she will receive KSh 100 for her airtime and the time she will take to respond to the SMS. At 12 months she will receive KSh 400 transport reimbursement when she retests for HIV and completes an exit interview about what made it easy or hard for her to access prevention services.

HIV-positive group: Your child will receive KSh 100 for her airtime and time she will take completing SMS surveys. For participating in the exit interview about what made it easy or hard for her to access care, your child will be compensated a total of KSh 400 for her time and travel. A randomly selected number of HIV positive youth will receive KSh 400 for transport to go for HIV care services.

Will it cost me anything for my child to participate? No, it will not cost you anything for your child's participation.

Please note that the U.S. National Institutes of Health (NIH) that is funding this study does not have a mechanism to provide direct compensation for research related injury.

A description of this clinical trial will be available on www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen to the results of the research study? The results of the study will be discussed and presented in a report at team meetings or as a publication. The information may be presented at a conference with other studies that relate to youth health promotion, sexual health and HIV prevention and treatment. Neither the report nor the presentation will show your name or your child's name.

Who has reviewed the study for ethical issues? This study has been reviewed and approved by the Institutional Review Boards at the **Kenyatta National Hospital/University of Nairobi (KNH/UON) and Yale University**.

What if I need more information? For any information about the study, you may contact the Study Coordinator, **Mr. Samwel Rao on 0713-687-399** at any time.

What if there is a problem? Any complaint about the way your child has been treated during the study or any possible harm she might suffer will be addressed. **Please contact the Principal Investigator of the study, Dr. Irene Inwani from the Kenyatta National Hospital on 0202-726-300 or Professor Chindia, Secretary to the KNH/UON Ethics and Research Committee on 0202-726-300.**

At this time, I want to make sure you understand the study and see whether you have any additional questions. After we discuss any questions you may have, we can discuss whether you are interested in your child participating in the study today.

Are you willing to permit your child to participate in the overall study (which includes HIV testing)? (Select one)

No ☐ **(if no, stop here)**

Yes ☐ **(if yes, continue below)**

SIGNATURE PAGE
GIRLS Study Information and Parental Informed Consent

Participant's parent/guardian: If you have read this consent form (or had it read and explained to you), all of your questions have been answered and you agree to have your child take part in this study, please sign this form or make your mark to indicate your willingness to allow your child to participate.

Study staff who conducted informed consent discussion: I confirm that I have personally explained the nature and extent of the planned research, study procedures, potential risks and benefits, and confidentiality of personal information.

Participant's parent/guardian name (print)	**Participant's parent/guardian signature/thumbprint and date**
Study staff conducting consent discussion (print)	**Study staff signature and date**
Witness's name (print) (if appropriate)	**Witness's signature and date (if appropriate)**

Appendix E: GIRLS Study Minor (15-17) Sample Assent Form

High-yield HIV testing, facilitated linkage to care, and prevention for female youth in Kenya (GIRLS Study)

Introduction

Hello, my name is ----------. You are invited to take part in a research study. Before you decide whether to participate, you need to understand why the research is being done and what it would involve. Please take the time to read or to listen as I read the following information. You may talk to others about the study if you wish. In order to participate in the **GIRLS Study**, participants under the age of 18 must bring a parent or guardian to give consent on their behalf, but they must also agree (give assent). Before receiving services, your parent/guardian will be asked to give written permission for you to participate and you must also agree (give assent). Please stop me at any time and ask if there is anything that is not clear, or if you would like more information. When all of your questions have been answered and you feel that you understand this study, you will be asked if you wish to participate in the study, and if you decide to join this research study, we will then ask you to give your written assent. Your participation is completely voluntary and you can withdraw your participation at any time with no penalty.

HIV testing services is an important gateway for HIV prevention, care, and treatment. Adolescent girls and young women in sub-Saharan Africa are the most at risk group for HIV infection. This is because of a number of reasons that include high fertility, young age at first sexual encounter, frequent intergenerational sex and low likelihood of partner circumcision. These reasons put many adolescent girls and young women at increased risk for HIV infection. It is therefore important to prioritize HIV testing for this population.

Purpose of the Study and Study Requirements

What is the study about? This study is being carried out by Impact Research and Development Organization in collaboration with Kenyatta National Hospital and Yale University. We are offering services to up to 1,200 female youth between the ages of 15-24 that help youth stay healthy and reduce chances of acquiring or transmitting HIV/AIDS. The study is called the **GIRLS Study**. We would like to know which testing services female youth prefer and if they like receiving services at home, in the community outside the health facilities or in the health facilities. The ultimate goal of this study is to improve the health and well-being of female adolescents and young women like you.

The study offers the following:

- HIV Testing Services
    - For those who will turn out HIV positive, they will be assisted to access care and treatment in a government facility
    - For those who are at risk of HIV infection, they will be assisted to access prevention services

- In addition, about 293 (about 185 negative and 108 positive) girls like you may be requested to be followed for one year.

The testing, referral, and follow-up services will be delivered by health teams, made of nurses and counselors, among others.

In order to participate in the **GIRLS Study**, you and your parent/guardian must agree for you to participate voluntarily after getting all the necessary information. You will give your permission to participate in the study in writing (undergo written assent procedures). You will sign two copies of this form, and will be given a copy to take with you if you wish. One copy will remain with the study staff. If you do not wish to take a copy with you, we will give you a piece of paper with information on whom to contact if you have questions about the study or your rights as a participant.

To be a participant, you must also agree to provide information on where/how you can be reached by the study staff, if needed.

Why have I been invited to take part? You have been invited to take part because you are a young girl between the ages of 15-17 living in Homa Bay County where the study is taking place.

What will happen if I take part? If you agree to take part in the study today, the following things will happen:

1. You will be asked to agree to HIV counseling and rapid testing using a little blood from your finger or saliva.

   You can choose any of the following testing approaches:

   a) Oral fluid HIV self-testing (OHIVST) at your convenience, where you carry out the test yourself using fluid from your mouth OR
   b) Staff-aided testing, where rapid testing using a little blood from your finger will be carried out either at home or at a mobile health event OR
   c) You go to a health facility where rapid testing using a little blood from your finger will be done by a health provider (standard health facility based testing)

   You will be contacted in 2 weeks via SMS regardless of your testing choice. You will be asked to answer a few questions about your HIV test experience for which you will receive KSh 100 for your airtime and for time you will take to respond to the SMS.

2. Study staff will ask you a few questions about yourself, your behaviors, and your knowledge of health promotion services and HIV prevention services using a questionnaire on a small hand-held computer called a tablet. This interview will be held in private where others cannot hear what you say and will take about 15 minutes.

3. We will collect information of how we can locate/contact you in case we need to follow-up with you during the study (we will not reveal your identity to anyone outside the study).

4. If you choose staff-aided HTS, you may choose to allow your parent or guardian to stay for your HIV test result. Once you receive the results of the HIV test, you will be told what additional services you may require and you will be offered appropriate referral. If your test result is positive, you must name a parent or guardian to whom you will share your result in order to be able to receive treatment for HIV.

If the HIV test is positive: If the oral fluid self-test, or staff-aided screening test, or facility-based screening test is **positive**, another test must be done to confirm the results. If one result is negative and one is positive, we will refer you to a health facility of your choice for HIV re-testing. If two HIV test results are positive, we will refer you to a local HIV care facility of your choice. We will also take blood (up to 4 mL, less than 1

teaspoon) to see how strong the body's defense system is (test your CD4 count) and how much of the virus is in your blood (HIV viral load level).

If the test is positive and you are also pregnant, we will refer you to a health facility of your choice where you can get care for both the pregnancy and HIV and help prevent the unborn baby from getting HIV.

All HIV infected girls will be invited to participate in a follow up for 12 months. We want to know what is the best way to support you in making sure that you receive the care you need. If you are positive and agree we will provide referral to a health care facility or referral plus SMS message to go for services, and after 2 weeks we will check with you and with the clinic to see if you were able to get services. Among those who will not have gone to the clinic, they will be randomized (have a 50/50 chance) to receive either SMS text reminder to attend the clinic, or provided transport reimbursement. This is to help us understand the best approach to link young girls to HIV care. If you have linked to HIV care, we will send you SMS every three months to find out how you are doing and if you are keeping your appointments. We will confirm your self-report of clinic attendance by reviewing your medical records at the health facility. At 12 months, you will be contacted and invited to have blood taken for a repeat viral load test. At this time, all HIV positive girls will be invited to participate in an exit interview looking at what makes it easy or hard to go for HIV care among young girls.

If the HIV test is negative: If you test HIV negative, you may be asked if you would be willing to provide your phone number. A randomly selected number of girls (≈185) will receive an SMS at 6 and 12 months with a health promotion message and asked to answer a few questions on their behaviors, condom use, and willingness to retest for HIV. At 12 months, they will be retested for HIV. and also complete an exit interview on what makes it easy or hard to access HIV prevention services.

If you select OHIVST: If you choose this approach, you will be counseled/explained to on how to use the self-test and some paper with explanation and pictures on how to do the test given to you. Once you complete the test, you will be asked to take a picture of the result with a study camera (non-identifiable barcode (unique lines) will be placed on each kit and camera so as to confirm that the kit and camera links with your study number). You will be given a number that you can contact once you complete the self-test. You will be sent a few questions about your testing experience via SMS within 2 weeks and will receive KSh 100 for your airtime and for time you will take to respond to the SMS. Also, by sending a message or calling the number listed, study staff will arrange for collection of the camera and used self-test kit. At the time of kit and camera collection, study staff will conduct a brief interview on your experience with self-testing. (Note, you should not discard the test kit or camera, they will be collected by study staff).

For those who have a positive or indeterminate test result with the self-test, and a randomly selected proportion of those who report testing negative, study staff will connect with you at a convenient location to help you get the confirmatory test. This may be at home, somewhere in the community, or at a health facility where you would be comfortable.

Risks

What are the risks of participating in the study? You may feel uncomfortable discussing your behaviors. Taking a finger stick blood sample for HIV testing may cause a little pain and poses minimal risk of infection, however we will use sterile equipment. We will ensure that infection control procedures are followed.

HIV Testing Services: You may become worried, anxious, or upset by learning the result of your HIV test is positive. You will be counseled and referred for care and support.

Social Harms: It is possible that your involvement in the study could lead to stigmatization, discrimination, disruption to social support network, and abuse (physical/verbal). We will monitor these and will protect confidentiality to reduce potential social harms. We will also provide you with information on where you can get support services. In addition, you can call the Study Coordinator on the number provided at the end of this form to report any harm you may experience.

Benefits

What are the benefits of participating in the study?

The direct benefits to you for participating in the study are that you will know your HIV status and this will help you in making decisions on how to remain negative or live positively, depending on the results. You will also have access to HIV prevention services and health services that have been shown to help reduce HIV risks. You may learn a few things from the discussion that could help you protect yourself or others against HIV and other sexually transmitted infections. Also, the results of this study may contribute to the implementation of future intervention programs to reduce the risk of HIV in female adolescents and youth.

Anyone found to be HIV positive will be linked with community support groups as well as life-saving care and treatment services for themselves. Those found pregnant will be supported to access prevention of mother-to-child transmission (PMTCT) services. Information regarding how to prevent infection or transmission of HIV to and from their sexual partners will also be offered.

Confidentiality

Will my participation in the study be kept confidential? We will take all steps necessary to ensure your privacy and confidentiality. Given that it is a mobile event/ home visit/ clinic visit, your attendance at any of these places may be known to other people. However, we will request all participants/ members of the homestead to keep information that they observe about others during the visit confidential and not to share it with anyone. The services will be offered in a place where other people cannot see you or hear what you say.

You will be assigned a unique number and your name will not appear on any information like your responses on the computer or services accessed. Safeguards for protecting confidentially of questionnaires and other data will be strictly enforced. All data will be kept in a secure location at the Kenyatta National Hospital and Impact Research and Development Organization and destroyed at the end of the study. Each participant will be asked to respect the participation of others and the confidentiality of others they see. This point will be stressed throughout.

Your study records (not your name) may be reviewed only by approved study staff and representatives of:

- Yale University
- Kenyatta National Hospital
- Impact Research and Development Organization
- Yale University Human Investigation Committee

- Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC)
- National Institutes of Health USA
- Office for Human Research Protections (OHRP)
- Division of AIDS (DAIDS)
- Ministry of Health Kenya
- Other local, US, and international regulatory entities

Voluntariness

What are my rights as a research participant/subject? Your participation in this study is completely voluntary. Significant new findings developed during the course of the research which may affect your willingness to continue participation will be provided to you. If you decide not to participate, you will not lose any existing benefits you may receive from **Impact Research and Development Organization or health facility**. If you decide to take part, you are free to refrain from answering any questions and you may end your participation at any time without penalty or loss of existing benefits to which you are entitled.

Involuntary Early Termination of Participation:
The field site investigators may withdraw a participant before their scheduled termination visit to protect their safety. Participants may be withdrawn from the study if the study sponsors, government or regulatory authorities, ethical/institutional review boards stop the study before its planned end date.

Voluntary Early Withdrawal:
If someone voluntarily withdraws from the study, a few brief questions will be asked. We will offer HIV testing for those initially negative, and if HIV positive we will collect a small amount of blood sample to test how much of the virus is in your blood and refer you for services.

Additional Information

What will I receive for participating? You will not be paid for your participation in the study. However, you will receive KSh 100 for your airtime and time taken in completing the SMS questions about your satisfaction with your HIV test experience.

HIV-negative group: If you are HIV negative and selected to complete SMS questions at 6 and 12 months, you will receive KSh 100 for your airtime and time you will take to respond to the SMS. At 12 months, you will receive KSh 400 transport reimbursement when you retest for HIV and complete an exit interview about what made it easy or hard to access prevention services.

HIV-positive group: You will receive KSh 100 for your airtime and time you will take completing SMS surveys. For participating in the exit interview about what made it easy or hard to access care, you will be compensated a total of KSh 400 for your time and travel. A randomly selected number of HIV positive youth will receive KSh 400 for transport to go for HIV care services.

Will it cost me anything to participate? No, it will not cost you anything to participate.

Please note that the U.S. National Institutes of Health (NIH) that is funding this study does not have a mechanism to provide direct compensation for research related injury.

A description of this clinical trial will be available on www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen to the results of the research study? The results of the study will be discussed and presented in a report at team meetings or as a publication. The information may be presented at a conference with other studies that relate to youth health promotion, sexual health and HIV prevention and treatment. Neither the report nor the presentation will show your name.

Who has reviewed the study for ethical issues? This study has been reviewed and approved by the Institutional Review Boards at both the **Kenyatta National Hospital/University of Nairobi (KNH/UON) and Yale University**.

What if I need more information? For any information about the study, you may contact the Study Coordinator, **Mr. Samwel Rao on 0713-687-399** at any time.

What if there is a problem? Any complaint about the way you have been treated during the study or any possible harm you might suffer will be addressed. **Please contact the Principal Investigator of the study, Dr. Irene Inwani from the Kenyatta National Hospital on 0202-726-300 or Professor Chindia, Secretary to the KNH/UON Ethics and Research Committee on 0202-726-300.**

At this time, I want to make sure you understand the study and see whether you have any additional questions. After we discuss any questions you may have, we can discuss whether you are interested in participating in the study today.

Are you willing to participate in the overall study (which includes HIV testing)? (Select one)

No ☐ **(if no, stop here)**

Yes ☐ **(if yes, continue below)**

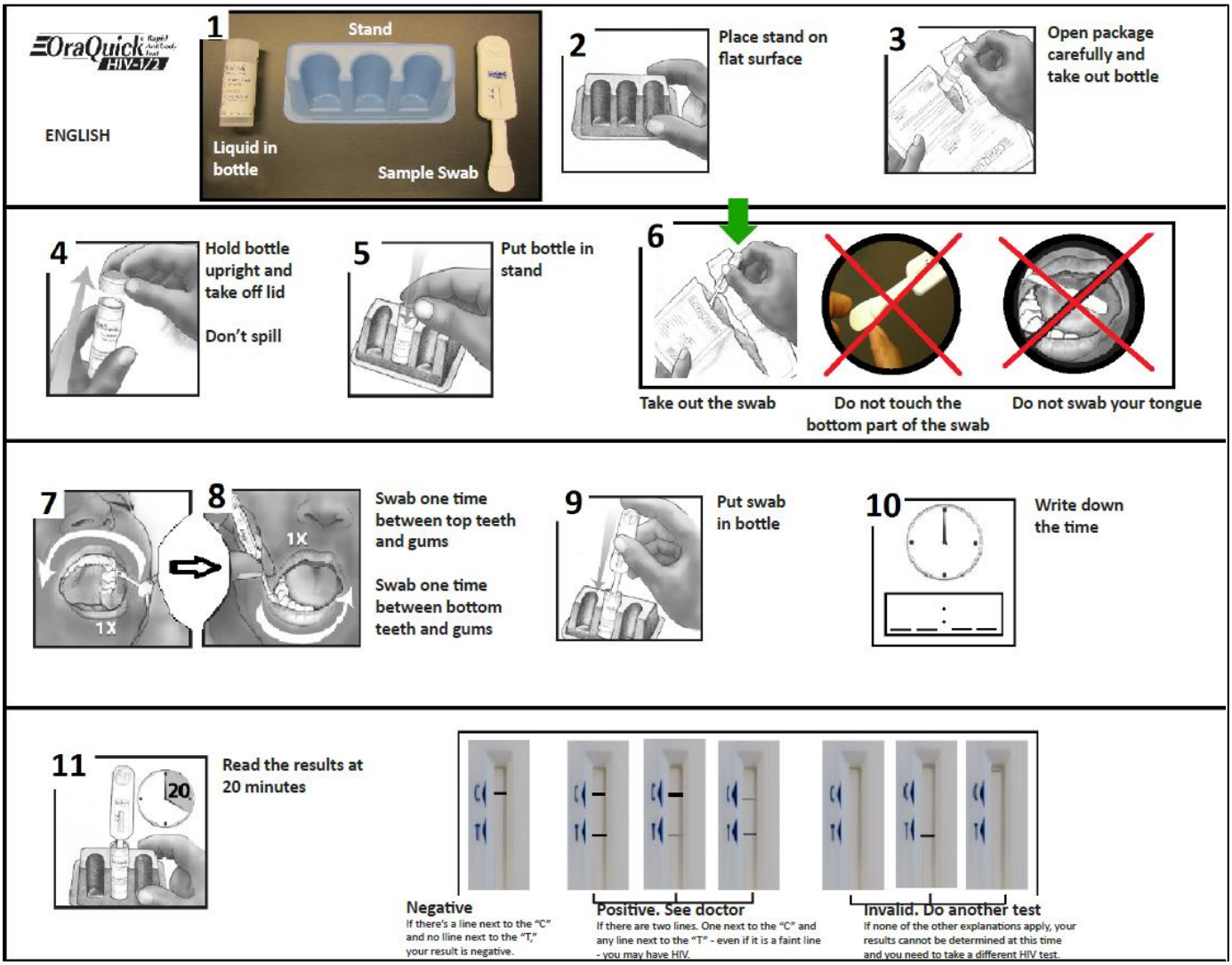
SIGNATURE PAGE
GIRLS Study Information and Informed Assent

Participant: If you have read this assent form (or had it read and explained to you), all of your questions have been answered and you agree to take part in this study, please sign this form or make your mark to indicate your willingness to participate.

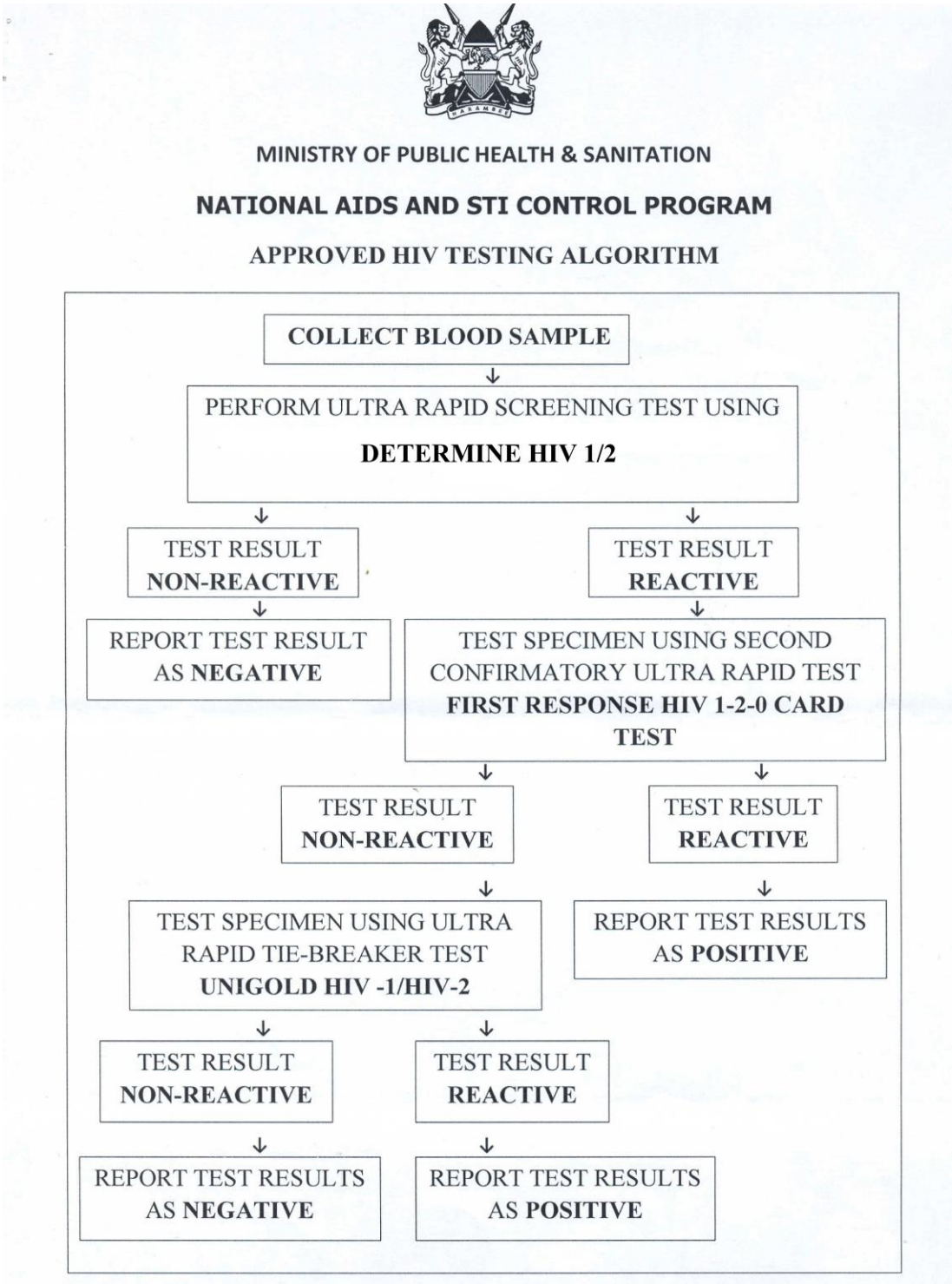
Study staff who conducted informed assent discussion: I confirm that I have personally explained the nature and extent of the planned research, study procedures, potential risks and benefits, and confidentiality of personal information.

Participant's name (print)	**Participant's signature/thumbprint and date**
Study staff conducting consent discussion (print)	**Study staff signature and date**
Witness's name (print) (if appropriate)	**Witness's signature and date (if appropriate)**

Appendix F: Oral HIV Self-testing Instruction Sheet



Appendix G: NASCOP HIV Testing Algorithm



*Updated 13th August 2015

MINISTRY OF HEALTH

OFFICE OF THE DIRECTOR OF MEDICAL SERVICES

Telegrams: "MINHEALTH". Nairobi
Telephone: Nairobi 2713395
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Ref. No. MOH/ADM/1/1/17

13th August, 2015

All CECs of Health
All County Chief Officers of Health
All County Health Directors
All CASCOS
All HIV Implementing Partners
All HIV Program Managers
All Medical Superintendents/Facility-in-Charges

RE: CHANGE IN HIV TESTING ALGORITHM

HIV Testing Services (HTS) is an essential gateway into HIV care and treatment programs and plays an important role in HIV prevention counselling to reduce HIV transmission risk among both HIV-infected and HIV-uninfected persons. The current Kenya AIDS Strategic Framework (KASF) stipulates ambitious targets for the Country for HIV prevention and control with HTC being a key entry point. Such targets include the attainment of 90-90-90 targets, the elimination of mother to child transmission of HIV, HIV prevention in health care setting and HIV control among key and vulnerable populations.

The Ministry of Health through the National AIDS &STI Control Program (NASCOP) remains committed to continually ensure that quality HIV Testing Services are available, when required, throughout the Country. HIV Testing algorithm determination is based on thorough country evaluations of test kits that have been pre-qualified by World Health Organization (WHO). The current national algorithm: Colloidal Gold **(KHB)®** as the first test, **First Response®** as the second test and **Unigold®** as the tie-breaker was rolled out in 2013. Recent communication from WHO indicates that KHB has been **delisted®** from the list of Prequalified HIV Rapid Test Kits (RTKs) because the manufacturer is making a number of major changes in the production of the product. WHO has however not documented any issues related to quality, safety or performance for KHB manufactured and distributed to date. In accordance with the WHO procedure for change notification, this makes it a new product that will require a new WHO prequalification assessment once all of these changes have been implemented.

Consequently the Ministry of Health recommends the following:

- Since there are no documented issues related to quality, safety or performance of the already manufactured and distributed KHB, the current stock of KHB will continue being used until stocks are exhausted.

- KHB will subsequently not be part of the country's HIV testing algorithm but may be re-considered in future for inclusion if re-listed by the WHO.

- Once KHB stocks are exhausted, the recommended interim national HTS algorithm will be **Determined® as the first test, First Response® as the second test and Unigold® as the tie-breaker**.

- Counties will carry out a rapid assessment of existing KHB stocks at facility level so that internal redistribution is done to ensure that all KHB stocks are utilized.

The Ministry of Health is working with stakeholders to ensure that HIV testing services are not interrupted during the changeover and through the procurement and supply of **Determine®**. We would also like to confirm Ministry's commitment to continued high quality HIV testing services; which includes regular evaluation of rapid tests kits in line with WHO guidance.

We request for your full support and commitment as we go through this transition period.

Dr. Nicholas Muraguri
DIRECTOR OF MEDICAL SERVICES

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