Impact of a Novel HIV-1 RNA Testing Intervention to Detect Acute and Prevalent HIV Infection and Reduce HIV Transmission — Tambua Mapema Plus

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SIGNATURE PAGE

We the principal investigators agree to conduct the study in accordance with the Institutional Review Board (IRB)-approved, current protocol and will not make changes to the protocol without permission of DAIDS, except when necessary to protect the safety, rights, or welfare of study participants.

We agree to personally conduct or supervise this study.

We will ensure that the requirements set out in 45 CFR 46 and ICH/GCP relating to obtaining informed consent and ethics committee or IRB review and approval are met.

We agree to report to the sponsor adverse experiences that occur during the course of this study.

We agree to maintain adequate and accurate study records and to make those records available for inspection by DAIDS, DAIDS' authorized representatives, and/or other applicable regulatory entities.

We will ensure that the Universities of Washington, and Oxford and KEMRI ethical review committees (ERC), in compliance with the requirements of 45 CFR Part 46, will complete continuing review and approval of the study. We also agree to promptly report to the ERCs all changes to the study and all unanticipated problems involving risks to human subjects or others. Additionally, we will not make any changes to the study without DAIDS and EC/IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

We agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Protocol Chair: Susan M. Graham, Associate Professor, University of Washington

Signed: _____ Date: _____

Protocol Co-Chair: Eduard J. Sanders, Associate Professor, University of Oxford

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4. LIST OF ABBREVIATIONS

AHI	acute HIV infection
AIDS	acquired immunodeficiency syndrome
aPS	assisted partner notification services
ART	antiretroviral therapy
CAPI	computer-assisted personal interview
CASI	computer-assisted self-interview
CEA	cost effectiveness analysis
CI	confidence interval
CRF	case report form
DALY	disability-adjusted life-year
FSW	female sex worker
GUD	genital ulcer disease
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IAVI	International AIDS Vaccine Initiative
ICER	incremental cost-effectiveness ratio
ICD	informed consent document
ID number	identification number
IPV	intimate partner violence
KCR	Kilifi community representatives
KEMRI/WTRP	Kenya Medical Research Institute/Wellcome Trust Research Programme
MoH	Ministry of Health
MSM	men who have sex with men
NASCOP	National AIDS & STI Control Programme
PEP	post-exposure (antiretroviral) prophylaxis
PITC	provider-initiated testing and counselling
POC	point-of-care
PrEP	pre-exposure (antiretroviral) prophylaxis
PTID	participant ID
REDCap	Research Electronic Data Capture
RR	relative risk
sSA	sub-Saharan Africa
STI/STD	sexually transmitted infection/sexually transmitted disease
TasP	treatment as prevention
TDR	transmitted drug resistance
WHO	World Health Organization

5. PROTOCOL SUMMARY

Full Title: Impact of a novel HIV-1 RNA testing intervention to detect acute and prevalent HIV infection and reduce HIV transmission

Short Title: Tambua Mapema Plus

Study Purpose: This is a proof-of-concept study comparing outcomes of a health facility-based acute HIV infection (AHI) and prevalent HIV testing intervention using point of care HIV-1 RNA detection, combined with assisted partner services (aPS) and follow-up in an antiretroviral therapy (ART) cohort for all newly diagnosed individuals and follow-up in a pre-exposure prophylaxis (PrEP) cohort for the uninfected partners of newly diagnosed individuals, compared to standard care.

Study Design: Randomized stepped-wedge study with prospective cohort follow-up of all individuals newly diagnosed with acute or prevalent HIV infection and of up to 300 identified partners of these persons. Individuals enrolled in the observation phase will be compared to those enrolled in the intervention phase at each facility, after undergoing the following procedures in each phase:

Observation Period	*Intervention Period*
HIV testing per Kenyan guidelines and clinician judgment	HIV-1 RNA testing followed by rapid tests if RNA positive
CASI/CAPI	CASI/CAPI
6-week follow-up visit (only if HIV-infected)	6-week follow-up visit (only if HIV-infected)
aPS using standard HIV testing offered at the 6-week follow-up visit (only if HIV-infected and partners not already notified)	ART cohort enrollment and enhanced aPS using HIV-1 RNA testing both offered at diagnosis (only if HIV-infected)
Referral of partners to local services for risk reduction counseling, with HIV care if infected	ART cohort for infected partners; PrEP cohort for uninfected partners in ongoing relationships with an index case

Study Population: The study population will be recruited from among male and female adult patients who present for care at 6 public or private outpatient clinics in coastal Kenya. Eligibility criteria for the HIV-1 RNA testing intervention include: 1) age from 18-39 years; 2) not previously diagnosed with HIV infection; and 3) a score ≥2 on our AHI risk score algorithm.

	Eligibility criteria for partners of newly diagnosed cases with acute or prevalent HIV infection include: 1) age over 18 years; and 2) not previously diagnosed with HIV infection.
Sample Size:	3,175 study participants total, including 2,875 participants in the stepped-wedge study (1,375 in the observation period and 1,500 in the intervention period). We estimate that approximately 2% of participants in the observation period (n=28) and approximately 5% of participants in the intervention period (n=75) will test positive for HIV infection and continue in the study. We estimate that up to 300 partners of newly diagnosed individuals will be offered enrollment and tested for HIV using standard tests (observation period) or HIV-1 RNA testing (intervention period).
Participating Sites:	KEMRI-Wellcome Trust Programme, Kilifi, Kenya (DAIDS-ES ID # 38181), with stepped wedge trial implementation at 6 community health facilities (2-4 public, 2-4 private) and ART and PrEP cohort follow-up at the nearest of our two KEMRI Research Clinics, located in Mtwapa and Kilifi, Kenya
Schedule of Procedures:	Individuals eligible for the HIV-1 RNA testing intervention will be offered enrollment when they seek care at one of the study facilities, with testing taking place on that same day. For individuals with negative test results for both acute and prevalent HIV infection, no further follow-up will occur. One 6-week follow-up visit will occur after testing for all individuals who are newly diagnosed with HIV. Procedures for the aPS intervention, the ART cohort, and the PrEP cohort are detailed in this protocol.
Study Duration:	Study enrollment will occur over 24 months. Following enrollment and study procedures (1-2 hours of time), all participants who test negative for HIV infection will have no further visits. All participants newly diagnosed with HIV will have a 6-week follow-up visit. All participants who enroll in the ART or PrEP cohort will be followed for a total of 12 months.
Intervention:	Testing for acute and prevalent HIV infection, followed by partner notification services and immediate ART (provided by the Kenya Kenyan National AIDS and STD Control Program [NASCOP]) for newly diagnosed individuals and PrEP (provided by Gilead) for uninfected partners in serodiscordant relationships.
Objectives:	<u>Primary Objective</u>: • ***HIV-1 RNA testing intervention:*** To conduct a proof-of-concept study to determine outcomes of a health facility-based HIV-1 RNA testing intervention to identify acute (i.e., RNA-positive, seronegative or discordant rapid test results) and prevalent (i.e., RNA-positive, seropositive) HIV infection, compared to standard care.

Secondary Objectives:

- ***Linkage to care:*** To determine the feasibility, acceptability, and uptake of offering immediate linkage and treatment to all newly diagnosed HIV-infected patients in the intervention period, comparing this approach to standard care.
- ***Partner testing:*** To determine the feasibility, acceptability, and uptake of aPS for partner identification and testing, comparing enhanced aPS with HIV-1 RNA testing in the intervention period to passive referral followed by delayed aPS with standard HIV testing in the observation period.
- ***Impact and cost-effectiveness:*** To model the potential impact of the HIV-1 RNA testing, linkage, immediate treatment, and aPS interventions on the Kenyan HIV epidemic, in terms of incremental costs per HIV infection averted, death averted, and disability-adjusted life-year (DALY) averted, using data on standard care outcomes from the observation period and data on intervention outcomes from the intervention period.

Exploratory Objectives:

- ***Barriers and facilitators:*** To conduct qualitative in-depth interviews with up to 60 newly diagnosed prevalent and AHI patients and seronegative partners in discordant relationships to gain insights into intervention uptake, including barriers and facilitators to ART or PrEP uptake and adherence in these groups.
- ***Staff views:*** To conduct interviews or focus groups with up to 60 individuals who work in the 6 health facilities where the trial will take place (up to 10 participants per facility), to obtain their views on HIV-1 RNA testing and the research carried out at the facility, including challenges to intervention scale-up.

Endpoints:

Primary Endpoints:

HIV-1 RNA testing intervention: Proportion of participants with the following outcomes in the observation and intervention periods:

- tested for HIV infection;
- newly diagnosed with prevalent HIV; and
- newly diagnosed with AHI (0 in the observation period).

Secondary Endpoints:

Linkage to care: Proportion of newly diagnosed patients with the following outcomes in the observation and intervention periods:

- successfully linked to care by week 6; and
- initiating ART by week 6 following HIV diagnosis.

For ART cohort participants (intervention period only) we will also assess:

- proportion initiating ART by month 3 following HIV diagnosis;
- proportion with viral suppression (<1,000 copies/mL) by month 6 and month 12 following ART initiation.

Partner testing: For newly diagnosed individuals with acute or prevalent HIV, we will also compare the following week 6 outcomes between the observation and intervention periods:

- number of partners reported;
- number of partners successfully contacted;
- number of partners tested;
- number of partners newly diagnosed with prevalent HIV infection;
- number of partners newly diagnosed with AHI (0 in the observation period);
- number of HIV-infected partners newly engaged in care; and
- number of HIV-uninfected partners initiating PrEP.

For PrEP cohort participants (intervention period only) we will also assess:

- proportion initiating PrEP by month 3 following cohort enrollment;
- proportion with adherence >80%, measured by self-report or MEMS® cap at months 3 and 6 following PrEP initiation.

Impact and cost-effectiveness: Model outputs will include the following:

- HIV infections averted
- Deaths averted
- Disability-adjusted life-years (DALY) averted
- Costs per HIV infections averted
- Costs per death averted
- Costs per DALY averted

Impact and cost-effectiveness will be evaluated by comparing these outputs for standard care (observation period) to these outputs for the HIV-1 RNA testing intervention (intervention period).

Barriers and facilitators: Qualitative results will present barriers and facilitators to the following components:

- HIV testing uptake
- aPS uptake
- ART uptake
- ART adherence
- PrEP uptake
- PrEP adherence

Staff views: Qualitative results will present staff views on the detection of AHI and the research carried out at the HIV-1 RNA testing intervention facilities, including challenges to intervention scale-up.

6. INTRODUCTION

6.1. Background Information

Most Individuals Who Acquire HIV-1 Infection in East Africa Have Symptoms and Many Seek Care. While some patients with acute HIV infection (AHI) remain asymptomatic, most experience an acute illness approximately 2 weeks following infection, and the majority of these patients seek urgent care [1-5]. Common symptoms of AHI include fever, joint and muscle pains, headache, fatigue, and rash, while a minority of patients have a mononucleosis-like illness with fever, sore throat, and oral ulcers [6]. In coastal Kenya, 81% of female sex workers (FSW) participating in a prospective cohort experienced symptoms with seroconversion and 44% were sick enough to prevent them from working [7]. The majority (69%) of HIV-1-seroconverters identified in a more recent cohort study in coastal Kenya sought care for symptoms prior to seroconversion, and 40% were incorrectly assumed to have malaria [3]. Unfortunately, most individuals who seek care in the setting of HIV-1 acquisition have not yet developed antibodies and are missed with provider-initiated testing and counselling (PITC) [8, 9].

Phylogenetic reconstruction of HIV-1 transmission networks in North America and Europe show that people with newly acquired HIV-1 are concentrated in specific populations and geographic areas [10, 11], and that transmission is often clustered both in heterosexual populations and in key populations such as men who have sex with men (MSM) [12, 13]. Although similar studies are not feasible in most African settings, a modelling study using data from Malawi estimated that 38.4% (95% credible interval, 18.6%-52.3%) of HIV transmissions were attributable to sexual contact with individuals with early infection [14]. Prompt diagnosis of acute and early HIV-1 infections, with risk reduction counselling and immediate provision of ART, could lead to important reductions in HIV-1 transmission, both for the general population and within key population groups.

Identifying Young Adults with Acute or Prevalent HIV-1 is a Key Opportunity to Interrupt Ongoing Transmission. Due to very high viral loads and characteristics of the infecting viral strain, AHI is a period of heightened risk for secondary HIV-1 transmission [15-18]. The proportion of transmission attributed to AHI varies with epidemic stage and other local factors, but has been estimated to range from 25% to 50% in studies using viral sequences. Unfortunately, no current HIV-1 prevention guidelines in sub-Saharan Africa (sSA) recommend evaluation for AHI among young adult patients seeking care who test negative on rapid HIV-1 antibody tests [19].

Kenya has the 4th largest HIV epidemic in the world, with approximately 1.4 million persons living with HIV infection [20]. In the 2012 AIDS Indicator Survey, Kenya had an adult HIV prevalence of 5.6%, and most (53.1%) seropositive individuals were unaware of their status, presenting a major challenge for epidemic control [21, 22]. Efforts to reach a greater proportion of undiagnosed individuals will be critical for attaining the 90-90-90 UNAIDS targets — that by 2020, 90% of all people living with HIV should know their HIV status, 90% of those who test positive should be provided therapy, and of those, 90% should achieve virologic suppression [23].

In a pilot study entitled "Tambua Mapema" (Kiswahili for "discover early"), we have shown that rapid ELISA testing combined with p24 testing can identify ≥90% of AHI and prevalent HIV cases who present for care in an African clinical setting [8]. Now that point of care (POC) RNA diagnostics designed for AHI detection are becoming available, real-time AHI diagnosis before the patient leaves the clinic is within reach [24, 25]. Guidance on the value of HIV-1 RNA or p24 antigen testing programs among adult patients seeking care for symptoms, and their

potential impact on the African HIV epidemic, is therefore needed. We have recently shown that targeted testing of adults at risk for AHI using a simple algorithm based on seven features (age 18-29 years, fever, fatigue, diarrhea, body pains, sore throat, and genital ulcer disease [GUD]) would substantially reduce the number of symptomatic HIV-1-seronegative patients requiring HIV-1 RNA or p24 antigen testing [26]. For this proposal, we will use this consensus risk score to identify at-risk young adults aged 18-39 years and test them for both acute and prevalent HIV infection using a POC HIV-1 RNA test. We will then offer to link all newly diagnosed individuals to care, to start ART immediately and to provide aPS using our HIV-1 RNA testing intervention so that the sexual partners of newly diagnosed individuals can be tested for acute and prevalent HIV infection as well.

Assisted Partner Notification Has Been Successful in sSA, But Has Not Been Attempted for Index Cases with AHI. Partner notification strategies have long been a fundamental component of STI prevention [27]. Standard care in most African settings involves passive referral, in which the person diagnosed (i.e., the index case) is encouraged to disclose results to sex partners without direct involvement of a healthcare provider. An alternative is aPS, in which the index case is allowed a short period in which to contact and refer partners, after which the provider notifies partners (i.e., contract referral); or the provider contacts sex partners directly, without a waiting period (i.e., provider referral). For both strategies, providers obtain consent to interview index patients about sexual partners and then locate partners to inform them about the exposure without revealing index case identity. The primary goals of aPS are to ensure that reported partners are notified, tested and successfully referred for care. Importantly, aPS can link HIV-infected partners to potentially life-saving treatment and prevent future transmission; in addition, aPS can identify seronegative individuals in discordant relationships, who might benefit from pre-exposure prophylaxis (PrEP).

Modelling and Cost-Effectiveness Analysis (CEA) Are Key Methodologies to Evaluate New Intervention Strategies. Funders including the National Institutes of Health, World Health Organization, and Gates Foundation have stressed the importance of CEA and modelling in recent years. CEA assesses the relative value of healthcare interventions and produces results that help policy makers make resource allocation decisions. Several recent publications in PLoS Medicine stressed the importance of modelling studies to support evidence-based decision-making about Treatment as Prevention (TasP) [28]. Network models are particularly well suited to addressing prevention questions in settings with complex relational dynamics such as those found in coastal Kenya and other urban or peri-urban centers in Africa [29]. Important questions of how to deliver services to maximize the impact of an intervention on HIV-1 transmission can be addressed through modelling, including how to increase coverage of HIV testing, when and where to conduct HIV testing, and how to link patients to care [28, 30].

6.2. Rationale

Detection and management of AHI has been called a "clinical and public health emergency" [18] and a "common occurrence overlooked" [31]. Because the cost of HIV-1 RNA testing is considerable, there is growing consensus that detection of AHI in resource-limited countries should be guided by algorithms that identify at-risk individuals [32]. While AHI cases have been identified by several research programs in sSA, an evidence-based programmatic approach to targeting testing for young, seronegative adult patients for AHI is lacking. Our novel pilot study (Clinicaltrials.gov, NCT01876199) demonstrating that AHI can be detected in ~1% of young adult patients seeking care forms the basis for this proposal [33]. Our newly developed consensus risk score algorithm will guide targeted AHI evaluation in

patients seeking care for symptoms [26, 33]. We will use a modified stepped wedge design to scale up our HIV-1 RNA testing intervention in a 'proof of concept' study, using the newly available *Xpert® HIV Qual* commercial assay (which has a lower limit of detection of 278 copies/mL in whole blood) to detect AHI in real time, offer to link patients to care immediately, and offer ART from the day of diagnosis. In addition, we will use aPS to maximize the impact of each new HIV infection diagnosed and linked to care, with standard HIV testing for partners of patients diagnosed in the observation period and the HIV-1 RNA testing intervention for partners of patients diagnosed in the intervention period. As in an ongoing demonstration study in Kenya [34], uninfected partners of all newly diagnosed patients will be provided with PrEP, if accepted, until viral suppression by ART in the index patient. This innovative intervention has the potential to greatly reduce ongoing transmission by making HIV-infected individuals aware of their status and linking them to care without delay, while at the same time identifying HIV-negative persons in discordant couples who would benefit from prevention interventions. If our novel intervention proves cost-effective and promising in terms of reducing HIV-1 transmission, we will use this data to design further research focusing on implementation of the intervention, including barriers and facilitators to its success.

6.3. Study Hypotheses

- Testing for prevalent and acute HIV infection (i.e. our HIV-1 RNA testing intervention) will increase rates of case-finding and linkage to care relative to standard PITC.
- aPS will identify additional cases of previously undiagnosed HIV infection, including small outbreaks in local sexual networks, with enhanced aPS using HIV-1 RNA testing identifying more infected partners than standard aPS using standard HIV rapid tests.
- Identification of previously undiagnosed acute and prevalent HIV infections will lead to a significant reduction in new HIV infections in Kenya and will be cost-effective under a range of assumptions.

6.4. Preliminary Studies

The proposed study builds on more than two decades of research conducted by the University of Washington (UW) in Kenya, and 10 years of collaborative research by the UW, the University of Oxford (UO) and the Kenya Medical Research Institute-Wellcome Trust Research Programme (KEMRI-WTRP), led by Drs. Graham and Sanders. Our collaborative research on the Kenyan coast has focused on identifying patients with AHI and ensuring access to care for key populations. In this section, we present our relevant work, along with data from aPS research by Dr. Farquhar; examples of work by Dr. Goodreau on a dynamic, network-based HIV-1 transmission models; and Dr. Babigumira's work using modeling methods to evaluate the cost and cost-effectiveness of healthcare services in general and HIV programs in particular in East Africa.

6.4.1. Care-seeking Prior to Seroconversion

Surprisingly, and until recently, evidence on the characteristics and care-seeking behavior of adults who acquire HIV-1 in sSA has been sparse. Our group conducted the first study of healthcare seeking prior to seroconversion among 72 participants who acquired HIV-1 while participating in a prospective cohort in coastal Kenya. Three quarters of these patients reported fever and 50 (69%) sought care for symptomatic illness, including 23 (32%) who sought care in a non-research setting. Twenty-nine (40%) patients received presumptive malaria treatment [3]. Healthcare seeking did not differ between men and women [3]. This

study demonstrated that AHI is frequently accompanied both by symptoms and by care-seeking, and is frequently misdiagnosed as "malaria."

6.4.2. Targeted Testing for AHI

The utility of developing a clinical algorithm to predict AHI was first reported in resource-rich settings [35], and only recently became a focus of attention in resource-limited areas [18]. In Malawi, the University of North Carolina-Malawi risk score (UMRSS) combining discrete clinical and behavioral characteristics was developed to identify AHI among STI clinic patients [36]. In this study, patients who were HIV-1 negative or had discordant rapid tests (i.e., one rapid test negative, one positive) received a score of 1 for fever, body ache, or multiple partners; 2 for diarrhea or GUD; and 4 for discordant rapid tests. Using this algorithm, Powers et al. could detect 95% of AHI cases identified in the entire sample by testing only patients with a score ≥2 (40% of the study population) [36]. We evaluated the UMRSS for detection of AHI in our cohort of Kenyan MSM with ~8% annual HIV-1 incidence. Three components (fever, diarrhea, and discordant rapid test results) were also independent predictors of AHI in our cohort. The predictive ability (i.e., area under receiver operating characteristics curve, AUC) of the UMRSS was 0.79. A cohort-derived risk score consisting of six characteristics (fever, diarrhea, discordant rapid tests, fatigue, age <30 years, and symptomatic STI) had a higher AUC of 0.85 [37]. This risk score was used in our recent study of targeted p24 antigen testing described below.

Because guidance exists for persons with discordant rapid test results (i.e., repeat testing is recommended after 2 weeks) [38], we aimed to evaluate the value of demographic factors, signs, and symptoms to detect AHI in patients with negative serologic test results, using data from four sites in Kenya, Malawi and South Africa [26]. In this study, AHI was defined as detectable plasma viral load or p24 antigen in an HIV-1-seronegative patient who subsequently seroconverted. We compared 122 AHI visits to 45,961 uninfected patient-visits. Using GEE, we identified predictors of AHI visits in a model including signs and symptoms, age group, sex, and site. Younger age (18-29 years) and reported fever, fatigue, body pains, diarrhea, sore throat, and GUD were independent predictors. We assigned a model-based score to each predictor, and calculated a risk score for each participant. GUD received a score of 3; all other predictors received a score of 1. We evaluated performance (i.e., AUC) of this algorithm, comparing its performance overall to its performance at each study site. The AUC for this algorithm overall was 0.78, with site-specific AUCs ranging from 0.61 to 0.89. A risk score ≥2 using our pooled-data algorithm would indicate HIV-1 RNA testing for 15%, 26%, 50%, and 5% of risk populations in Mombasa, Kilifi, Lilongwe, and Durban, respectively. Sensitivity was highest for this algorithm in Kilifi and Lilongwe (90.0% in Kilifi, 92.9% in Lilongwe), where the pooled-data algorithm improved AHI detection over the published algorithms from these two sites [36, 37]. We will use this recently developed pooled-data algorithm in the study proposed in this application.

6.4.3.Detecting AHI and Prevalent HIV-1 in the Private and Public Sectors in Kenya

We hypothesized that targeted evaluation for AHI among young adults (<30 years of age) seeking health care at local health facilities for symptoms and behavior characteristics compatible with our cohort-derived risk score (discussed above) would result in an AHI detection rate of ~3%. We therefore proposed to test all patients who met our targeting criteria and had negative or discordant rapid test results, using a p24 antigen assay and repeat HIV-1 rapid ELISA testing 2 weeks after first presentation. Our pilot study (Clinicaltrials.gov, NCT01876199) was conducted from April–July 2013 at a network of 5

health facilities and 5 pharmacies selected from the 26 health facilities and 26 pharmacies located in the study area, Mtwapa/Shanzu town (total population ~100,000) [33]. This area, known for its busy night life, sex work, and tourist industry, has been the site of a KEMRI HIV/STI Research Clinic since 2005 [39]. In this study, 3,602 adults were evaluated for prevalent HIV-1 infection (prevalence: 3.9%). Patients with fever were more likely to have prevalent HIV-1 infection than those without fever (9.1% vs. 3.3%, p<0.001), and HIV prevalence in febrile patients was higher than that of the general population in Kenya (5.6% in 2012) [21]. Since we excluded known HIV-positive patients, this prevalence among undiagnosed individuals is noteworthy. AHI was diagnosed in 5 of 506 patients with negative or discordant rapid test results who met risk criteria and were completely evaluated, for an AHI prevalence of 1.0%. Of the 5 AHI cases, 4 were diagnosed among the 241 patients with a documented fever (prevalence 1.7%), vs. 1 among 265 non-febrile patients (prevalence 0.4%, p=0.1). Malaria was confirmed by PCR in 4 (1.7%) of the 241 febrile patients [33]. Ongoing qualitative work based on interviews with these individuals over several weeks' follow-up reveals challenges with accepting the diagnosis, understanding the value of immediate treatment, and incorporating an HIV diagnosis into daily life (van der Elst, in preparation); specific counseling may be required to optimize linkage and treatment outcomes for individuals with an AHI diagnosis.

In summary, this pilot study enabled us to test our novel approach to HIV testing for adults seeking health care, fine tune our intervention procedures, and set up a scalable intervention for use in Kenyan health facilities. We now propose to focus our HIV-1 RNA testing intervention on young adults 18-39 years of age, as the latest Kenya AIDS indicator survey shows a steady increase in HIV prevalence over this age range [40]. We will use our pooled-data consensus risk score algorithm (described above), as most likely to identify undiagnosed persons with AHI in a range of clinical settings.

6.4.4.Partner Notification in Kenya

In 2012, Dr. Farquhar was awarded an R01 grant (NIH/PEPFAR R01 A1099974) to investigate the effectiveness of aPS among newly diagnosed HIV-infected persons at 18 rural and urban Kenyan HIV voluntary counseling and testing (VCT) facilities, including an analysis of cost-effectiveness. The protocol for this trial has been published [41]. Enrollment began in August 2013 and was completed in August 2015. Results demonstrating that aPS in the Kenyan setting was both safe and effective were published in the Lancet HIV in 2016, and are summarized here [42]. Immediate aPS was compared to aPS deferred for 6 weeks, and primary outcomes were assessed at 6 weeks and 3 months from enrolment of the index case. Briefly, 1,119 index cases enrolled and mentioned 1,872 partners, for an average of 1.67 partners per index case. Overall HIV prevalence among the 1,292 (69.0%) partners enrolled was 48.0%. Immediate aPS increased HIV test rates four-fold (incidence rate ratio [IRR] 3.78, 95% confidence interval [CI] 3.08–4.65) and new HIV test rates over eleven-fold (IRR 11.50, 95% CI: 5.56–23.78). Immediate aPS also increased the number of partners testing positive and those enrolled in HIV care (IRR 3.22, 95% CI: 2.26–4.61, and 3.95, 95% CI: 2.48–6.28, respectively) [42]. Only two cases of intimate partner violence (IPV) possibly related to the study were reported, one in each arm. Both occurred before staff contacted any partners and well before the 6-week follow-up visit; it is plausible that knowledge of the pending aPS may have influenced the intervention arm participant. In December 2016, the WHO published new guidelines on HIV testing that include the recommendation to provide assisted partner notification; these guidelines can be found at:

http://www.who.int/hiv/pub/vct/hiv-self-testing-guidelines/en/. These guidelines were informed by the success of Dr. Farquhar's intervention.

Currently, Dr. Farquhar is collaborating with the Kenyan Ministry of Health to establish a nationwide monitoring system to evaluate why Kenyans are tested for HIV infection and define the contribution of aPS to HIV case-finding at the population level. The Kenyan Ministry of Health is scaling up aPS at HIV testing sites, under the leadership of Dr. Martin Sirengo (a co-investigator on this protocol) and with support from the PEPFAR program. Dr. Farquhar's experience and ongoing collaborative work with Dr. Sirengo and his colleagues at NASCOP provide a foundation upon which to build our novel HIV-1 RNA testing intervention, in which enhanced aPS (i.e., aPS using HIV-1 RNA testing) will be offered to individuals newly diagnosed with acute or prevalent HIV infection. Of note, 50% of the primary sex partners of AHI patients were contacted in our pilot study in 2013; we hope to increase this rate by collaborating with Dr. Farquhar and Dr. Sirengo to improve our partner notification training and procedures.

6.4.5.Collection of Sexual Behavior and Network Data Optimized for Modeling

Dr. Goodreau has extensive experience in the design of surveys for the collection of sexual network data [43, 44] and in the analysis of sexual behavioral data for the parameterization of epidemic models among a variety of populations, including MSM and heterosexuals in sSA [45-48]. Dr. Goodreau has collaborated with Dr. Sanders and integrated sexual history data from coastal Kenyan MSM to parameterize the one African case study in a combination prevention model published in a recent special issue of the *Lancet* on the future of HIV among MSM [49]. Dr. Goodreau's modeling expertise and the rest of the team's collective experience working in East Africa will ensure our ability to collect the sexual network data needed to parameterize a model of the potential impact of our combined testing and aPS intervention.

6.4.6.Collection of Cost Data in Kenya

Dr. Babigumira has extensive experience conducting cost and cost-effectiveness evaluations and collecting health outcomes data in East Africa, where his research focus is on improving access to safe and cost-effective diagnostic technologies, medicines, and healthcare delivery platforms. He has performed studies of health technology assessment in low-income countries, cost-effectiveness and scale-up of rapid diagnostic tests for malaria, and incentives for seeking and receiving services to prevent HIV [50-55]. He will be responsible for collecting and analyzing data on costs related to the novel interventions we will test, contributing along with Dr. Goodreau, to the cost-effectiveness study.

7. OBJECTIVES

7.1. Primary Objective

- ***HIV-1 RNA testing intervention:*** To conduct a proof-of-concept study to determine outcomes of a health facility-based HIV-1 RNA testing intervention to identify acute (i.e., RNA-positive, seronegative or discordant rapid test results) and prevalent (i.e., RNA-positive, seropositive) HIV infection, compared to standard care.

7.2. Secondary Objectives

- ***Linkage to care:*** To determine the feasibility, acceptability, and uptake of offering immediate linkage and treatment to all newly diagnosed HIV-infected patients in the intervention period, comparing this approach to standard care.
- ***Partner testing:*** To determine the feasibility, acceptability, and uptake of aPS for partner identification and testing, comparing enhanced aPS with HIV-1 RNA testing in the intervention period to passive referral followed by delayed aPS with standard HIV testing in the observation period.
- ***Impact and cost-effectiveness:*** To model the potential impact of the HIV-1 RNA testing, linkage, immediate treatment, and aPS interventions on the Kenyan HIV epidemic, in terms of incremental costs per HIV infection averted, death averted, and disability-adjusted life-year (DALY) averted, using data on standard care outcomes from the observation period and data on intervention outcomes from the intervention period.

7.3. Exploratory Objectives

- ***Barriers and facilitators:*** To conduct qualitative in-depth interviews with up to 60 newly diagnosed prevalent and AHI patients and seronegative partners in discordant relationships to gain insights into intervention uptake, including barriers and facilitators to ART or PrEP uptake and adherence in these groups.
- ***Staff views:*** To conduct interviews or focus groups with up to 60 individuals who work in the 6 health facilities where the trial will take place (up to 10 participants per facility), to obtain their views on HIV-1 RNA testing and the research carried out at the facility, including challenges to intervention scale-up.

8. STUDY DESIGN

We will use a modified stepped wedge design to evaluate the yield of the HIV-1 RNA testing intervention at 6 public or private health facilities in Kenya, before (1,375 patients) and after (1,500 patients) intervention delivery. This study will be conducted in two phases at each site.

The first phase is the **observation period** in which all testing and treatment will be per Kenyan Ministry of Health guidelines and primary care clinician judgment. Adults seeking care at primary health care clinics who have never been diagnosed with HIV and have a risk score of 2 or higher will be offered participation. HIV testing will only be done if ordered by the primary care clinician. Research procedures in the observation period will consist of a CASI/CAPI at baseline (all participants) and a home visit at 6 weeks (only for those diagnosed with HIV at baseline). The 6-week visit will include a second CASI/CAPI and follow-up on uptake of care and treatment and partner notification. Those who have not yet notified partners will be offered assisted partner notification with standard HIV testing (i.e., standard aPS). Participants found to be HIV negative and those not tested will end their participation at the baseline visit. Those diagnosed HIV positive (estimated to be about 2%) will have 2 visits, baseline and 6 weeks.

In the **intervention period**, there are four major interventions being tested: testing for acute and prevalent HIV infection, aPS using our HIV-1 RNA testing intervention (i.e., enhanced aPS), an ART cohort at KEMRI, and a PrEP cohort at KEMRI. Again, adults seeking care at primary care clinics with no history of HIV and a risk score of 2 or more will be offered enrollment. In the intervention phase, all participants will undergo HIV testing consisting of testing for HIV-1 RNA initially, followed (if positive) by testing with 2 rapid HIV tests per Kenyan HIV testing guidelines. Those who test negative end participation at the baseline visit after the CASI/CAPI as above. Those who test positive (either AHI or prevalent case, estimated to be about 5% for this combined outcome) are offered enhanced aPS and participation in the ART cohort at KEMRI and can accept or decline each one. Those who decline follow-up at KEMRI will end their participation at the 6-week visit (as described above for the observation period), those who accept will be followed at KEMRI for 12 months. Those who test positive will also be offered participation in qualitative interviews, which they may accept or decline without influencing other components.

Partners of observation phase HIV-positive participants (i.e., index cases with prevalent HIV infection) will be offered referrals for risk reduction counseling and for HIV care, if infected. Partners of intervention phase HIV-infected participants (i.e., index cases with newly diagnosed acute and prevalent HIV infection) will be offered the HIV-1 RNA testing intervention (as described for participants in the intervention phase above) and enrollment into the KEMRI ART cohort or PrEP cohort based on their test results. If they accept either cohort, they will be followed for 12 months. If they decline and are HIV positive, their participation will end after a 6 week visit as above. If they decline and are HIV negative, their participation will end at the baseline visit after the CASI/CAPI as above. In the intervention period, partners newly diagnosed with HIV through the enhanced aPS intervention will also be offered the enhanced aPS intervention to identify and test their partners. Identified partners of these individuals will be offered the same options as partners of index cases diagnosed in the stepped wedge trial.

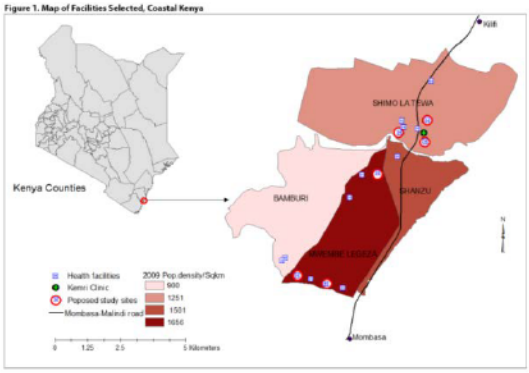
Opening of the observational phase at each site will be staggered in 3-month intervals so that no more than 2 sites will be in each phase at any given time. Each phase will last 3-6 months per site with the exception of the first site having only 3 months of observation to allow the study to

proceed more efficiently. Each site is anticipated to enroll approximately 125 participants per 3-month block for a total enrollment of 2875.

We expect to diagnose over two-fold more HIV infections through the HIV-1 RNA testing intervention than are currently diagnosed through PITC. Assisted partner notification should identify at least two-fold more previously undiagnosed individuals for each index case diagnosed than passive referral strategies (the current standard of care), augmenting intervention impact. We also expect that enhanced aPS will identify more previously undiagnosed individuals for each index case diagnosed than delayed standard aPS. Through modelling, we will estimate the impact of this combined intervention on HIV transmission (i.e., HIV infections averted) and clinical outcomes (i.e., deaths averted, DALYs averted) and evaluate the potential cost-effectiveness of this approach under a wide range of estimations. We expect this work to provide invaluable data that will help improve HIV testing and treatment as prevention in sSA.

Our HIV-1 RNA testing intervention network will include both private and public health facilities in a large, peri-urban area (population >100,000) in coastal Kenya (Figure 1). We will select six health facilities (2-4 public, 2-4 private) for inclusion in this study due to their size, central location (within 20 kilometers of one of our two KEMRI Research Clinics, located in Mtwapa and Kilifi), patient volume (>500 patients 18-39 years of age seen over 3 months), availability of HIV rapid testing on-site, availability of a private room for consenting participants, and willingness to collaborate with the research team. Four such facilities (2 private and 2 government) participated in AHI studies conducted by KEMRI in 2013 and 2014.

Figure 1. Map of Facilities Selected, Coastal Kenya



We have chosen a modified stepped wedge trial design for the following reasons: (1) we predict that the intervention will do more good than harm and (2) for logistical reasons, it is not practical to deliver the intervention simultaneously to all participants. Rolling out the intervention in a staggered fashion will ensure that there is adequate time for individual site preparation and staff training, as well as oversight of study activities. Before study initiation, the six participating clinics will be randomized to observation and intervention periods, as presented below in Figure 2.

Figure 2. Stepped Wedge Design at Six Sites

Clinic	0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24
Site 1	O	I	I					
Site 2	O	O	I	I				
Site 3		O	O	I	I			
Site 4			O	O	I	I		
Site 5				O	O	I	I	
Site 6					O	O	I	I
N enrolled	250	375	500	500	500	375	250	125

I = intervention period, N = number, O = observation period

Randomization will be performed using a random number generator to assign each clinic to one of the six positions, with stratification by facility type (public vs. private). Due to practical limitations, allocations will be unblinded. We will recruit 125 participants per clinic per 3-month time block, for 2,875 total participants (1,375 in the observation period and 1,500 in the intervention period) in the HIV-1 RNA testing intervention. By the end of the trial, each facility will have undergone an observation period of 3-6 months and received the intervention for 3-6 months. Thus, each health facility or "cluster" will act as its own control, with comparison of those patients enrolled during the observation period to those patients enrolled during the intervention period. Using this design, we can model the effect of time on the intervention, adjusting for temporal variations in HIV incidence [56, 57].

9. STUDY POPULATION

9.1. Inclusion Criteria for the Stepped Wedge Trial

The stepped wedge trial of the HIV-1 RNA testing intervention will be carried out in 6 outpatient health facilities in an area with a high prevalence of sex work, among both men and women. While sex work and other high-risk sexual behaviors are not part of the eligibility criteria for the study, data on sexual risk behaviors will be collected from all eligible patients.

The eligibility criteria target young adults, in whom HIV incidence is highest in Kenya, and focuses on symptoms and signs compatible with AHI, identified through our previous work (reviewed in Section 6.4).

Eligibility criteria for participation in the stepped wedge trial include:

- age from 18-39 years;
- not previously diagnosed with HIV infection; and
- a score ≥2 on our risk score algorithm to identify persons at higher risk for AHI, with scoring as follows:
  - age 18-29 years (1),
  - fever (1),
  - fatigue (1),
  - body pains (1),
  - diarrhea (1),
  - sore throat (1), and
  - GUD (3).

Eligibility criteria for partners of newly diagnosed cases with prevalent or acute HIV include:

- age over 18 years; and
- not previously diagnosed HIV infection.

9.2. Exclusion Criteria for the Trial

Patients not meeting inclusion criteria or those who are not willing or able to participate (e.g., due to illness or time constraints, or at the discretion of the study clinician) will be excluded.

Individuals at high risk for IPV are excluded from the aPS intervention, but eligible for all other components of the study.

9.3. Eligibility Screening for the Trial

Eligibility screening will be carried out using the screening form in section 21.6. This form has a permission script that research staff will read to participants. For those who consent verbally to screening, staff will initial the form and complete verification and documentation of eligibility. Individuals who refuse screening or do not meet eligibility criteria will not be enrolled into the study. All screening data obtained prior to written consent will be verified after the consent is signed.

9.4. Inclusion Criteria for Staff

Interviews or focus groups will be held for up to 60 individuals who work in the 6 health facilities where the trial will take place (up to 10 participants per facility). These individuals can work for the facility in any role, but will be required to have the following

characteristics in order to participate: 18 years of age or older, planning to remain with the facility for the duration of trial implementation at that site, and willing to provide views on the detection of acute HIV infection and the research carried out at the facility, including challenges to intervention scale-up.

10. INTERVENTIONS

10.1. Biomedical Interventions

10.1.1. Testing for Acute and Prevalent HIV Infection

- During the intervention period, a blood sample will be obtained and tested for AHI using the *Xpert® HIV Qual* assay (Cepheid, Sunnyvale, California, USA), with testing conducted on-site at the health facility where the participant was recruited and enrolled. This assay has been found to be easy to use and feasible in a community-based facility with limited or no laboratory infrastructure [58].
- For participants in whom HIV-1 RNA is detected, a laboratory technician will conduct rapid HIV-1 testing (currently Determine®, Abbott Laboratories, Abbott Park, Illinois, USA; and First Response®, Premier Medical Corporation, Kachigam, Nani Daman, India) in accordance with Kenyan HIV testing guidelines.
- HIV test results will be provided to participants in real-time, with post-test counselling by research staff and detailed documentation of results.

10.1.2. ART and HIV Care per Kenyan Guidelines

- Participants in the HIV-1 RNA testing intervention who are newly diagnosed with acute or prevalent HIV will be invited to participate in the ART cohort based at the nearest KEMRI Research Clinic (the KEMRI HIV research program has active research clinics in Kilifi, where the KEMRI-Wellcome Trust headquarters and reference laboratory are located, as well as in Mtwapa, which is within a one-hour drive from Kilifi). A map of the KEMRI clinical sites is in the appendices (Section 21.11).
- Treatment in the ART cohort will follow the most recent Kenyan MOH ART guidelines, with medications supplied by the Kenyan MOH through NASCOP.
- Concomitant medications, including co-trimoxazole prophylaxis and STI/STD treatment as needed, will be administered according to the most recent Kenyan MOH guidelines.
- Adherence will be monitored by pharmacy logs, pill counts, and multiple self-report measures.

10.1.3. PrEP and Risk Reduction Counseling per Kenyan Guidelines

- Partners of newly diagnosed patients in the intervention period will be asked to undergo HIV counseling and testing and, if seronegative, will be invited to participate in the PrEP cohort based at the nearest KEMRI Research Clinic (described below).
- PrEP administration and monitoring will follow WHO and Kenyan MOH guidelines.
- Medications will be supplied by Gilead through a contract agreement.
- Adherence will be monitored in all PrEP cohort participants by pharmacy logs, pill counts, and multiple self-report measures. In a subset of PrEP cohort participants, MEMS® electronic caps will be used as an additional measure of adherence.

10.2. Behavioral Interventions

10.2.1. HIV Counseling and Testing Messages

- Standard HIV counseling and testing per Kenyan guidelines will be used in the observation period.
- For participants diagnosed with acute HIV infection during the intervention period, counselors will provide additional counseling messages regarding the high likelihood of recent infection and need for confirmatory testing.
- These individuals will be told of the high infectiousness that is usual during AHI, and the high risk of transmitting HIV to their sexual partners or, for pregnant women, their child in utero.

10.2.2. Counseling for ART or PrEP Uptake and Adherence

- All newly diagnosed individuals will be counseled to initiate ART for their own health and to reduce their risk of transmission to others.
- Counseling to promote the uptake of and adherence to ART for HIV-infected individuals and PrEP for HIV-uninfected individuals in serodiscordant relationships will be both informational and motivational.
- Counselors at the KEMRI clinics have been trained in motivational interviewing following a modified version of Next Step Counseling that has been used successfully in Dr. Graham's ongoing study of adherence among HIV-positive MSM on the Kenyan coast (1R34MH099946).
- This counseling approach includes the identification of each individual's barriers and facilitators to pill-taking and uses interactive exercises to ask the patient to help think through the possible solutions to his or her specific adherence barriers [59].

11. PROCEDURES

An overview of the schedule of visit procedures for each study component (observation period participants, intervention period participants, partners, ART cohort, and PrEP cohort) is included in the Appendices. Presented below is additional information for visit-specific study procedures for each component of the study. Detailed instructions to guide and standardize all study procedures across sites will be provided in the SSP Manual.

11.1. Recruitment Process

11.1.1. Recruitment and assessment of study eligibility

- Eligible subjects will be recruited from among young (18-39 years of age) adults who present to any of the six health facilities in our HIV testing network.
- At each facility, we will aim to enroll 2-4 participants per day, for a minimum of 10 and maximum of 20 per week. Staffing schedules will be developed in collaboration with each health facility, with a goal to ensure that recruitment targets are attained and that a range of time periods (e.g., daytime, evening, weekend) are covered. While research staff are present at the facility, we will approach consecutive patients for screening.
- After obtaining verbal permission from the patient, facility clinicians or research staff present in the clinical room will screen patients to determine eligibility and ask if they are willing to discuss participation with the research team after their consultation. The screening form to be used for this purpose is presented in appendix 21.6. This form includes a permission script to be read to potential screenees and a space for research staff to initial that verbal consent for screening was provided. If a patient refuses screening, sex and estimated age will be recorded and the rest of the form will be blank. No identifying information will be obtained from screenees. All screening outcomes (i.e., screening refused, screened out, screened in but refused participation, screened in and consented) will be documented using the screening form.
- Facility clinicians will then provide symptom-directed treatment to patients as per standard care and current Kenyan guidelines.
- Upon completion of the consultation, and before any HIV testing is conducted, patients who meet eligibility criteria will be approached by the research team and invited to participate in the study. Individuals recruited during the intervention period will be shown a brief 2-minute explainer video that presents the study rationale and overview in English or in Kiswahili (please see https://www.youtube.com/watch?v=C7A_AatfKr4&feature=youtu.be).[1]
- Patients will then be consented to the study by research staff. During the consent process, staff will explain the purpose and design of the study, taking care to inform patients that participation is voluntary and will not influence their access to diagnostic testing or care.
- During the observation period, we will use a consent (Consent 1) that focuses on the CASI/CAPI collection of data, collection of data on tests performed during the clinic visit, and permission for a follow-up visit at 6 weeks if newly diagnosed with HIV infection by the clinic.

[1] The script for this video was reviewed and approved by our three ethical review boards.

- During the intervention period, we will use a consent (Consent 2) that informs participants that diagnostic testing is offered as part of the study and may reveal a diagnosis of acute or prevalent HIV infection. The intervention period consent will therefore focus on testing for acute and prevalent HIV infection, CASI/CAPI collection of data, and permission to discuss results and further research participation options with individuals who are newly diagnosed with HIV infection by the research team.

11.1.2. Recruitment for ART Cohort

- Trial participants newly diagnosed with acute or prevalent HIV infection in the intervention period (estimated at 75 total) and any partners of these individuals who are newly diagnosed through partner testing will be offered follow-up at the nearest KEMRI Research Clinic.
- At the research clinic, these individuals will be offered immediate ART (provided by NASCOP) to prevent secondary transmission and adverse health outcomes, with follow-up for 12 months.
- A separate consent (Consent 5) will be used for this follow-up. This consent will be reviewed at an intake appointment at the nearest KEMRI Research Clinic, so that newly diagnosed individuals have time to process their diagnosis and care options.
- If these individuals prefer not to participate in the KEMRI ART cohort, they will be offered referral. Several clinics offering HIV care, including ART, are available in the study area.
- Persons testing positive for HIV during the observation period will not be eligible for the ART cohort, but will be provided counseling and offered referral to any of several local care facilities.

11.1.3. Recruitment for APS Intervention

- All individuals newly diagnosed with HIV in the intervention period (both trial participants and partners) will be offered participation in the enhanced aPS intervention (i.e., aPS with testing for acute and prevalent HIV infection), using Consent 3. Newly diagnosed individuals can opt out of enhanced aPS and still be followed in the ART cohort, according to their preference.
- During the observation period, standard aPS (i.e., aPS with standard HIV testing) will be offered to newly diagnosed individual who have not yet informed their partners at the 6-week visit (detailed below).
- Counselors will make it clear that participation in the aPS intervention involves providing contact information about recent sexual partners. Individuals who are not willing to disclose partner information will be excluded from aPS.

11.1.4. Recruitment of Partners

- Partners identified through the aPS intervention will be offered HIV testing according to the period in which the associated index patient was diagnosed (i.e., standard rapid HIV tests in the observation period, testing for both acute and prevalent HIV infection in the intervention period).

- During the intervention period, partners who are newly diagnosed with HIV will be offered enrolment in the ART cohort at the nearest KEMRI Research Clinic and will also be offered participation in the enhanced aPS intervention.
- In this same period, partners who are uninfected and in an ongoing serodiscordant partnership will be offered enrolment in the PrEP cohort at the nearest KEMRI Research Clinic.
- Consent 4 will be used for enrolment of partners for standard HIV testing (observation period) or for the HIV-1 RNA testing intervention (intervention period).
- Consent 5 will be used for enrolment of partners into the ART cohort, and Consent 6 will be used for enrolment of partners into the PrEP cohort

11.1.5. Qualitative Interviews

- All individuals newly diagnosed with HIV in the intervention period (both trial participants and partners) and seronegative partners who enroll in the PrEP cohort described above will be offered participation in the qualitative interviews, using Consent 7. These individuals can opt out of the interviews and still be followed in the ART or PrEP cohort, according to their preference.
- During the observation period, individuals will not be recruited for interviews.

11.2. Stepped Wedge Trial

Figure 3 provides a flow diagram of procedures in the observation period and intervention period. The schedule of procedures for these visits is in Appendix 21.1 for the observation period and Appendix 21.2 for the intervention period.

11.2.1. Observation Period, Enrolment visit

- Consenting patients will take a brief computer-assisted self-interview or personal interview (CASI/CAPI) on a hand-held tablet computer. This survey will capture demographic information, onset of illness, and data on sexual behavior including partner numbers (with detailed questions on three most recent partners), relational timing (i.e., concurrent vs. sequential), transactional sex, and same-sex behavior. CASI/CAPI length will be monitored to ensure that the time required (target ≤20 minutes) is not an undue burden on participants.
- After the CASI/CAPI, research staff will help patients who have a request form for PITC to find the laboratory. PITC results will be recorded, and facility staff will refer patients with a positive result to care as per their standard practice.
- At the conclusion of their study visit, participants will be asked about the last time they tested for HIV as well as the costs they incurred for the health facility visit.
- All study participants who are newly diagnosed with HIV at this visit will be asked for contact details in order to arrange a 6-week follow-up visit. Research staff will stress the importance of linking to care, the availability of ART regardless of CD4 cell count, and the need to inform partners that they should be tested.

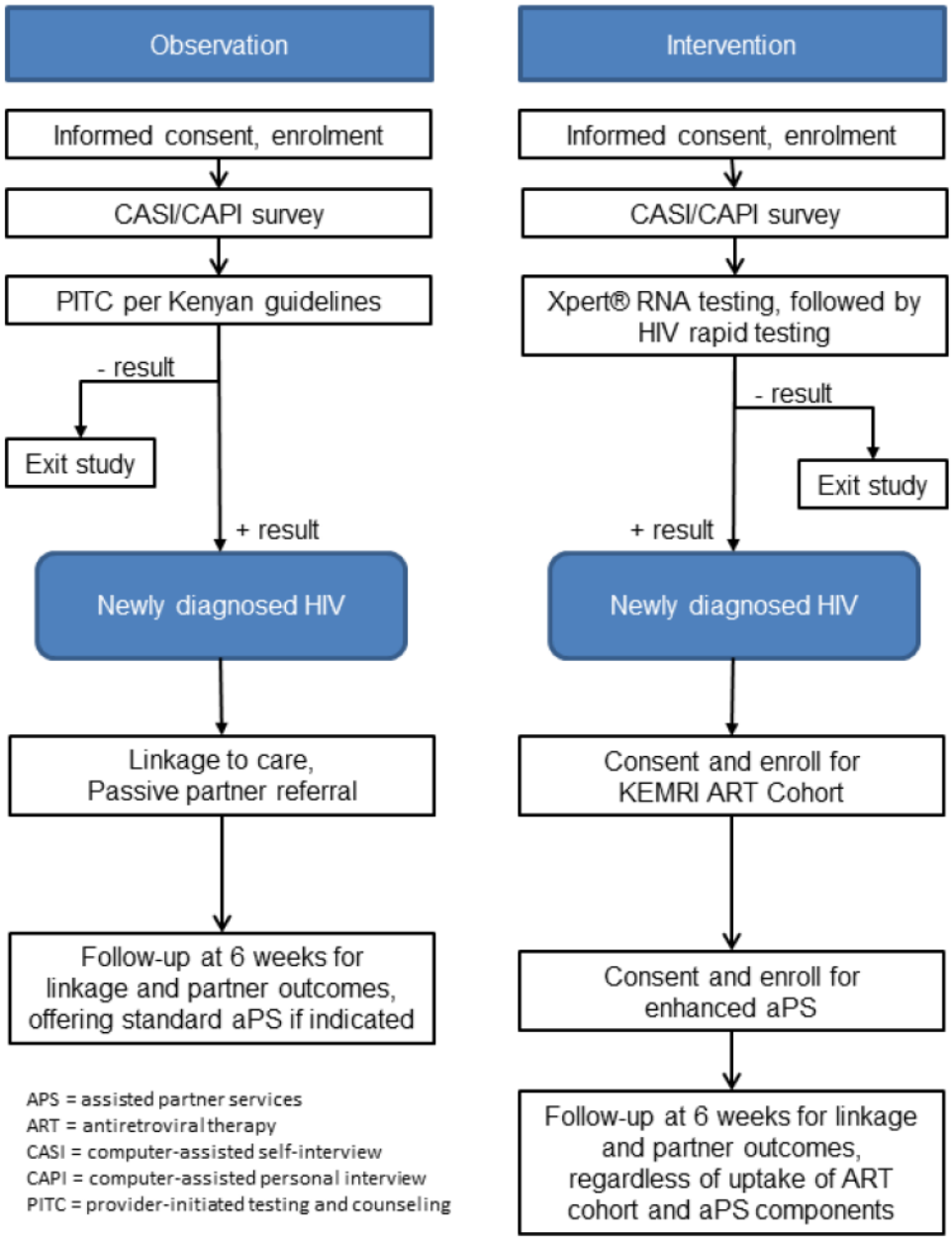
11.2.2. Observation Period, 6-Week Follow-up Visit

- Individuals with a new diagnosis of HIV infection made in the observation period will be visited in person or seen to at the health facility from which they were

recruited 6 weeks after diagnosis to repeat the CASI/CAPI and ascertain data on linkage to care, ART status, and partner notification outcomes. Linkage will be verified by demonstration of a clinic registration card, and ART status will be confirmed by demonstration of a regimen card and/or the patient's pills. Partner notification outcomes will be self-reported by the index patient.

- Participants who have not linked to care, started ART, or disclosed their HIV status will be offered counseling and referrals at this time.
- At the conclusion of this data collection and counseling, these index patients will be offered standard aPS. For those that accept, standard HIV rapid testing will be offered to all identified and successfully contacted partners.

Figure 3. Flow Diagram, Observation and Intervention Periods



11.2.3. Intervention Period, Enrolment Visit

- After consent is obtained, research staff will draw a 4-mL blood sample from participants for intervention HIV testing, which will be conducted by a research laboratory technician in the facility laboratory or at the nearest KEMRI research laboratory.
    - For all participants, a sample of blood will be tested on-site or at the nearest KEMRI research laboratory for HIV-1 RNA using the *Xpert® HIV Qual* assay (Cepheid, Sunnyvale, California, USA). This assay has been found to be easy to use and feasible in a community-based facility with limited or no laboratory infrastructure [58].
    - For participants with HIV-1 RNA detected, rapid HIV tests will be conducted, to determine whether the participant has prevalent HIV (i.e., seropositive results) or acute HIV (i.e., seronegative or discordant results).
- During wait time for this testing (up to 90 minutes), participants will take the brief CASI/CAPI survey described above. After the CASI/CAPI, research staff will help patients who have a request form for lab tests other than HIV to find the laboratory. In any time remaining, a brief educational video on HIV will be shown.
- HIV test results will be provided in real-time, with post-test counseling by KEMRI research staff. Results will also be shared with the facility clinician.
- At the conclusion of their study visit, participants will be asked about the last time they tested for HIV as well as the costs they incurred for the health facility visit.
- All study participants who are diagnosed with acute or prevalent HIV infection by the KEMRI research team will be asked for contact details in order to arrange a 6-week follow-up visit. ART cohort participation will also be offered at this time, and IPV assessment will be conducted to determine eligibility for the enhanced aPS intervention.
- Each health facility will work out a collaborative arrangement with KEMRI to ensure that these steps are fulfilled. There may be slight variations in the order of the above procedures, in order to ensure that patients and facility staff are minimally inconvenienced by the study.

11.2.4. Intervention Period, 6-Week Follow-up Visit

- Individuals with a new diagnosis of HIV infection made in the intervention period will be visited in person or seen at the KEMRI Research Clinic nearest to them 6 weeks after diagnosis to repeat the CASI/CAPI and ascertain data on linkage to care, ART status, and partner notification outcomes. Linkage will be verified by demonstration of a clinic registration card, and ART status will be confirmed by demonstration of a regimen card and/or the patient's pills. Partner notification outcomes will be self-reported by the index patient.
- Of note, additional data will be available on linkage, ART status, and partner notification outcomes for those participating in the enhanced aPS intervention and/or the ART cohort. However, the 6-week follow-up visit will serve to document

outcomes at the same time point in all trial participants, regardless of their uptake of other components of the Tambua Mapema Plus intervention.

11.3. ART Cohort for Newly Diagnosed Patients

- During the intervention period, all trial participants and partner participants with newly diagnosed acute or prevalent HIV infection will be offered referral to the nearest KEMRI Research Clinic, with study staff accompanying individuals to the Research Clinic if possible. At this site, these individuals will receive counselling about immediate ART initiation and partner notification (see below). The provision of immediate treatment, or TasP, to all newly diagnosed patients including those diagnosed with AHI has been approved by NASCOP and the Kilifi County Health Office.
- Medications will be provided at no cost through PEPFAR. Standard Kenyan first-line regimens will be used (currently tenofovir/lamivudine/efavirenz), with monitoring in accordance with Kenya MoH guidelines, continuing treatment indefinitely.
- Newly diagnosed persons who do not present to the research clinic within 3 days of their diagnosis will be contacted for a discussion of linkage to care at our research clinic or elsewhere if non-research options are preferred.
- Newly diagnosed patients enrolled at each KEMRI Research Clinic will be followed for 12 months at this site, with collection of data as follows for each visit:
    - Baseline visit
        - Confirmation of ART cohort eligibility and informed consent
        - Confirmation of contact details
        - Sociodemographic questionnaire
        - Risk assessment questionnaire
        - HIV testing to confirm status for seropositive patients and determine if seroconversion has occurred in AHI patients
        - IPV assessment
        - Risk reduction counseling
        - Mental health assessment
        - HIV cohort enrolment form
        - Medical history, including assessment for TB symptoms
        - Physical examination with collection of vaginal and/or rectal swabs as indicated for STI testing
        - Hepatitis B vaccine (if male-male sex or sex work reported)
        - ART counseling and initiation if prepared
        - Co-trimoxazole initiation
        - Isoniazid preventive therapy counseling and initiation if ART refused

- Urine collection for tests per ART Cohort Schedule (Appendix 21.4)
- Blood collection for tests per ART Cohort Schedule (Appendix 21.4), including plasma viral load to confirm AHI

- Week 2
  - Confirmation of contact details
  - HIV testing to determine if seroconversion has occurred in AHI patients
  - Risk reduction counseling
  - Qualitative interview (if consents to this procedure)
  - ART counseling, adherence assessment, and refills
  - TB assessment, isoniazid counselling, and isoniazid preventive therapy if eligible
  - Urine pregnancy testing if applicable and indicated
- Months 1, 2, 4, 5, 7, 8, 10, 11
  - Confirmation of contact details
  - HIV testing to determine if seroconversion has occurred in AHI patients (months 1 and 2)
  - Risk reduction counseling
  - Hepatitis B vaccine dose 2 if indicated (month 1)
  - ART counseling, adherence assessment, and refills
  - TB assessment, isoniazid counselling, and isoniazid preventive therapy if eligible
  - Other medication refills as needed
  - Urine pregnancy testing if applicable and indicated
- Week 6
  - Confirmation of contact details
  - IPV assessment
  - Risk reduction counselling
  - ART adherence counseling
  - TB assessment, isoniazid counselling, and isoniazid preventive therapy if eligible
  - Urine pregnancy testing if applicable and indicated
- Months 3, 6, 9, and 12
  - Confirmation of contact details

        - HIV testing to determine if seroconversion has occurred in AHI patients (months 3 and 6)
        - Risk assessment questionnaire
        - IPV assessment
        - Risk reduction counseling
        - Medical history, including assessment for TB symptoms
        - Physical examination with collection of vaginal and/or rectal swabs as indicated for STI testing
        - Qualitative interview (if consents to this procedure)
        - Hepatitis B vaccine dose 3 if indicated (month 6)
        - ART counseling, adherence assessment, and refills
        - TB assessment, isoniazid counselling, and isoniazid preventive therapy if eligible
        - Other medication refills as needed
        - Urine pregnancy testing if applicable and indicated
        - Urine collection from men for STI testing
    - Additional at Months 6 and 12
        - Blood collection for tests per ART Cohort Schedule (Appendix 21.4)
        - Urine collection for urinalysis
    - Additional at Month 12
        - Repeat mental health assessment
- Interim visits may occur at any time during ART cohort follow-up. All interim contacts and visits will be documented in participants' study records and on applicable case report forms (CRFs).
- Mental health assessment at baseline will be conducted by CASI/CAPI, with results followed up by our counselors to ensure referral for mental health problems such as depression and problem drinking. Our counsellors and clinicians have been trained in motivational interviewing and working with peer navigators [59], and will encourage patients to take advantage of these services in support of their ART uptake and adherence.
- All ART cohort participants will undergo a repeat CASI/CAPI and collection of data on linkage, ART status, and partner outcomes at week 6, as described above. This 6-week assessment will occur at the research clinic or at another location of the patient's choice.
- If a patient does not accept enrolment in the KEMRI ART Cohort, he or she will be offered referral to one of several large ART programs available in Mombasa, Mtwapa, or Kilifi. As described above, we will contact these individuals at week 6 to

repeat the CASI/CAPI and collect data on linkage results, ART status, and partner outcomes.

11.4. Assisted Partner Services (aPS)

11.4.1. Observation Period Participants Diagnosed with HIV Infection (Index Cases)

- Standard HIV care guidelines in Kenya recommend testing of partners of the index case through passive partner referral. Patients diagnosed with HIV infection during the observation period will be encouraged to refer their partners for this testing.
- Partner outcomes will be self-reported by these patients at the 6-week follow-up visit, after which all observation period index patients will be offered standard aPS (with research staff, instead of index cases, contacting named partners), using procedures summarized in section 11.4.2. Partner outcomes among observation period participants who agree to provide names for standard aPS will be documented by study staff as described below. Of note, testing of partners of index patients diagnosed in the observation period will not include the *Xpert® HIV Qual* test, but will consist solely of standard HIV rapid tests conducted according to Kenyan National Guidelines.

11.4.2. Intervention Period Participants Diagnosed with HIV Infection (Index Cases)

- During the intervention period, we will administer our enhanced aPS intervention to all consenting index patients on the day of diagnosis, either at the health facility where the case was diagnosed or at the nearest KEMRI Research Clinic, depending on the patient's preference.
- Research staff will describe the rationale for providing aPS and procedures for having providers immediately notify partners without directly revealing the index patient's identity. Specifically, staff will indicate that index patients who wish to inform partners themselves will be allowed up to 3 days to do so, after which research staff will notify partners following the aPS procedures. In addition, if an index patient requests that a certain partner not be contacted, the research team will respect the patient's wish and only contact partners for whom the index patient has given permission.
- We will use an assessment form adapted from Dr. Farquhar's completed aPS study to identify and exclude any individual from aPS who is determined to be at high risk of IPV, defined as reporting IPV within the last 1 month. Of note, partner notification following these eligibility criteria in Dr. Farquhar's completed trial at VCT sites in Kenya showed no difference in IPV in the control and intervention arms.
- Staff will then ask whether the patient (if eligible) accepts aPS, and have the patient provide written informed consent for the aPS procedures, which include the collection of detailed information on the aPS participant's recent sexual partners.
- Prior to initiating aPS interviews, research staff will explain that all information collected through the aPS process will be kept confidential, and reminded that staff will not reveal index cases' identities when contacting their partners.
- Index patients who accept aPS will be interviewed using structured interview forms that will be used to obtain partner contacts and track partner outcomes.

- Research staff will use a timeline-follow back instrument to elucidate the number of unique sex partners that participants have had in the past 1 year for prevalent infection and the past 3 months for AHI. If any participant reports injection drug use, information about needle-sharing partners will also be elicited.
- For each identified sex partner, staff will collect information including demographic characteristics, contact information, case's relationship to the partner, case's sexual behavior with the partner, and case's knowledge of the partner's HIV status. All data will be collected using structured interview forms and recorded as numerical or categorical outcomes.
- Index cases will be assigned unique identification (ID) numbers and their partners will be assigned corresponding numbers that include a random prefix (to protect index case confidentiality) and an additional sequential number for each partner, allowing partners to be linked to index cases in our dataset.
- aPS intervention participants who are assessed as having a moderate risk for IPV, as described in section 13.3.3 under "Rating System for IPV" will undergo special monitoring after the aPS consent visit, as described in that section.

11.4.3. Partners of Index Cases Who Consent to APS

- The schedule of procedures for partner testing is detailed in Appendix 21.3.
- When notifying partners, research staff will counsel the partner about HIV and encourage them to test at the nearest KEMRI Research Clinic.
- Partners who are successfully contacted in person will be given a study card with a unique ID number linked to the index case's unique ID number to present at the nearest KEMRI Research Clinic.
- If contact is established by telephone and the partner agrees to come to the VCT site at the nearest KEMRI Research Clinic for HIV-testing, we will send an SMS with an ID number linked to the index case's unique ID number, to be used when the partner presents for HIV testing.
- Partners who agree to testing in this study will undergo informed consent using an informed consent document (ICD) developed for this purpose (Consent 4). If a partner refuses to participate in the research study, he or she will be offered VCT in a non-research context (i.e., without data collection).
- After consent, the same CASI/CAPI used in the stepped wedge trial (described in section 11.2) will be administered, in order to capture demographic and sexual risk behavior data from participating partners.
- After the CASI/CAPI, the partner will then undergo HIV testing, using standard rapid HIV tests (i.e., standard aPS) for partners of observation period index patients and using the HIV-1 RNA testing intervention (i.e., enhanced aPS) to detect acute and prevalent HIV infection for partners of intervention period index patients.
- If a partner refuses to come to the clinic but consents to enrolment and HIV testing at home, field staff will conduct rapid HIV testing in the home and note the result. For partners of intervention period index patients, blood collected at the partner's home will be transported to the nearest KEMRI Research Clinic laboratory for the *XPert*®

HIV Qual test. Field staff will provide these results to intervention period partners within 48 hours and offer further research options (i.e., ART or PrEP cohort enrolment, enhanced aPS if HIV-infected) or referral to HIV prevention services or care as indicated.

- Partners of observation period index patients who are found to be seropositive will be offered referral to the local HIV care facility of their preference and will not be eligible for the ART cohort at the KEMRI Research Clinics. Partners who test seronegative in the observation period will also be referred to local facilities for follow-up counseling, and will not be eligible for the PrEP cohort at the KEMRI Research Clinics.
- Partners of index patients newly diagnosed with acute or prevalent HIV in the intervention period will be managed as follows:
    - Any partner of an intervention period index patient who is newly diagnosed with acute or prevalent HIV infection will be invited to the nearest KEMRI Research Clinic for enrolment into the ART cohort or offered referral for HIV care, if ART cohort enrolment is declined.
    - All partners of intervention period index patients who are newly diagnosed with acute or prevalent HIV will also be offered enhanced aPS, and their partners will also be offered enhanced aPS, enabling us to thoroughly investigate local sexual networks in which recent transmission occurred.
    - Partners who are uninfected but in an ongoing partnership with any individual newly diagnosed with acute or prevalent HIV infection in the intervention period will be offered enrolment in the PrEP cohort described below.
- All partners who are newly diagnosed with HIV in either study period will be assessed at a 6-week follow-up visit to determine linkage to care, ART uptake and disclosure to partners.
- At baseline and at the 6-week visit, research staff will counsel newly diagnosed individuals to disclose their HIV status to sexual partners and potential treatment supporters, and provide referral to counseling if needed for that purpose.

11.5. PrEP Cohort for Uninfected Partners in Discordant Partnerships

- Uninfected partners in discordant partnerships will be invited to enroll in the KEMRI Research Clinic PrEP cohort using Consent 6, with prospective follow-up as outlined below. These individuals and their partners will be encouraged to mutually disclose HIV status, in order to avoid potential unintentional disclosures from participating in research at the same research clinic.
- PrEP will be offered as a bridge to virologic suppression by ART in the index patient [34]. PrEP will be continued for at least 6 months, or until the HIV-positive partner has achieved virologic suppression.
- PrEP medications will be provided at no cost by Gilead, which has agreed to provide PrEP medication for up to 75 participants in this study. Standard tenofovir/emtricitibine dosing will be used, and WHO and Kenyan guidance on PrEP delivery and safety monitoring will be followed.

- We will use MEMS® electronic caps to monitor PrEP adherence in a subset of patients who agree to use these devices. We have approximately 50 MEMS® devices available from a prior study to use for this purpose. At each refill for participants with MEMS® cap pill containers, the electronic data on pill bottle openings since the last refill will be uploaded to a database.
- All women who enroll in the PrEP cohort will undergo a family planning assessment and offered contraception with injectable depot medroxyprogesterone acetate or oral contraceptive pills, both of which are available in the KEMRI Research Clinics. In addition, the use of a barrier methods such as condoms will be recommended.
- Patients who enroll in the PrEP cohort will be followed for 12 months, with collection of data as follows for each visit:
    - Baseline visit
        - Confirmation of PrEP cohort eligibility and informed consent
        - Confirmation of contact details
        - Sociodemographic questionnaire
        - Risk assessment questionnaire
        - HIV counseling and testing
        - IPV assessment
        - Risk reduction counseling
        - Mental health assessment
        - Medical history, including family planning assessment
        - Physical examination with collection of vaginal and/or rectal swabs as indicated for STI testing
        - Hepatitis B vaccine (if male-male sex or sex work reported)
        - PrEP counseling and education
        - Counseling and education for contraception (if female)
        - Urine collection for tests per PrEP Cohort Schedule (Appendix 21.5)
        - Blood collection for tests per PrEP Cohort Schedule (Appendix 21.5)
    - Week 2
        - Confirmation of contact details
        - Risk reduction counseling
        - Qualitative interview (if consents to this procedure)
        - PrEP counseling and initiation
        - MEMS® issuance if willing to use and MEMS® cap available
        - Urine pregnancy testing if applicable

- Months 1, 2, 4, 5, 7, 8, 10, 11
  - Confirmation of contact details
  - HIV counseling and testing (month 1 only)
  - Risk reduction counseling
  - PrEP counseling, adherence assessment, MEMS® data upload (if applicable), and refills
  - Hepatitis B vaccine dose 2 if indicated (month 1)
  - Urine pregnancy testing if applicable
  - Blood collection for creatinine check (month 1 only)
- Months 3, 6, 9, and 12
  - Confirmation of contact details
  - Risk assessment questionnaire
  - HIV counseling and testing
  - IPV assessment
  - Risk reduction counseling
  - Medical history
  - Physical examination with collection of vaginal and/or rectal swabs as indicated for STI testing
  - PrEP counseling, adherence assessment, MEMS® data upload (if applicable), and refills
  - Counseling and education for contraception (if female)
  - Qualitative interview (if consents to this procedure)
  - Hepatitis B vaccine dose 3 if indicated (month 6)
  - Urine pregnancy testing if applicable
  - Urine collection from men for STI testing
  - Blood collection for creatinine check (months 3, 6, and 12) and syphilis testing (month 12)
- Month 6 and thereafter
  - Review of need for continued PrEP (i.e., partner ART status and plasma viral load results)
- Additional at Month 12
  - Repeat mental health assessment
  - Urine collection for urinalysis

- Interim visits may occur at any time during PrEP cohort follow-up. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.
- If a study participant presents to a scheduled or interim visit with symptoms suggestive of acute HIV-1 infection syndrome, an *Xpert® HIV Qual* test will be performed and study medication will be held if the patient is newly HIV infected. Any PrEP cohort participant who seroconverts will be offered enrolment in the ART cohort, with 12 months of follow-up, or referred to the HIV care clinic of their choice.
- Mental health assessment at baseline will be conducted by CASI/CAPI, with results followed up by our counselors to ensure referral for mental health problems such as depression and problem drinking. Our counsellors and clinicians have been trained in motivational interviewing and working with peer navigators [59], and will encourage patients to take advantage of these services in support of their PrEP uptake and adherence.
- If an uninfected partner in a serodiscordant relationship does not accept enrolment into the PrEP cohort, he or she will be counseled on how to reduce HIV transmission risk and referred to another clinic for ongoing follow-up and regular HIV testing in the event that risk persists. PrEP is not currently offered outside of research settings in Kenya, but is expected to become available through government-funded research centers, including to seronegative individuals in serodiscordant partnerships, in the coming months to years. Several PrEP demonstration projects targeting various risk groups (e.g., sex workers, adolescent girls, MSM) are currently at various stages of planning and implementation in Kenya, including in the catchment area for this study.

11.6. Qualitative Interviews

- We will invite all participants who enroll in the ART or PrEP cohorts and some individuals who are eligible but refuse such enrolment to participate in paired or personal in-depth qualitative interviews to gain insights into intervention uptake, including barriers and facilitators to ART or PrEP uptake and adherence in these groups. Consent 7 will be used for this purpose.
- Those who are willing to have an in-depth interview will be given an appointment at the nearest KEMRI Research Clinic within two weeks of their HIV diagnosis and will undergo brief follow-up interviews at each quarterly visit during the 12-month follow-up period (if a cohort participant).
- Interviews will include questions about whether and to whom the interviewee has disclosed his or her status (if HIV-infected), whether the interviewee has had recent unprotected sex, and the interviewee's experiences and opinions about taking antiretroviral medications to treat or prevent HIV infection.
- Initial interviews will take approximately one hour, and be conducted at a separate appointment. Participants will be reimbursed KSh 500 for their time and travel expenses for this interview.

- Follow-up interviews for cohort participants will take approximately 15 minutes and will be integrated into regular study visits. No separate reimbursement will be provided for these brief follow-up interviews.
- Interviews will be tape-recorded if the participant consents to this. Notes will be taken by the interviewer at all interviews. Names and other identifying information will not be included in notes and will be expunged from transcriptions of recordings.
- Paired interviews will only be conducted if both partners have mutually disclosed status and agree to a join interview.

11.7. Participant Retention

- Our outreach team has many years' experience tracing patients who miss visits or have laboratory results needing follow-up. Because residential locations are very difficult to find due to poor maps and the lack of a formal numbering system, the team has used GPS mapping to locate a participant's home or workplace for future contacts; this service is provided to participants who agree to show the home or workplace to the study team member after a clinic visit. In addition, we collect tracking information that includes participant cell phone numbers. The outreach team will use SMS reminders before visits, cell phone calls in the event of questions or missed visits, and home visits as needed to encourage retention and complete follow-up.
- Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason at any time. Should a participant indicate that he or she would like to withdraw, study staff will request completion of a short assessment survey characterizing reasons for withdrawal.
- The PIs also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the DAIDS Medical Officer and KEMRI Trials Monitor. Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or IRBs/ECs terminate the study prior to its planned end date.
- Cohort participants who decide to withdraw from the study prior to the last follow-up visit will be asked if they will complete the procedures that would have been completed at this visit, but will not be required to do so. Additionally, study staff will record the reason(s) for all withdrawals from the study in participants' study records (regardless of whether participants fill out the short questionnaire) to further understand reasons for withdrawal.

11.8. Views of Health Facility Staff

- We will hold interviews or focus groups discussions with up to 60 facility staff (10 at each participating facility) before and after the intervention is conducted. KEMRI research staff will schedule interviews or focus group discussions at facilities or at an off-site location, depending on facility and staff preferences.
- We will ask facility staff members about their views of the importance of early detection of HIV infection and the prevention of transmission through finding and testing partners of newly diagnosed individuals. In addition, we will ask about the

impact the Tambua Mapema Plus study has had on the health facility in general, and any challenges encountered during the study. We will also ask views about what might make it easier or more difficult to scale up a similar intervention in other health facilities in Kenya.

- If participants agree, interviews and focus group discussions will be tape-recorded. Recordings and notes from the interview or focus group discussions will be used to assist later in fully writing up the information. We expect that these sessions will last about 1 hour.

11.9. Community Engagement

- KEMRI's research in Mtwapa and Kilifi is shared with KEMRI community representatives (KCR) during regular meetings. For this study, KCR members will be informed about the study goals, duration of study, health facilities selected, and benefits of the study to the wider community, including the benefits to partners who will be contacted and offered HIV testing. For Mombasa County and specifically the communities in Shanzu and Bombululu, community leaders, including area chiefs and other representatives will be invited to the KEMRI Research Clinics and informed about the study.

12. LABORATORY

12.1. HIV Testing at Health Facilities and in the aPS Intervention

12.1.1. HIV Testing, Observation Period

- The only laboratory testing during the observation period will be conducted as part of standard care by facility staff at the health facility where the participant has sought care.
- As described above, the results of any HIV rapid testing conducted will be recorded by study staff.
- No specimens will be collected for research testing in the observation period

12.1.2. HIV Testing, Intervention Period

- During the intervention period, a 4-mL sample of blood will be collected by research staff to test for acute and prevalent HIV at enrolment visits.
- For all intervention period participants, a blood sample will be tested on-site for AHI using the *Xpert® HIV Qual* assay (Cepheid, Sunnyvale, California, USA). Detailed procedures for this testing are described in a study-specific procedure (SSP).
- For participants with positive HIV-1 RNA test results, a laboratory technician will perform HIV-1 testing using two rapid test kits (currently Determine®, Abbott Laboratories, Abbott Park, Illinois, USA; and First Response®, Premier Medical Corporation, Kachigam, Nani Daman, India) in parallel, to distinguish prevalent (i.e., seropositive) HIV infection from acute (i.e., seronegative or discordant rapid HIV test results) HIV infection.
- Details of this testing and QA/QC procedures for serologic HIV testing using standard rapid tests and for *Xpert® HIV Qual* testing are described in KEMRI standard operating procedures (SOPs).
- Any remaining sample will be stored for quantitative HIV-1 RNA testing and drug resistance testing, as described below.

12.1.3. HIV Testing for Identified Partners in the aPS Intervention

- All identified partners of index patients diagnosed in the observation period will be tested with standard HIV rapid tests, in accordance with Kenyan guidelines.
- All identified partners of index patients diagnosed in the intervention period will undergo the same screening laboratory tests as described for HIV testing in the intervention period.

12.2. ART Cohort Laboratory Testing

- Urine pregnancy testing will be performed for all women at baseline and thereafter as clinically indicated [60].
- A urinalysis will be conducted for all participants at baseline and month 12 to monitor for kidney disease [60].
- Blood samples will be collected for ART safety monitoring according to current Kenyan guidelines [60], which recommend HBsAg, hemoglobin, creatinine, glucose, and cholesterol at baseline, plus a repeat creatinine, glucose, and cholesterol annually. ALT will be monitored in participants with concern for liver disease [60].

- ART response will be monitored according to current guidelines. CD4 counts and plasma viral load testing will be conducted at baseline and at 6 and 12 months after ART initiation. Further details are in the most recent WHO and Kenyan ART guidelines, in which our clinical staff have been trained [60].
- At each quarterly visit for the ART cohort, urine, vaginal swabs, or rectal swabs (depending on gender and whether anal sex is reported) will be collected to test for chlamydia and gonorrhea using nucleic acid amplification testing (Cepheid's *Xpert® CT/NG* test).
- Syphilis testing will be conducted at baseline and annually thereafter, or as clinically indicated.

12.3. PrEP Cohort Laboratory Testing

- PrEP eligibility will be determined by HIV testing, creatinine, and HBsAg testing at baseline. Contraindications to PrEP for this cohort will be a creatinine clearance <50 mL/minute or a positive HBsAg (because hepatitis treatment and monitoring programs are not yet available on the Kenyan coast) [60].
- Urine pregnancy testing will be performed for all women at baseline and thereafter at each follow-up visit [60].
- HIV testing will be conducted at month 1 and then every 3 months after PrEP initiation. Individuals who defer PrEP initiation will undergo HIV testing and counseling every 3 months.
- PrEP safety monitoring will consist of repeat creatinine testing at month 1, month 3, month 6, and month 12, as in the Partners PrEP Demonstration Project [61]. Of note, this is more frequent than is recommended per Kenyan PrEP guidelines [60].
- At each quarterly visit for the PrEP cohort, urine, vaginal swabs, or rectal swabs (depending on gender and whether anal sex is reported) will be collected to test for chlamydia and gonorrhea using nucleic acid amplification testing (Cepheid's *Xpert® CT/NG* test).
- Syphilis testing will be conducted at baseline and annually thereafter, or as clinically indicated [60].

12.4. Drug Resistance Testing

- Using separate funding available through IAVI, *POL* genotype tests will be performed on stored samples collected from patients newly diagnosed with HIV infection to detect transmitted drug resistance (TDR). For these analyses, plasma samples from HIV-positive patients will be sent to the Contract Laboratory Services (CLS) in South Africa, and for deep sequencing of minority resistance species to Lund University, Lund Sweden.

12.5. Quality Control and Quality Assurance Procedures

- The KEMRI laboratory participates in locally-approved External Quality Assurance (EQA) programs. The DAIDS staff and its contractors will conduct periodic visits to each site to assess the implementation of on-site Quality Control (QC) procedures, including proper maintenance of laboratory testing equipment and use of

appropriate reagents. The PI will follow-up directly with site staff to resolve any problems identified through QA/QC process.

- The main KEMRI laboratory in Kilifi and its satellite branch in our KEMRI Mtwapa Research Clinic, where testing will be performed for this study, is accredited by Qualogy LTD, UK and compliant with good clinical and laboratory practice (GCLP).
- Laboratory staff adhere to KEMRI standard and study-specific operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens.
- Specimen storage will be documented using a KEMRI database developed in PHP MySQL and stored in a server with remote back-up by the KEMRI IT department.
- International AIDS Vaccine Initiative laboratory staff and contractors who oversee specific laboratory tests at KEMRI also conduct periodic visits to assess the implementation of laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. These monitors follow up directly with site staff to resolve any QC or QA problems identified through proficiency testing and/or on-site assessments.

12.5.1. QC for HIV Serologic Testing

- Before performing diagnosis using HIV serologic tests, all health facilities in our HIV testing network will be trained on study procedures and on the most recent HIV testing and counseling guidelines for Kenya. During the observation period, these facilities will perform standard rapid tests following Kenyan Ministry of Health Guidelines (provided in the KEMRI HIV Testing SOP). All study clinics will be encouraged to participate in an EQA program for HIV serologic testing.
- In accordance with Kenyan National Guidelines, HIV status will be confirmed at linkage to care and before ART initiation.
- The KEMRI laboratory performs EQA for HIV serologic testing with the National Health Laboratory Service of South Africa and with the Royal College of Pathologists of Australasia.

12.5.2. QC for Xpert® HIV Qual and HIV Viral Load Testing

- The KEMRI laboratory will participate in the DAIDS Virology QA (VQA) program, with EQA results that are deemed satisfactory by DAIDS and its contractors.

12.5.3. QC for CD4 Count Testing

- CD4 count testing will be performed at the KEMRI laboratory for all participants in the ART cohort. The KEMRI laboratory participants in EQA for CD4 count testing with the National Health Laboratory Service of South Africa.

12.5.4. QC for Safety Monitoring

- Safety monitoring for ART and PrEP will be performed at the KEMRI laboratory for all participants in the ART or PrEP cohorts. The KEMRI laboratory participates in EQA for hematology and chemistry laboratories with the Royal College of Pathologists of Australasia.

12.6. Laboratory Specimens and Biohazard Containment

12.6.1. Laboratory Specimens

- The following specimens will be collected for the tests and procedures at the 6 health facilities in the intervention period:
    - Blood (4 milliliters, which is the smallest available tube side that allows for this testing and storage) for *Xpert® HIV Qual* testing for HIV-1 RNA and standard HIV testing with rapid tests
- The following specimens will be collected for the tests and procedures at the KEMRI Research Clinics for participants in the ART or PrEP cohorts:
    - Blood (20 or 10 milliliters) for testing per the ART and PrEP Cohort Schedules (Appendix 21.4 and 21.5, respectively) and for plasma storage (discussed in 12.7)
    - Urine for urinalysis and (for women) pregnancy testing
    - Urine (for men), vaginal swabs (for women), or rectal swabs (for participants reporting receptive anal intercourse) for STI testing
- Some initially uninfected partners in the PrEP cohort may become HIV infected during the study period. HIV testing algorithms, including tests required to confirm HIV acquisition, are described in the SSP Manual.
- All HIV seroconversion events will be confirmed retrospectively, using established procedures at the KEMRI Research Clinics. CD4 cell count testing will be performed at the HIV confirmatory visit.
- Research staff will adhere to standards of good clinical laboratory practice, and local SOPs for specimen management, including proper collection, processing, labeling, and transport of specimens to the nearest KEMRI Laboratory (main laboratory in Kilifi or satellite laboratory in Mtwapa). Samples will be transported from the KEMRI Mtwapa Laboratory to the main KEMRI Laboratory in Kilifi for storage.
- Specimen collection, testing, and storage will be documented using the Laboratory Data Management System (LDMS) as described in the SSP Manual.

12.6.2. Biohazard Containment

- 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 collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the United States Centers for Disease Control and Prevention and National Institutes of Health, and the WHO.
- Shipping is not necessary for the testing funded by this NIH study, but samples will be shipped for the drug resistance sequencing work at Lund University. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Good Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. In addition, all infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

12.7. Specimen Storage and Possible Future Research Testing

- KEMRI will store all plasma collected in this study in its main laboratory in Kilifi at least through the end of the study and until all assessments have been completed, for quality testing and repeat testing should a test fail. In addition, study participants will be asked to provide written informed consent for their plasma specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed after all QA and protocol related testing has been performed.
- Testing on stored specimens will include:
  - Extended QA for HIV diagnostic testing, including confirmation HIV acquisition during follow-up in the PrEP Cohort
  - Testing for antiretroviral drug levels (if funding permits)
  - Phylogenetic and linkage analysis (if funding permits)
  - Stored samples may also be used to characterize HIV viruses (e.g., for HIV subtyping, viral diversity analysis) and the host response to viral infection (e.g., immune activation markers, immunoglobulins, cytokines).

13. SAFETY ASSESSMENT

13.1. Safety Assessment Overview

- This study is divided into several components as described above. Potential adverse events are described below for each intervention component:
  - *Screening and Enrolment, Observation Period*. No biomedical intervention is provided and no sample is collected. Social harms could result if confidentiality is breached.
  - *Screening and enrolment, Intervention Period.* No biomedical intervention is provided. HIV testing is conducted on 4 mL of collected blood. Social harms could result if confidentiality is breached.
  - *aPS Intervention.* No biomedical intervention is provided. HIV testing is conducted on 4 mL of collected blood. Social harms could result due to partner notification, and IPV is a possible adverse outcome.
  - *ART Cohort.* ART is provided to HIV-infected participants in accordance with Kenyan National Guidelines. No research-related adverse medical event is expected that would be different from the provision of standard care. Social harms could result if confidentiality is breached.
  - *PrEP Cohort.* PrEP is provided to HIV-uninfected partners in serodiscordant relationships according to WHO and Kenyan Guidelines. No research-related adverse medical event is expected that would be different from the provision of standard care. Social harms could result if confidentiality is breached.

13.2. Adverse Event Definitions

- Based on the above summary of potential adverse events, we will use the definitions below:
  - *Clinical adverse event:* A clinical adverse event is any untoward medical occurrence in a study participant administered a pharmaceutical product (i.e., ART or PrEP) and which does not necessarily have a causal relationship with this treatment. A clinical adverse event can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of ART or PrEP, whether or not related to these medications.
  - *IPV:* As defined previously, IPV refers to physical, sexual, or psychological harm by a current or former sexual partner.
  - *Social harm:* A social harm is any untoward social event in a study participant during study participation. This occurrence does not necessarily need to have a causal relationship with the intervention.
  - *Unanticipated problem:* The Office for Human Research Protections generally defines *unanticipated problems* as "any incident, experience, or outcome that meets **all** of the following criteria:
    - unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and ICD; and (b) the characteristics of the subject population being studied;
    - related to participation in the research (i.e., there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

13.3. Adverse Event Procedures

13.3.1. Clinical Adverse Events

- Clinical symptoms will be systematically assessed in a structured medical history administered to ART and PrEP cohort participants.
- Clinical adverse events on ART will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Appendix 21.4) and managed according to Kenyan and WHO guidelines [60, 62].
- Clinical adverse events on PrEP will also be graded as above. In addition:
  - A serum creatinine elevation of Grade 1 or greater that is confirmed on a second sample drawn for follow-up of an abnormal result will result in temporary hold of PrEP.
  - A participant with a Grade 2 or higher creatinine or a calculated creatinine clearance of <50 mL/min will have PrEP temporarily withheld, and a second sample will be drawn for confirmation; confirmed Grade 2 or higher creatinine events or confirmed creatinine clearance <50 mL/min will result in permanent PrEP discontinuation.
  - SAEs felt to be related to PrEP will result in temporary hold of PrEP. In the case of temporary holds, the hold will continue until the event is stabilized or resolved. If the event resolves, PrEP may be reinitiated at the discretion of the Investigator, resuming safety monitoring.
  - Decisions to hold PrEP due to clinical and/or other laboratory safety reasons, or in the event of overdose, will be at the discretion of Principal Investigators. Reporting on adverse events to relevant IRBs will be according to relevant regulations.

13.3.2. Social Harms

- It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities.
- The study team will collect and report all social harms that are reported to study staff members, using a study-specific incident report form. This form will query common social harms such as altered personal relationships, forced change in housing, and physical violence. The form will also include space for a written narrative to document additional details of any social harm experienced. All research staff will be trained to properly complete the form.
- In the event that a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. As a part of study training, research staff will also be trained on the provision of referrals to counseling and social service support.

- While maintaining participant confidentiality, KEMRI may also engage with the KEMRI community representatives (KCR) in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such a harm.

13.3.3. IPV Monitoring

- As in Dr. Farquhar's completed study of aPS in Kenya, we will use the CDC definition of IPV, which has been adapted from the CDC website below, and can be found at http://www.cdc.gov/ViolencePrevention/intimatepartnerviolence/definitions.html
    - The term "intimate partner violence" describes physical, sexual, or psychological harm by a current or former partner or spouse. This type of violence can occur among heterosexual or same-sex couples and does not require sexual intimacy. IPV can vary in frequency and severity. It occurs on a continuum, ranging from one hit that may or may not impact the victim to chronic, severe battering.
    - There are four main types of IPV:
        - Physical violence is the intentional use of physical force with the potential for causing death, disability, injury, or harm. Physical violence includes, but is not limited to, scratching; pushing; shoving; throwing; grabbing; biting; choking; shaking; slapping; punching; burning; use of a weapon; and use of restraints or one's body, size, or strength against another person.
        - Sexual violence is defined as the use of physical force to compel a person to engage in a sexual act against his or her will, whether or not the act is completed or abusive sexual contact.
        - Threats of physical or sexual violence use words, gestures, or weapons to communicate the intent to cause death, disability, injury, or physical harm.
        - Psychological/emotional violence involves trauma to the victim caused by acts, threats of acts, or coercive tactics. Psychological/emotional abuse can include, but is not limited to, humiliating the victim, controlling what the victim can and cannot do, withholding information from the victim, deliberately doing something to make the victim feel diminished or embarrassed, isolating the victim from friends and family, and denying the victim access to money or other basic resources.
- When we use the term IPV in this protocol, we are referring to all 4 types of IPV listed above. However, when we use the term physical IPV, we are referring only the first type of IPV, physical violence.
- *Identification of IPV during the study:* We will collect IPV data on CRFs from all participants in the study. Face-to-face interviews to collect this data will be conducted by trained study clinicians, counselors, and field workers at the following time points and will be accompanied by counseling and referrals for care and/or additional counseling as needed:
    - aPS Eligibility Screening: all participants providing written informed consent for the aPS intervention will undergo assessment for IPV to determine aPS eligibility
    - aPS Enrollment Visit – for all participants meeting eligibility criteria and consenting to be enrolled

  - Weekly for the first month after aPS intervention enrolment and as needed if problems arise – enrolled participants categorized as being at moderate risk (per the rating system described below) for IPV
  - 6-week Follow-up Visit – all participants newly diagnosed with HIV infection in any intervention component of this study
  - ART and PrEP cohort visits following the schedules detailed in Appendices 21.4 and 21.5.

- IPV monitoring forms will include instructions to describe in detail any situation reported and the plan developed to resolve the current problem and prevent any future abuse.
- More intensive monitoring will be conducted if a participant expresses concerns or reports any incident.
- Emergency contact numbers for study staff will be provided to all participants who undergo the aPS intervention.
- Prior to study initiation, all clinicians, counselors, and field workers will be trained to collect data on IPV, recognize IPV, and provide IPV counseling and referrals. Training will be based on training modules that have been created and implemented successfully by Dr. Farquhar and her team. This will ensure that we are identifying all participants at risk for IPV, collecting accurate data on IPV to inform scale-up of this intervention, and addressing the needs of participants with respect to IPV.
- *Rating System for IPV:* At the aPS Eligibility Screening Visit, participants who provide written informed consent for the aPS intervention will be asked several questions to determine their eligibility for the aPS intervention component of our study and to classify them as at high, moderate, or low risk for IPV.
  - Participants will be classified as at high risk for IPV if they report a history of IPV within the last 1 month. *These participants will be **excluded** from the aPS intervention.*
  - Participants will be classified as at moderate risk for IPV if they report 1) history of IPV during their lifetime either from a current or past partner; and/or 2) fear of IPV if they participate in the study. *These participants will receive **special monitoring** as described below.*
  - Participants will be classified as at low risk for IPV if they report 1) no history of IPV during their lifetime either from a current or past partner; and 2) no fear of IPV if they participate in the study. *These participants will undergo aPS procedures without special monitoring.*
- *Mitigation Plan for Risks:* Our mitigation plan includes 1) special monitoring for participants at moderate risk for IPV; 2) formation of a Protocol Safety Review Team to monitor IPV, as described below; 3) stopping rules for the study.
- *Special monitoring*: Participants at moderate risk for IPV will be eligible for the aPS intervention, but will be monitored by the study team more closely than those at low risk. Special monitoring involves an additional meeting with a counselor or field worker at a mutually agreed upon location 1 week after the aPS intervention to:

- interview participants about IPV
- provide individual or couple counseling
- make referrals for additional care/counseling as needed
- schedule additional monitoring visits as needed

- All monitoring visits will be documented and reported by the counselor or field worker to the study coordinator at the end of each week. Any episodes of IPV will be reported immediately by the study coordinator to the Safety Review Team as described below.
- The decision to schedule additional follow-up visits after 1 week (or after a shorter interval) will be made by the research team at the time of the first monitoring visit, by the study coordinator after receiving the field staff weekly report, or by the Safety Review Team at any time.

13.4. Protocol Safety Review Team

- A protocol safety review team to monitor adverse events will be formed and will include the following individuals:
  - Dr. Susan Graham, co-PI and protocol chair
  - Dr. Eduard Sanders, co-PI and protocol co-chair
  - Dr. Clara Agutu, Program Manager
  - Dr. Carey Farquhar, Co-investigator
  - A KEMRI Clinical Trials Unit representative, TBN
  - NIAID Medical Officer
  - KEMRI Community Engagement Officer
  - Study Field Worker, TBN
- The Safety Review Team is responsible for reviewing written reports prepared by the study data manager and distributed by the study coordinator. These will include summaries of baseline data, special monitoring data, and 3-month follow-up data.
- Reports will be distributed and reviewed monthly and the committee will meet via teleconference at least twice annually to discuss any safety issues or concerns.
- Because we expect IPV to be a rare event, any IPV reported by research staff that is determined to be related to the intervention will prompt an ad hoc report to be distributed and may result in an ad hoc teleconference for the entire committee.
- The Safety Review Team will also be responsible for determining whether the aPS intervention needs to be stopped, as discussed in more detail in the following section.

13.5. Stopping Rules

- The Safety Review Team will also be responsible for stopping the aPS intervention (both standard and enhanced aPS) if this becomes necessary. The following "stopping rules" are proposed to guide the Safety Committee in decision-making:
  - More than 3 episodes of *physical IPV* at a *single study site* may warrant stopping aPS procedures at that study site if the violence is deemed related to this intervention.

- More than 5 episodes of *physical IPV* in the study overall may warrant stopping aPS procedures at all study sites if the violence is deemed related to this intervention.

- While the Safety Review Team will be discussing every episode of IPV in detail, special attention will be given to these 2 scenarios which will trigger discussions about stopping the aPS intervention, either in an isolated study site or overall.

13.6. Reporting Requirements

- Information on clinical adverse events, social harms, and IPV will be reported by the PI and study coordinator to the Safety Review Team and to the UW, Oxford, and KEMRI IRBs.

- Study participants will be instructed to contact the study site staff to report any AEs they may experience at any time between enrollment and completion of their participation. In the case of a life-threatening event, they will be instructed to seek immediate emergency care.

- Study staff will record all AEs on CRFs. Study staff will obtain written permission from the participant to obtain and use records from non-study medical providers to complete any missing data element on a CRF related to an adverse event.

- All participants reporting an untoward medical occurrence will be followed clinically, until the occurrence resolves (returns to baseline) or stabilizes. The Safety Committee will determine AE resolution or stabilization in their best clinical judgment.

13.7. Serious Adverse Events

- Serious adverse events (SAEs) will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) and include any AE that:
  - Results in death
  - Is life-threatening
  - Results in persistent or significant disability/incapacity
  - Is a congenital anomaly/birth defect
  - Requires inpatient hospitalization or prolongation of existing hospitalization

    Note: Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event. Thus, hospitalization in the absence of an adverse event is not regarded as an AE, and is not subject to expedited reporting.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

- A social impact that is reported to the Safety Review Team will be considered serious if significant social harm occurs (e.g., loss of a job, social ostracism).

- Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

- The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.
- For questions about DAERS, please contact NIAID CRMS Support at
- CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.
- For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

13.8. Adverse Event Relationship to Study Procedures

- The relationship of all AEs to study procedures will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) and clinical judgment. Per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010), the relationship categories that will be used for this study are:
  - *Related*: There is a reasonable possibility that the AE may be related to the study procedures
  - *Not related*: There is not a reasonable possibility that the AE is related to the study procedures

13.9. Grading Severity of Events

- The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1, July 2017) will be used.

13.10. EAE Reporting Period

- The AE reporting period for this study is defined as the entire study duration for an individual participant (from study enrollment until the participant's final study contact (Follow-Up Phone Assessment Visit/Termination Visit).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

14. SAMPLE SIZE CONSIDERATIONS

The proposed work is powered for the stepped wedge design (Figure 2). Based on our pilot work, we estimate that 50%-60% of adults aged 18-39 at the six participating facilities will be eligible for the study and approximately 50%-80% of these will accept study participation. Our preliminary data shows that approximately 2% of young adults in this age range are diagnosed with prevalent HIV-1 infection under standard care, while approximately 5% will be newly diagnosed with acute (1%) or prevalent (4%) HIV-1 infection in the intervention period. If these estimates are correct, with 1,375 subjects in the observation period and 1,500 subjects in the intervention period and a type I error probability of 0.05, assuming a coefficient of variation (k) of 0.25, we will have >90% power to reject the null hypothesis that the HIV diagnosis rates for experimental and control subjects are equal [57]. This power is more than adequate for multivariable analysis related to the testing of this null hypothesis. Because facilities will not have the laboratory capacity to diagnose HIV before seroconversion during the observation period, the base rate of AHI detection is 0, and power to detect AHI during the intervention period is >90% even if AHI prevalence is well below 1%. The table below presents power for a range of coefficients of variation and acute/prevalent HIV prevalence in the intervention period, given our chosen sample size.

Table. Power for Evaluation of Null Hypothesis that HIV Diagnosis Rates are Equal

Diagnosed HIV, Observation Period	Diagnosed HIV, Intervention Period	Kappa	Power
2.0%	5.0%	0.20	94.4%
2.0%	4.3%	0.20	82.2%
2.0%	5.0%	0.25	93.0%
2.0%	4.3%	0.25	80.0%
2.0%	5.0%	0.30	91.4%
2.0%	4.3%	0.30	77.3%
2.0%	5.0%	0.35	89.4%
2.0%	4.3%	0.35	74.6%

Accounting for correlation within sites (i.e., facilities participating in the randomized trial), precision for the estimated rate of AHI detection is ±0.54%, assuming a prevalence of 1% and k=0.25; if AHI prevalence is 2%, precision will be ±0.81%. For the evaluation of impact and cost-effectiveness, precision is more important than power, since estimates will be used as ranges for modelling. Assuming 150 partners tested as a result of the aPS intervention, we can estimate their HIV prevalence with reasonable precision (binomial confidence limits [CL], 39.8%–56.3%, for 48.0% prevalence); in addition, we will have 80% power to detect a relative risk (RR) of 1.58 or higher for HIV infection in the partners of AHI patients (n=30), compared to partners of prevalent HIV patients (n=120). Assuming 75 new HIV diagnoses from the HIV-1 RNA testing intervention to detect acute and prevalent HIV infection, we can estimate the proportion attaining virologic suppression with reasonable precision (binomial CL, 69.2%–88.3% if 80.0% achieve suppression by month 12); we will have 80% power to detect an RR of 2.84 or higher for failure to suppress among AHI patients (n=15) compared to prevalent HIV patients (n=60).

15. DATA ANALYSIS

15.1. HIV Testing Uptake and Diagnoses

We will compare the age and sex of individuals who accept vs. refuse screening, using Student t and Chi-square tests. In addition, we will tally reasons for refusal to participate among those eligible, and compare eligible individuals who refuse vs. consent to study enrolment, using Chi-square or Fisher exact tests for categorical variables and Student t tests or Mann-Whitney U tests for continuous variables. Proportions of individuals who accept screening, are determined eligible, and enroll will be presented, with exact binomial CI.

We will compare the proportion of patients with the following outcomes in the observation and intervention periods: (1) tested for HIV infection; (2) newly diagnosed with prevalent HIV infection (i.e., HIV seropositive); (3) newly diagnosed with AHI. Because we expect 0 AHI cases in the observation period, we will use a combined outcome (i.e., newly diagnosed acute or prevalent HIV-1) to model the effect of the intervention, so that models will converge. We will conduct analyses on the individual-level data, using log-binomial generalized estimating equation (GEE) models to account for clustering by health facility. We will use a small-sample variance correction to handle the small number of clusters [63]. Models will include indicator variables for calendar time period to control for trends in HIV incidence in the study area.

We will compare baseline characteristics between individuals in the observation and intervention groups, using Chi-square or Fisher exact tests for categorical variables and Student t tests or Mann-Whitney U tests for continuous variables. Where imbalances are identified, we will control for these potential confounders in secondary analyses using GEE models as above. We will also conduct exploratory analyses to identify predictors of the combined outcome (i.e., newly diagnosed acute or prevalent HIV-1) in the intervention group, including age, sex, marital status, symptom or symptoms reported, sex of partners, number of partners, condom use, transactional sex work, and other risk behaviors. We will test for interactions between the intervention and other variables such as sex, and will present stratified analyses if meaningful interaction is observed. In analyses in which multiple null hypotheses are tested, p values will be adjusted using the Holm–Bonferroni method.

15.2. Linkage to Care

During the intervention period, participants with newly diagnosed HIV infection will be offered referral to our research clinic, and enrolled in ongoing HIV care cohorts. We will evaluate the following outcomes for prevalent HIV, acute HIV, and the combined outcome (acute or prevalent HIV infection): (1) proportion successfully linked to care by week 6; (2) proportion initiating ART by week 6 and month 3 following HIV diagnosis; (3) proportion with viral suppression (<1,000 copies/mL) by month 6 and month 12 following ART initiation. All proportions will be calculated with exact binomial CI, assuming independence between individuals. We will compare these outcomes between prevalent HIV and AHI cases using Pearson Chi square or Fisher exact tests, as appropriate. We will also compare these proportions to outcomes in HIV-infected partners using the same methods. As above, in analyses in which multiple null hypotheses are tested, p values will be adjusted using the Holm–Bonferroni method.

15.3. Partner Testing

We will compare the following week 6 outcomes between the observation and intervention periods: (1) number of partners reported; (2) number of partners successfully contacted; (3) number of partners tested; (4) number of partners newly diagnosed with prevalent HIV

infection; (5) number of partners newly diagnosed with AHI (0 in the observation period); (6) number of HIV-infected partners newly engaged in care; (7) number of HIV-uninfected partners initiating PrEP. For PrEP cohort participants (intervention period only) we will also assess the proportion initiating PrEP by month 3 following cohort enrollment and the proportion with adherence >80%, measured by self-report or MEMS® cap at months 3 and 6 following PrEP initiation. The median, inter-quartile range, and range will be presented for each outcome in each period.

Outcomes will also be compared across study periods using Poisson GEE models with a small-sample variance correction [63]. Potential predictors, adjustment for confounding by calendar time, and interaction testing will be as described for the HIV-1 RNA testing intervention analysis above. We will also analyze local sexual network characteristics including the composition of individuals' personal sexual networks by attributes, relational type, relational timing, and relational duration. Characteristics will be compared for partners of index cases with AHI vs. prevalent HIV and for networks that include or do not include one or more AHI cases, using Pearson Chi square or Fisher exact tests for binary outcomes and non-parametric tests for continuous outcomes. We will also conduct a subset of these comparisons to the sexual networks of HIV-negative respondents provided through their CASI/CAPI data. Point estimates and standard errors for each behavioral parameter will be used to parametrize the modelling efforts described below. As above, in analyses in which multiple null hypotheses are tested, p values will be adjusted using the Holm–Bonferroni method.

15.4. Impact and Cost-Effectiveness

We will develop a stochastic, network-based model of HIV-1 transmission within the region. The general approach will follow that developed by Goodreau for modelling HIV-1 transmission among MSM in multiple international settings, including coastal Kenya [47], extended to a two-sex population. In essence, the model will simulate individuals distinguished by the following attributes: age, sex, sex of partners (males, females, both); sex worker status; circumcision status; HIV status; diagnosis status; time since infection; CD4 count; and treatment status, among possible relevant others revealed by our fieldwork. Individuals will be capable of undergoing any or all of the following transitions: enter the sexually active population; depart from the sexually active population; age; become infected; experience symptoms of AHI; become diagnosed; disclose HIV status to primary or secondary partners; change CD4 count; initiate treatment; change level of treatment adherence; cease treatment; experience opportunistic infections; or die.

Network dynamics will be modelled using the temporal exponential random graph model approach that Dr. Goodreau has co-developed [64]; this allows for complex dependences among relations to be modelled explicitly, in forms that preserve multiple features from observed data (e.g., proportion of males with concurrent partners, age mixing matrix) simultaneously. A range of partnership types is common in some parts of Eastern Africa, and likely maintains the persistence of transmission at observed levels, and the model will include these types. Our model will also explicitly include men who have sex with men only, women only, or both, given the epidemiological importance of all three populations in this area.

Population-specific birth and death rates, including general mortality and HIV survival trajectories, will be used to parameterize vital dynamics. Data on population structure will be drawn from the 2014 Kenya Demographic and Health Survey [65] and 2012 Kenya AIDS Indicator Survey [21], or more recent surveys when available. Existing rates of HIV testing,

treatment initiation, adherence, and disease progression and morbidity will be estimated from the latest available literature at the time of model-building. Parameters for sexual network modules will be derived from the partner testing and related network analysis. The impact of the HIV-1 RNA testing intervention and the enhanced aPS intervention on diagnosis and linkage to care for index cases and their partners will be estimated from study data; our model will then layer these onto the baseline model to estimate potential population-level impact. Sensitivity analyses will be conducted, especially around key parameters of the individual-level intervention impact. Model outcomes will include life-years lived with HIV or clinical AIDS, life-years lost, incident HIV cases averted, deaths averted, and DALYs averted. We will validate the HIV model using available Kenyan surveillance data [40].

The model will be used to predict the potential impact of our testing and aPS interventions on HIV incidence, disease progression, and mortality, with additional assessment of the value added by enhanced aPS for newly diagnosed patients with acute HIV infection. Five main scenarios will be modelled:

1. Baseline model (current guidelines and practice): no HIV-1 RNA testing, low use of PITC
2. Testing for acute and prevalent HIV infection with immediate linkage to care (intervention period)
3. Addition of enhanced aPS for newly diagnosed prevalent HIV infections (intervention period)
4. Addition of enhanced aPS for newly diagnosed acute HIV infections (intervention period)
5. Addition of PrEP provision to eligible partners tested through the enhanced aPS intervention (intervention period)

We will perform CEA from both the governmental (MoH) and societal perspectives. The governmental perspective includes only direct medical and non-medical costs that would be incurred by the Kenyan government if they implemented the intervention. The societal perspective includes all opportunity costs (i.e., medical costs from the governmental perspective plus costs incurred by patients for transportation and upkeep while seeking care, and costs of lost productivity while traveling to seek care, waiting in line, and seeking care). Costs will be divided into costs of the intervention and costs of HIV treatment. Costs of the intervention will be estimated separately for the HIV testing and enhanced aPS interventions. Direct medical costs of HIV testing will include costs of testing supplies, personnel, transportation, and communication. Costs of testing supplies are a factor of resource use for testing and unit costs obtained from local medical price lists. Costs of personnel are a factor of wages for clinical, laboratory, counselling, and field workers, and the time spent performing different activities. Time spent performing different activities, including partner tracing, will be obtained by conducting a primary time-and-motion surveys for HIV testing. Transportation cost for aPS will be estimated using the mean distance travelled and the travel cost per kilometer based on WHO Choice program data for Kenya [66]. Communication cost will be obtained by estimating the number of minutes per call, the mean number of calls, and costs per call-minute. Costs of HIV treatment include the costs of immediate ART during the intervention period, costs of other medications, and the projected lifetime costs of HIV treatment under different HIV testing and aPS scenarios. Indirect costs will be estimated using data from patient interviews and publically available data. Questions on patient transport costs, transport time, upkeep costs, and wages will be added to data collection forms. These will be combined with data on patient waiting and

patient contact time with health workers to estimate the indirect costs. For unemployed individuals, wages will be estimated based on Kenya's gross domestic product per capita.

We will combine effectiveness estimates from the HIV-1 RNA testing intervention, linkage to care, and aPS interventions with the cost estimates of each intervention to calculate cost per HIV-infected person identified and treated, and the incremental cost-effectiveness ratio (ICER) measured as cost per incident HIV case averted, cost per death averted, and cost per DALY averted. Disability weights for calculation of DALYs will be obtained from the latest global burden of disease study [67]. Following WHO guidelines, interventions will be judged to be cost-effective if the ICER is <3 times local GDP and very cost-effective if the ICER is <1 times local GDP per DALY averted [68]. Univariate and probabilistic sensitivity analyses will be performed to determine model robustness and the impact of varying different parameters through their plausible ranges on the estimate of cost-effectiveness.

15.5. Barriers and Facilitators

For newly diagnosed patients or uninfected partners who decline cohort enrolment but consent to an in-depth interview, we will conduct a single interview. For those who enroll in the ART or PrEP cohorts, we will aim to conduct four in-depth interviews per interviewee. The first one will take place approximately 2 weeks after diagnosis of acute or prevalent HIV infection or confirmation of uninfected status in an ongoing discordant partnership. Subsequent interviews will take place at months 3, 6, 9, and 12, coinciding with cohort follow-up visits. A grounded theory framework will be used for analysis. Audio recordings of the in-depth interviews will be transcribed verbatim; identifying information will be omitted from transcripts. Transcribed interviews will be entered into NVivo, and analysis will aim to identify and categorize the attitudinal, psychosocial, and contextual factors associated with ART or PrEP use. Data analysis will be iterative, and include open coding, axial coding, marginal remarks, comparisons, and memo-writing. Themes will be analyzed and triangulated. The next stage of analysis will relate concepts in order to identify factors that can enhance quality of health services and counselling for HIV-infected patients and their partners. Data will be collected confidentially, secured and stored in study offices. Audio recordings of the interviews will be destroyed after transcription. Personally identifiable information opinions and quotations will not be used in publications arising from this work.

15.6. Views of Health Facility Staff

We aim to conduct in-depth interviews or focus group discussions for up to 60 staff at the 6 health facilities (i.e., up to 10 staff members per facility) at which our HIV-1 RNA testing intervention will take place. These interviews or discussions will take place before and after each facility's participation in the intervention phase of this study, in order to get staff views of the importance of early detection of HIV infection, the impact this research had on the facility in general, and any challenges that were encountered that might make scale-up difficult. As for participant interviews, a grounded theory framework will be used for analysis. Audio recordings of the in-depth interviews and focus group discussions will be transcribed verbatim; identifying information will be omitted from transcripts. Transcribed interviews and focus group discussions will be entered into NVivo, and analysis will aim to identify and categorize knowledge, attitudes, and contextual factors associated with the HIV-1 RNA testing intervention evaluated. Data analysis will be iterative, and include open coding, axial coding, marginal remarks, comparisons, and memo-writing. Themes will be analyzed and triangulated. The next stage of analysis will relate concepts in order to identify factors that can enhance uptake of the HIV-1 RNA testing intervention at similar health facilities around Kenya. Data

will be collected confidentially, secured and stored in study offices. Audio recordings of the interviews and focus group discussions will be destroyed after transcription. Personally identifiable information opinions and quotations will not be used in publications arising from this work.

16. DATA MANAGEMENT

16.1. Data Management Responsibilities

- Source data/documents will be maintained in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials at https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf.
- The investigators will maintain and store securely complete, accurate and current study records on site throughout study implementation. Study records will be retained for at least 3 years after the research is completed, in compliance with DAIDS policy of storage and retention of clinical records. No study records may be moved to an off-site location or destroyed prior to receiving approval from both DAIDS and the Sponsor.

16.2. Screening IDs, Participant ID Numbers (PTIDs), and Unique Barcodes

- Screening IDs consisting of a health facility code and a sequential screening number will be assigned to all potential study participants who are approached for enrollment.
- Screening IDs are assigned regardless of whether or not the potential participant completes screening for the study.
- PTIDs are assigned at Enrollment and are separate from the Screening ID.
- The KEMRI Mtwapa Data team 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.
- Barcode labels will be procured from a vendor, and printed by the Data Manager/Designee. Study staffer will place a pre-printed barcode label (with a unique barcode number) on all data collection forms for that participant, on the HIV rapid tests and *Xpert® HIV Qual* test kits used in the intervention period. Study staff 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 test kits used for each participant in the intervention period.
- Any further laboratory testing conducted in the context of ART or PrEP cohort follow-up will also be labelled with the unique barcode assigned to that participant.
- Additional information on organization, types of data, and storage of study files can be found in the SSP.

16.3. Procedures for Organization of Files

16.3.1. Screening Data (Form 1)

- Form one (appendix 21.6) will be completed for each participant who is approached for study screening.
- Hard copy screening forms will be stored in a lockable cabinet at each KEMRI Research Clinic.

- The hard copy screening forms of participants who do not enroll in the study will be stored separately.
- Electronic screening data will be stored in a password protected database.

16.3.2. Participant Binders

- Enrolled participants will each have a Participant Binder, which will be collected daily and stored at the KEMRI Research Clinic where the participant is enroled.
- Participants will be identified only by Screening ID or PTID on documents in these binders.
- Forms from screening visits, which do not contain participant names or identifiers will be transferred to the Participant Binders. Forms from screening visits will have a pre-printed PTID sticker attached.
- Participant Binders will be stored in a lockable cabinet in the data room.
- Participant Binder will be stored in cabinets which are separate from the Link Log and ICD binders.

16.3.3. ICD Binders and Tracking Information

- ICDs for each component of the study will be stored separately in a specific binder for each ICD (numbers 1-8)
- Locator Forms (names and contact information) and Tracer Forms for each PTID will be filed in binders in a separate storage area, and be updated regularly.
- ICD binders and PTID locator binders will be stored in separate lockable cabinets in the data room.
- These materials will be stored in cabinets which are separate from the Link Log and Participant Binders.

16.3.4. Link Log

- A paper Link Log will link the participant name and ID/PTID. Names will not be collected at screening.
- The link between participant name and PTID will also be stored in a password protected database (Participant Tracking Database).
- The paper Link Log will be stored in a lockable cabinet with limited access by study coordinator, principle investigators and representatives of the regulatory bodies only.
- The Participant Tracking Database will be stored on a password protected computer in the Data Manager's office.
- Only the Data Manager and Data Manager backup/Designee, Study Coordinator, and Principal Investigators will have access to the Participant Tracking Database. The electronic database will be backed up daily on a centrally located KEMRI server.

16.4. Data Management Process

16.4.1. Quality Assurance (QA)/Quality Control (QC)

- KEMRI will conduct quality control and quality assurance procedures in accordance with the revised DAIDS "Requirements for Clinical Quality Management Plans" available at: https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf.
- The CASI/CAPI 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.
- Hard copy forms will be checked for completeness at the end of every visit, with capture of any missing data prior to the participant's departure.
- 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.

16.4.2. Data Revision

- 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.
- 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.

16.4.3. 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 tablets using CASI/CAPI will be encrypted such that only password-authorized study staff can access the data.
- All participant study files will be retained at the KEMRI Research Clinics for at least 3 years after study completion.
- The Master Database will be stored onsite and also backed-up on a separate server at the main KEMRI facility in Kilifi at the end of each day.
- Information entered and stored in the Participant Tracking Database — which is not considered source data — will be maintained at the KEMRI Research Clinics and backed-up on the KEMRI (Kilifi) server at the end of each day.

16.4.4. Confidentiality

- **De-identified data:** Participant study files will be stored as described in the previous sections. 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 each KEMRI Research Clinic, with access limited to study staff. The data room is accessible only to Data Management staff, who are issued card keys for access. 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 Data Manager is present, and care will be taken to ensure that participant records are not in view.
- **Access to the Participant Tracking 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. 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.*

16.5. Data Capture Methods

16.5.1. Data Collection

- All participants who are eligible, consented, and enrolled in the stepped wedge trial will be required to complete a baseline CASI/CAPI survey. Participants who are newly diagnosed with HIV infection will complete a 6-week follow-up survey by CASI/CAPI. Participants who consent for the aPS intervention will undergo procedures as described in this protocol, with data collection by face-to-face interviews. Participants who consent to enroll in the ART or PrEP cohort will complete CASI/CAPI for data on sexual behavior and adherence, and face-to-face interviews for medical history, according to the schedules provided in the appendices.

16.5.2. Administering CASI/CAPI Surveys in the Field

- **Data Collection Setup:** The CAPI will be self-administered (if participant is capable) or staff-administered (if participant is unable to self-administer) on a tablet computer. All survey questions will be pre-programmed in tablet by the Data Manager, who will be responsible for training the research staffers and on their use.
- **Data Collection Procedures:** All CASI/CAPI surveys will be administered after informed consent has been given. Surveys should be completed in one sitting. For sensitive questions administered by CAPI (i.e., with staff support), the participant can input the answer without the interviewer viewing the computer screen, to reduce discomfort. The research staff member assigned to the tablet will be responsible for it. When not in use, the tablet will be locked in a lock box at each KEMRI Research Clinic.
- **Data Transfer Process:** All data will be temporarily saved on the hard-drive of the tablet. The data from the tablets will then be securely uploaded to the Data Office Data Computer where the study database is housed. This transfer will occur within 12 hours after completion of data collection. Data will not be deleted from the tablets before it is uploaded and transferred.
- A **Research Electronic Data Capture (REDCap) database** will be designed to store data using range limits and data-links to optimize data consistency and accuracy at entry. CASI/CAPI data will be uploaded daily using an encrypted connection by research staff assigned to each health facility and backed up on a daily basis at the central research clinic. Data captured through CRFs instead of CASI/CAPI will be entered directly into a

REDCap database after every study visit. Staff will verify this data weekly via line listing. Information in the tablets will be identified only by the PTID.

16.5.3. Data Collection in the Clinic

- **Data Collection Setup:** During cohort follow-up in the KEMRI Research Clinics, CASI/CAPI data will be collected as above. Face-to-face interview data will be collected by a counsellor or clinician in a private clinic room.
- **Data Collection Procedures:** All surveys and questionnaires will be administered after informed consent has been given. All surveys and questionnaires for a given study visit should be completed before the participant leaves the research clinic. As above, for sensitive questions administered by CAPI (i.e., with staff support), the participant can input the answer without the interviewer viewing the computer screen, to reduce discomfort.
- **Data Transfer Process:** CASI/CAPI data will be transferred as described above. Data collected on hard-copy data forms will be entered by Data Section staff on the same day of the study visit, using the Data Office Computer where the study database is accessed. Data staff will file all hard copy data collection forms in binders filed sequentially according to the PTID. Information on the data forms will be identified only by the PTID.

16.6. Laboratory Data

- Laboratory data will be entered manually with back-ups stored weekly at an off-site location in Kilifi. Data verification and analysis will be performed weekly to ensure prompt quality control and assurance. Computerized sample inventories will be maintained at the KEMRI Research Clinics.
- Electronic data is stored in a Primary data center server in Kilifi and backup is done every day between 11:55 pm and 12:05 am.
- The Netapp Storage technology used for data backups provides backups both in Kilifi and in an offsite data center in Nairobi.

16.7. Types of Data

- Examples of data to be collected from HIV-infected individuals include behavioral data, HIV test results, sexual partner data, linkage to care, ART uptake and adherence, CD4 count, viral load, and adverse events. From HIV-uninfected individuals, data to be collected includes behavioral data, HIV test results, linkage to prevention services, and PrEP uptake and adherence.

16.8. Access to Source Documents

- The KEMRI Research Clinics and main KEMRI campus in Kilifi 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. No research records will be maintained at the six health facilities where the stepped wedge trial will be conducted.
- The data management team, study coordinator, and Principal Investigators will have access to the data. De-identified data will be shared with the rest of the scientific team as appropriate.

- KEMRI will permit authorized representatives of the NIH, Gilead (for PrEP-relevant data), and regulatory agencies 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.

16.9. Protocol Deviations

- All protocol deviations will be immediately reported to the IRBs as well as the study sponsor (see section *16.4.1 QA/QC*). Regular (monthly or more frequently as necessary) communication will provide a consistent and regular forum to examine protocol compliance (see section 13.0 Safety Assessment).
- Intensive trainings on the study specific protocol and intermittent in-service trainings will be scheduled to ensure protocol compliance by all study staff.
- DAIDS Critical Events Policy, as detailed in the Critical Events Manual found at: https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf, will be adhered to at all times.

17. HUMAN SUBJECTS PROTECTIONS

17.1. Institutional Review Boards

Ethical approval will be sought from KEMRI Scientific & Ethics Review Unit (SERU), and by the Human Subjects Research Committees (HSRC) at the Universities of Washington (UW) and Oxford.

17.2. Vulnerable Participants

Pregnant women who consent to participate will be included in this research, due to the importance of HIV diagnosis, linkage to care if infected, and prevention of HIV acquisition if uninfected. Pregnant women will not, however, be eligible for PrEP due to the limited experience with PrEP in this population to date and our provision of this intervention as a research procedure. Prisoners and children will not be included. Precautions are taken as below regarding potential subjects with low literacy.

17.3. Consent Procedures

- Screening procedures have been developed to minimize inconvience to patients at the health facilities where the study will be conducted, thereby removing potential barriers to screening participation. All screening will be conducted in a private clinical consultation room with only the facility clinician, the patient seeking care, and one member of the research team present, with care to ensure screenee privacy and confidentiality. Talking points reviewed by our ethical review boards will be used to ensure that all screenees receive the same basic information on the study (Appendix 21.7).
- Patients may refuse to be screened, in which case the research team member will leave the consultation room. If a patient accepts screening but prefers that it be done by the facility clinician, the research team member will leave the consultation room and the facility clinician will complete the screening form, sending this to the research team member with the patient after the clinical consultation is completed.
- All screening will be conducted only after verbal consent is received from the patient. Because screening for this study presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, we will request a waiver of documentation of informed consent from our ethical review boards. Instead of formal documentation with a written screenee signature on an informed consent document, the research staff member present will enter his or her initials after the permission script on our screening form, to indicate that the screenee gave his or her verbal consent for screening.
- Seven different patient ICD will be used, each corresponding to either the observation period (ICD #1) or to different components of the intervention period (ICD #2-#7). In addition, there is an ICD for facility staff to provide feedback on the intervention tested (ICD #8). An overview of the consents is presented in the table below, which gives the ICD number, short title, description, number of expected participants in that study component, and site of consenting:

Number and short title:	ICD Description	Number of participants / Facilities where ICD will be presented
1. Observation	Observation period consent	N=1375 / 6 health facilities
2. Intervention	Intervention period consent	N=1500 / 6 health facilities
3. Assisted partner notification	Assisted partner services consent for all newly diagnosed	N= 75 / 6 health facilities or KEMRI clinic
4. Partner testing	Partner testing consent	N=300 / partner home or KEMRI clinic

5. Immediate treatment	Cohort follow-up for HIV positive patients and partners	N= 75 (and unknown HIV infected partners) / KEMRI clinic
6. PrEP	Cohort follow-up for HIV negative (with PrEP)	N=75 / KEMRI clinic
7. Qualitative	Personal interview	N=60 / KEMRI clinic
8. Staff	Personal interview or focus group	N=60 / 6 health facilities

- Each ICD document will describe the purpose of the specific component of the study described, the procedures to be followed, and the risks and benefits of participation.
- During the consent process with each ICD, staff will explain the purpose and design of the specific study component, taking care to inform patients that participation is voluntary and will not influence their access to care or any other services to which they are entitled.
- Consent forms will be available in Swahili and English, and a copy will be given to each participant in the language of his or her choice.
- If an individual is illiterate, we will explain all procedures, risks, and benefits and offer the option of having a friend, family member, or paid consultant who is not a member of the research staff be present to further explain the study.
- Written informed consent will be obtained from all participants; persons incapable of consenting are excluded.
- Potential participants who would like to take additional time to consider their enrolment will be encouraged to do so.
- The informed consent process will be conducted by staff members trained in the ethical treatment of human subjects. This process involves presenting a detailed verbal description of the study as described on the printed, IRB-approved consent form.
- Staff will emphasize that participation is voluntary, and that participants can refuse to answer any question or undergo any procedure or can discontinue participation at any time without penalty.
- Participants will be informed of the procedures for ensuring confidentiality, including use of unique non-personally identifying ID numbers instead of names on research materials, and the maintenance of data in encrypted computer databases and locked filing cabinets in locked rooms.
- Participants will be provided with a signed and dated copy of the ICD before they leave the study site.

17.4. Risks to Human Subjects

Medical risks associated with ART are no different than if this intervention was started in a non-research setting. Of note, although immediate ART (i.e., regardless of CD4 count) will expose individuals to potential adverse side effects from these medications, evidence and current guidelines now support the initiation of immediate ART both for clinical benefit for the patient (reduced morbidity and mortality risk) and for the patient's sexual partners (reduced transmission risk). Also of note, ART for all HIV-infected persons is currently recommended by both the World Health Organization and the Kenya Ministry of Health. Individuals who wish to postpone ART due to concerns about their health or readiness for long-term medications will be provided ongoing clinical care, with counselling about medication readiness and sexual risk reduction.

Medical risks associated with PrEP are no different than if this intervention was started in a non-research setting. However, PrEP is not yet widely available in Kenya, despite being recommended for persons at high risk for HIV infection by the World Health Organization and the Kenya Ministry of Health. Truvada®, the drug used for PrEP, may cause side effects including headache, nausea, diarrhoea, vomiting, rash, depression and mild, painless darkening of the skin on their palms and/or soles of feet. In addition, if adherence to PrEP is suboptimal, there is a risk of acquiring HIV infection despite taking PrEP.

There may be several non-physical risks associated with this research:

- There is a small risk of loss of privacy or confidentiality for participants related to study visits, in-depth interviews, or contacts by staff or field workers. This study will include questionnaires and counselling on sensitive topics including sexual risk behavior. The ICDs will bring confidentiality risks to participants' attention.
- Participants may also experience psychological discomfort during discussion and disclosure about sexual behavior and sex partners. In addition, participants who are diagnosed with acute or prevalent HIV may experience distress. We will take steps to minimize any psychological discomfort. Counsellors will be rigorously trained on study protocols, and will receive close supervision by the investigators.
- Participants may experience stigma or discrimination if their HIV-positive status or if stigmatized sexual risk behavior (e.g., male-male sex) is revealed. We will take steps to minimize the risk that participants' HIV status or risky sexual behavior might be revealed, develop individualized procedures for study-related contacts in collaboration with each participant, and continually develop further safeguards to protect participants' confidentiality.
- While IPV has the potential to cause harm, IPV has not increased in other US or African studies when aPS has been implemented. We will provide training on IPV counselling for study staff and ensure that resources have been identified so we can refer individuals who report abuse or are concerned for their safety. With these precautions and the exclusion of individuals who reported IPV during the last month from the aPS intervention, we believe these potential risks are reasonable compared to the potential benefit to the individual and the broader community. Please see section 13 for further details on planned IPV and safety monitoring.
- Contacting partners for HIV testing could potentially involve community leaders or representatives who may have an opinion about KEMRI's work in Mtwapa or Kilifi as mainly focusing on the sex worker community. We will use the KEMRI Community Representative meetings to brief community stake holders that this study involves any community member seeking care for symptoms and that all patients seeking care are entitled to PITC. Invitations to partners for HIV testing is a strategy approved by the Ministry of Health and will extend care and prevention options to partners with undiagnosed HIV infection.

17.5. Protections against Risk

Every effort will be made to minimize the risks associated with study participation. Experienced research staff will counsel participants prior to enrolment, so that they are aware of the risks described above. All HIV testing will be accompanied by pre- and post-test counselling as per Kenyan national guidelines. In addition, experienced research staff will oversee all computer-

assisted interviews and perform examinations and blood collection. Appropriate clinical and laboratory monitoring will minimize the risk of severe adverse events related to antiretroviral medications during clinic follow-up. Participants will be assured that their clinical care will not be affected by their participation status in any of the aims, nor by their responses in questionnaires. Participants will be enrolled only after written informed consent is given, and have the right to withdraw or refuse an examination or sample collection at any point. We will ask any participant who withdraws from the study to complete a questionnaire regarding his or her reason for withdrawal, care and referral needs, and (if HIV-infected) intent to establish care elsewhere.

In addition, HIV-uninfected partners will all be offered PrEP in this study. Immediate ART and PrEP have both been approved for this study by the Kenyan National AIDS and STD Control Programme (NASCOP), in the context of testing this new intervention. We will stress to participants that this is a pilot program with the goal to detect and manage acute and prevalent HIV infection with the maximum impact on reducing HIV transmission risk. Patients who agree to research follow-up but do not want to initiate ART or PrEP immediately will receive ongoing counselling. Patients who refuse research participation will be offered referral to one of several other HIV clinics in the area and followed as per standard care in Kenya.

Of note, the laboratory test we will use for AHI detection (i.e., the Cepheid *Xpert® HIV Qual* assay) has obtained European Conformity in vitro diagnostic (CE-IVD) status in April 2015. For this proposal, we are supported by the Kenyan Ministry of Health in offering immediate ART to all persons with positive *Xpert® HIV Qual* results. Therefore, all participants who test positive for AHI will be given post-test counselling, advised to abstain from sex or use condoms, and offered immediate ART. All AHI diagnoses by the *Xpert® HIV Qual* assay will be followed up by serial HIV rapid tests at week 2, month 1, month 2, month 3, and month 6. In addition, HIV-1 RNA testing will be conducted at ART initiation and followed every 6 months in the ART cohort.

Staff who participate in the staff interviews or focus group discussions will be informed that their names and identifying information will not be associated with any of the feedback received. They will also be informed of the procedures to protect recordings and transcripts, by keeping these files on an encrypted, password-protected computer only accessible by the research team.

17.6. Potential Benefits of Participation

Although participants in this study may not personally benefit, the following may be considered potential benefits to participants:

- Participants in the stepped wedge trial may benefit from the following:
  - Participants may contribute to and learn from research that will evaluate a unique combination HIV prevention intervention.
  - Participants have access to free diagnosis of AHI through testing that is specific to the research, and would not be included in regular HIV care.
  - Improvement of HIV awareness, diagnostic practices, and clinical care at participating health facilities is a likely side benefit of this research.
  - Diagnosis of acute or prevalent HIV will enable the patient to take measures to avoid infecting their sexual partners and register for HIV care.

- Participants will receive intensive HIV prevention counselling, which includes both sexual risk reduction and ART adherence promotion for participants diagnosed with acute or prevalent HIV.
- Provision of immediate ART to newly diagnosed patients may prevent transmission to their sexual partners and, for women, to their children.
- Provision of PrEP to uninfected partners of HIV-infected individuals may protect them from HIV-1 acquisition.
- Anonymous partner referral services may benefit HIV-infected individuals who do not wish to notify partners themselves. In addition, partners of participants will receive notification of the exposure to HIV, be counselled about HIV prevention, and be offered HIV testing and counseling.

- Staff at the 6 health facilities that participate in the HIV-1 RNA testing intervention trial may benefit from the following:
  - Staff will contribute to and learn from research that will evaluate a unique combination HIV prevention intervention.
  - Staff may have an opportunity to improve HIV awareness, diagnostic practices, and clinical care at their facility.
  - Staff will have the opportunity to provide their views and insights on the value of identifying HIV as early as possible.

18. PUBLICATION POLICY

- Publication of the results of this study will be governed by NIAID and KWTRP publication policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to DAIDS and to the KWTRP Manuscript Review Committee for review prior to submission.
- 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 R01AI124968****. 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.

19. ADMINISTRATIVE PROCEDURES

19.1. Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by their 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.

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 RSC. 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.

19.2. Regulatory Oversight

Regulatory oversight will be provided by DAIDS PRO, and local IRB/ethics committee at KEMRI and at the Universities of Washington and Oxford.

19.3. Study Implementation

Pending successful protocol registration and submission of all required documents, DAIDS will "activate" the KEMRI site.

Study implementation may not be initiated until a study activation notice is provided to the KWTRP by the DAIDS PRO. In addition, if study "activation" is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the KEMRI site by the DAIDS PRO.

19.4. ClinicalTrials.gov

This protocol will be registered in ClinicalTrials.gov.

19.5. Study Coordination

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual will outline procedures for conducting study visits; data and forms processing; social harm assessment, management and reporting; and other study operations.

Study CRFs and other study instruments will be developed by the protocol team. Data will be captured in a Research Electronic Data Capture (REDCap) database for data entry. Data cleaning, reporting and analysis will be done in STATA. Quality control reports and queries will be generated and distributed to the KEMRI site on a routine schedule for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and social harm incidence will be monitored closely by the team.

KWTRP staff will address issues related to study eligibility and social harm management and reporting as needed to assure consistent case management, documentation, and information-sharing.

19.6. Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the KEMRI site and study implementation sites to:

- Verify compliance with human subjects and other research regulations and guidelines;
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- Confirm the quality and accuracy of information collected at the study sites and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., ICDs, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures.

Investigators also will allow inspection of all study-related documentation by authorized representatives of NIAID, IRBs/ethics committees, and US regulatory authorities (i.e., the Office for Human Research Protections). A visit log will be maintained at KEMRI to document all site visits.

19.7. Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the DAIDS Regulatory Support Center (RSC) prior to implementing the amendment.

19.8. Investigator's Records

All Investigators of Record (IoR) will be responsible for maintaining, and storing in a secure manner, complete, accurate, and current study records throughout the study. Under HHS regulations, the IoR is required to retain all study records relating to research for at least three [3] years after completion of the research, or longer if needed to comply with local regulations. Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects;
- All protocol-required data collection of identifiable private information described in the IRB/ethics committee-approved research plan;
- All analysis of identifiable private information described in the IRB/ethics committee-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

Study records include administrative documentation (including protocol registration documents and all reports and correspondence relating to the study), as well as documentation related to each

participant screened and/or enrolled in the study (including ICDs, locator forms, CRFs, notations of all contacts with the participant, and all other source documents).

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21. APPENDICES

21.1. Schedule of Procedures, Observation Period HIV Testing Cohort

SCHEDULE OF PROCEDURES - OBSERVATION PERIOD

Procedures Visit week	Visit 1 WK0	Visit 2 WK 6[1]
Date of visit	**X**	**X**
Eligibility Screening	X	
Informed Consent (Consent 1)	X	
Contact Information	X	
Sociodemographic Questionnaire	X	
Risk Assessment Questionnaire	X	
HIV Counseling and Testing[2]	±	
Assessment of Linkage to Care, ART, Disclosure, and Self-report of Partner HIV Status[3]		X
Offer Standard Assisted Partner Services (aPS) if Eligible (Consent 3)[3]		X

1) Week 6 procedures will be conducted for HIV-positive participants only.
2) HIV testing will be performed at the discretion of the health facility provider, using standard rapid antibody tests to confirm prevalent (i.e., seropositive HIV status) in accordance with current Kenyan Ministry of Health testing guidelines.
3) Standard aPS uses standard rapid antibody tests to confirm prevalent (i.e., seropositive HIV status) in accordance with current Kenyan Ministry of Health testing guidelines

21.2. Schedule of Procedures, Intervention Period POC HIV-1 RNA Testing Cohort

SCHEDULE OF PROCEDURES - INTERVENTION PERIOD

Procedures	Visit 1	Visit 2
Visit week	**WK0**	**WK 6[1]**
Date of visit		
Eligibility Screening	X	
Informed Consent (Consent 2)	X	
Contact Information	X	
Sociodemographic Questionnaire	X	
Risk Assessment Questionnaire	X	
HIV Counseling and Testing[2]	X	
Intimate Partner Violence Assessment[3]	X	
Offer Enhanced Assisted Partner Services if Eligible (Consent 3)[3]	X	
Offer ART Cohort Enrolment (Consent 5)[3]	X	
Sample storage	X	
Assessment of Linkage to Care, ART, Disclosure, and Self-Report of Partner HIV Status[3]		X
Total Blood Volume per Visit (mL)	4	

1) Week 6 procedures will be conducted for HIV-infected participants only.
2) HIV testing will be performed with X-pert testing, followed with rapid antibody tests in RNA positive samples to confirm prevalent (i.e., seropositive HIV status).
3) Only for HIV-infected patients (both AHI and prevalent cases). Enhanced aPS includes POC X-pert HIV-1 RNA testing, followed with rapid antibody tests in RNA positive samples to confirm prevalent (i.e., seropositive HIV status).

21.3. Schedule of Procedures, Partner Testing

SCHEDULE OF PROCEDURES for PARTNER TESTING – OBSERVATION AND INTERVENTION PERIODS

Procedures	Visit 1	Visit 2
Visit week	**WK0**	**WK 6[1]**
Date of visit		
Confirmation of partner's identity	X	
Informed Consent (Consent 4)	X	
Contact Information	X	
Sociodemographic Questionnaire	X	
Risk Assessment Questionnaire	X	
HIV Counseling and Testing[2]	X	
Intimate Partner Violence Assessment[3]	X	
Offer Assisted Partner Services if Eligible (Consent 3)[3]	X	
Offer ART Cohort Enrolment if HIV Positive (Consent 5)[4]	X	
Offer PrEP Cohort Enrolment if HIV Negative (Consent 6)[4]	X	
Sample storage[4]	X	
Assessment of Linkage to Care, ART, Disclosure, and Self-Report of Partner HIV Status[3]		X
Total Blood Volume per Visit (mL)	4	

1) Week 6 procedures will be conducted for HIV-infected partners only.
2) In the observation period, HIV testing will be performed with standard rapid antibody tests to confirm prevalent (i.e., seropositive HIV status). In the intervention period, HIV testing will be performed with standard rapid antibody tests when tested at home or another private location, and with X-pert testing, followed with rapid antibody tests in RNA positive samples to confirm prevalent (i.e., seropositive HIV status) when tested at the research clinic.
3) Only for HIV-infected partners in the intervention period
4) Only for partners of patients in the intervention period

21.4. Schedule of Procedures, Immediate ART Cohort

SCHEDULE OF PROCEDURES, IMMEDIATE ART COHORT

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Visit Month (Study Month = 28 days)	**M0**	**WK 2**	**M1**	**WK 6**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Date of visit															
Eligibility Screening	X														
Informed Consent (Consent 5)	X														
Contact Information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sociodemographic Questionnaire	X														
Risk Assessment Questionnaire	X					X			X			X			X
HIV Counseling and Testing[1]	X	X	X		X	X			X						
Intimate Partner Violence Assessment	X			X		X			X			X			X
Risk Reduction Counselling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mental Health Assessment	X														X
HIV-Positive Cohort Enrolment Questionnaire	X														
Medical History	X					X			X			X			X
Physical Exam, including collection of vaginal and/or rectal swabs as indicated	X					X			X			X			X
Hepatitis B Vaccination[2]	X		X						X						
Qualitative Interview (if consented for this procedure, Consent 7)		(X)				(X)			(X)			(X)			(X)
ART Initiation and Refills	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ART Adherence Counselling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ART Adherence Assessment		X	X		X	X	X	X	X	X	X	X	X	X	X
Co-trimoxazole Counseling and Refills	X		X		X	X	X	X	X	X	X	X	X	X	X
TB Assessment, Isoniazid Counseling and Preventive Therapy if Eligible[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test (women only)[4]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Urinalysis[5]	X														X

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Urine collection for STI testing (men only)	X					X			X			X			X
Hepatitis B Surface Antigen	X														
Hepatitis C Antibody[6]	X														
RPR with TPHA if Positive	X														X
Cryptococcal Antigen[7]	X														
Complete Blood Count[5]	X														
Creatinine[5]	X														X
Glucose[5]	X														X
Cholesterol[5]	X														X
ALT[5]	X														
CD4 Count	X								X						X
Viral Load	X								X						X
Sample Storage	X								X						X
Total Blood Volume per Visit (mL)	20	0	0	0	0	0	0	0	10	0	0	0	0	0	20

1. HIV testing will be performed with standard rapid antibody tests baseline to confirm prevalent (i.e., seropositive HIV status). For AHI cases, standard rapid antibody tests will be performed at baseline, week 2, month 1, month 2, month 3, and month 6 as needed, to document seroconversion.
2. HBV vaccination (with doses at baseline, month 1, and month 6) should be provided if at high risk for HBV transmission (i.e., FSW, MSM, or male sex worker), as evaluated by the Risk Assessment Questionnaire administered at the baseline and follow-up visits as above.
3. Isoniazid preventive therapy will be considered for ART-naïve individuals who defer ART and for persons taking ART for at least 3 months, in order to avoid potential difficulties with medication adherence and adverse drug effects. Assessment for active TB will be conducted at every cohort visit, as per Kenya National Guidelines.[1]
4. Pregnancy testing should be performed at baseline and as clinically indicated thereafter, as per Kenya National Guidelines.[1]
5. Per Kenya National guidelines, we will assess hemoglobin (as a complete blood count), creatinine, glucose, lipids, and a urinalysis at baseline. ALT will not be ordered at baseline unless there is a specific indication, such as a history of hepatitis, signs or symptoms of liver disease, or risk of liver disease due to alcohol abuse, chronic HBV or HCV infection, or concomitant hepatotoxic drug use. Safety monitoring labs with abnormal values at baseline will be repeated if clinically indicated.[1]
6. If injection drug use history, as per Kenya National Guidelines.[1]
7. If CD4 count <100 cells/µL.

[1] Ministry of Health. **Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya, 2016**. National AIDS and STI Control Programme. Nairobi, Kenya: 2016.

21.5. Schedule of Procedures, PrEP cohort

SCHEDULE OF PROCEDURES, PREP COHORT

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Visit Month (Study Month = 28 days)	**M0**	**WK 2**	**M1**	**M2**	**M 3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Date of visit														
Eligibility Screening	X													
Informed Consent (Consent 6)	X													
Contact Information	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sociodemographic Questionnaire	X													
Risk Assessment Questionnaire	X				X			X			X			X
HIV Counseling and Testing[1]	X		X		X			X			X			X
Intimate Partner Violence Assessment	X				X			X			X			X
Risk Reduction Counselling	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mental Health Assessment	X													X
Medical History	X				X			X			X			X
Physical Exam, including collection of vaginal and/or rectal swabs as indicated	X				X			X			X			X
Hepatitis B vaccination[2]	X		X					X						
Qualitative Interview (if consented for this procedure, Consent 7)		X			X			X			X			X
PrEP Initiation and Refills[3]		X	X	X	X	X	X	X	X	X	X	X	X	X
PrEP Adherence Counselling[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PrEP Adherence Evaluation[3]		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test (women only)[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X													X
Urine collection for STI testing (men only)	X				X			X			X			X
Hepatitis B Surface Antigen	X													

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
RPR with TPHA if Positive	X													X
Creatinine	X		X		X			X						X
Sample storage	X		X		X			X			X			X
Total Blood Volume per Visit (mL)	10	0	4	0	8	0	0	8	0	0	8	0	0	10

1. HIV testing will be performed with standard rapid antibody tests at all visits. At baseline, HIV testing will include *X-pert® HIV Qual* testing to test for AHI.
2. HBV vaccination (with doses at baseline, month 1, and month 6) should be provided if at high risk for HBV transmission (i.e., FSW, MSM, or male sex worker), as evaluated by the Risk Assessment Questionnaire administered at the baseline and follow-up visits as above.
3. PrEP will be offered after review of baseline test results (creatinine, HBsAg) to all participants in this seronegative cohort. PrEP will be continued until the seropositive partner has achieved virologic suppression on ART or until the partnership has dissolved, provided the participant does not have a new HIV-infected partner. PrEP counseling will be offered at each visit regardless of uptake. After PrEP initiation, each visit will include adherence counselling, adherence evaluation, and refills until PrEP is discontinued. A MEMS electronic cap will be issued to a subset of participants in order to monitor adherence.
4. Pregnancy testing should be provided at every visit. PrEP will be discontinued for any woman who becomes pregnant in the study. Such individuals will be provided HIV risk reduction counseling and referred for antenatal care.

21.6. Screening Form

Form 1: AHI STUDY ELIGIBILITY FORM

Start time: _____ **End time:** _____ Volunteer ID:

Screening ID: *5-digits auto generated* **Facility name:** _____

Date: ____/ ____/ ____

Gender: ____ Male ___ Female

Estimated age: ____ (yrs)

Permission script: We are currently conducting a study in this facility for which only some patients are eligible. We don't need your name or contact information in order to see if you're eligible. Is it OK if I ask a few questions to see if you are eligible? This will take about one minute.

Research staff initials documenting verbal permission to screen: _____

Axillary temperature: _____

DOB: (dd/mmm/yyyy): ____/ ____/ ____ Actual age: ____ (yrs)

(For participants aged 18 and 39, please calculate the exact age in years and months and document in the comments section on the flip side of the form)

HIV status:

Ever tested for HIV? __Yes __ No

HIV Status: __ Positive __ Negative/ Unknown

If HIV positive: registered in care: __Yes __ No

If HIV positive: on ART: __Yes __ No

Patients not in care or on ART should be counselled accordingly.

Have you previously enrolled in this study? __Yes __ No

If yes, which facility: _____ Date: (dd/mmm/yyyy): ____/ ____/ ____
(Do not proceed with screening and enrolment if the patient has been enrolled in TMP within 6 months at any of the TMP study sites)

If between 18 and 39 years of age and not known HIV positive, calculate risk score below:

Characteristic	**Present = Yes (circle score)**	**Absent = No (circle score)**
Age **18-29 years**	1	0
Reported **fever**	1	0
Reported **diarrhoea**	1	0
Reported **fatigue**	1	0

Reported **body aches**	1	0
Reported **sore throat**	1	0
Reported **genital ulcer**	3	0
TOTAL SCORE		

If score is 2 or more (≥ 2), invite patient for Tambua Mapema Plus study.

Research staff Initials: _____

If enrolled, place sticker with participant ID number in box in right hand corner above. Please confirm all screening data above after written consent is obtained:

Research staff Initials: _____

Please capture reason not enrolled in the table below.

Reason	**Check all applicable**
Not eligible	
Too ill	
Too busy, in a hurry	
Need to ask partner	
Temporary visitor (<2 weeks in study area)	
Outside catchment area (>30 km from the KEMRI Mtwapa or Kilifi Research Clinic)	
Never been sexually active	
Doesn't want to participate in research	
Patient enrolled in TMP study within 6 months at any of the TMP study sites	
Patient found to be under or over age [correct age and initial above]	
Patient found to have known HIV-positive status [correct and initial above]	
Patient does not want to take a HIV test	
Other, describe: _____ _____	

Comments:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

21.7. Talking Points, Recruitment and Screening

Observation Period

The following talking points will be made:

1. The Kenya Medical Research Institute (KEMRI) is conducting a study to find better ways of preventing and treating illnesses common in Mombasa and Kilifi counties.
2. In this study, we want to see how young adults (18-39 years of age) who seek urgent health care are evaluated upon care seeking. We are interested in what tests and treatments are offered, including whether HIV testing is performed.
3. If you know your HIV status and are HIV-infected, this study is not for you, since different tests and treatments may be offered to persons living with HIV.
4. If you are eligible, the study involves a short computer survey on your reason for seeking care, the last time you tested for HIV, and whether you have any HIV risk factors. We will also ask permission ascertain whether you receive an HIV test as part of your care today, and to contact you for further information on care options if you test HIV positive.
5. May we ask you a few questions to determine whether you are eligible to participate? Participation is voluntary and will not affect your care today.
6. Please note that we will not collect your name or any other information that could identify you in order to see if you are eligible.

Intervention Period

The following talking points will be made, and formed the basis for the script of the brief 2-minute explainer video (see Section 21.10) that will be used to present the study rationale and overview:

1. The Kenya Medical Research Institute (KEMRI) is conducting a study to find better ways of preventing and treating illnesses common in Mombasa and Kilifi counties.
2. In this study, we want to see how young adults (18-39 years of age) who seek urgent health care are evaluated upon care seeking. We are providing HIV testing as part of this study, including tests for very recent HIV infection that may cause symptoms similar to the flu.
3. If you know your HIV status and are HIV-infected, this study is not for you, since different tests and treatments may be offered to persons living with HIV.
4. If you are eligible, the study involves a short computer survey on your reason for seeking care and any HIV risk factors you have. We will then test you for HIV using the Xpert HIV test to check for very recent infection. If you test positive on the Xpert HIV test, we will carry out an additional test for HIV using standard rapid tests as at all VCT sites in Kenya. If you test positive for HIV on either test, we will review care options and make sure you are well taken care of.
5. May we ask you a few questions to determine whether you are eligible to participate? Participation is voluntary and will not affect your care today.
6. Please note that we will not collect your name or any other information that could identify you in order to see if you are eligible.

21.8. Informed Consent Documents

Number and short title:	ICD	Number of participants / Facilities where ICD will be presented
1. Observation	Observation period consent	N=1375 / 6 health facilities
2. Intervention	Intervention period consent	N=1500 / 6 health facilities
3. Assisted partner notification	Assisted partner services consent for all newly diagnosed	N= 75 / 6 health facilities or KEMRI clinic
4. Partner testing	Partner testing consent (prevalent and AHI evaluation)	N=300 / partner home or KEMRI clinic
5. Immediate treatment	Cohort follow-up for HIV positive patients and partners	N= 75 (and unknown HIV infected partners) / KEMRI clinic
6. PrEP	Cohort follow-up for HIV negative (with PrEP)	N=75 / KEMRI clinic
7. Qualitative	Personal interview	N=60 / KEMRI clinic
8. Staff	Personal interview or focus group	N=60 / 6 health facilities

1. Observation Period

KEMRI-Wellcome Programme Information Sheet and Consent Form for Observation Period

IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION
TAMBUA MAPEMA PLUS

INSTITUTION	INVESTIGATORS
KEMRI – Wellcome Trust	Dr. Eduard Sanders, Dr. Susan Graham, Dr. Elise van der Elst, Mr. Evans Gichuru, Dr. Amin Hassan, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Drs. Steven Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?
KEMRI is a government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. We are conducting a study called Tambua Mapema Plus, which aims to determine how health facilities assess symptoms in young adults seeking care. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?
In this component of the Tambua Mapema Plus study, we want to see how young adults who seek urgent health care for symptoms including fever, fatigue, body pains, diarrhoea, sore throat or genital ulcer disease, are evaluated upon care seeking. We are interested in whether HIV testing is performed and for whom this is done.

We are enrolling **up to 2875 persons** who are between **18-39** years of age and who are seeking urgent health care for symptoms. In 1375 people seeking health care we would like to make observations only. If you consent to participate today, you will be part of this observational study.

If you know your HIV status and are HIV-infected, this study is not for you, since different tests and treatments may be offered to persons living with HIV. If you need a referral for care, we will provide a referral to you today.

In the observation phase, we would like to learn:

1. What symptoms are present upon care-seeking and what tests and treatments are offered by health facility staff.
2. What proportion of people presenting with symptoms will be HIV tested during care-seeking.
3. What proportion of those who test positive for HIV infection would be linked into care, and have their partner invited for testing.

What will it involve for me?
Computer-assisted questionnaire: You will be given a computer-assisted questionnaire about your current symptoms and reason for seeking care, the last time you were tested for HIV, if you know the status of your partner(s), and your recent sexual activity. If you do not want to take the computer-assisted questionnaire, a counsellor will ask questions in person. The interview may take approximately 20 minutes.

The study counsellor would also like to ascertain if you will get tested for HIV today by staff of the health care facility, and what the outcome of the test is.

If you test positive for HIV infection, the counsellor would like to assess if your partner or partners were invited for an HIV-test, and if you were linked to care. To do this, the counsellor will make a follow up assessment at home, at this health facility, or at a venue of your choice approximately 6 weeks after today's visit and ask if you have linked to care, started treatment, and disclosed to your sexual partners. To help us find you, we would like to ask for your contact information (e.g., where you live and your phone number). Study staff will only contact you or visit your home with your permission.

For your time and fare reimbursement, you will be provided with KSh 350 today. If you are found to be HIV-positive and complete the 6-week follow-up visit, you will be provided with KSh 350 for your time and fare reimbursement then as well.

Are there any risks or disadvantages of taking part?
Sharing information about your sexual risk behaviour may seem unrelated to your symptoms, but we appreciate your participation and the minor inconvenience of your completion of our questionnaire.

You may feel embarrassed or uneasy while answering some questions which may be sensitive, for example; "Have you used intravenous drugs in the past 2 months", "When you last had sex with this partner, did you use a condom?" etc. The study counsellors have been trained to ask the questions with respect. You are free to answer or not to answer any question without penalty.

The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are in the study and assume you have a health problem because of your participation. In our recruitment at the site, we will make it clear that we are enrolling young adults seeking care for a variety of symptoms and not recruiting based on any specific diagnosis. We will ensure that the information you provide will remain confidential.

Are there any advantages of taking part?
There are no direct benefits to you for taking part in this study.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you choose not to participate, this will not affect your access to care, including HIV testing and counselling, offered at the health facility you have chosen. We will ask you to give us a reason for choosing not to participate, but you are free not to give us a reason. If you do agree to participate, you can change your mind and withdraw from the study at any time without any consequences.

Who will have access to the information I give?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. Only if you test positive at today's visit will your contact information be obtained on a locator form, to ensure we can follow up with you. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. All of our documents are stored securely in locked cabinets and on password protected computers.

In future, information collected or generated during this study may be used to support new research related to HIV. In all cases, the knowledge gained from this research will be shared in summary form, without revealing individuals' identities. We will not publish or discuss in public anything that could identify you.

Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected.

Who has approved this research?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI has to be approved before it begins, by committees in Kilifi and, the KEMRI scientific and ethics review committee in Nairobi. These committees make sure that every research study is important, and that participants' safety and rights are respected. A description of this clinical trial will be available on http://www.clinicaltrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What if I have any questions?
You are free to ask me any question about this research. If you have any further questions about the study or if you have been harmed by participating in this study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator
KEMRI- Wellcome Trust, Kilifi
P.O. Box 230, Kilifi
Telephone: 0723-593762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi Telephone: 0723-342780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FORM –Observation Period

Impact of a novel HIV-1 RNA testing intervention to detect acute and prevalent HIV infection and reduce HIV transmission –Tambua Mapema Plus

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily

I agree to participate in the study ☐ **Yes** ☐ **No**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to obtain consent from the participant. He or she apparently understood the nature and the purpose of the study and consents to the participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Investigator/designee Signature: _____ **Date:** _____

Investigator/ designee Name: _____ **Time:** _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____
Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

2. Intervention Period

KEMRI-Wellcome Programme Information Sheet and Consent Form for Intervention Period

IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION

TAMBUA MAPEMA PLUS

Institution	INVESTIGATORS
KEMRI – Wellcome Trust	Dr. Eduard Sanders, Dr. Susan Graham, Dr. Elise van der Elst, Mr. Evans Gichuru, Dr. Amin Hassan, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Drs. Steven Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?

KEMRI is a government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?

In this component of the Tambua Mapema Plus study, we want to see if young adults who seek urgent health care for symptoms including fever, fatigue, body pains, diarrhoea, sore throat or genital ulcer disease, are HIV-tested upon care seeking. Early detection of HIV infection is important as immediate treatment will improve the patient's health, and learning one's status may help reduce onward transmission.

We are targeting **up to 2875 persons** who are between **18-39** years of age and who are seeking urgent health care for symptoms. In 1500 people seeking health care we will offer HIV testing, and that is the group we invite you to participate.

If you know your status and are HIV-infected, this study is not for you, since different tests and treatments may be offered to persons living with HIV. If you need a referral for care, we will provide a referral to you today.

In the intervention study, we would like to learn:

1. What symptoms are present upon care-seeking.
2. What proportion of people presenting with **symptoms** such as fever, fatigue, body pains, diarrhoea, sore throat or genital ulcer disease will be HIV-infected.
3. What proportion of those who test positive are willing to start immediate ART, and have their partner invited for testing.

What will it involve if I agree to participate?

Computer-assisted questionnaire: You will be given a computer-assisted questionnaire about your current symptoms and reason for seeking care, the last time you were tested for HIV, if you know the status of your partner(s), and your sexual activity in the last two months. If you do not want to take the computer-assisted questionnaire, a counsellor will ask questions in person. The interview may take approximately 20 minutes.

HIV counselling: You will be given confidential pre- and post- HIV test counselling by a trained counsellor.

HIV test: We will obtain a 4-mL blood sample (a teaspoon) for HIV testing and for storage.

***HIV testing will involve the following*:**

1. An *X-pert® HIV Qual* test will be done today. This test detects HIV in the blood, even in people who were very recently infected. The test will take about 90 minutes to provide your result. Only a small proportion (~1%) of patients with symptoms similar to yours will be found to have acute HIV infection.
2. After the *X-pert® HIV Qual* test, we will test any samples with evidence of HIV infection using standard tests according to Ministry of Health guidelines. These tests will help determine whether the HIV infection is acute (very recent) or prevalent (acquired months or more ago).

The remainder of your sample will be stored for additional tests. If HIV is detected, we will test the amount of virus in the blood and whether this virus is resistant to any medications used to treat HIV. Samples from patients not infected with HIV will be stored for additional tests to identify other infections that may have caused your acute illness. If you give permission, the researchers will store your samples for up to 10 years. However, you can change your mind and withdraw your permission any time.

If you test positive for HIV, we will offer enrolment at the KEMRI clinic nearest you. We will also discuss how we can invite your recent sex partner or partners to come forward for HIV testing at KEMRI. We will evaluate your risk of intimate partner violence, or physical, sexual, or psychological harm by a current or former partner or spouse, and discuss with you another component of the Tambua Mapema Plus study called "assisted partner notification." If you prefer to discuss options to access comprehensive care in the clinic where you will test today or in one of the nearby clinics of your choice, we will support this.

Regardless of your choice about clinical care, we would like to follow up in 6 weeks to determine whether your partner or partners were invited for an HIV-test, and if you were linked to care, and started ART. To do this, the counsellor will make a follow up assessment at home, at this health facility, or at a venue of your choice approximately 6 weeks after today's visit. To help us find you, we would like to ask for your contact information (where you live and your phone number). Study staff will only contact you or visit your home with your permission.

For your time (about 2 hours total) and fare reimbursement, you will be provided with KSh 500 today. If you are found to be HIV-positive and complete the 6-week follow-up visit, you will be provided with KSh 500 for your time and fare reimbursement then as well.

Are there any risks or disadvantages of taking part?
Drawing blood may cause pain, and a bruise may form where the needle enters the vein. Learning about HIV infection may cause stress, and, if you are found to be infected, you may feel isolated. The counsellor will help you prepare for an HIV test and counsel you about the test results.

You may feel embarrassed or uneasy while answering some questions which may be sensitive, for example; "Have you used intravenous drugs in the past 2 months", "When you last had sex with this partner, did you use a condom?" etc. The study counsellors have been trained to ask the questions with respect. You are free to answer or not to answer any question without penalty.

The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are in the study and assume you have a health problem because of your participation. In our recruitment at the site, we will make it clear that we are enrolling young adults seeking care for a variety of symptoms and not recruiting based on any specific diagnosis. We will ensure that your privacy is protected and that your test results will only be known by you, your clinician and the counsellor.

Are there any advantages of taking part?
If you are HIV-infected, you may benefit from additional counselling about care options available in the KEMRI Research Clinics. If you don't know your status or if you have previously tested HIV negative, you may want to test again, especially if you have had unprotected sex. The Kenyan MOH recommends that adult Kenyans test every year, with more frequent testing (every 3 months) for those at higher risk, such as persons with an HIV-positive partner, men who have sex with men, and sex workers. If you are found to be acutely infected with HIV, you will benefit from learning about the HIV infection and how to protect your partners and yourself.

There will be no direct benefit to you from future research using your stored samples and information. However, the information learned may help others. It may take the researchers many years to have any results. In most cases, you will not receive future research results from the researchers.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you choose not to participate, this will not affect your access to care, including HIV testing and counselling, offered at the health facility you have chosen. HIV testing and counselling is available outside of study participation at this facility and at many other facilities in the study area.

We will ask you to give us a reason for choosing not to participate, but you are free not to give us a reason. If you do agree to participate, you can change your mind and withdraw from the study at any time without any consequences.

What happens to the samples?
After the specialized test, the remainder of your sample (about 2 milliliters) will be stored for additional testing such as detection of other viruses that may have caused your acute illness. If HIV infection is diagnosed, additional testing will be performed to determine the amount of virus in the blood and whether this virus is resistant to any medications used to treat HIV. If any sample remains, we ask your permission to use that sample for research related to HIV and how it affects the body. If you give permission, researchers will store your sample for up to 10 years. If you decline to have your sample stored, the sample will not be analyzed further and will be discarded. Future research must first be approved by a KEMRI independent expert committee to ensure that participants' safety and rights are respected.

Who will have access to the information I give?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. Only if you test positive at today's visit will your contact information be obtained on a locator form, to ensure we can follow up with you. This form will be accessed in the event you fail to register for care or miss your 6-week follow-up visit. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. All of our documents and tapes are stored securely in locked cabinets and on password protected computers.

In future, information collected or generated during this study may be used to support new research related to HIV. In all cases, the knowledge gained from this research will be shared in summary form, without revealing individuals' identities. We will not publish or discuss in public anything that could identify you.

Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected.

Who has approved this research?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI has to be approved before it begins, by committees in Kilifi, and the KEMRI scientific and ethics review committee in Nairobi. These committees make sure that every research study is important, and that participants' safety and rights are respected. A description of this clinical trial will be available on http://www.clinicaltrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What if I have any questions?
You are free to ask me any question about this research. If you have any further questions about the study or if you have been harmed by participating in this study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator
KEMRI- Wellcome Trust, Kilifi
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi Telephone: 0723-342780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FORM – Intervention Period

Impact of a novel HIV-1 RNA testing intervention to detect acute and prevalent HIV infection and reduce HIV transmission – Tambua Mapema Plus

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily

(Please tick)

I agree to participate in the study and undergo a test for acute HIV infection

☐ **Yes** ☐ **No**

Sample storage

I agree to have a sample of my blood (i.e. plasma) stored at KEMRI and used to test for other infections causing acute illness, and other tests related to HIV infection, if present.

☐ **Yes** ☐ **No**

Sample shipment

I agree to have a sample of my blood (i.e. plasma) to be transported outside Kenya and used for future testing related to HIV infection. ☐ **Yes** ☐ **No**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to obtain consent from the participant. He or she apparently understood the nature and the purpose of the study and consents to the participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Investigator/ designee Signature: _____ **Date:** _____

Investigator/ designee Name: _____ **Time:** _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____

Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

3. **Assisted Partner Notification**

KEMRI-Wellcome Programme Information Sheet and Consent Form
for Index Patient – Assisted Partner notification

IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION

TAMBUA MAPEMA PLUS

INSTITUTION	INVESTIGATORS
KEMRI – Wellcome Trust	Dr. Eduard Sanders, Dr. Susan Graham, Dr. Elise van der Elst, Mr. Evans Gichuru, Dr. Amin Hassan, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Drs. Steven Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?

KEMRI is a government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?

As you have recently been diagnosed with HIV, you are invited to participate in this part of the study in which we are assessing whether partners of newly diagnosed HIV patients would benefit from prompt notification and evaluation of their HIV status. We would like to enrol up to 75 newly diagnosed patients for this part of the Tambua Mapema Plus study.

In this research, we will assist you in telling your partner or partners about their possible exposure to HIV infection, and their need to confirm their status, without revealing your identity. This process of telling the sexual partners of an HIV-positive person that they have been exposed to HIV is called "assisted partner notification services." Partner notification will be useful to both you and your partner or partners. If a partner is infected with HIV, he or she would benefit from early antiretroviral treatment (ART) if diagnosed. If a partner is not found to be infected, he or she might benefit from pre-exposure prophylaxis (PrEP), which is a medication against HIV that can protect an HIV-negative person from getting infected.

In this study, we want to find out three things:

1. Does assisted partner notification increase the number of people testing for HIV and receiving care?
2. Do the benefits of assisted partner notification services outweigh the costs?
3. Finally, could assisted partner notification lead partners to protect themselves when they test negative for HIV?

What will it involve for me?

Before you agree to participate in this study, we will assess your risk for intimate partner violence (IPV), or physical, sexual, or psychological harm by a current or former partner or spouse. If you have experienced IPV within the past 1 month, you will not be eligible for this component of the Tambua Mapema Plus study. If you are eligible and agree to take part in this component of the study, the following procedures will be carried out at today's visit after you read, discuss, and sign this form.

- We will ask you to provide information on how to contact you, including your address and the address of one or two other people who could help us to locate you if we are unable to reach you through your own contact information.
- You will be asked to take part in the assisted partner notification process by giving us contact information about your sexual partners, in the past one year if your rapid test results are positive or in the past 3 months if your lab results suggest very recent infection. We will keep the contact information secret. The people you identified as your past sexual partners will also be kept secret. Only the staff conducting the study will know that you gave us contact information for your past sexual partners and that you identified these people as your past sexual partners.
- If you inject drugs and share needles, we will ask about persons you have shared needles with in the time periods as described above according to your lab results.
- Next, we will attempt to contact your sexual or needle-sharing partners that you have identified. We will tell them that we have information that they may have been exposed to HIV. We will not reveal your identity when contacting your past partners.
- We will contact your partner or partners by phone or in person and ask that they come to KEMRI for an HIV test at the KEMRI VCT as he or she may have been exposed to HIV. We will not mention any other information. When your partner agrees to come to KEMRI, we will send an SMS with a unique code for each partner to present to VCT; this helps us track the results of our notification service.
- If your partner has no telephone, we will contact your partner based on the name and home or work location information you provide, and invite him or her to present to the KEMRI VCT for testing.
- If we are not able to reach your partner(s) after three attempts or they refuse to be in the study, we will destroy the contact information you provided within 3 months of data collection.
- If you prefer to inform your partner without our assistance, we will request that you give him or her a numbered invitation card to present to the KEMRI VCT for testing. This card will not reveal any other information.
- If we believe you may be at risk for physical, sexual, or psychological harm by a current or former sexual partner or spouse (or a needle-sharing partner, if applicable), we will schedule follow-up visits with you at your home, the KEMRI clinic, or a venue of your choice every week for the first month after enrolment in this study and as needed for any problems that arise, to monitor your risk and provide support and counselling. These follow-up visits will last about 30 minutes. If you report any harm during this study, you will be offered referral to local intimate partner violence (IPV) services.
    - If you feel threatened by IPV and need help, contact the clinician on call, who can be reached 24 hours a day on our helpline at 0715 059254 or through our community section at 0700 471087.
    - If you need to come to the clinic for more intensive IPV monitoring and counselling, you will be reimbursed KSh 500 for your travel costs.
- If you don't want to register at the KEMRI clinic for care, you will be asked to come to the KEMRI once for a follow-up visit 6 weeks after enrolling in this study. At this visit, we will ask you questions about any harm you may have experienced since your HIV test. We will ask you about IPV, if you have disclosed your HIV status to anyone, your sexual behaviours,

and if you have begun any HIV care or treatment. If you are unable to come to the KEMRI clinic for this follow-up visit, we can come meet you at your home or other location you suggest.

- If you miss your follow-up visit, we will try to contact you by telephone to come for the visit. If we can't reach you by telephone, we will go to your home for the follow-up visit. If you don't agree for us to visit your home, you can still participate in the study.
- The enrolment visit for this partner notification study will be reimbursed only if not combined with another visit (your screening visit or a cohort enrolment visit).
- Each 6-week follow-up visit will last about one hour. We will compensate you KSh 500 for your time and for the cost of transportation to follow-up visits.

Are there any risks or disadvantages of taking part?

- Answering questions about your sexual partnerships, including questions about any violence by a partner, may be stressful. An example of such a question is, "Are you in a relationship with a person who forces you to participate in sexual activities that make you feel uncomfortable?" You are free to skip any questions if you do not want to answer them.
- If you participate in the study you may be at risk for IPV from a current or former sexual or needle-sharing partner. As discussed above, we will offer counselling and special monitoring to assist if this happens to you.
- The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are in the study. Because of this, they may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.
- Our staff who contact your partner(s) will not tell your partner(s) who you are, but your partner(s) may be able to guess that it is you. We offer counselling to both you and your partner to address issues that may arise from your HIV testing and partner notification services.
- Participating in this study may cause you to reflect upon your sexual relations. It may result in you deciding to end a sexual partnership. Your sexual partner may also choose to end their relationship with you.
- You have the right to discontinue participating at any time. Your decision to participate will not affect the services that we provide to you.

Are there any advantages of taking part?

You may get no direct benefit from being in this study. The benefits of having partners get tested for HIV infection may apply only to your partners, but may help protect the health of these partners and their sexual partners. There may be other benefits of assisted partner notification that we don't know about now. You or others may benefit in the future from information learned in this study.

What happens if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want to take part or not. If you choose not to participate, this will not affect your access to care or HIV treatment offered at the health facility you have chosen. We will ask you to give us a reason for choosing not to participate, but you are free not to give us a reason. If you do agree to participate, you can change your mind and withdraw from the study at any time without any consequences.

Who will have access to the information about me in this research?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. Only a locator form with your contact information will contain your name; this form will be accessed in the event we need to contact you about results or if you fail to return for your repeat testing. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. All of our documents are stored securely in locked cabinets and on password protected computers.

In future, information collected or generated during this study may be used to support new research related to HIV. In all cases, the knowledge gained from this research will be shared in summary form, without revealing individuals' identities. We will not publish or discuss in public anything that could identify you.

Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Who has approved this research?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI has to be approved before it begins by several national committees who look carefully at planned work. They must agree that the research is important, relevant to Kenya and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.

What if I have any questions?
You are free to ask me any question about this research. If you have any further questions about the study or if you have been harmed by participating in this study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator
KEMRI- Wellcome Trust,
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi Telephone: 0723-342780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FOR STUDY PARTICIPATION

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily.
(Please tick)

I agree to participate in the assisted partner notification process	☐ **Yes**	☐ **No**
I agree to telephone contact if I fail to come for my study visits	☐ **Yes**	☐ **No**
I agree to home visits if I fail to come for my study visits	☐ **Yes**	☐ **No**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to obtain consent from the participant. He or she apparently understood the nature and the purpose of the study and consents to the participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Investigator/ designee Signature: _____ **Date:** _____

Investigator/ designee Name: _____ **Time:** _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____
Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

KEMRI-Wellcome Programme Information Sheet and Consent Form for Partners of Index Patients

IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION

TAMBUA MAPEMA PLUS

INSTITUTION	INVESTIGATORS
KEMRI - Wellcome trust	Dr. Eduard Sanders, Dr. Susan Graham, Dr. Amin Hassan, Mr. Evans Gichuru, Dr. Elise van der Elst, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Dr. Steve Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?

KEMRI is a government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?

You are invited to participate in this study in which we are assessing the impact of notifying and evaluating partners of newly diagnosed HIV patients in reducing HIV-transmission. We would like to enrol up to 300 partners of newly diagnosed patients for this part of the Tambua Mapema Plus study. Early recognition of HIV infection can provide benefits to individuals and society. Many people do not know their HIV status so do not benefit from early treatment. Starting HIV treatment early can improve the body's immune response and protect the health of people with HIV, and can also help reduce the chances of infecting others with HIV. Telling the sexual partners of an HIV-positive person that they have been exposed to HIV is called "assisted partner notification services." Knowing that a sexual partner has tested HIV-positive allows people to know they have been exposed to HIV and that they should get tested.

In this study, we want to find out three things:

1. Does assisted partner notification increase the number of people testing for HIV and receiving care?
2. Do the benefits of assisted partner notification services outweigh the costs?
3. Finally, could assisted partner notification lead partners to protect themselves when they test negative for HIV, or start ART when they test positive for HIV?

What will it involve for me?

Your first visit will continue today after you read, discuss, and sign this form.

- We will offer you HIV testing and counselling either at your home, at a nearby voluntary counselling and testing (VCT) clinic, or at the KEMRI clinic nearest you. You may choose to undergo HIV testing even if you do not want to participate in the study.
- Next, you will complete interview answering questions about your background and health. You may refuse to answer any question.
- If you test positive for HIV infection, there are several services that we will offer you:
    - First, we will offer to link you to care at the clinic of your choice so that you can start ART.

- Second, we will offer help with contacting your sexual partners without revealing your identity. This is called assisted partner notification process. This will require us to interview you about your sexual partners in the last year and locate these partners to inform them about the exposure without revealing your identity.
- Third, you will be asked to participate in a follow-up visit 6 weeks after enrolling in this study. At this visit we will ask you questions about any harm you may have experienced since your HIV test. We will ask you if you have disclosed your HIV status to anyone and if you have begun any HIV care or treatment.
- Fourth, as part of the enrolment process, we will assess your risk for intimate partner violence (IPV), or physical, sexual, or psychological harm by a current or former partner or spouse. If we believe you may be at risk for IPV, we will schedule follow-up visits with you at the KEMRI clinic every week for the first month after enrolment in this study and as needed for any problems that arise, to monitor your risk and provide support and counselling. These follow-up visits will last about 30 minutes. If you report any IPV during this study, you will be offered referral to local IPV services.
- If you miss your follow-up visit, we will try to contact you by telephone to come for the visit. If we can't reach you by telephone, we will go to your home for the follow-up visit. You can still participate in the study even if you don't agree for us to contact you or visit your home.

- If you are contacted as part of the observation period of the Tambua Mapema Plus study, you will receive standard HIV testing and counselling, with referral to counselling and, if you test positive, offer to link you to the HIV care facility of your choice.
- If you are contacted as part of the intervention period of the Tambua Mapema Plus study, the following procedures will be offered:
  - HIV testing will include testing using standard HIV rapid tests as well as a special test for acute HIV infection (very recent infection so the rapid tests are not yet positive). If you agree, a blood sample (4 mL) will be taken for both of these tests and for storage.
  - <u>If you test positive for HIV infection</u>, you are eligible to enrol in a KEMRI study offering antiretroviral therapy (ART) to treat your infection. In addition, we will do a test to see if the drugs used to treat HIV infection (ART) will be effective for you. We may send your blood sample to a collaborating laboratory in South Africa or the UK to do the test for us. If you prefer to be referred for non-research care, we will offer to link you to the HIV care facility of your choice.
  - <u>If you test negative for HIV infection</u>, you are eligible to enrol in a KEMRI study offering medication (Pre-Exposure Prophylaxis, PrEP) to prevent you from getting HIV from your partner.
- Regardless of your test result today, we will compensate you KSh 500 for your time and for the cost of transportation to this study visit and the 6-week follow-up visit, each of which will last about one hour.

Are there any risks or disadvantages of taking part?

- Drawing blood may cause pain, and a bruise may form where the needle enters the vein.
- Answering questions about your background and health, especially questions about sexual health, may be stressful. An example of such a question is, "Are you in a relationship with a person who forces you to participate in sexual activities that make you feel uncomfortable?" You are free to skip any questions if you do not want to answer them.

- The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are in the study. Because of this, they may treat you unfairly or discriminate against you.
- Participating in this study may cause you to reflect upon your sexual relationships, and may result in your or your sexual partners dissolving the relationship.
- You have the right to discontinue participating at any time. Your decision to participate will not affect the services that we provide to you.

Are there any advantages of taking part?
The benefits of being tested are very personal. By learning your status, you may be able to take better care of yourself, partners and/or your family. There may be other benefits of assisted partner notification that we don't know about now. You or others may benefit in the future from information learned in this study.

If you are tested in the intervention period of Tambua Mapema plus and agree to sample storage, there will be no direct benefit to you from future research using your stored samples and information. However, the information learned may help others. It may take the researchers many years to have any results. In most cases, you will not receive future research results from the researchers.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you choose not to participate, this will not affect your access to HIV testing and counselling or to HIV care if needed. HIV testing and counselling, as well as care for HIV-positive individuals, is available outside of study participation at many facilities in the study area. We are happy to provide information on the facilities nearest to you.

We will ask you to give us a reason for choosing not to participate, but you are free not to give us a reason. If you do agree to participate, you can change your mind and withdraw from the study at any time without any consequences.

What happens to the samples?
If you are tested in the intervention period of Tambua Mapema plus and agree to storage, the researchers will store the remainder of your samples (about 2 milliliters) for up to 10 years. However, you can change your mind and withdraw your permission any time. The remainder of your sample after HIV testing for this study will be used for additional tests to identify other viruses to which you may have been exposed. If HIV is detected, the sample will be used for HIV viral load and drug resistance testing. If any sample remains, we ask your permission to use that sample for research related to HIV and how it affects the body. If you give permission, researchers will store your samples for up to 10 years. If you decline to have your sample stored, the sample will not be analysed further and will be discarded. Future research must first be approved by a KEMRI independent expert committee to ensure participants' safety and rights are respected.

Who will have access to information about me in this research?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. Only a locator form with your contact information will contain your name; this form will be accessed in the event we need to contact you about results or if you fail to return for the follow up visit. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be

destroyed. All of our documents are stored securely in locked cabinets and on password protected computers.

In future, information collected or generated during this study may be used to support new research related to HIV. In all cases, the knowledge gained from this research will be shared in summary form, without revealing individuals' identities. We will not publish or discuss in public anything that could identify you.

Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Who has approved this research?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI has to be approved before it begins by several national and international] committees who look carefully at planned work. They must agree that the research is important, relevant to Kenya and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected. A description of this clinical trial will be available on http://www.clinicaltrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What if I have any questions?
You are free to ask me any question about this research. If you have any further questions about the study or if you have been harmed by participating in this study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator
KEMRI- Wellcome Trust,
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi Telephone: 0723-342780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FOR STUDY PARTICIPATION

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily.
(Please tick)

I agree to participate in the study, and undergo an HIV test ☐ **Yes** ☐ **No**

If I test positive for HIV, I agree to telephone contact if I fail to come for my 6-week follow-up visit
☐ **Yes** ☐ **No**

If I test positive for HIV, I agree to a home visit if I fail to come for my 6-week follow-up visit
☐ **Yes** ☐ **No**

For partners contacted as part of the intervention period only,

I agree that my sample will be tested for AHI with a special test at KEMRI. ☐ **Yes** ☐ **No**

I agree to have a sample of my blood (i.e. plasma) stored at KEMRI for tests related to HIV infection (e.g. viral load and drug resistance testing) or other infections causing fever. ☐ **Yes** ☐ **No**

I agree to have a sample of my blood (i.e. plasma) to be transported outside Kenya and used for future testing related to HIV infection. ☐ **Yes** ☐ **No**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to obtain consent from the participant. He or she apparently understood the nature and the purpose of the study and consents to the participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Investigator/ designee Signature: _____ **Date:** _____

Investigator/ designee Name: _____ **Time:** _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____
Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

KEMRI-Wellcome Programme Information Sheet and Consent Form for Participants in the ART Cohort – Immediate Treatment

IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION
TAMBUA MAPEMA PLUS

INSTITUTION	INVESTIGATORS
KEMRI - Wellcome Trust	Dr. Eduard Sanders, Dr. Susan Graham, Dr. Amin Hassan, Mr. Evans Gichuru, Dr. Elise van der Elst, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Dr. Steve Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?
KEMRI is a government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?
You have been diagnosed with HIV infection. This infection may lower your immunity and increase your risk for additional infections in your skin, lungs, gut, or other parts of the body. In addition, you can pass HIV to other people by having unprotected sex with them or by sharing needles used for drug injection.

Starting immediate ART will improve your health and can prevent transmission of the virus to sex partners. In this study, all patients who are newly diagnosed with HIV will be offered immediate antiretroviral therapy (ART). The Kenyan Ministry of Health has recently recommended that all patients with HV infection start ART, regardless of their CD4 count (a marker for how active HIV infection is), due to evidence that early treatment protects health and prevents the spread of HIV.

In this study we want to find out if patients with a new HIV diagnosis will initiate immediate HIV treatment (ART), take their medication correctly, and are able to reduce the HIV virus until it is undetectable in their blood.

You have been invited to participate in this study at the KEMRI Research Clinic nearest you, and if you agree, you will be followed up for 12 months and offered treatment and care as is described below. We would like to enrol up to 75 newly diagnosed patients for this part of the Tambua Mapema Plus study.

What will it involve for me?
If you are eligible and agree to take part in the study, your first visit will continue today after you read, discuss, and sign this form.

- As part of your clinical care, we will provide counselling for immediate ART initiation. During this first ART initiation session today, you will speak to a clinician who will explain the benefits of immediate ART and assess if you are prepared to start. You will then be issued with a starter

pack of drugs for 2 weeks. Two more adherence counselling sessions will be planned if necessary with members of our counselling and clinical team.

- You will be asked to return in two weeks to check whether you are coping well with the drugs and adhering as advised. If no problems are reported, your drugs will be dispensed monthly.
- Co-trimoxazole prophylaxis and isoniazid preventive therapy, if indicated, will also be provided as part of standard clinical care for persons living with HIV infection.
- Your week 6 visit after HIV diagnosis, which we ask of all Tambua Mapema Plus participants regardless of participation in the ART cohort, can be conducted at the nearest KEMRI Clinic or at another location of your choice. At this visit, we will update contact information if needed, and continue counselling and support regarding intimate partner violence (IPV), risk reduction, and ART adherence. We will also screen for TB symptoms or the need to conduct pregnancy testing, if applicable.
- You will be asked to return for follow-up research visits every 3 months. At monthly ART and other medication refills, we will assess your adherence through a questionnaire and pill counts of any pills remaining.
- We would also like to collect data on your health problems and the number of STDs you might have over the next 12 months. If you would like to participate, you will be asked to attend the clinic every 3 months. You are free to attend clinic at any time between your scheduled study visits.
- As part of the enrolment process, we will collect information on your age, marital status, and other sociodemographic characteristics. We will also assess your risk for IPV, or physical, sexual, or psychological harm by a current or former partner or spouse. If we believe you may be at risk for IPV, we will schedule follow-up visits with you every week as needed. These follow-up visits will last about 30 minutes. If you report any IPV during this study, you will be offered referral to local IPV services. We will repeat IPV assessments at week 6 and at months 3, 6, 9, and 12 to monitor for any problems you may experience.
- At every research visit, we will ask you questions about your sexual behaviour and use of condoms. We will use a trained interviewer or a computer to ask you questions about your risk for spreading HIV. Examples of the most personal kinds of questions we may ask include "How many times have you had sexual intercourse in the last week?" and "Have you used intravenous drugs in the past 3 months?" We will also ask if you have smoked, drunk alcohol, or used other recreational drugs since your last visit. We will also offer counselling to reduce your risk of transmitting HIV infection to others at every visit.
- Once a year, you will be asked to undergo an audio-computer assisted self-interview (ACASI) about depression, substance abuse, stigma, and other mental health challenges. You are free not to answer any questions you do not wish to answer. These interviews should take about 20 minutes of your time.
- At each visit, we will also ask questions about your medical history and symptoms. You will have a complete physical examination and a genital exam. For women, we will collect a vaginal swab to test for STDs. For men, we will collect a urine sample to test for STDs. Please note that while the STD testing offered in this study is recommended by the World Health Organization, it is not standard care in Kenya. If you have any STD symptoms at any time during follow-up you can come to the clinic to be examined, and receive treatment.
- Urinalysis will be conducted at baseline and month 12. Women will be offered urine pregnancy testing at any visit on which this is indicated

- For individuals who report anal receptive sex, we will also offer an examination to identify anal ulcers or proctitis, and collect a quarterly rectal swab for gonorrhoea testing and drug sensitivity testing (i.e., testing to find out if the prescribed drugs for gonorrhoea are effective).
- HIV testing to confirm your status will be conducted once at baseline and at week 2 and months 1, 2, 3, and 6 or until seroconversion, if your infection was very recent and you have not yet seroconverted. This is done as part of routine clinical care.
- Blood will be collected at enrolment (20 mL, or ≈2 tablespoons), month 6 (10 mL, or ≈1 tablespoon) and month 12 (20 mL, or ≈2 tablespoons). This blood will be used to test for infections such as syphilis and hepatitis; test the health of your kidneys and liver; and check for common problems such as anaemia, diabetes, and high cholesterol. Your CD4 count (a marker for how active your HIV infection is) and plasma viral load (the amount of HIV in your blood) will also be tested on a regular schedule (every 6 months). We will store the rest of this sample at the KEMRI laboratory for additional tests such as drug resistance testing, as funding permits.
- Because hepatitis B is an important infection in people living with HIV infection, we will test your blood for hepatitis B infection when you enrol in this study. If you are not infected for hepatitis B virus (HBV) and are at risk for this infection (i.e., through male-male sex or sex work), we will offer HBV vaccination, which is recommended for persons at risk for this infection but not currently available in most HIV care clinics in Kenya.
- The medical visit and STD testing should take about 20 minutes of your time. Results of your tests will be available for you 5-10 days after your visit. If you have an STD, you will be given treatment.
- At each scheduled visit, you will receive a travel reimbursement of 400 Kenyan shillings. As for other ongoing studies at the clinic, persons who come to the clinic on the day of their scheduled appointment will receive an additional 100 Kenyan shillings in appreciation of their adherence to the study protocol. All laboratory tests conducted expressly for the purpose of this study will be provided at no cost to you.
- Participants who withdraw from the study early will be asked to complete final visit procedures early if possible and will also be requested to complete a short assessment survey on their reasons for leaving the study.
- Participants may be withdrawn from the study if the study is terminated. The Principal Investigators may withdraw a participant in order to protect his or her safety and/or if he or she is unwilling or unable to comply with required study procedures.

To summarize, if you participate in the study, you will be asked to attend the clinic every 3 months to:

- answer questions about your sexual risk behaviour
- answer questions about symptoms you may have
- have a physical exam that includes inspection of the genital area
- undergo testing for STDs and monitoring of your HIV infection
- receive any medical care that you need at the time
- receive counselling on how to adhere to your ART treatment

Please note that the ART we provide at the clinic, as well as other interventions such as assessment for tuberculosis and isoniazid preventive therapy to prevent tuberculosis, will be provided according to the latest Kenyan guidelines and are therefore standard for care in Kenya.

Procedures to Improve Research Participation

Once you enrol in the study, we will offer 3 strategies to improve the research participation:

1. *Home visits*: If you grant permission, clinic staff will make an appointment to visit you once at your home. During this visit, they will update your tracing locator form with landmarks in the vicinity of your home and take a GPS-way point. This is done in order to help research locate your home on future visits, since descriptions and sketched maps are often not adequate for staff to find you. A GPS machine looks like a big mobile telephone and can take coordinates of any location with a precision of about 5 meters. These coordinates will be used by KEMRI staff only if we need to trace you for an abnormal lab results or missed visit. We believe this technology will help us trace you more discretely, since tracing staff will need to ask fewer questions to locate your residence. Study staff will only come to your home with your permission.
2. *SMS-reminder message*: If you provide us with a mobile phone number, we will send you a reminder message for your clinic appointment 1 day in advance. If you do not want to receive such a message, please let us know either now or at any time in the future.
3. *Fingerprint scan*: To help us keep track of who is enrolled in our clinic, we will ask you to put your right index finger on a small machine that can scan your finger print. This will be done at each clinic visit and will take less than 5 seconds. This scan will translate into a unique identification number that will be added to your study ID card, and will be accessible only to our staff.

Are there any risks or disadvantages of taking part?
The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are in the study. Because of this, they may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

Drawing blood may cause pain, and a bruise may form where the needle enters the vein. The genital or pelvic examination may also cause minimal discomfort or be stressful, as can collection of genital samples (and rectal samples, if anal sex is reported). In addition, the questionnaires and physical examination may be stressful for some people. We recognize that participating in these research procedures may involve more stress and discomfort than you might experience if you were not participating.

Are there any advantages of taking part?
If you chose to participate in this study, you will help us to learn how HIV is being spread in Kilifi County and how you can help stop it. You will also help us to learn about the problems and needs of HIV-infected patients at our clinic. By having regular (every 3 months) testing and treatment for STDs, you may decrease the risk that you could transmit HIV infection to other people. By participating in detailed interviews and the audio computer-assisted self-interview, you may learn more about your own risk of transmitting HIV to others than you would in a less intensive counselling visit. However, it is also possible that you will have no direct personal benefit and will only contribute to an increase in knowledge about HIV in the community.

There will be no direct benefit to you from future research using your stored samples and information. However, the information learned may help others. It may take the researchers many years to have any results. In most cases, you will not receive future research results from the researchers.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you choose not to participate, this will not affect your access to HIV care and treatment. We will ask you to give us a reason for choosing not to participate, but you are free not to give us a reason. If

you do agree to participate, you can change your mind and withdraw from the study at any time without any consequences.

If you choose not to participate in the study, you will be offered referral for comprehensive HIV care, including ART, and risk reduction counselling in one of the many clinics that now offer these services free of charge. If you have symptoms of an STD or are concerned about a recent sexual exposure, you may also receive STD testing in our laboratory free of charge.

What happens to the samples?
With your permission, the remainder of your blood samples (about 2 milliliters) will be stored for up to 10 years at the KEMRI laboratory for additional tests such as HIV viral load and drug resistance testing, as funding permits. If the storage period will need to be extended, we will seek for approval from the ethics committee.

Your samples will be labelled only with your study identification number and the code linking this number to your name will be kept in a computer with restricted access. Future research on your specimens will involve research on HIV, other infectious diseases associated with HIV, common viruses and infections people in this community are exposed to, and the body's response to infection.

Your stored blood may also be sent to other expert laboratories that are not based in KEMRI, for more specialized tests. It is not known at this time to which laboratories these samples will be shipped. However, we will only use the stored blood to do useful studies on HIV and permission will be obtained from the KEMRI/National ethics committee. In all cases your privacy is protected because blood is stored with a number not a name on it. If you decline to have your sample stored, the sample will not be analysed further and will be discarded.

Who will have access to information about me in this research?
Your identity and test results will remain confidential, known only to the investigators. Your information will be kept in your study file and be marked with your study ID number. To protect your confidentiality, your name will not appear anywhere in this file. Your signed consent and locator forms which have your name will be locked separately from your file. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. Our computerized databases are also password-protected, so any unauthorized cannot access them.

In our clinic, only study staff involved directly in patient care and research will have access to your record. In addition, Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

In future, information collected or generated during this study may be used to support new research on HIV prevention and care by other researchers in Kenya and other African countries. In all cases, we will only share information with other researchers in ways that do not reveal individual participants' identities. For example, we will remove information that could identify people, such as their names and where they live, and replace this information with number codes. Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected by our staff.

Who has approved this research?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI has to be approved before it begins by several national and international] committees who look carefully at planned work. They must agree that the research is important, relevant to Kenya and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.

If you have any further questions about the study, or if you have been harmed by participating in this study, you are free to ask questions of any staff at any time and you can also contact:

Dr. Eduard Sanders
KEMRI- Wellcome Trust,
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi Telephone: 0723-342780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FOR STUDY PARTICIPATION

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily.
(Please tick)

I agree to participate in the study, and to complete study procedures ☐ **Yes** ☐ **No**

I agree to have a sample of my blood (i.e. plasma) stored at KEMRI and used for tests related to HIV infection (e.g. viral load and drug resistance testing) or other infections causing fever.
☐ **Yes** ☐ **No**

I agree to have a sample of my blood (i.e. plasma) to be transported outside Kenya and used for future testing related to HIV infection. ☐ **Yes** ☐ **No**

I agree to telephone or SMS contact ☐ **Yes** ☐ **No**

I agree to home visits if I fail to come for my study visits ☐ **Yes** ☐ **No**

I agree to having my fingerprint scanned each time I visit the clinic ☐ **Yes** ☐ **No**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to obtain consent from the participant. He or she apparently understood the nature and the purpose of the study and consents to the participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Investigator/ designee Signature: _____ **Date:** _____

Investigator/ designee Name: _____ **Time:** _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____
Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

6. PrEP for Seronegative Partners in Discordant Partnerships

KEMRI-Wellcome Programme Information Sheet and Consent Form for Participants

in the PrEP Cohort

IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION
TAMBUA MAPEMA PLUS

INSTITUTION	INVESTIGATORS
KEMRI - WELLCOME TRUST	Dr. Eduard Sanders, Dr. Susan Graham, Dr. Amin Hassan, Mr. Evans Gichuru, Dr. Elise van der Elst, Dr. Clara Agutu, Mr. Peter Mugo
UNIVERSITY OF WASHINGTON	Dr. Steve Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?
KEMRI is a government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?
In this component of the Tambua Mapema Plus study, we want to study the uptake of, and adherence to, pre-exposure prophylaxis (PrEP) for reducing HIV transmission in the uninfected partners of persons recently diagnosed with HIV. As your partner has been diagnosed with HIV, you have an increased chance of getting HIV if you have unprotected sexual intercourse. You can reduce this chance if you start PrEP. PrEP is the use of antiretroviral medicines to prevent infection in uninfected persons who are at risk of infection, and is similar to what is done in government programs to prevent HIV transmission from an infected mother to her baby. PrEP is approved for use by the HIV negative partner in a serodiscordant sexual partnership (in which one partner is HIV negative and the other partner is HIV positive). PrEP has been shown to reduce the risk of getting HIV when taken at every day as prescribed.

In this study, uninfected persons with an HIV-infected partner diagnosed through our HIV-1 RNA testing intervention (Tambua Mapema Plus) will be invited to enrol at the nearest KEMRI Research Clinic. These partners will be counselled to mutually disclose HIV status in order to support each other, and will be provided ongoing couples counselling and support throughout their study participation. PrEP will be offered to these persons during the time it takes for their HIV-infected partners to start and continue ART until the virus becomes undetectable. This usually takes 6-12 months. ART will be offered to your partner, who may also be enrolled at the nearest KEMRI Research Clinic. We would like to enrol up to 75 uninfected partners of newly diagnosed HIV patients for this part of the Tambua Mapema Plus study.

What will it involve for me?

If you are eligible and agree to take part in the study, your first visit will continue today after you read, discuss, and sign this form.

- At this enrolment visit, you will be asked to provide information on how to contact you, including your address and the address of one or two other people who could help us to locate you if we are unable to reach you through your own contact information.
- We will then interview you to find out more about your past and present sexual behaviours and partnerships. This may include sensitive questions about past or current physical or sexual violence against you. Examples of questions you may be asked include: "With how many different people, including your spouse (s) have you had sex in the past week?" and "In past 3 months: have you used intravenous drugs?" You may refuse to answer any question.
- As part of the enrolment process, collect information on your age, marital status, and other sociodemographic characteristics, provide risk reduction counseling to decrease your risk of acquiring HIV infection, and conduct a baseline mental health assessment to determine if you need referral for depression or for alcohol or other drug abuse. We will also assess your risk for intimate partner violence (IPV), or physical, sexual, or psychological harm by a current or former partner or spouse. If we believe you may be at risk for IPV, we will schedule follow-up visits with you every week as needed. These follow-up visits will last about 30 minutes. If you report any IPV during this study, you will be offered referral to local IPV services.
- Before starting PrEP, we will check your overall health to see if it is safe for you to take PrEP. A blood specimen (10 mLs) will be taken to test for HIV infection, check your kidney function, screen for syphilis, and to determine whether you have chronic hepatitis, which would make you ineligible for PrEP.
- A urinalysis will be conducted for all patients (both men and women), and urine pregnancy testing will be conducted for all women, as pregnant women are also not eligible for PrEP in this study.
- If you are not ready to start PrEP at this time, we will continue to follow you and offer advice about the benefits and risks of taking PrEP for you and your partner.
- If you are not infected for hepatitis B virus (HBV) and are at risk for this infection (i.e., through male-male sex or sex work), we will offer HBV vaccination, which is recommended for persons at risk for this infection but not currently available in most HIV care clinics in Kenya.
- If you are interested to start PrEP, we will arrange that you speak to a member of our counselling and clinical team who will discuss with you the drug regimen for PrEP, and provide adherence counselling. Your lab results will be checked, and if you have no contraindication to PrEP, you will receive a starter pack of drugs at a return visit in 2 weeks. You will be asked to return 2 weeks after that visit (i.e., one month after enrolment) for HIV counselling and testing, blood collection (4 mLs) to test your kidney function, and to check that you are taking the drugs as advised. We will give you adherence counselling so that you will be motivated to take the drug every day.
- At medication refills, we will assess your adherence through a questionnaire and pill counts of any pills remaining. For a subset of participants, we will monitor adherence using a special pill bottle that records openings of the pill cap. We will also provide brief counselling to support adherence and promote risk reduction at every study visit. If you are doing well, your drugs will from then on be dispensed monthly, for the first three months, and then be provided for 3 months at a time.

- We will invite you for four quarterly follow up visits after your enrolment visit. These visits may be planned in conjunction with your partner if you wish. You will have the following procedures as part of your study visits:
    - Medical history and physical examination
    - Collection of a vaginal swab for women, a urine sample for men, and a rectal swab (if anal sex is reported) to test for sexually transmitted infections.
    - HIV testing and counselling, risk assessment and risk reduction counselling and family planning counselling.
    - Assessment for the risk of intimate partner violence (IPV)
    - Blood specimens will be collected at month 1 (4 mLs); months 3, 6, and 9 (8 mLs); and month 12 (10 mLs). These specimens will be used for HIV testing at months 3, 6, 9, and 12; kidney function tests at months 1, 3, 6, and 12; and repeat syphilis testing at month 12.
    - In women, a urine pregnancy test will be conducted at every study visit to ensure that pregnant women do not take PrEP in the study.
    - For all participants (men and women), a urinalysis will be repeated at month 12.
- Once a year, you will be asked to undergo an audio-computer assisted self-interview (ACASI) about depression, substance abuse, stigma, and other mental health challenges. You are free not to answer any questions you do not wish to answer. These interviews should take about 20 minutes of your time.
- At each clinic visit, you will receive a travel reimbursement of 400 Kenyan shillings. As for other ongoing studies at the clinic, persons who come to the clinic on the day of their scheduled appointment will receive an additional 100 Kenyan shillings in appreciation of their adherence to the study protocol. All laboratory tests conducted expressly for the purpose of this study will be provided at no cost to you.
- If you do not come back within two weeks of a follow-up visit, we will try to contact you by telephone to come for the visit. If we can't reach you by telephone, we will go to your home for the follow-up visit. You can still participate in the study even if you do not agree for us to visit your home when you miss follow-up visits.
- Participants who withdraw from the study early will be asked to complete final visit procedures early if possible and will also be requested to complete a short assessment survey on their reasons for leaving the study.
- Participants may be withdrawn from the study if the study is terminated. The Principal Investigators may withdraw a participant in order to protect his or her safety and/or if he or she is unwilling or unable to comply with required study procedures.

PrEP will be continued for at least 6-12 months after your partner starts ART, or until the virus becomes undetectable in your partner.

Are there any risks or disadvantages of taking part?

- Drawing blood may cause pain, and a bruise may form where the needle enters the vein. The genital or pelvic examination may also cause minimal discomfort or be stressful, as can collection of genital samples (and rectal samples, if anal sex is reported). In addition, the questionnaires and physical examinations may be stressful for some people. We recognize

participation in these research procedures may involve more stress and discomfort than you might experience if you were not participating.

- Answering questions about your sexual partnerships, including questions about any violence by a partner, may be stressful. An example of such a question is, "Are you in a relationship with a person who forces you to participate in sexual activities that make you feel uncomfortable?" You are free to skip any questions if you do not want to answer them.
- The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are in the study. Because of this, you may experience discrimination or personal problems such as interpersonal violence (IPV). If you do, let the study staff know and we will try to help you with these issues. For example, family or friends may worry, get upset or angry, or assume you are HIV infected and treat you unfairly, especially when they are not aware of your study participation and learn about it later.
- Participating in this study may cause you to reflect upon your sexual relations. It may result in you deciding to end a sexual partnership. Your sexual partner may also choose to end their relationship with you.
- FOR WOMEN: If you become pregnant during the study we will stop providing you with PrEP, counsel you about how to reduce your HIV risk, and refer you to antenatal care.
- Truvada®, the drug used for PrEP, is usually safe and causes few side effects. The most commonly reported side effects include headache, nausea, diarrhoea, vomiting, rash, depression and mild, painless darkening of the skin on their palms and/or soles of feet. Additional side effects you may experience include generalized weakness, dizziness, abdominal pain, kidney damage or failure, liver problems, shortness of breath, allergic reaction, bone pain or changes, muscle pain and weakness, or sleeping problems.
- Even with very high adherence, you will continue to be at low risk for HIV infection, since PrEP is not 100% effective. If you don't take PrEP daily as prescribed, there is a possibility that you will become HIV-infected while taking PrEP, which could potentially happen with a drug-resistant HIV strain.
- If you get infected while taking PrEP, you will need HIV care and treatment with a combination of at least three HIV drugs to which the infected virus is sensitive. PrEP will be stopped if HIV infection is detected and drug resistance testing will be performed.
- If drug resistance to one or both drugs in Truvada® is present, you have the option of taking different ART drugs that are available in Kenya. We will provide you with treatment here at the study research clinic, or we can refer you to another health facility of your choice where you may receive care and treatment.
- You have the right to discontinue participating at any time. Your decision to participate will not affect the services that we provide to you.
- You may also want to stop taking PrEP if the partnership with your HIV-positive partner ends and you are not sexually active with another partner who could have HIV infection.
- You will be counselled on reducing your risk for getting HIV and protecting yourself.

Procedures to Improve Research Participation

Once you enrol in the study, we will offer 3 strategies to improve the research participation:

1. *Home visits*: If you grant permission, clinic staff will make an appointment to visit you once at your home. During this visit, they will update your tracing locator form with

landmarks in the vicinity of your home and take a GPS-way point. This is done in order to help research locate your home on future visits, since descriptions and sketched maps are often not adequate for staff to find you. A GPS machine looks like a big mobile telephone and can take coordinates of any location with a precision of about 5 meters. These coordinates will be used by KEMRI-staff only if we need to trace you for an abnormal lab results or missed visit. We believe this technology will help us trace you more discretely, since tracing staff will need to ask fewer questions to locate your residence. Study staff will only come to your home with your permission.

2. *SMS-reminder message*: If you provide us with a mobile phone number, we will send you a reminder message for your clinic appointment 1 day in advance. If you do not want to receive such a message, please let us know either now or at any time in the future.
3. *Fingerprint scan*: To help us keep track of who is enrolled in our clinic, we will ask you to put your right index finger on a small machine that can scan your finger print. This will be done at each clinic visit and will take less than 5 seconds. This scan will translate into a unique identification number that will be added to your study ID card, and will be accessible only to our staff.

Are there any advantages of taking part?
PrEP is known to prevent getting HIV when taken correctly. The information we collect from this study will add to the knowledge to protect people from contracting HIV. You and or your partner may benefit from information learned in this study.

There will be no direct benefit to you from future research using your stored samples and information. However, the information learned may help others. It may take the researchers many years to have any results. In most cases, you will not receive future research results from the researchers.

What will happen if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you choose not to participate, this will not affect your access to HIV testing and counselling services or to HIV care should you become infected. Unfortunately, PrEP is not yet available outside of research settings in Kenya, but you will have access to other prevention methods, including risk reduction counselling. We will ask you to give us a reason for choosing not to participate, but you are free not to give us a reason. If you do agree to participate, you can change your mind and withdraw from the study at any time without any consequences.

What happens to the samples?
After using the blood sample for the HIV test, kidney function test, and syphilis test, the remaining sample (about 2 milliliters) will be stored. We ask your permission to use that sample for research related to PrEP adherence and to HIV and how it affects the body. If you give permission, researchers will store your samples for up to 10 years in the laboratory at KEMRI for future testing either in Kenya or at a partner laboratory abroad. If you decline to have your sample stored, the sample will not be analysed further and will be discarded. Future research must first be approved by a KEMRI independent expert committee to ensure that participants' safety and rights are respected.

Who will have access to information about me in this research?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. Only a locator form with your contact information will contain your name; this form will be accessed in the event we need to contact you about results or if you fail to return for your study visits. We will retain a link between your study number and your contact information for 6

years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. All of our documents/tapes are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research will be shared in summary form, without revealing individuals' identities. We will not publish or discuss in public anything that could identify you. Study monitoring and regulatory staff, including KEMRI and other local, US, international regulatory entities, and the company (Gilead) that is supplying the Truvada® used for this study may review study records to make sure that study procedures are being done safely and ethically. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Who has approved this research?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI has to be approved before it begins by committees in Kilifi and by the KEMRI scientific and ethics review committee in Nairobi. These committees make sure that every research study is important, and that participants' safety and rights are respected.

What if I have a research-related injury?
The study staff will monitor your health while you are in this study. If you have any health problems between visits, please contact the study staff. If they are not immediately available, leave a voice message. If you have a medical emergency that requires immediate care, please report to the nearest health facility or to the clinician on call, who can be reached 24 hours a day on our helpline at 0715 059254 or through our community section at 0700 471087.

If you have a reaction to the medications or incur an injury as a result of participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of the team of researchers at this clinic if you feel that you had such a reaction or injury because of taking part in this study. There is not a program of monetary compensation through this institution. In addition, the U.S. National Institutes of Health (NIH) does not have a mechanism to provide compensation for research-related injury. If you require medical care that the study clinic cannot provide, the study doctors will refer you to the appropriate services or organizations that can provide care for the injury. You do not give up any legal rights by signing this consent form.

What if I have any questions?
You are free to ask me any question about this research. If you have any further questions about the study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator
KEMRI- Wellcome Trust,
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi Telephone: 0723-342780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FOR STUDY PARTICIPATION

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily.
(Please tick)

I agree to participate in the study, and to complete study procedures ☐ **Yes** ☐ **No**

I agree to have a sample of my blood (i.e. plasma) stored at KEMRI for tests related to HIV infection (e.g. viral load and drug resistance testing) in the event that I acquire this infection, or to test for other infections causing fever. ☐ **Yes** ☐ **No**

I agree to telephone or SMS contact ☐ **Yes** ☐ **No**

I agree to home visits if I fail to come for my study visits ☐ **Yes** ☐ **No**

I agree to having my fingerprint scanned each time I visit the clinic ☐ **Yes** ☐ **No**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to obtain consent from the participant. He or she apparently understood the nature and the purpose of the study and consents to the participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Investigator/ designee Signature: _____ **Date:** _____

Investigator/ designee Name: _____ **Time:** _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____
Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

7. Qualitative Interview

KEMRI-Wellcome Programme Information Sheet and Consent Form for Patient Interviews
IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION
TAMBUA MAPEMA PLUS

Institution	INVESTIGATORS
KEMRI – Wellcome Trust	Dr. Eduard Sanders, Dr. Susan Graham Dr. Elise van der Elst, Mr. Evans Gichuru, Dr. Amin Hassan, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Dr. Steven Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?
KEMRI is a Government organisation that carries out health research to learn more about diseases that affect children and adults in Kenya. Sometimes research only involves asking questions of patients about what they know, feel or do. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?
In this component of the Tambua Mapema Plus research, we want to learn more about your knowledge and understanding of what HIV infection is, how transmission can be reduced or prevented. We hope to hold interviews with up to 60 Tambua Mapema Plus study participants in Coastal Kenya. If you are willing to have an in-depth interview, you will be given an appointment at the KEMRI research clinic nearest you within two weeks of your or your partner's HIV diagnosis. If you enroll in the KEMRI ART or PrEP cohort, we will also ask you to undergo brief follow-up interviews at each quarterly visit during the 12-month follow-up period.

Why do you want to talk to me and what does it involve?
You or your partner have recently been found to be infected with HIV as a result of testing performed for the study "Tambua Mapema Plus." We would like to ask you about your understanding of HIV infection, aspects of prevention, and knowledge of available care in an interview. The interview will include questions about whether and to whom you or your partner have disclosed your recent HIV test results, if you have had unprotected sex, and your experiences and opinions about taking antiretroviral medications to treat or prevent HIV transmission.

If you enroll in the KEMRI ART or PrEP cohort, we would also like to ask you questions about how your understanding of HIV infection changes over your follow-up. If you agree to have these follow-up interviews, we would like to invite you for subsequent interviews quarterly (every 3 months over the next 1 year) coinciding with your medical follow-up visits.

If your regular partner is also participating in Tambua Mapema Plus, we will give you both the option of interviewing together. If either of you prefers a separate interview, we will interview you separately.

If you do not want to answer any of the questions you may say so and the interviewer will move on to the next question. The discussions will take place in a private location in the KEMRI clinic nearest you, or a location of your choice. No-one else but the interviewer will be present unless you would like someone else there.

The discussions will be tape-recorded and notes from the interviews will be used to assist later in fully writing up the information. The first interview will last about 1 hour. Any subsequent interviews may take 15 minutes. No-one will be identified by name on the tape or notes. The tapes of these discussions will be destroyed after your words have been transcribed, within 12 months of each interview. If you choose not to join the ART or PrEP cohort, your study participation will end today. If you choose to join the ART or PrEP cohort, the duration of the study will be 12 months.

You will be provided with KSh 500 for your time and travel expenses at the first interview only, since this interview will take place at a scheduled appointment separate from your scheduled research visits. For subsequent brief follow-up interviews, you will receive KSh 400 reimbursement as part of the scheduled full research visit, and an additional KSh 100 if you report on your scheduled visit date.

Are there any risks or disadvantages of taking part?
The study staff will make every effort to protect your privacy and confidentiality while you are in the study. However, it is possible that others may learn you are participating in an interview and make assumptions about your health. We will conduct all interviews in a private room in the clinic, and will not include your name or other identifying information in transcripts of the recordings. All recordings and transcripts will be stored as electronic files on a password-protected and encrypted computer only available to research staff.

Some questions can be confidential or sensitive to some individuals. You may refuse to answer any question you are unhappy to answer.

Are there any advantages of taking part?
There are no individual benefits to taking part, but in answering our questions you will help us improve our understanding of young adults' knowledge of HIV, sexual risk behaviour, and ways to prevent HIV transmission.

Who will have access to the information I give?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. All of our documents/tapes are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research will be shared in summary form, without revealing individuals' identities. We will not publish or discuss in public anything that could identify you.

Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Who has allowed this research to take place?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI, including those involving only interviews, are approved by committees in Kilifi, and by national independent expert committees in Nairobi to make sure that participants' safety and rights are respected.

What will happen if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree you can change your mind at any time. Your ability to participate in other parts of the Tambua Mapema Plus research will not be affected by your decision.

What if I have any questions?
If you have any further questions about the study, or if you have been harmed by participating in this study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator

KEMRI- Wellcome Trust,
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi.
Telephone: 0723-342 780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FORM – INDIVIDUAL INTERVIEWS

Impact of a novel HIV-1 RNA testing intervention to detect acute and prevalent HIV infection and reduce HIV transmission – Tambua Mapema Plus

Personal interview of patients or their partners participating in Tambua Mapema Plus study

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I may change my mind at any stage, and that this will not affect the benefits due to me.

I agree to participate in the interview and it to be tape-recorded ☐ **Yes** ☐ **No**

I agree that notes from the interview or counselling notes may be reviewed ☐ **Yes** ☐ **No**

Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to explain this study to the participant, and that he or she understands the nature and the purpose of the study and consents to participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Signature: _____ **Date** _____

Designee/investigator's Name: **Time:**
_____ _____
(please print name)

I affirm that the Informed Consent Document has been read to the volunteer and he or she understands the study, had his or her questions answered, and I have witnessed the volunteer's consent to study participation. *(Only necessary if volunteer was not able to read and understand this informed Consent Document)*

_____ _____
Impartial Witness signature **Date**

Impartial Witness Name: _____ **Time:** _____
(please print name)

Thumbprint of participant if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

8. Staff

KEMRI-Wellcome Programme Information Sheet and Consent Form for Staff
IMPACT OF A NOVEL HIV-1 RNA TESTING INTERVENTION TO DETECT ACUTE AND PREVALENT HIV INFECTION AND REDUCE HIV TRANSMISSION
TAMBUA MAPEMA PLUS

Institution	INVESTIGATORS
KEMRI – Wellcome Trust	Dr. Eduard Sanders, Dr. Susan Graham Dr. Elise van der Elst, Mr. Evans Gichuru, Dr. Amin Hassan, Dr. Clara Agutu, Mr. Peter Mugo
University of Washington	Dr. Steven Goodreau, Dr. Deven Hamilton, Dr. Joseph Babigumira, Dr. Carey Farquhar

Who is carrying out this study?
KEMRI is a Government organisation that carries out health research to learn more about diseases that affect children and adults in Kenya. Sometimes research only involves asking questions of health facility staff about what they know, feel or do. We are conducting a study called Tambua Mapema Plus, which aims to determine whether HIV can be diagnosed in patients seeking care at health facilities, with immediate referral and care for HIV-infected patients and their partners. The study will be conducted at selected health facilities located within Mombasa and Kilifi Counties, in collaboration with the nearby KEMRI Research Clinics.

What is this study about?
In this component of the Tambua Mapema Plus research, we want to learn more about how staff at the health facilities where the study is conducted view the Tambua Mapema Plus intervention. We hope to hold interviews or focus groups discussions with up to 60 facility staff (up to 10 at each participating facility) before and after the intervention is conducted. If you are willing to participate, KEMRI research staff will schedule an interview or focus group discussion at your facility or an off-site location (depending on facility and staff preferences).

Why do you want to talk to me and what does it involve?
The Tambua Mapema Plus study is a public health intervention that tests individuals with symptoms compatible with acute HIV infection using a point of care test to detect HIV virus particles before an antibody response develops. The intervention will also identify individuals with undiagnosed HIV infection who have already developed an antibody response. Our overall goal is to detect HIV infection as early as possible in order to start immediate antiretroviral therapy and prevent further transmission. We will also test the partners of newly diagnosed individuals for HIV infection so that they can take action to prevent HIV transmission as well.

We would like to ask you about your views of the importance of early detection of HIV infection and the prevention of transmission through finding and testing partners of newly diagnosed individuals. In addition, we would like to ask about the impact the Tambua Mapema Plus study has had on your health facility in general, and any challenges that were encountered during the study. We are particularly interested in things that might make it easier or more difficult to scale up a similar intervention in other health facilities in Kenya.

If you prefer to have an individual interview, we will arrange that with you, at your work site or at another site of your preference. During the interview, if you do not want to answer a question, you may say so and the interviewer will move on to the next question. If you would like to participate in a group discussion with your colleagues, we will arrange that instead. Focus group discussions will

take place at the health facility or at the KEMRI clinic nearest you, depending on what your health facility group prefers.

If participants agree, interviews and focus group discussions will be tape-recorded. Recordings and notes from the interview or focus group discussions will be used to assist later in fully writing up the information. We expect that these sessions will last about 1 hour. No-one will be identified by name on the tape or notes. The tapes of these discussions will be destroyed after your words have been transcribed, within 12 months of each discussion.

If you participate, you will be provided with KSh 350 for your time.

Are there any risks or disadvantages of taking part?
Some questions can be confidential or sensitive to some individuals, as personal views will be requested. You may refuse to answer any question you are unhappy to answer.

We will ask focus group participants not to share views and opinions stated in the focus group discussions outside of those discussions, but there is a risk that your views and opinions will become known to others or that confidentiality of information disclosed there will be breached. Our research staff who conduct the interviews and focus group discussions must take an oath of confidentiality to protect all private and confidential information.

Are there any advantages of taking part?
There are no individual benefits to taking part, but in answering our questions you will help us improve our understanding of the importance of early detection of HIV infection, HIV prevention, and your experience working at a clinic that participates in the Tambua Mapema Plus study.

Who will have access to the information I give?
We will not share individual information about you or other participants with anyone who is not directly involved in the research. Your research data will be identified with a study number and not your name. We will retain a link between your study number and your contact information for 6 years after the close of the study in the event we need to contact you for a result, after which time the link will be destroyed. All of our documents/tapes are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research will be shared in summary form, without revealing individuals' identities We will not publish or discuss in public anything that could identify you.

Study monitoring and regulatory staff, including KEMRI and other local, US, and international regulatory entities, may review this study to make sure that study procedures are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Who has allowed this research to take place?
This research study is funded by the United States National Institutes of Health and carried out by KEMRI. All research at KEMRI, including those involving only interviews, are approved by committees in Kilifi, and by national independent expert committees in Nairobi to make sure that participants' safety and rights are respected. A description of this clinical trial will be available on http://www.clinicaltrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What will happen if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree you can change your mind at any time. Your decision will not impact your employment status.

What if I have any questions?
If you have any further questions about the study, or if you have been harmed by participating in this study, you are free to contact the research team using the contacts below:

Dr. Eduard Sanders, Principal Investigator
KEMRI- Wellcome Trust,
P.O. Box 230, Kilifi
Telephone: 0723-593-762

If you want to contact someone not involved in this study to ask about this research, please contact
Community Liaison Manager, KEMRI – Wellcome Trust
P.O. Box 230, Kilifi.
Telephone: 0723 342 780 or 0705-154386

If you want to contact someone about your rights as a research subject, please contact
The Head, KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi
Telephone: 0717-719477 or 0776-399979, e-mail: seru@kemri.org

CONSENT FORM – STAFF INTERVIEWS AND FOCUS GROUPS

Impact of a novel HIV testing intervention to detect acute and prevalent HIV infection and reduce HIV transmission – Tambua Mapema Plus

Interviews or focus groups for health facility staff participating in Tambua Mapema Plus study

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I may change my mind at any stage, and that this will not affect the benefits due to me.

I agree for my interview or focus group discussion to be tape-recorded ☐ **Yes** ☐ **No**

I agree that notes from the interview or focus group discussion may be reviewed ☐ **Yes** ☐ **No**

Signature: _____ **Date** _____

Participant Name: _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to explain this study to the participant, and that he or she understands the nature and the purpose of the study and consents to participation in the study. He or she has been given opportunity to ask questions which have been answered satisfactorily.

Signature: _____ **Date** _____

Designee/investigator's Name: _____ **Time:** _____
(please print name)

Thumbprint of the participant as named above if they cannot write: _____

THE PARTICIPANT SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

21.9. Grading the Severity of Adverse Events

We will use the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1, July 2017) ("DAIDS AE grading table") for Adverse Event (AE) reporting and grading of severity for each AE term (please see http://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2). Potential clinical AEs most relevant to this protocol include systemic symptoms, acute infectious illness, injection site reactions (e.g., after a penicillin injection for treatment of syphilis), skin-dermatological, gastrointestinal, neurological, musculoskeletal, and genitourinary. Laboratory tests that fall outside the normal range will also be graded according to this table. If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), we will select the higher of the two grades for the clinical AE. The severity of IPV and social harms will be graded as discussed in section 13 of this protocol.

21.10. Explainer Video Script

Shot	Script
1	When an adult person is ill in Kenya….he or she often seeks health care. ***Mtu mzima anapokuwa mgonjwa nchini Kenya, yeye mara nyingi hutafuta huduma za afya***
2	Common symptoms for which health care is sought include fever, fatigue, sore throat, diarrhoea, body pains, or sometimes genital ulcer disease. ***Dalili za kawaida ambazo hutafutiwa matibabu ni kama vile joto mwilini, uchovu, vidonda vya koo, kuhara, maumivu ya viungo na wakati mwingine ugonjwa wa vidonda katika sehemu ya siri.***
3	Unfortunately, the root cause of these illnesses is not always tested for. ***Mara nyingi, sababu kuu ya magonjwa haya haithibitishwi kwa vipimo vya maabara***
4	In Africa, people often assume the symptoms are due to Malaria ***Barani Africa, watu hudhania kuwa dalili hizi zimetokana na ugonjwa wa malaria***
5	That is why The Tambua Mapema Study is evaluating a new HIV testing intervention for adult patients with symptoms that could be related to HIV. ***Hii ndiyo sababu mradi wa utafiti wa Tambua Mapema unachunguza kuhusishwa kwa kifaa kipya cha upimaji wa HIV kwa watu wazima walio na dalili ambazo zinaweza kuwa na uhusiano na maambukizi ya HIV***
6	In the Tambua Mapema Plus study we will ask questions about when your symptoms started, when you were last tested for HIV, and if you know your partner's status. ***Katika utafiti wa tambua Mapema, tutauliza maswali kuhusu muda wa tangu dalili zilipoanza, mara ya mwisho kupimwa HIV, na iwapo unajua hali ya mwenzio***
7	Questions can be answered in privacy by making use of a computer ……or in person with a counsellor ***Maswali yanaweza kujibiwa faraghani kwa kutumia kompyuta…au ana kwa ana na mshauri***
8	Participating in the study may take up to 2 hours. And You will get Ksh 500 to compensate for your time. ***Kushiriki kunaweza kuchukua hadi masaa mawili. Na utapata Ksh 500 kufidia wakati wako.***
9	The study will help patients link to care if they have HIV,

	Utafiti utasaidia wagonjwa kuunganishwa na huduma za matibabu iwapo wana HIV.
10	*And we will offer access to immediate treatment.* ***Na tutatoa uwezekanaji wa kupata matibabu ya papo kwa hapo***
11	We also assist with HIV testing of your partners, and make sure your partners can benefit from prevention options such as pre-exposure prophylaxis medication if they are not infected. ***Pia tutasaidia kupima wenzi wako, na kuhakikisha kuwa wanaweza kunufaika na njia za kujikinga kama vile dawa ya PrEP iwapo hawajaambukizwa.***
12	TAMBUA MAPEMA! You want to discover your HIV status early! TAMBUA MAPEMA! ***Unataka kujua hali yako ya HIV Mapema, sio?***
13	Thank you for considering participation in the study. ***Shukran kwa kuzingatia kushiriki katika utafiti.***

21.11. Map of KEMRI Sites