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Title of Thesis

OPTIMIZATION OF THE HIV CARE CASCADE IN RURAL UGANDA AND KENYA

Thesis for the degree of doctor of philosophy in Epidemiology at the University of Antwerp to be defended by James AYIEKO

Promoter:
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Dedication

I dedicate this thesis to my dear wife Tabitha, loving son Joseph and my beloved parents.

Acknowledgement

The journey towards completing the PhD program has been exciting and intense, paved with many selfless individuals who have shaped my career and continue to have profound influence on me. I will forever be indebted to them.

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Finally, I thank my wife Tabitha and son Joseph who have given me immense support during my studies. I thank my dad and mum for their deep inspiration and confidence in me.

List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti retroviral Therapy
CD	Cluster of differentiation
CDC	Center for Disease Control
CIS	Combination Intervention Strategy
CHC	Community Health Campaign
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
HAART	Highly Active Anti Retroviral Therapy
HBT	Home Based Testing
HIV	Human Immunodeficiency Virus
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PEP	Post Exposure Prophylaxis
PITC	Provider Initiated Testing and Counseling
PLWH	People Living With HIV
PMTCT	Prevention of Mother to Child Transmission
POC	Point of Care
PRECEDE	Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation.
PrEP	Pre-Exposure Prophylaxis

RCT	Randomized Controlled trial
RNA	Ribonucleic Acid
SEARCH	Sustainable East African Research for Community Health
SMS	Short Message Service
TasP	Treatment as Prevention
TB	Tuberculosis
UNAIDS	The Joint United Nations Programme on HIV and AIDS
WHO	World Health Organization

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Executive summary

By 2017, an estimated 36.9 million (31.1million - 43.9 million) people globally were living with HIV. The HIV epidemic remains uncontrolled with 1.8 million people reported to have been newly infected in the same year, and 940,000(670,000-1.300,000) dying from AIDS-related illnesses globally. In the absence of an effective vaccine and curative treatment, other control measures are needed urgently. The therapeutic and preventive benefits of ART highlight the importance and urgency to identify all people living with HIV, link them to care, initiate them on ART, attain and maintain viral suppression among them. The progress towards achieving this has been evaluated using the care cascade, which unfortunately demonstrates massive drop-offs along the cascade in almost all care settings. To achieve the goals of the WHO test and treat strategy, each step of the cascade must be optimized. The losses from the cascade in the test and treat era need therefore to be quantified, the steps suffering the largest dropouts identified, the reasons for these dropouts analysed, and novel interventions designed.

This thesis explores the barriers to care engagement along the HIV care cascade and evaluates the effectiveness of a streamlined patient centered care model in addressing the barriers along the cascade within the context of an ongoing test and treat trial called SEARCH (Sustainable East African Research for Community Health) conducted in rural Uganda and Kenya. The studies included in this thesis were conducted among 16

intervention communities with the exception of the qualitative analysis that sampled participants from 4 control and 4 intervention communities.

In the first study, qualitative methods were used to explore the barriers to care engagement. Our findings demonstrated multiple barriers along the cascade with stigma in its different manifestations (anticipated, internalized and enacted) appearing as a major barrier across multiple steps of care engagement. Other barriers identified were behavioral (treatment fatigue, forgetting to take medications), structural (distance to clinics, poverty), health system (poor health provider attitudes, patient-unfriendly clinic set-up), social (work interference, lack of social support), and drug related (drug side effects, pill burden). With this array of barriers, a combination intervention strategy with multiple interventions targeting different barriers and different phases on the cascade simultaneously to improve outcomes among PLWH was identified as the optimal approach to improve the care cascade. We thus designed and applied a streamlined patient centered multi-component strategy to improve patient outcomes along the care cascade.

Our second study evaluated linkage to care among patients not engaged to care at the first round of HIV testing as part of the SEARCH study. Our patient centered multicomponent intervention comprised building rapport with patients at diagnosis, sharing clinic contact details, phone call reminders a day prior to the linkage appointment date and physical tracing if the appointment was missed. The intervention achieved 73% linkage to care at one year with half of those eligible for the

intervention linking to care within 7 days if testing. Rapid linkage, engagement to care and ART initiation is a highly desirable outcome if ART is to control the epidemic.

Our third study, moved further to attempt and link the "difficult to engage" and newly diagnosed patients who had not linked by year two of the study. We designed a randomized controlled trial that used a patient centered intervention to explore individual barriers to care engagement and involved patients in developing solutions on how to overcome their barriers to engage in care via a clinical officer led phone call. This intervention still achieved a low overall linkage rate (41%) in this difficult to engage group. However, twice as many individuals who received the intervention linked to care as compared to those who did not receive the intervention. This demonstrates the value of individualized and personalized approaches in complement to a public health approach to engage all people with HIV in care.

Our fourth study focused on retention in care applying a patient centered streamlined care model comprising of appointment reminders, clinic hours flexibility, short wait times, warm and friendly services by health providers and spaced out visits. This resulted in very high retention rates: 95.5 % retention at 12 months among all participants and 89.3% among those newly linked to care.

Our final study evaluated the streamlined patient centered care model against the UNAIDS 90-90-90 targets. Our intervention exceeded the UNAIDS 90-90-90 targets by

the follow up year two of the study with a population-wide viral suppression of 80.2% as compared to the 73% target set by the UNAIDs.

In conclusion, the streamlined patient centered care model improved outcomes along all components of the HIV care cascade. However, the cascade still has dropouts in specific population groups. Innovative, targeted interventions to seal the leaks need to be developed to help end the HIV epidemic.

Title of thesis in Dutch

Optimalisatie van de HIV zorgcascade in Uganda en Kenya

Samenvatting

In 2017 leefden naar schatting 36,9 miljoen (31,1 miljoen - 43,9 miljoen) mensen wereldwijd met HIV, 1,8 miljoen mensen werden geïnfecteerd en 940.000 (670.000-1.300.000) mensen stierven aan AIDS-gerelateerde ziekten. Bij afwezigheid van een effectief vaccin en een curatieve behandeling zijn andere strategieën dringend nodig. De therapeutische en preventieve voordelen van antiretrovirale behandeling benadrukken het belang en de urgentie om alle mensen die leven met HIV te identificeren en koppelen aan zorg, alle patiënten te initiëren op antiretrovirale behandeling, en virale suppressie te bereiken en behouden in iedereen die antiretrovirale behandeling neemt. De vooruitgang in het bereiken van deze doelstellingen wordt best geëvalueerd met behulp van de HIV-zorgcascade. Om de doelen van de WHO 'test- en -behandel' strategie te bereiken, moet elke stap van de cascade worden geoptimaliseerd. Om nieuwe interventies te ontwerpen moeten de tekorten in de HIV-zorgcascade in het 'test- en behandel' tijdperk gekwantificeerd worden, de stappen die de grootste deficiënties vertonen vastgesteld worden, de redenen die leiden tot de tekorten geanalyseerd worden.

Dit proefschrift onderzoekt de barrières in de HIV-zorgcascade en evalueert de effectiviteit van een gestroomlijnd patiëntgericht zorgmodel voor het aanpakken van deze barrières in het kader van een klinische studie genaamd SEARCH (Sustainable East African Research for Community Health). Deze studie werd uitgevoerd op het platteland van Oeganda en Kenia. De studies opgenomen in dit proefschrift betreft deelnemers uit de 16 interventiegemeenschappen van de SEARCH trial, met uitzondering van de kwalitatieve analyse die deelnemers uit 4 controle- en 4 interventiegemeenschappen includeerde.

In de eerste studie werden kwalitatieve methoden gebruikt om de barrières te onderzoeken. Onze bevindingen toonden meerdere barrières langs de HIV zorg-cascade, met vooral verschillende vormen van stigma (verwacht, geïnternaliseerd en vastgesteld) die een belangrijke barrière lijken te vormen op meerdere momenten van zorgbetrokkenheid. Andere barrières die geïdentificeerde werden zijn gedrag (behandelingsvermoeidheid, vergeten medicijnen in te nemen), structureel (afstand tot klinieken, armoede), gezondheidssysteem (attitudes van zorgverleners, patiëntonvriendelijke klinieken), sociaal (werkinterferentie, gebrek aan sociale ondersteuning) en medicatie gerelateerde factoren (bijwerkingen van medicijnen, de belasting gerelateerd aan het innemen van de medicatie). Omwille van het bestaan van multiple barrières werd geopteerd voor een combinatie-interventiestrategie, met meerdere interventies gericht op verschillende barrières en verschillende fasen in de HIV zorgcascade om zo de uitkomsten van patiënten te verbeteren. Er werd daarom een

gestroomlijnde, patiëntgerichte multi-componentstrategie ontworpen en toegepast om de patiënt-gerelateerde resultaten van de HIV-zorgcascade te verbeteren.

De tweede studie evalueerde de zorg koppeling van patiënten die geen behandeling gestart waren een eerste HIV-test (uitgevoerd als onderdeel van de SEARCH-studie). Onze patiëntgerichte multi-component interventie gericht op het verwijzen van mensen naar formele gezondheidscentra bestond uit het opbouwen van een vertouwensrelatie met patiënten bij diagnose, het delen van contactgegevens van klinieken, herinneringen via telefoon een dag voorafgaand aan de afspraak, en fysieke tracering als de afspraak werd gemist. De interventie bereikte 73% koppeling aan zorg op een jaar, waarbij de helft van degenen die in aanmerking kwamen voor de interventie zich aanmeldde bij een kliniek binnen 7 dagen na een HIV test. Snelle start van antiretrovirale behandeling is een uiterst belangrijk om de HIV epidemie te bestrijden.

De focus van de derde studie betrof het koppelen van de 'moeilijk te bereiken' patiënten, gedefinieerd als patiënten die niet gekoppeld waren aan een behandeling bij het begin het tweede jaar van de SEARCH studie. We zetten een gerandomiseerde gecontroleerde studie op voor de evaluatie van een patiëntgerichte interventie waarbij, via een telefoongesprek met een arts, individuele belemmeringen voor zorgbetrokkenheid onderzocht werden en patiënten betrokken werden bij het ontwikkelen van oplossingen voor het overwinnen van hun individuele barrières. Resultaten toonden een suboptimale koppeling aan zorg (41%) in deze moeilijk te bereiken groep. Toch werden twee keer zoveel personen in de interventiegroep

gekoppeld aan zorg in vergelijking met patiënten in de controlegroep. Dit toont de waarde aan van geïndividualiseerde en gepersonaliseerde benaderingswijze, complementair aan een volksgezondheidsstrategie.

De vierde studie richtte zich op retentie in de zorg via een patiëntgericht gestroomlijnd zorgmodel, bestaande uit afspraakherinneringen, flexibiliteit in kliniekuren, korte wachttijden, warme en vriendelijke diensten door zorgverleners, en gespreide kliniekafspraken. Dit resulteerde in zeer hoge retentiepercentages: 95,5% retentie na 12 maanden bij alle patiënten en 89,3% bij nieuwkomers.

De laatste studie vergeleek de resultaten behaalde met het gestroomlijnde patiëntgerichte zorgmodel met de doelen van UNAIDS 90-90-90. Onze interventie overschreed de doelen van UNAIDS 90-90-90, met een populatie-brede virale onderdrukking van 80,2%. Dit was hoger dan 73%, het doel dat door de UNAIDS nagestreefd wordt.

In conclusie, het gestroomlijnde patiëntgerichte zorgmodel verbeterde de resultaten HIV zorgcascade. De cascade is echter nog steeds suboptimaal, vooral in specifieke bevolkingsgroepen. Er moeten dus innovatieve interventies ontwikkeld worden die gericht zijn op specifieke doelgroepen om de 'lekken' te dichten en de HIV epidemie te beëindigen.

Introduction

Human Immunodeficiency Virus infection

Unexplained occurrence of *Pneumocystis jirovecii* in five healthy homosexual men in Los Angeles and of Kaposi Sarcoma with or without *P. jirovecii* in 26 homosexual men in New York and Los Angeles marked the first recognition of AIDS in 1981[1,2]. In 1983, the human immonodeficiecy virus (HIV), a single stranded RNA lentivirus that belongs to the family *Retroviridae* was isolated from a man with lymphadenopathy. One year later HIV was identified as the causative agent of AIDS [3-5].

HIV-1 is primarily a sexually transmitted disease but can also spread via percutaneous, intravenous, and perinatal routes [6,7]. Following exposure, 80% of adult individuals get infected [6,7].

Upon entry of the virus, there is rapid local propagation of infection on CD4+T cells followed by dissemination into draining lymph nodes. Systemic circulation rapidly follows, with establishment of CD4 T-cell viral reservoirs [7]. Replication of the virus leads to markedly elevated levels of the virus in peripheral blood. This is accompanied by a marked decline in CD4+ T cells. Over time, HIV infection causes the Acquired Immunodeficiency syndrome (AIDS) by progressive depletion of CD4 +T cells, which is associated with progressive weakening of the immune system and host susceptibility to opportunistic infections. The median time from infection to development of AIDS among untreated cases is 8-10 years [8]. The survival period from the time of initial infection is estimated to be 9 to 11 years depending on the viral subtype [9], but often

shorter in children with 50% of untreated cases likely to die before their second birthday [10].

The early phase acute viremia is associated with activation of CD8+ T cells that kill HIV-infected cells and antibody production. Figure 1 shows the six stages following HIV-1 infection based on the sequential appearance in plasma of HIV-1 viral RNA; the gag p24 protein antigen and antibodies which bind to viral proteins [7]. The laboratory diagnosis of HIV is based on detection of these antibodies, viral components, or virus in blood. Following primary infection it takes about 9-11 days for viral RNA and 21-25 days for antibodies against HIV to be detected. Current assays employ a mixture of synthetic peptides and recombinant viral protein to detect antibodies against HIV within three to four weeks of infection. Fourth generation assays allow detection of p24antigens and antibodies against HIV increasing sensitivity to recent infection to one week [11].

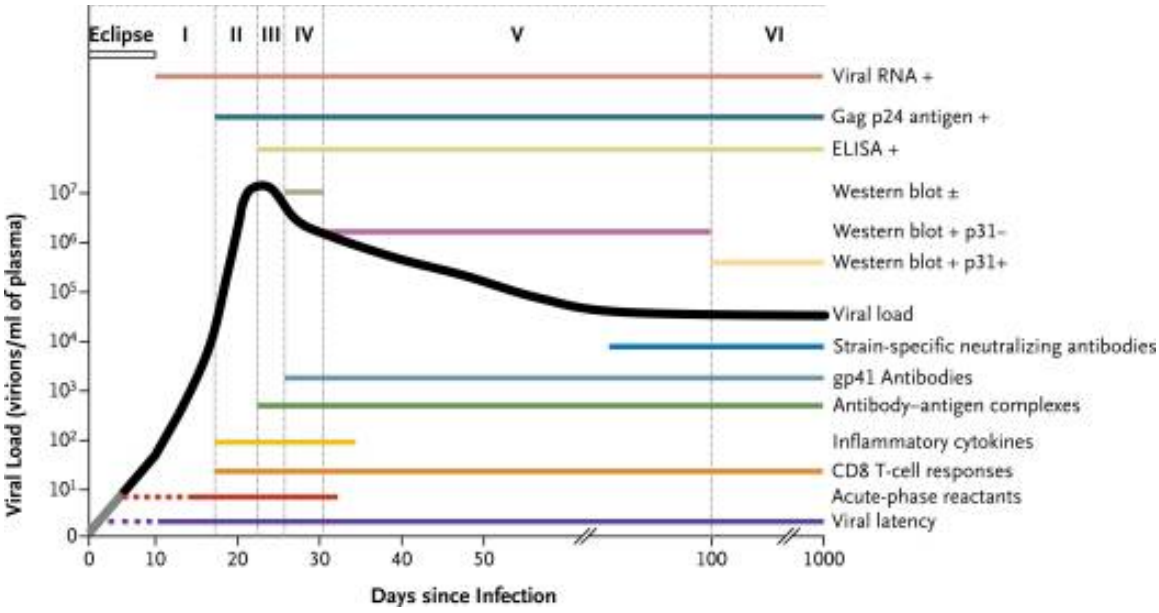

Figure 1. The Natural History and Immunopathogenesis of HIV-1
Progression of HIV-1 infection can be depicted as six stages [12](indicated on top of the graph). The stages are defined according to standard clinical laboratory tests results(note above the viral load curve). The stages are based on sequential appearance in plasma of HIV-1 viral RNA; the gag p24 protein antigen; antibodies specific for recombinant HIV-1 proteins, these are detected with the use of an enzyme-linked immunosorbent assay (ELISA); and antibodies that bind to fixed viral proteins, including p31, detected on Western immunoblot. The lines shown below the viral-load curve correspond to the timing of events and immune responses that cannot be measured with standard clinical laboratory assays, beginning with establishment of viral latency.(Adapted from Cohen MS 2011[7])

The first antiretroviral agent, Azidothymidine (AZT), was approved in 1987 following its discovery [13]. Soon after its discovery, it became clear that due to the ability of the virus to generate drug-resistant mutants rapidly, therapy would require a combination of agents. This marked the beginning of highly active antiretroviral therapy (HAART), developed and approved in 1996 [14,15]. HAART uses a combination of antiretroviral agents to slow the emergence of drug-resistant virus and suppress the virus. Several antiretroviral medications have since been developed and are classified based on the viral cycle step that they act on (Figure 2) or their chemical structure [16]. Current HIV treatment consists of HAART, which comprises a combination of three medications

from at least two classes of antiretroviral medications (Table 1) targeting distinct steps in the HIV replication cycle (Figure 2).

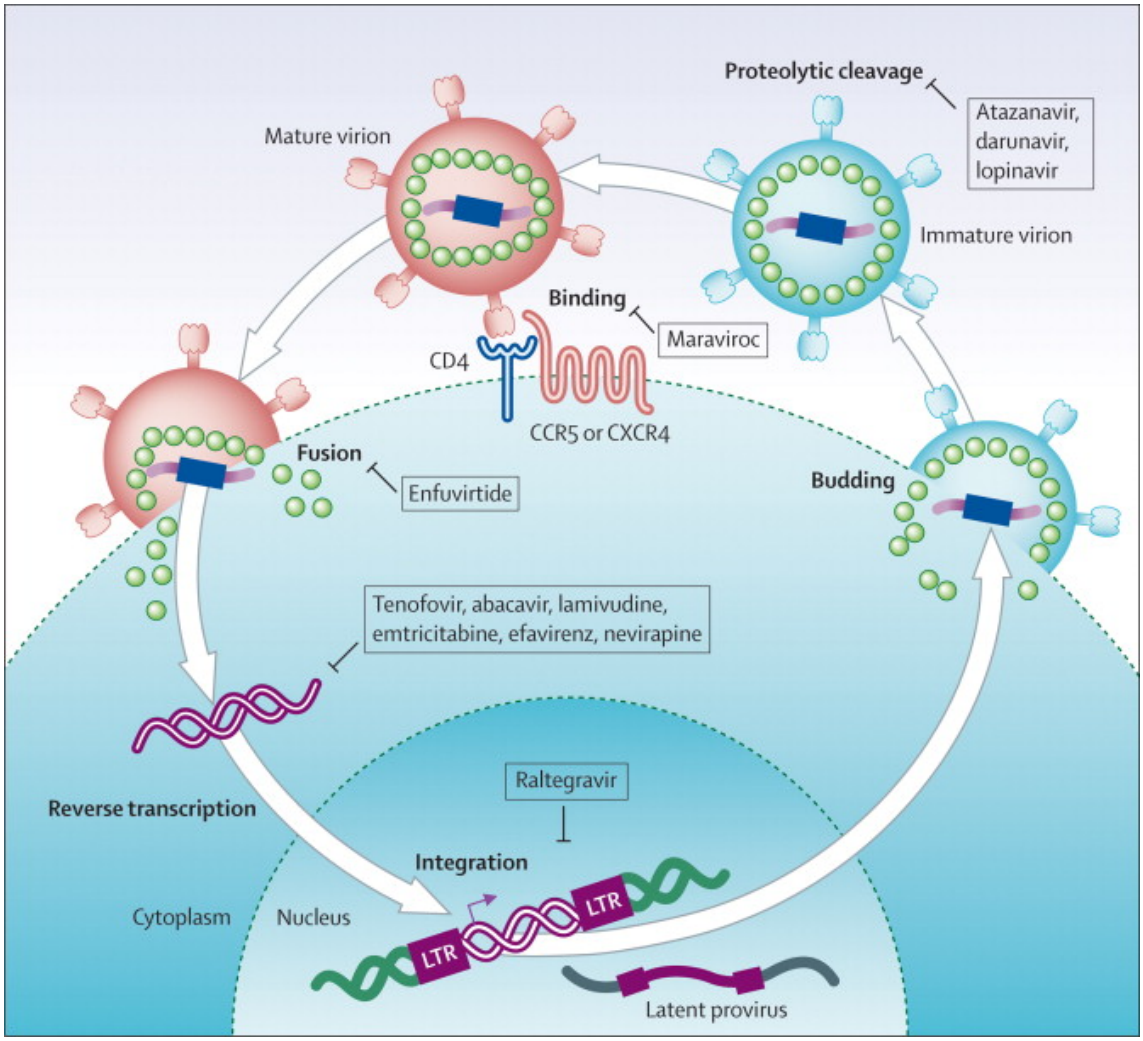

Figure 2. The HIV life cycle and antiretroviral drug targets
Current antiretroviral drugs are categorized into six classes that target five unique steps in the HIV life cycle (binding, fusion, reverse transcription, integration, and proteolytic cleavage). Virions enter their target cell through a three-step process, consisting of (1) attachment to the CD4 receptor, (2) binding to the CXCR4 or CCR5 coreceptors, or both, and (3) membrane fusion. Maraviroc acts by blocking CCR5 binding and enfurvitide prevents fusion. The enzyme HIV reverse transcriptase, catalyses transcription of HIV RNA into double-stranded HIV DNA, this step is inhibited by nucleoside analogues and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The HIV integrase enzyme acts to incorporate HIV DNA into host chromosomes , this step is inhibited byintegrase inhibitors. Following transcription and translation of HIV, immature virions are produced and bud from the cell surface. The enzyme HIV proteasecleaves polypeptide chains, enabling the virions to mature. Protease Inhibitors act on this last step(Adapted from Volberding et al 2010)

Class	Drugs
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	Tenofovir, abacavir, zidovudine, lamivudine, emtricitabine
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz, nevirapine,etravirine, rilpivirine
Integrase inhibitors	Raltegravir,dolutegravir, elvitegravir
Protease inhibitors	atazanavir darunavir, lopinavir,
CCR5 inhibitors	Maraviroc
Fusion inhibitors	Enfuvirtide
Post Attachment inhibitors	Ibalizumab
Pharmacokinetic Enhancers	Cobicistat

Table 1. Antiretroviral drugs classification

HAART does not cure HIV infection but can suppress plasma HIV RNA concentrations within a few weeks to months of treatment below values that are detectable with commercially available assays (around 50 copies per mL)[17]. Figure 3 illustrates the virological and immunological response to antiretroviral therapy over time. Antiretroviral therapy (ART) has changed the course of the HIV/AIDS epidemic. It has caused a dramatic reduction in AIDS-related morbidity and mortality, and has converted HIV/AIDS into a manageable chronic illness for those living with HIV who are engaged in care and remain adherent to treatment. Administration of HAART results in

increased survival with life expectancies that can be close to those of HIV-uninfected individuals [18,19].

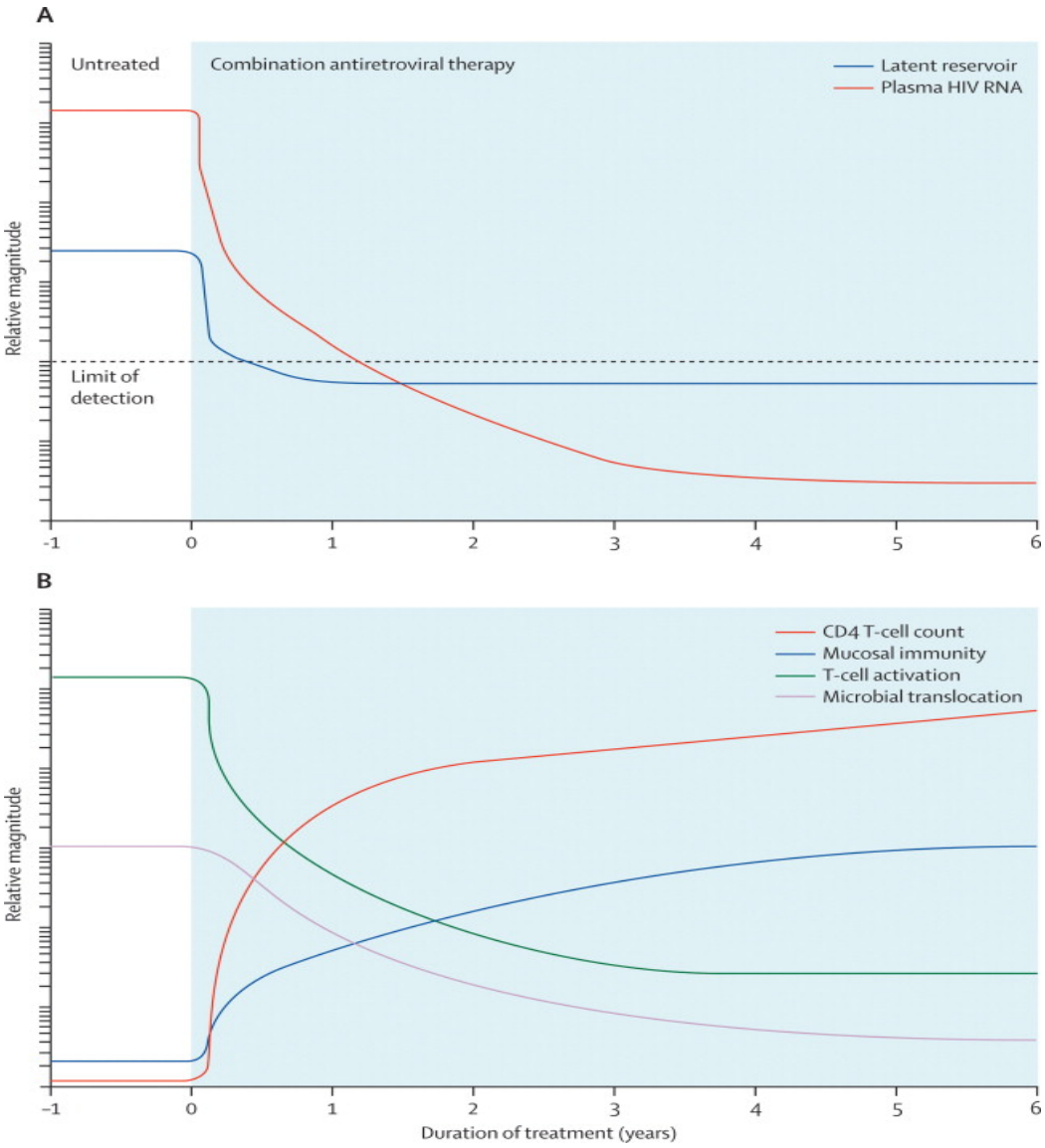

Figure 3. Virological and immunological response to antiretroviral therapy
(A) Combination antiretroviral therapy results in more than 100-fold reduction in HIV RNA within the first two weeks of treatment, this is followed by a slow decline over time, with a new markedly low steady-state being attained within a few years of therapy. The levels of the latent reservoir (long-lived cells containing replication competent HIV) reduce as well. (B) ART-mediated suppression of HIV replication is associated with sustained but variable increases in CD4 T-cell counts (both peripheral and mucosal, the former being of greater magnitude). (Adapted from Volberding 2010[16])

The global HIV epidemic

HIV/ AIDS has become one of the most devastating infectious diseases in recent history. Since its identification close to four decades ago, more than 77 million infections and at least 35 million deaths have been reported [20,21] with developing countries bearing the largest burden of morbidity and mortality [20]. The global HIV-1 prevalence and HIV-1 incidence peaked worldwide in the late 1990s and has been declining since [22]. Although ART has lowered mortality and morbidity associated with HIV, coverage of ART has not been universal, hampering the potential benefits from this powerful intervention in a setting where the prospects of effective vaccines and curative treatment still remain unclear [23,24].

In 2017, an estimated 36.9 million (31.1million - 43.9 million) people globally were living with HIV, 1.8 million people became newly infected, and 940,000(670,000-1.300,000) died from AIDS-related illnesses globally [20]. Figure 4 shows the HIV burden based on prevalence globally. Sub-Saharan Africa bears the largest burden of the disease (Figure 4). The Eastern and Southern Africa region accounts for more than half (19.6 million/36.9 million) of all people living with HIV and 44% (0.8 million/1.8 million) of all new infections.

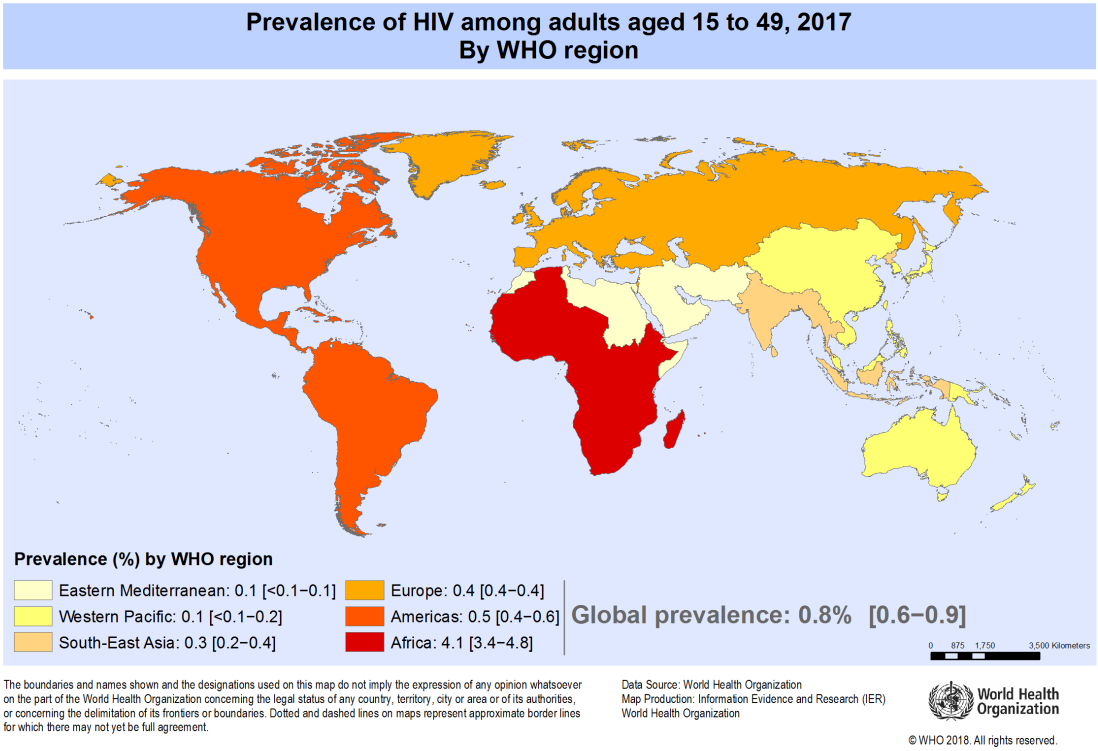

Figure 4Global HIV prevalence in 2017 among adults aged 15-49 years old.(Adapted from WHO 2018[25])

The HIV-1 epidemic is not homogeneous; two distinct epidemiological patterns are evident. Most countries have *concentrated* epidemics where HIV is seen in certain high risk groups such as sex workers, men-who have sex with men, and injection drug users. In many sub-Saharan Africa the distribution is different, the epidemics are *generalized* and therefore self-sustaining [22]. The approaches for controlling these different epidemics may have slight modifications but largely remain similar.

The control of the epidemic was initially solely anchored on disease prevention. The first prevention methods to be broadly implemented were behavioral interventions focused on delayed sexual debut, use of clean needles among intravenous drug users

[26] and the ABC of sexual abstinence [27], being faithful (single sexual partners), and condom use [28]. Later on, other preventive interventions such as male circumcisions were implemented, following the results of three male circumcision randomized controlled trials conducted in Africa which revealed a nearly 60% reduction in female to male HIV transmission [29-31]. By 2010, the concept of combination prevention was introduced. This approach as defined by the UNAIDS Prevention Reference Group on December, 2009 comprises "... rights-based, evidence-informed, and community-owned programmes that use a mix of biomedical, behavioural, and structural interventions, prioritized to meet the current HIV prevention needs of particular individuals and communities, so as to have the greatest sustained impact on reducing new infections."[32].

The role of ART changed rapidly over time, with increasing expansion of eligibility. About a decade ago, focus was on individual patients with scientists stating that "the absolute benefit of treatment in patients with early-stage disease is probably not large, provided that treatment is not deferred until more advanced stages of disease (<350 cells/μL) "[16]. Over time, the role of antiretrovirals has been redefined beyond treatment of the infected individual to prevention of transmission. Since early 1990's, ART has been used as post-exposure prophylaxis (PEP) among exposed health care workers and victims of rape, with official WHO guidelines on PEP being released in 2007 [33]. In 2006, following evidence from multiple studies, WHO released guidelines on use of ARVs medications in pregnant women for their own health and prevention of HIV transmission to the unborn babies and infants, a concept referred to as prevention

of mother to child transmission (PMTCT) [34]. In 2012, WHO offered guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. In 2015, the WHO expanded its recommendation for oral PrEP to those considered to be "at substantial risk of HIV infection"[35]. The latest change in public health approach is TasP (treatment as prevention) coupled with a test and treat strategy to prevent transmission of HIV from people living with HIV to their sexual partners

Uptake of HIV testing and ART and the HIV care cascade

While massive scale-up of HIV testing, and engagement of patients for treatment has succeeded in increasing the numbers of people on ART with more than 19 million individuals initiated on ART in sub-Saharan Africa [36], the success of these programs has been significantly hindered by high patient attrition with high drop outs both before and after ART initiation [37-42]. Delays in the utilization of HIV test and treatment services and failure to adhere to life-long continued engagement in care remain a major problem and are associated with poor individual patient outcomes and missed opportunities for preventing onward HIV transmission [43]. The importance of high ART coverage at population level was demonstrated by several observational studies. Tanser et al. showed that HIV uninfected individuals living in a community with an ART coverage of 30-40% was 38% less likely to acquire HIV as compared to individuals living in a community with less than 10% ART coverage [44]. In Rakai, Uganda, Kong et al. showed that increased ART coverage among women was associated with decreased HIV incidence in men[45]. Using mathematical models, important

reductions in transmission are predicted to occur in the presence of in high uptake of regular HIV testing and universal treatment [46]. Four ongoing cluster-randomized trials in Botswana (BCPP study NCT01965470), Kenya and Uganda (SEARCH StudyNCT01864603), Zambia and South Africa(HPTN 071 PoPART study NCT01900977)(ANRS 12249 TasP Study NCT01509508) aim to quantify the effect on HIV testing and ART coverage on HIV incidence.

In 2012, CDC reported that only 25% of individuals living with HIV in the United States achieved viral suppression [47]. This report introduced the concept of the HIV care cascade, a concept that has since become an important way of analyzing and describing the process from HIV diagnosis to the ultimate goal of viral suppression on ART [40,48]. Care cascade analysis has helped to quantify patient attrition from care at different points, thus identifying the time points of greatest drop-off that offer opportunity for innovation of interventions to address the losses [40,43].

Initially, four stages of the care cascade were defined: the three pre ART phases of testing to staging or receipt of CD4+ T cells result (Stage 1), staging to ART eligibility (Stage 2), ART eligibility to ART initiation(Stage3), and retention on treatment (stage 4) [40]. Data evaluating this four-stage cascade have shown high attrition at every stage, resulting in massive cumulative drop-off along the care cascade [40,43]. Figure 5 shows the percentage of patients completing each of the stages on the HIV care cascade according to reviews conducted by Rosen S and Kranzer [40,43]. The purple bars depict the long-term retention in care after ART initiation (Stage 4) as observed in a review by Fox M [49].

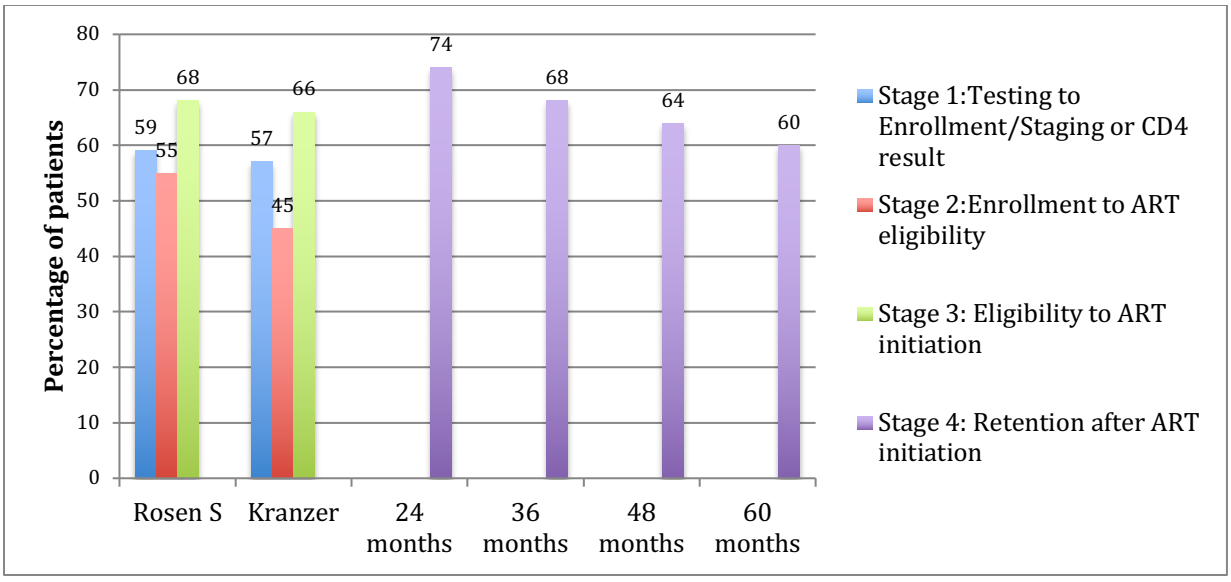

Figure 5: HIV care cascade

The Pre-ART phase of the cascade has recently changed with the release of the recent WHO recommendations and treatment guideline for test-and-treat [35] as the "treat all" strategy renders Stage 2 of the Pre-ART care phase (enrollment to ART eligibility) obsolete. Figure 6 shows the revised cascade and highlights the opportunities to become lost to care under the new treatment model. The Pre-ART period is now reduced to two stages with HIV testing to linkage to care (Stage 1) and linkage to care to ART initiation (Stage 2). The third and final stage is retention on ART [50]. Fox and Rosen propose that this third stage be split and treated as two stages of retention on ART within the first year of treatment (Stage 3-early retention in care) and lifelong retention on treatment for later years [50].

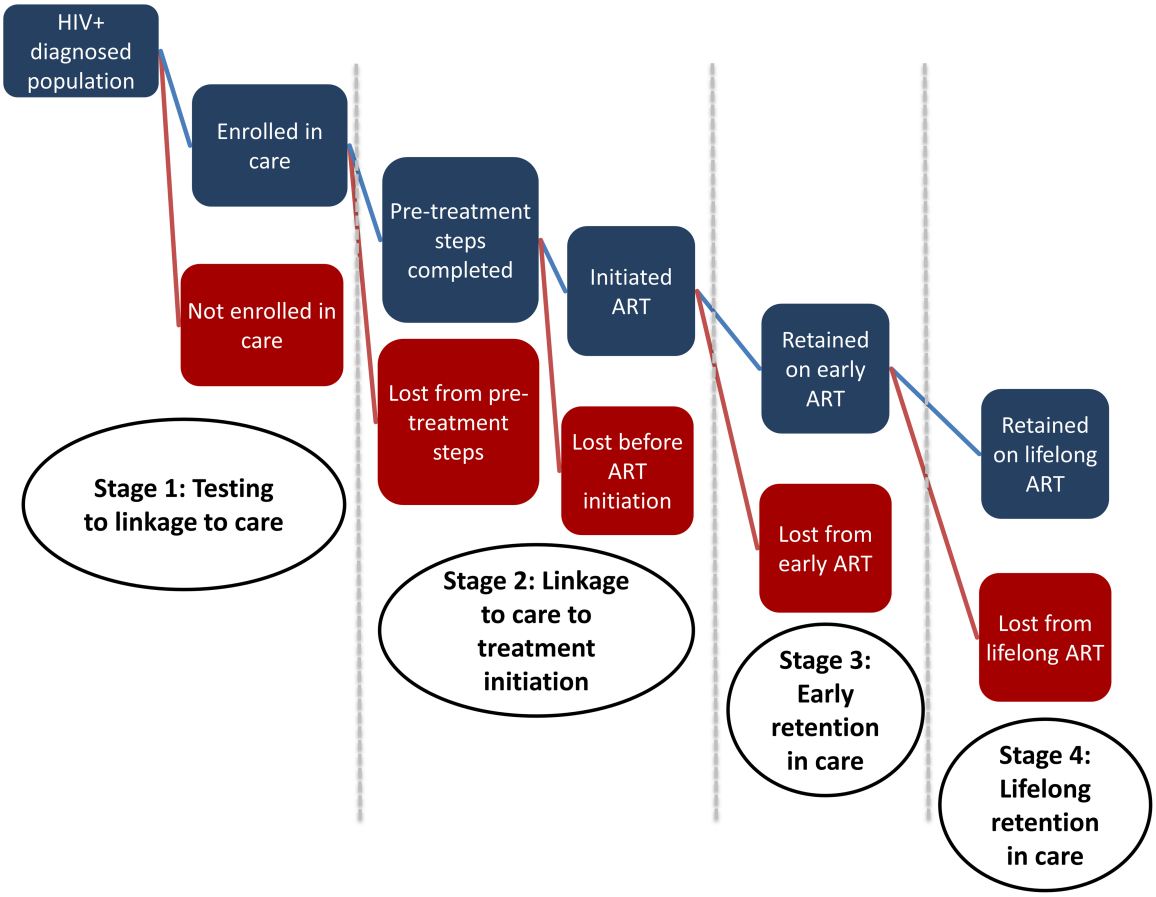

Figure 6: The New HIV Care Cascade in the context of test and treat and Opportunities of dropping-off Care (Adapted from Fox 2017[50])

The test-and-treat era continues to suffer from patient attrition along the HIV care cascade. One of the large test-and-treat trials reporting no reduction in HIV incidence, a finding that was attributed by the investigators to the low linkage to care rates [51]. Another study evaluating the care cascade in a test and treat setting reported highest attrition (17% drop) in the retention in care stage with factors such as incarceration (45% drop) and use of illicit drugs (32% drop) making this worse [52]. In the US, the dropouts along the cascade, even with test and treat, remain disturbingly high with only

86% of PLWH getting to know their status and only 30% achieving viral suppression [53].

The UNAIDS 90-90-90 targets

Building upon the HIV care cascade, UNAIDS developed its 90-90-90 targets (Figure 7). The goal is by 2020 to have 90 % of all people living with HIV to know their status, place 90 % of all those diagnosed with HIV on ART, and attain viral suppression in 90% of those on ART. Achieving these targets is dependent on success of the care cascade. The UNAIDS targets aim at shutting the HIV epidemic by achieving a population-wide viral suppression of at least 73% if the three targets (testing, ART initiation and viral suppression) are achieved [54]. The care cascade is thus a crucial piece of the puzzle that is expected to end the HIV epidemic.

In 2017, it was estimated that 75% (55%-92%) of all people living with HIV (PLWH) globally knew their HIV status, 59% (21.7 million) were on ART, and among those on ART, 81% were virally suppressed [20].

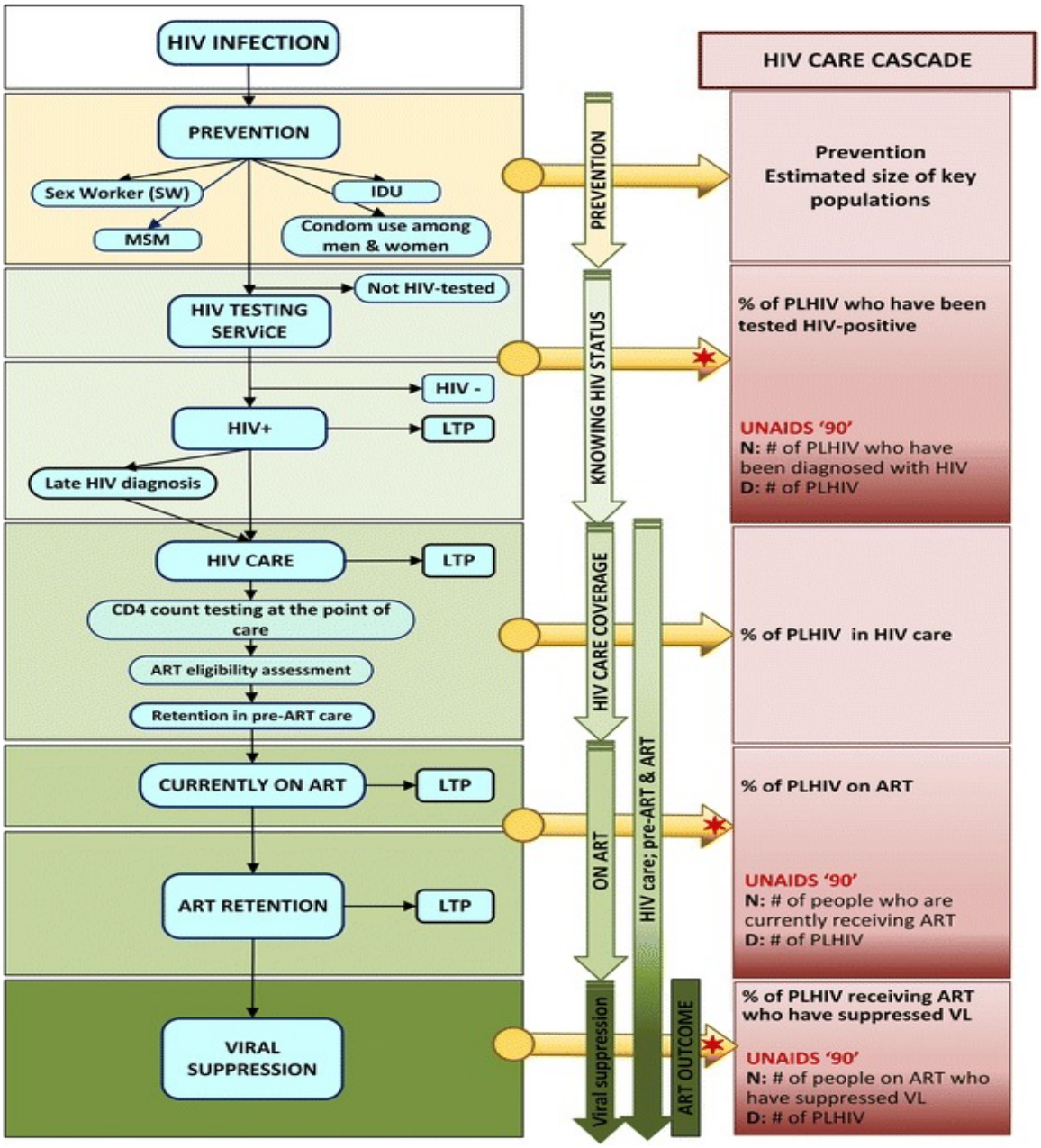

Figure 7 The HIV care cascade (Adapted from WHO 2015 guidelines(Consolid strategic Info))
ART, antiretroviral therapy; IDU, injection drug use; LTP, loss to program; MSM, men who have sex with men; PLHIV, people living with HIV; VL, viral load

Research on intervention to improve the HIV cascade

Cascade research has focused on addressing the barriers to care engagement such as structural barriers (long distance to clinic, transport costs, work constraints) health system barriers (multiple clinic visits, poor health provider attitudes,) and behavioral barriers (forgetting appointments, poor understanding of treatment) [55-60].

Cascade interventions have broadly been classified into six classes [61]:

(i) Service delivery: mobile testing, point-of care, navigator, integration, home-based care

(ii) Infrastructure/management: task shifting, guidelines, health worker training, clinic operations

(iii) Counseling

(iv) Social/Behavioral: peer interventions, reminders

(v) Technology: mobile phone interventions such as SMS, call reminders, mHealth

(vi) Demand creation: behavioral economics, incentives, food supplementation.

Prior to the test and treat era, interventions aimed at reducing patient attrition along the cascade achieved mixed results [62,63]. Interventions such as improved clinic operations [64-65], rapid/point-of-care (POC) CD4 count technology [66-72], a package of patient-directed services [73,74], interventions within home-based testing [76,77], HIV/TB service integration [78-80] have been associated with increased ART initiation in some studies. However, in a review [63] pooling three provider-initiated testing interventions (PITC) [81-82], PITC was observed to be associated with reduced ART initiation while counseling and support interventions [70,71,83,84] had no impact on

ART initiation. Peer interventions have been shown to have positive outcomes on linkage and retention, however there are limited data on the impact of peer intervention on adherence to ART, viral suppression and mortality [85,86].

Many studies have focused on one barrier at a single point of the cascade, for example, use of a phone short message service (SMS) to improve linkage to care at time of HIV diagnosis [74], or the use of point of care CD4 to improve retention among patients in care [66]. In their model, Gardner and colleagues demonstrate that an improvement on one step of the cascade will have little impact on viral suppression, which is the ultimate goal [43].More efficient multi-component approaches comprising several interventions that are practical and evidence-based, simultaneously targeting multiple and recurrent barriers that PLWH face as they navigate across the HIV care continuum are thus needed to maximize patient outcomes in care. Combination intervention strategy (CIS) has shown promise in improving outcomes along the cascade [86] and application simultaneously along the entire cascade is likely to have even greater impacts.

Rationale and objectives of the thesis

The question that must now be asked is "Are there missed opportunities in controlling HIV that treatment can offer?" Focus needs to move to using what we have in an optimized fashion to yield best individual outcomes and control of the epidemic. Given the impressive progress made on HIV testing coverage, the new cascade guides research to two important points of intervention likely to have greatest impact: linkage

to care and life-long adherence to ART. There is a need for efficiency and innovation to address these.

A comprehensive intervention on the HIV cascade to optimize outcomes and minimize losses arguably becomes the most important intervention in controlling HIV, and currently holds the promise of shutting down the epidemic. This thesis evaluates the contribution made by a patient-centered streamlined care intervention within the context of a universal test-and-treat trial on all the steps of the cascade, from linkage to care to ART initiation, retention in care, and viral suppression.

Specific objectives are:

Aim 1: To evaluate the barriers to engagement in care across the entire HIV cascade

Aim 2: To describe the linkage to care in a universal test and treat trial offering a patient centered linkage intervention.

Aim 3: To evaluate the effect of a phone call by a clinical officer at the time of HIV testing on linkage to care

Aim 4: To evaluate the impact of a patient centered streamlined care on HIV care retention.

Aim 5: To evaluate the impact of a patient centered streamlined care model on viral suppression.

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Methods

Study design

All studies represented in this PhD thesis were nested within the SEARCH trial (NCT01864603). The acronym SEARCH stands for Sustainable East African Research in Community Health. SEARCH is a large community-based cluster randomized HIV test-and-treat trial aimed at evaluating approaches to reduce HIV incidence and improve other health outcomes such as mortality, TB incidence, non-communicable diseases (diabetes and hypertension), maternal and child health.

The SEARCH trial was performed in 32 rural communities (20 in Uganda and 12 in Kenya) selected from 54 candidate communities that met initial eligibility criteria of a rural community, defined as one or more national geopolitical units, just above the village level (i.e., a parish in Uganda and a sub-location in Kenya), with a population of about 10,000 people. Based on ethnographic mapping data, national census and epidemiological data, 32 communities were selected on the basis of region, population density, occupational mix, access to transport routes, and number of trading centers [1]. Each of the 32 communities were randomized as matched pairs resulting in 16 intervention and 16 control communities. For each of the 32 communities, resident enumeration was conducted between July 2012 and June 2013 via a door-to-door census.To achieve high uptake of community-wide testing following the census, mobile, multi-disease Community Health Campaigns (CHC) lasting 2 weeks per community were augmented with home-based HIV testing (HBT) for those residents who did not attend the CHC in their community [2]. Baseline HIV testing was conducted between June 2013 and June 2014. Following the baseline testing, annual community-wide

testing was conducted in all the intervention communities to capture new cases and engage them in care using the hybrid-testing model comprising the CHCs and HBT.

Intervention

The intervention aimed to engage participants in care through linkage to care and retention in care with the goal of viral suppression. A patient-centered streamlined care model based on the social cognitive theory [3] was developed using the PRECEDE-PROCEED framework (Fig 1)[4] designed to reduce barriers to care for each step of the cascade. The patient-centered streamlined care components included were designed to target structural, health system and behavioral barriers that hinder care engagement [5-7]. The goal of the intervention was to impact the entire HIV testing and care cascade and impact health.

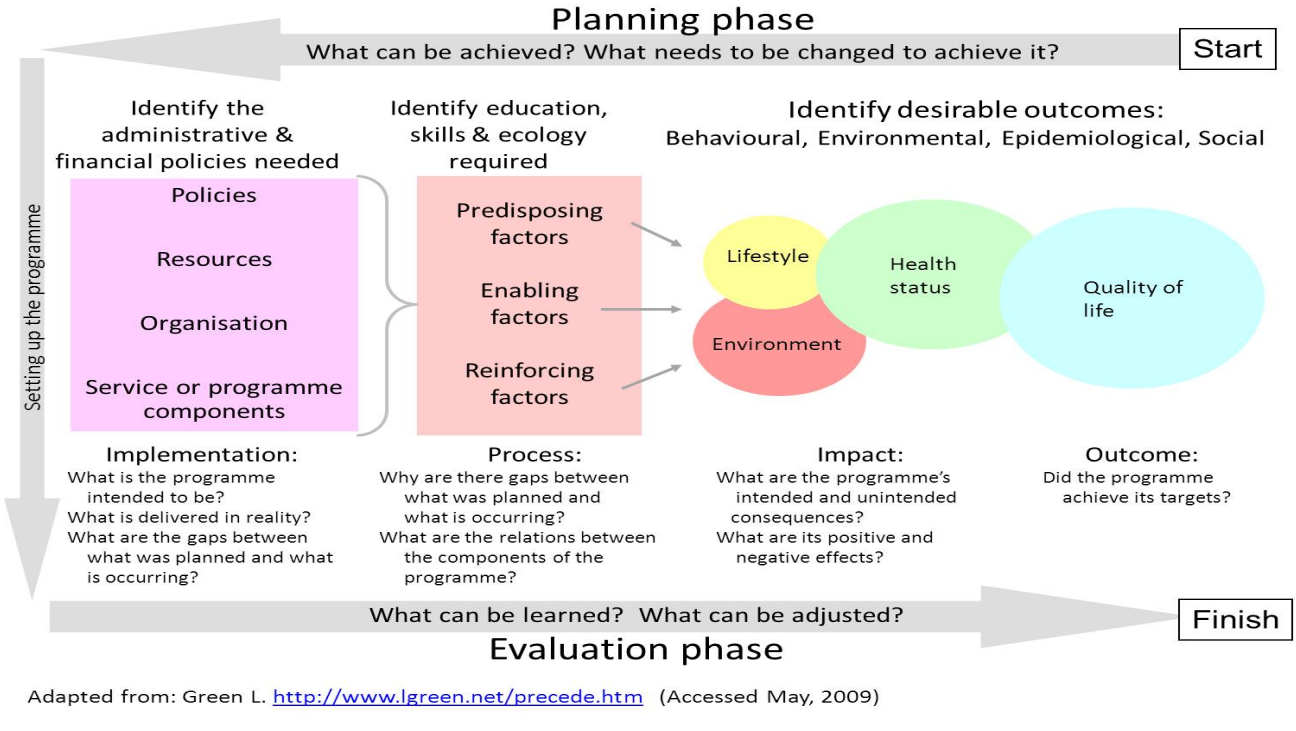

Figure 1: The PRECEED-PROCEED framework as described by Green L (4)

To improve linkage to care, the intervention introduced those eligible at the time of HIV testing to clinic staff either in person for those who tested at a community campaign or using a study-provided phone for those who tested at home. These personal introductions served to: i) established personal rapport between participant and clinic staff; ii) address participant questions about HIV or care provided in clinic; iii) assured participants of a patient-centered warm friendly environment with flexible clinic hours; and, iv) provided patients with a telephone "hot-line", a number that patients could call or text to ask questions or request support, such as rescheduling clinic appointments. Second, patients were provided a one-time transport reimbursement upon linkage. Third, patients received an appointment reminder call a day prior to their clinic appointment date. Finally, those who missed their linkage appointment were tracked.

To improve retention in care, the interventions implemented were same day ART start was offered, visits with reduced wait time [8], spaced out quarterly follow-up visits for stable patients, a patient-centered approach to care in which staff were trained to provide care in a welcoming and empathetic environment, a telephone "hotline" for patients with questions and appointment scheduling enquiries, appointment reminders via phone, and provision of viral load results through a structured viral load counseling protocol [9,10]. Those who missed clinic visits were tracked. No financial incentives were provided for retention in care.

I serve as a co-investigator in the study and the clinical services director for Kenyan sites on the study. My role in the study included participating in the design of the overall study intervention, recruiting and training study staff on delivery of the

intervention, supervision of participant enrollment and delivery of the study intervention, protocol amendments for revision in study design, review of difficult clinical cases and overall study administrative duties such as budgeting and resource planning.

All studies reported in this PhD were either nested within the SEARCH trial or performed as ancillary studies to the SEARCH trial. All papers included only focus on the intervention communities of the trial.

Primary data was collected for two of the five publications included in this thesis:

- Chapter 1. A qualitative analysis of barriers to engagement in care. In total, 63 participants were enrolled for in-depth interviews. I designed this study, worked with field staff in data collection and performed all analyses.
- Chapter 3. A randomized controlled trial (RCT) evaluating the effectiveness of a clinical officer phone call in improving linkage to care. In total, 208 individuals participated in the trial. I designed this study, supervised all field activities, and performed all analyses

Chapter 2 consisted of a secondary analysis of the SEARCH trial data collected at the baseline year of the study (1st author). I designed the concept of the secondary analysis and performed all analyses.

Chapters 4 and 5 were primary analyses of the SEARCH trial data. As a co-investigator of the trial, I was involved in the delivery of the intervention, assisted in the data

collection, participated in conception of the ideas on the manuscripts, and contributed to the writing and review as a co-author on these two manuscripts.

PhD Study setting

The studies were conducted in rural communities in Southwest Uganda, East Uganda and West Kenya three regions of East Africa. The economic activities of the participants varied across the regions but most were farmers with a higher proportion of fishermen among Kenya participants living around Lake Victoria than the other two regions. Majority of participants were Christians.

The estimated HIV prevalence across the three regions was 6.5%, 3.5% and 20.1% respectively with an average prevalence of 10.1%.

In 2015, an estimated 1,517,707 people in Kenya were living with HIV, 77,407 new infections were reported and 35,821 HIV related deaths occurred [11]. Of all the new infections observed, 51% of them occurred in individuals aged 15-24 years. Figure 1 shows the distribution of the HIV prevalence.

In 2013, about half of people living with HIV in Kenya were unaware of their HIV status [12] and only 897,644 (59%) were on ART. The ART coverage is not homogeneous, with vast portions of the country having coverage of less than 80% (Figure 2). A 40 % increase in the number of people living with HIV on ART has been noted between 2013 and 2015 (from 656,359 to 897,644) [11].

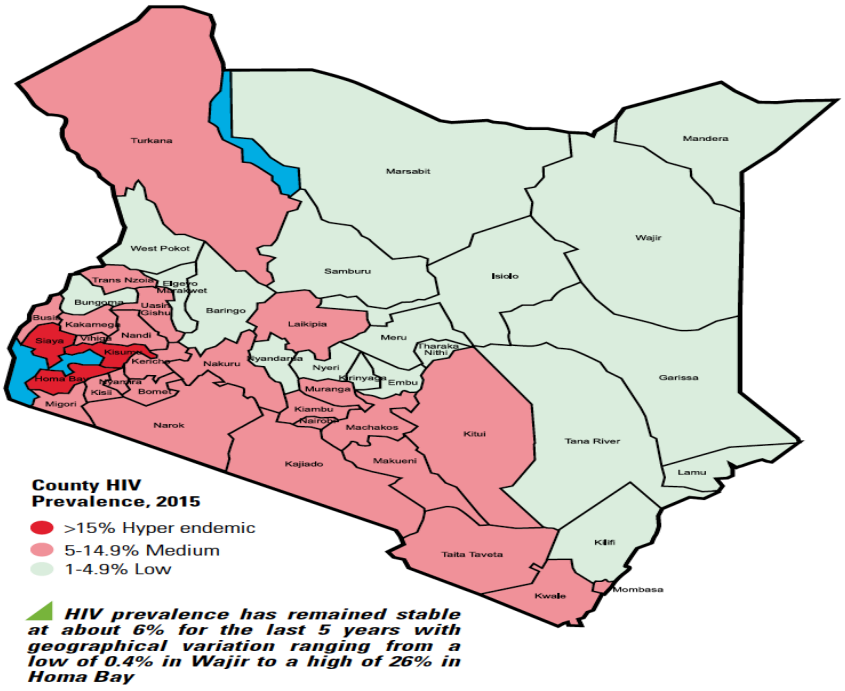

Figure 2: HIV prevalence in Kenya (Adapted from NACC 2016[11])

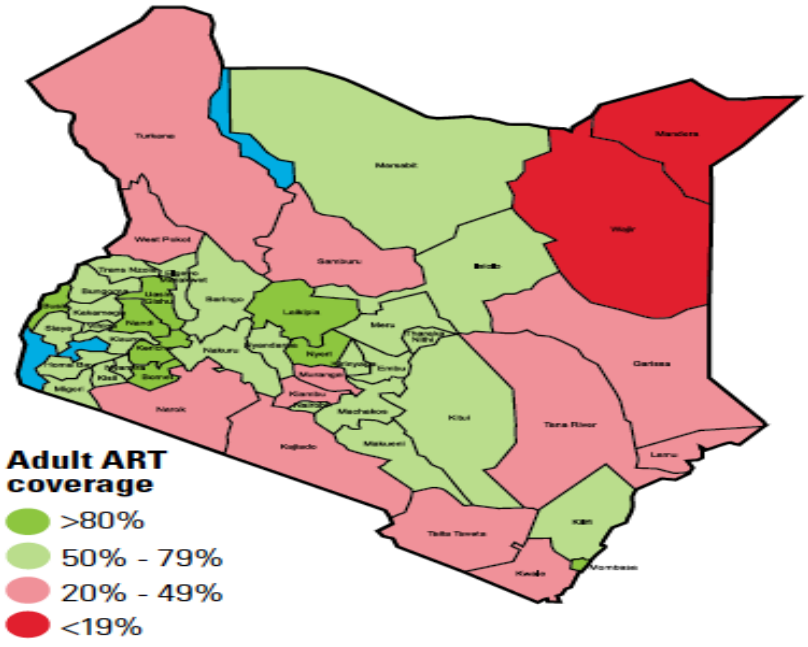

Figure 3: ART Coverage in Kenya as at 2015 (Adapted from NACC 2016[11])

In Uganda, it is estimated that 1,300,000 were living with HIV in 2017 [13]. The prevalence of HIV is 6.2 among adults aged 15-64 years [14]. Figure 3 shows the distribution of the disease burden by prevalence. Approximately 50,000 (42,000-59,000) new infections were reported in 2017, 48% (24,000) of these occurred among women aged 15 years and over. A total of 26,000(20,0000-34,0000) deaths occurred as a result of HIV [13].

In 2017, 81% (1,100,000) of those living with HIV knew their HIV status yet only 56% (760,000) were virally suppressed. ART coverage was estimated at 72% (68% -77%), with 969,569 of the 1,300,000 people living with HIV were receiving ART. About 42,489 persons were newly initiated on ART that year, a 5% increase from the previous year. Only 78% of people initiated on ART were still on ART 12 months after initiation [13].

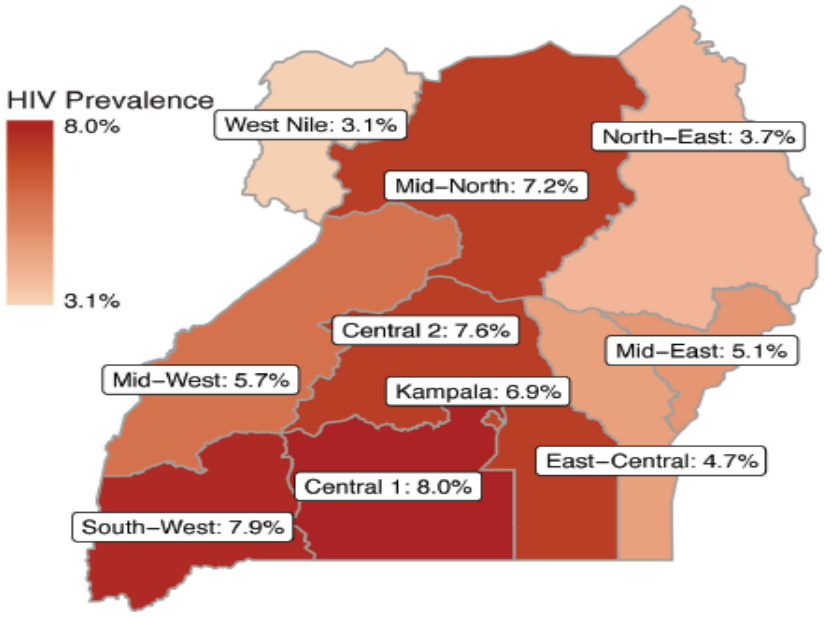

Figure 4: HIV prevalence of Uganda by region (Adapted from UPHIA progress report[14])

PhD Study population

All studies included in this thesis involve participants from the SEARCH trial.

The first manuscript is a qualitative analysis of barriers to care engagement. This was conducted using in-depth interviews at baseline, prior to roll-out of the intervention, with 63 study participants at various stages of the care cascade. Participants were randomly selected from 8 of the 32 trial communities.

The analysis for the second chapter (linkage to care) was limited to HIV positive participants who had never engaged in care after enrolment in the SEARCH trial.

For the third chapter (phone call randomized controlled trial) eligibility was limited to those participants who were not engaged in care at year 2 of the SEARCH trial. Eligible participants included i) those who were newly diagnosed with HIV at the year 2 testing (and thus had either not participated in HIV testing in year one or had not linked to care after previous testing at baseline or year 1of the study) and ii) those identified to have dropped out of care for more than six months at the time of follow up in year 2 testing.

The fourth chapter (retention) was focused on all participants who engaged in care, including both those who were newly linked to care and those already in care prior to study commencement.

The fifth chapter (testing, treatment and viral suppression), describes testing coverage among all community members and treatment, retention and viral suppression analysis among all participants engaged in care, both newly linked and those who were previously engaged in care already. The study population was an open cohort and includes those newly diagnosed with HIV during annual testing activities and linked to care as well as those who moved into the community. Individuals who moved out of the community within the first three years of the study were excluded.

Statistical analysis

The data analyses for the results presented in this thesis were done using standard techniques. Details of the analytic methods used can be found in detail in the method sections of each relevant chapter.

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Chapter 1

"Hurdles on the path to 90-90-90 and beyond": Qualitative analysis of barriers to engagement in HIV care among individuals in rural East Africa in the context of test-and-treat

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Abstract

Background

Despite substantial progress, gaps in the HIV care cascade remain large: globally, while about 36.7 million people were living with HIV in 2015, 11.9 million of these individuals did not know their HIV status, 12.7 million were in need of antiretroviral therapy (ART) and 13.0 million were not virally suppressed. We sought to deepen understanding of the barriers to care engagement at three critical steps of the care cascade proposed to make greatest impact for attaining the UNAIDS 90-90-90 targets aimed at shutting down the HIV epidemic.

Methods

Analyses were conducted among HIV-infected adults in rural East Africa. Qualitative data were collected using in-depth interviews among 63 individuals participating in an ongoing test-and treat trial (NCT01864683) in its baseline year (July 2013-June 2014). Audio recordings were transcribed, translated into English, and coded using Atlas.ti software. Data were analyzed using a thematic framework for explaining barriers to care engagement that drew upon both theory and prior empirical research in similar settings.

Results

Multiple barriers to engagement in care were observed. HIV-related stigma across dimensions of anticipated, internalized and enacted stigma manifested in denial and

fears of disclosure, and influenced lapses in care engagement across multiple steps in the cascade. Poverty (lack of food and transport), lack of social support, work interference, prior negative experiences with health services, drug side effects, and treatment fatigue also negatively affected ART adherence and viral suppression. Gender differences were observed, with work interference and denial disproportionately affecting men compared to women.

Conclusion

Multiple barriers to HIV care engagement still pervade rural sub-Saharan settings threatening the realization of the UNAIDS 90-90-90 targets. To control the epidemic, efforts need to be accelerated to combat stigma. Patient economic empowerment, innovative drug formulations, as well as more patient-responsive health systems, may help overcome barriers to engagement in care.

Key words: HIV care cascade, HIV test-and-treat, HIV care engagement, HIV care retention, community-based interventions

Introduction

Antiretroviral therapy (ART) has become more potent, better tolerated, and less complex, enabling people living with HIV (PLWH) adhering well to treatment to achieve viral suppression [1,2]. ART not only improves quality of life [3,4] but also prevents transmission of infection [5,6,7]. Several large trials are underway to test whether the HIV "test-and-treat" strategy [8] can reduce HIV incidence, as suggested by mathematical models [9] and observational studies [10,11]. The 90-90-90 UNAIDS targets envision that if 90% of PLWH are tested, 90% of those tested are initiated on ART, and 90% of those on ART achieve viral suppression, a high population-level viral suppression will be attained [12]— the key to the promise of the test-and-treat strategy to 'shut down' the HIV epidemic. For test-and-treat to succeed, early diagnosis coupled with linkage to and retention in ART care is required. Yet in many settings, late and low rates of HIV testing, poor linkage and retention, and suboptimal adherence to ART [13,14,15] continue to impede optimal outcomes. The barriers to effective engagement across every step of the HIV care cascade must be well understood in order to be successfully addressed; this is of greatest importance now as the scale up of test-and-treat takes place in sub Saharan Africa and other developing countries with an aim of achieving the UNAIDS 90-90-90 targets.

In this qualitative study, we sought to better understand barriers to engagement in HIV care, with a particular focus on the testing, ART initiation

and viral suppression steps of the cascade, during the baseline year of an ongoing HIV test-and-treat trial, the Sustainable East African Research for Community Health (SEARCH) study (NCT01864683)[16]. These data were collected prior to full implementation of SEARCH, and thus reflect conditions in communities prior to full 'rollout' of the test-and treat intervention.

Methods

Study design and sampling

Data are from a qualitative study embedded within the SEARCH trial, a community-level cluster randomized HIV test-and-treat trial currently being implemented in 32 rural communities in Uganda (10 in southwestern Uganda, 10 in eastern Uganda) and western Kenya (12). SEARCH aims to increase HIV testing and care uptake through community-led, multi-disease and patient-centered approaches, including community health campaigns followed by tracking and home-based testing, along with streamlined HIV care delivery; study details are published elsewhere [16].The qualitative study is conducted within 8 of the 32 SEARCH communities: 2 matched intervention and control communities in southwestern Uganda, 2 in eastern Uganda, and 4 in western Kenya.The overall aims of the qualitative study in SEARCH are to ascertain how a large test and treat effort influences community norms, beliefs, attitudes and behaviors related to HIV and, in turn, how these changes influence the uptake and success of this effort.

Purposive and stratified random sampling techniques were used to establish three longitudinal in-depth interview cohorts: community members, community leaders, and HIV care providers; this analysis uses only the data collected from HIV-positive members of the community cohort, which was composed via random selection from household rosters established by the SEARCH socio-economic survey. Within strata defined by gender and HIV care status (ascertained during baseline testing in SEARCH), 5 HIV-negative and 9 HIV-positive adults (aged 15 or over) per community (3 with CD4 count above 500 cells/mm^3 and not on ART, 3 on ART, and 3 eligible for ART by CD4 (<500 cells/mm^3) but not linked to care at sampling) were selected for recruitment for the qualitative study. A total of 63 HIV-positive individuals were successfully found and consented to enrollment in the study. Data were collected after baseline testing, during the first year of SEARCH (July 2013-June 2014). At the time of interview, among the 63 participants, 42 were engaged in HIV care, with 21 already on ART; a total of 21 were not engaged in care. The median age of the 63 participants was 37 years (IQR 30-44); 34 were female, 46 were married, 36 were from Kenya and 27 were from Uganda.

Data collection and analysis

In-depth semi-structured interview guides were used for data collection. A team of six trained researchers conducted the interviews in participant's preferred language (Lusoga, Lugwero, Ateso, Runyankole and Luo).

Interviewers and study participants were matched by gender and language. Audio recordings were transcribed verbatim and translated into English. Data analysis followed techniques from thematic and framework analysis [17,18], and also drew upon theories of stigma [19,20], and prior empirical research on barriers to care engagement among PLWH in similar East African settings [21]. In that study, six underlying factors were identified by confirmatory factor analysis to explain barriers to care engagement among out-of-care patients: poverty, inconvenience/work interference, poor treatment/quality at clinic, fear of disclosure of HIV status, healthy family provider/migrant worker, and treatment fatigue/seeking spiritual healing. We used the six-factor framework as a starting point for reduction and synthesis of the data for these analyses. Where new themes were emergent, the team of researchers discussed and modified the existing framework for inclusion of new codes. We drew upon socio-ecologic systems theory [22] for the organization of findings of this analysis.

Ethical approval

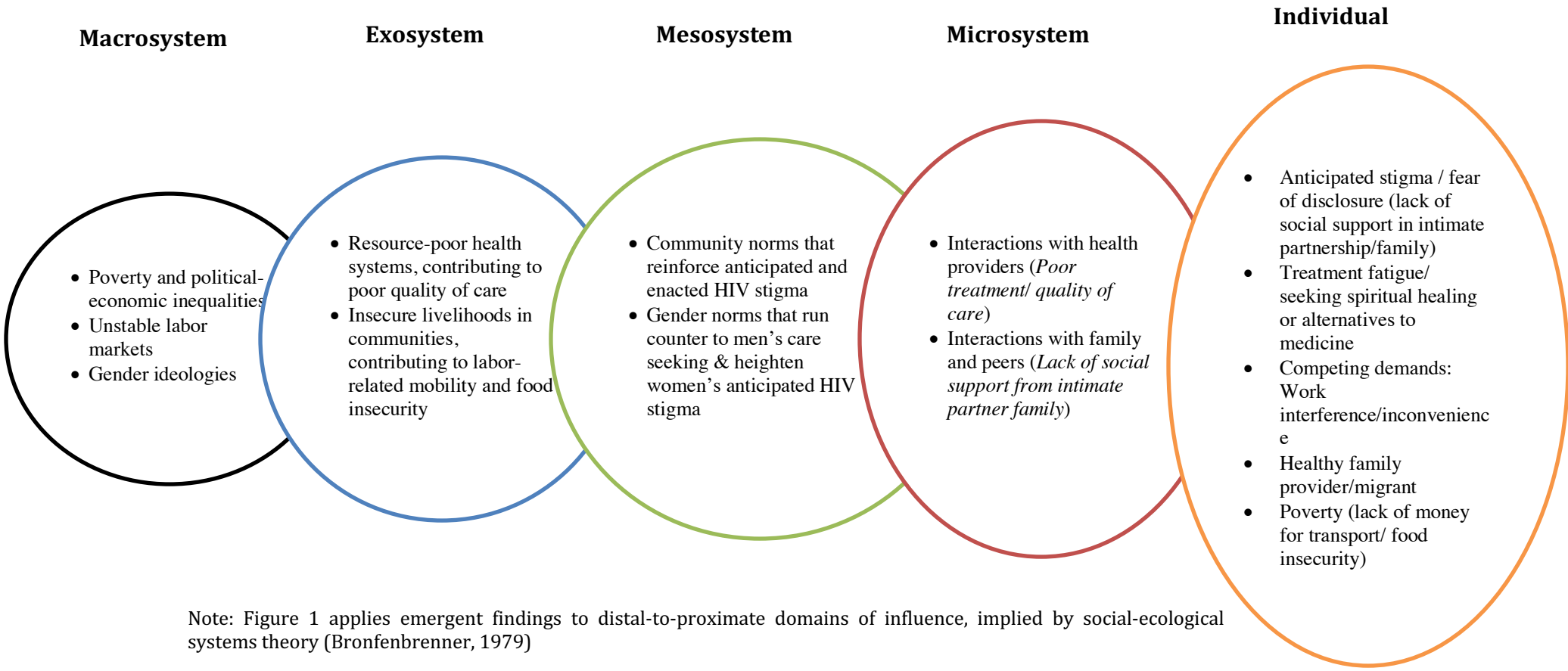
The study received ethical approvals from University of California, San Francisco Committee on Human Research, Makerere University School of Medicine Research and Ethics Committee, Uganda National Council for Science and Technology, and the Ethical Review Committee of the Kenya Medical Research Institute.

Results

In the results below we describe the principal emergent findings related to barriers to engagement in care across the care cascade among the participants. In Fig 1, we have organized these emergent findings into distal-to-proximate domains of influence using a social-ecological framework [22]. The socio-ecological perspective implies that these barriers to care engagement that are experienced by individuals (as documented in the excerpts presented below), are predicated by higher-level domains of influence: the microsystem includes interactions, roles and relations in the individual's immediate circle of partner, family and peers, including their interactions with health care providers; the mesosystem is made up of interconnections among microsystems, and is often the domain of community norms and values that are perceptible by individuals; the exosystem includes distal systems that affect an individual indirectly, including health systems-level factors that influence quality of care, and socio-economic conditions in settings that affect individuals' livelihoods, mobility and food insecurity; and finally the macrosystem, which is the broader environmental and political-economic context that influence cultural norms and values, and material conditions. We present direct empirical evidence in support of the individual, microsystem, and mesosystem level influences and barriers to care engagement in the results below. While some barriers appeared to impact upon specific steps in the cascade, others cut across multiple stages (from diagnosis to viral suppression). Gender

dimensions to the barriers to care engagement were observed; we describe below how men and women experienced some barriers differently.

Fig 1:Barriers to care engagement among PLWH organized from distal-to-proximate domains of influence using social-ecological framework



Note: Figure 1 applies emergent findings to distal-to-proximate domains of influence, implied by social-ecological systems theory (Bronfenbrenner, 1979)

HIV-related stigma

Participants' narratives revealed that three dimensions of stigma (anticipated, enacted and internalized, or 'self-stigma') [19] continue to impede successful engagement in care at every step of the cascade, with its impact felt across the entire HIV care cascade from testing, linkage to, and retention in care due to its diverse manifestations and expressions. PLWH did not want to be seen attending HIV clinics, because of anticipated stigma. Some only felt comfortable accessing care at non-ART clinic times (i.e. after hours) or in settings where no one knew them. Some said they would rather miss their scheduled appointments than meet people who would disclose their status. Clinics were sometimes not set up to help patients to cope with stigma, exacerbating patients' fears because of inadequate provisions to protect privacy:

> " They put it [*the HIV clinic tent*] in a bad location […], in the middle of the compound […] where everyone is watching you go. That tent! Everyone knows that it is for people that have HIV. When I go there, I try to hide, because if someone from this village sees you there, when you come back you find when they have announced to the whole village that you have HIV [*Laughs*]. So it all loses meaning. Whoever brought that virus really killed us." *(24-year-old married female from Uganda, engaged in care and on ART)*

Enacted stigma was observed in participants' accounts of discrimination because of their HIV status. PLWH reported that terms such as "useless", "dead", "walking dead", "finished", were used to refer to them, and that they were viewed as "promiscuous" and "immoral":

> "They comment and say that people with HIV are moving corpses and are useless."*(44-year-old married male, Uganda, not engaged in care)*

> "They say '*so and so has practiced immorality till she has contracted HIV'.* Sometimes I was not involved in immorality but it is my partners who brought in the infection." *(27-year-old divorced female from Kenya, engaged in care, not on ART)*

> "You can hear of some people saying that those who are using ARVs are immoral. They can talk about such in their own groupings, but can also say directly to the infected in case there is a disagreement between them, when one might abuse another while referring to his or her positive status."*(46-year-old divorced female from Kenya, engaged in care and on ART)*

Patients perceived that members of their communities viewed HIV infection as a 'death sentence' and equated an HIV- positive diagnosis with death:

"They [*community members*] feel that when they have HIV their life has suddenly stopped and death is the only option.**"** *(36-year-old married male from Kenya, not engaged in care)*

"Once one has tested positive, then what they think of next is death and this notion is what disturbs the community most." *(41-year-old married female from Kenya, engaged in care and on ART)*

PLWH also expressed internalized stigma, as they described feeling judged, ashamed and embarrassed. These feelings sometimes led to depression, low self-worth, and a loss of interest and motivation for self-care.

"People are still feeling embarrassed about the scourge and the majority are still hiding their status.**"** *(44-year-old divorced female, Kenya, engaged in care and on ART)*

"At times you may feel bad and angry with those people but then you decide to keep quiet. At times you hear a person say in public that you have HIV, and you start to feel embarrassed. You see this disease does not cure and everyone thinks it is the worst disease; in fact the people in my village think that way.**"** *(28-year-old married female from Uganda, not engaged in care)*

Anticipated stigma: Fear of HIV status disclosure

Fear of disclosure of HIV status is a major manifestation of anticipated stigma, and stood out as a distinct barrier to care engagement, especially at the cascade steps of linkage to and retention in care including drug adherence. Fear of disclosure to spouses or intimate partners as well as other members of the community negatively affected care engagement. These two circumstances are described in turn below:

Fear of disclosure to partner

Men feared to be blamed by their spouses for infidelity and bringing "death" to them. Some opted not to engage in care for fear that their spouse may suspect them having HIV if they were to take daily medications, or if they frequently visited the clinic despite appearing well:

> "I can say it is my own liking for not having received treatment yet. You know in that house I am living with my wife and the house belongs to the wife, so there is no place I can keep these drugs without her finding out. Exactly, that is what is hindering me [*from enrolling in care*]. I will keep the drugs somewhere and in that house she will definitely get them. Secondly, if I start taking drugs in the morning and evening she will ask me "*I thought you went to the hospital— which disease is this that drugs are just taken continuously?*"

So if she asks me like that, how will I respond?"*(36-year-old married male from Kenya, not engaged in care)*

This barrier appeared to differ by gender, based on commonly held gender role expectations. Men tended to avoid care more than women, sometimes leading to their deterioration and death, while women more often got into care, yet successfully kept their status a secret from their spouses:

"Men do not readily accept HIV care as compared to women. […] Men generally have a difficult understanding on life matters as compared to a woman…"*(38-year-old widowed female, Kenya, engaged in care and on ART)*

<u>Fear of disclosure at clinics</u>

Out of fear to be labeled with derogatory tags such as "corpses" or "dead", individuals with HIV choose to only disclose to a few individuals whom they perceived as safe custodians of their "secret". This presented a challenge in seeking care and getting drug refills, as individuals did not want other members of the community to know their status— especially in the early stages of accessing care in HIV clinics:

"… At first I was scared of going there [*the localHIV clinic*] to meet people there that I know or that know me, but I did not have

transport go to Mbarara— I would not be saving any money. I decided that come what may, because I am not the only one that has HIV [*I would seek treatment at the local clinic*]. However, when I board a motorbike, I tell the person riding me to take me to town— I do not tell him to take me directly to the health center. So when I get to town, I walk to the health center on foot so that no one sees me." *(41-year-old married female from Uganda, engaged in care and on ART)*

Denial

Denial of HIV-positive status after testing was a major barrier to linkage to and retention in care and resulted in delayed initiation of treatment, with some refusing to take their medication after being initiated on ART. Some individuals described having been in psychological denial, while others described having avoided care more as a manifestation of negative coping.

"Some normally wait to the final stages of HIV/AIDS for them to act and they must be pushed hard to do so."*(31-year-old widowed female from Kenya, engaged in care and on ART)*

> "[*I took*] about five years [*before enrolling into care*] and in between I used to go for repeated tests which all tested positive."*(42-year-old married male from Kenya, engaged in care and on ART)*

> "…Because I was in denial, I threw the drugs in the water while I was on my way home from the hospital. I later became sicker and my mother-in-law now talked to the doctors to come for me since she did not want to lose yet another person in the family after the son [*my husband*] had passed on." (*41 year-old widowed female, Kenya, engaged in care and on ART*)

Participants said that men, especially young men, were disproportionately affected by denial:

> "Men will only visit the hospitals when critically sick […] Most of them [those who die as a result of HIV] are young men"*(38-year-old widowed female, Kenya, engaged in care and on ART)*

Poverty

Poverty strongly affects linkage to and retention in care, both through food insecurity and also difficulty with paying for transportation to and from clinic. PLWH require adequate nutritious food for best outcomes on

treatment, and patients report aggravated side effects when medications are taken on an empty stomach. Poverty, as a driver of food insecurity, therefore emerged as a salient barrier to drug adherence:

> "I don't like taking these drugs when there is no food. When I have nothing to eat, I don't take them..."*(36-year-old married female, Kenya, engaged in care and on ART)*

Secondly, HIV is a chronic condition and requires money for transportation for multiple follow-up visits at health facilities:

> "Transport is a burden. At times you do not have money and you have exceeded your appointment dates. […] It is only transport that disturbs me, because I do not have where to get it from." *(24-year-old married female, Uganda, engaged in care and on ART)*

Poor quality of health services

A hostile treatment environment, including negative attitudes from healthcare providers and long wait times, was also found to hinder retention in care. Some participants described encounters with health care providers with a 'bad attitude', who humiliated patients. This resulted in some patients stopping care, and others changing health facilities:

> "These service providers are sometimes not friendly […] The providers make noise to the clients who have either come late or defaulted and send them back home without drugs. This sometimes is humiliating to the clients who sometimes get demoralized and just stop going for drugs completely."*(31-year-old widowed female, Kenya, engaged in care and on ART)*

> **"**I know that they [*antiretroviral medications*] are really helping people a lot. I also know that they are harmful if not used correctly, though this could come as a result of many factors, like distance to the health facility and even the way the providers handle those who have defaulted. They are punished by the facility for defaulting. They either go without drugs, or quarreled [*with*] by the providers, and this in turn discourages people— they just continue defaulting because they do not want to go through the negative attitude from the providers." *(41-year-old divorced female from Kenya, engaged in care and on ART)*

Some viewed the long clinic visit due to wait times as an additional expense, since they have to spend additional money on a meal while waiting to be attended to:

"We spend a lot of time at the health facility. If you do not have money to buy tea and food, you can collapse."*(28-year-old single male, Uganda, engaged in care and on ART)*

Competing demands: Care-seeking interfering with work

Engagement in chronic care is demanding in this high-poverty, rural setting, both in terms of time and money spent in attending clinic appointments. Attending clinic may take a whole day and thus interfere with income generating activities; patients had to weigh losing a day's income against attending a clinic appointment. In addition, the livelihoods that patients are involved in, such as fishing, sometimes involved expeditions that took days or weeks, presenting a challenge to drug adherence:

"… sometimes I may leave for the [town] center with the aim of not going to the lake knowing that[…]I will go back home and take my drugs— but I find people at the center who force me to take them inside the lake. Something I didn't prepare for…."*(38-year-old married male, Kenya, engaged in care and on ART)*

"The fact that I must collect my drugs sometimes bar me from undertaking some personal activities, but I must collect them because

this is where my help comes from." *(30-year-old married male from Kenya, engaged in care and on ART)*

Feeling healthy

Feeling healthy, especially among those whose health had improved after ART, also emerged as a barrier to retention in care and drug adherence. Some dropped out of care because they felt that they did not need the medication any longer:

> "… there is somebody who truly is sick and has been on drugs for two years— but because he thinks that he has recovered, since he is looking healthy and feeling normal […], [*he*] puts drugs aside. Taking the dose morning and evening is not easy."*(45-year-old married male, Kenya, engaged in care and on ART)*

> "These people just refuse going to the hospital for drugs because they think that they are now healthy. Others just stop because they are tired of taking drugs"*(31-year-old married female from Kenya, engaged in care and on ART)*

Treatment fatigue

For a lifelong condition requiring daily oral medication, treatment fatigue is a key barrier. Some PLWH referred to themselves as "prisoners" to the medication. This theme emerged as a barrier to drug adherence, a necessary component for viral suppression. Some got tired along the way and stopped their medication altogether:

> "It is like being in a jail, because it has to be taken daily." *(49-year-old married male, Kenya, engaged in care and on ART)*

> "We feel like prisoners to the drugs, because all the time we are supposed to have them with us no matter where we are and where we go, as well as to adhering to the time, which is the greatest challenge." *(45-year-old married female from Kenya, engaged in care and on ART)*

Drug side effects

Participants reported experiencing side effects especially at the beginning of treatment, which subsided in most cases. The severe or protracted forms are most worrying to patients, and without reassurance, patients were likely to stop their medications hampering drug adherence, with resultant viral non-suppression:

"….When I swallowed these drugs for the first time, I used to have bad dreams and get nausea[…] I used to feel so weak and I would collapse and so I called the providers.[…] I told them […] 'it seems these drugs that you gave me are going to kill me.' " *(30-year-old married male, Uganda, engaged in care and on ART)*

Negative beliefs and attitudes about ART

Firmly held beliefs, whether true or false, and negative experiences emerged as barriers to linkage to care, ART initiation and drug adherence. Most of the beliefs were centered around ART, mostly associated with negative effects to the patient on treatment.

"I was in a group of 30 members who all died in succession only three of us are still alive. This made me plead with the doctors not to initiate me on ARVs since I knew those on ARVs die sudden deaths." *(51-year-old married male, Kenya, engaged in care and on ART)*

Discussion

This qualitative study documented a conceptually-coherent set of factors hindering positive outcomes at three stages in the HIV care cascade proposed to yield greatest impact in shutting down the HIV epidemic, per the UNAIDS 90-90-90 targets. These ranged from psychosocial factors such as

dimensions of HIV-related stigma, especially as manifested in fear of disclosure that hindered individuals from being seen at HIV clinics as has been documented previously [23,24], to structural factors related to poverty such as food insecurity and a lack of money for transport, to health systems barriers which hindered drug adherence and clinic retention. In some instances these factors were inter-related, as viewing clinic attendance as a competing demand that interfered with income-generating activities interacted with health systems factors such as long wait times (a marker of poor quality of care).

These qualitative findings mapped well to a previously empirically-derived set of factors explaining barriers to care engagement among out-of-care patients, using health systems data from programs in several East African countries [21] and provide theoretical validation of this framework to explain barriers to care engagement. The empirically-derived six-factor structure was not, however, comprehensive; this qualitative study suggested that in addition to the key six domains previously identified (anticipated stigma and fear of disclosure; treatment fatigue, and seeking spiritual healing or alternatives to medicine; competing demands, or work interfering with care-seeking; being a healthy provider for one's family, often as a migrant; poverty, manifested as lack of money for transport and food insecurity; and poor quality of care at clinics), there were two additional emergent themes related to barriers: psychological denial/negative coping; and having

negative experiences (including side effects), beliefs and attitudes about ART. Further work should be done to develop instruments to predict threats to care engagement that can be used by health care workers to identify patients at risk of dropout, or by health systems to evaluate progress towards addressing barriers to care engagement in resource-poor settings.

While both men and women in the communities experienced high levels of anticipated stigma, our study reveals a gender dimension to these barriers. We found that, while both men and women feared disclosure, women more readily engaged in care despite the fact that the negative consequences of disclosure that they anticipated (abandonment or violence) were more severe. Men avoided care more readily than women in response to fears of being blamed and shamed. In addition, men's livelihoods that involved mobility (e.g. fishing), combined with male gender norms that reinforced men's needs to uphold their status as breadwinners, made perceived work interference a particularly potent barrier. These findings are consistent with those we have previously described in a larger qualitative study of HIV status disclosure experiences in SEARCH communities [25].

Our findings underscore the persistence of HIV-related stigma in rural East African settings. Though rapid advancements have been made in HIV treatment, negative perceptions associated with HIV disease have not evolved as rapidly [26,27]. Our study confirms findings of other recent

studies [23,24] that stigma remains a major barrier to successful care engagement. Various approaches are needed to directly address stigma, including stronger social support structures for patients, clinic integration, spaced out clinic appointments for stable patients, and mental health care services that have been shown to improve retention [28,29]. Other interventions, including education programs to enhance understanding of HIV disease, connecting PLWH with their peers and the community, and skills-building through peer coaching, have shown some promise for addressing stigma [30,31,32].

Quality of care, including patient-provider interactions, is an important facilitator of care engagement that is amenable to intervention. Our findings were consistent with prior studies showing that poor health services, health provider attitudes and clinic set-ups deterred care engagement [23,24]. Patient-friendly services are needed, accommodating patient desires such as confidentiality, flexibility in clinic appointments and friendly interactions with patients [23]. Streamlined care models designed to provide more flexible, patient-centered care have been shown to produce favorable outcomes among HIV patients in diverse settings [33].

Other factors may pose a more stubborn threat to successful care engagement, including treatment fatigue. Therapy simplification including alternative drug formulation as well as reduced frequency of drug dosing and

pill burden are known to improve adherence to treatment translating to better outcomes in HIV management [34]. First line treatment with one pill a day and development of injectable long acting ART are hopeful developments in this respect, more still needs to be done to address this concern.

Our study was subject to limitations. This analysis drew information from PLWH, and did not include perspectives from other parties such as healthcare providers, family members or other community members. However, we view this focus as a necessary step to ensure conceptual rigor in analyzing themes emergent from the data, foregrounding voices and experiences of PLWH. Interviews are susceptible to social desirability bias. Our interviewers were trained to reaffirm confidentiality and avoid judgmental reactions, which aided in minimizing this bias. Our study does not present data on certain key populations such as men who have sex with men (MSM), sex workers and injection drug users, data that may be of interest in other settings due to unique care engagement barriers experienced by these groups. The scope of this analysis was limited to barriers of care engagement, and did not include analyses of facilitators, permitting us to present findings in depth. The findings are strengthened by the breadth and regional heterogeneity of our data sources, composed of interviews with PLWH living in communities across three regions of Uganda and Kenya; thus, findings are potentially applicable to other rural settings in developing countries. With respect to the reflexive nature of this research,

the investigators in this study comprised a multidisciplinary cross-regional team including African researchers living the study settings, an asset for inclusion of multiple perspectives in the interpretive process. Finally, this analysis explores barriers along the entire cascade of care, demonstrating the impact of specific barriers across several points in the care cascade, as well as their distal to proximate levels of influence.

Conclusions

Achieving the 90-90-90 targets promises both to optimize individual health and prevent onward HIV transmission. As universal treatment is expanded in sub-Saharan Africa it will be essential to address the barriers at critical steps of the HIV care cascade. Sustained efforts to decrease HIV-related stigma as a major impediment to meaningful engagement are still required. Additionally, health care systems and policy makers must make deliberate efforts to deliver patient-centered, patient-sensitive and patient-responsive care to promote sustained engagement.

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Chapter 2

A patient-centered multi-component strategy for accelerated linkage to care following community-wide HIV testing in rural Uganda and Kenya

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Abstract

Introduction: As countries move towards universal HIV treatment, many individuals fail to link to care following diagnosis of HIV. Efficient and effective linkage strategies are needed.

Methods: We implemented a patient-centered, multi-component linkage strategy in the SEARCH "test-and-treat" trial (NCT 01864603) in Kenya and Uganda. Following population-based, community-wide HIV testing, eligible participants were (1) introduced to clinic staff after testing, (2) provided a telephone "hot-line" for enquiries, (3) provided an appointment reminder phone call, (4) given transport reimbursement upon linkage, and (5) tracked if linkage appointment was missed. We estimated the proportion linked to care within one year and evaluated factors associated with linkage at 7, 30 and 365 days using logistic regression.

Results: Among 71,308 adults tested**,** 6,811(9.6%) were HIV-infected; of these, 4,760(69.9%) were already in HIV care. Among 2,051 not in care, 58% were female, median age was 32 (IQR 26-40) years, and median CD4 count was 493 (IQR 331-683)cells/μL. Half (49.7%) linked within one week, and 73.4% within one year. Individuals who were younger (15-34 vs. >35 years, aOR 0.69, 95%CI:0.55-0.88), tested at home vs. community campaign (aOR=0.61, 95%CI:0.49-0.76), had a high-HIV-risk vs. low-risk occupation (aOR=0.51, 95% CI:0.40-0.65) and were wealthier (aOR 0.66, 95% CI:0.49-0.88) were less likely to link. Linkage did not differ by marital status, stable residence, level of education or having a phone contact.

Conclusion: Using a multicomponent linkage strategy, 73% of people living with HIV but not in care linked within a year, and half linked within one week of HIV testing.

Key words: Linkage to HIV care, factors associated with linkage, test-and-treat, linkage strategy, risk factors, HIV care continuum

Introduction

The therapeutic and preventive benefits of antiretroviral therapy (ART) highlight the need and the urgency to identify individuals living with HIV, link them to care, and initiate them on ART.[1-3] However, many people diagnosed with HIV fail to link to HIV care following diagnosis, or link after long delays.[4-6] Poor linkage to care is reported across sub-Saharan Africa, the region most heavily burdened by the HIV epidemic,[7-9] posing a threat to the 90-90-90 UNAIDS strategy, which aims to ensure 90% of those living with HIV are aware of their status, 90% of those diagnosed are on ART, and 90% of those on ART achieve virological suppression.[10, 11]Linkage to care may prove an even greater challenge in the context of population-based HIV testing and the current World Health Organization's (WHO) treatment guidelines, under which every person living with HIV is eligible for ART.[12] In this context, the population in need of linkage may increasingly be recently infected individuals, individuals who previously failed to link, or who have dropped out of care, and individuals who have characteristics, such as mobility, that pose a challenge to both testing and linkage. Recently completed and ongoing test-and-treat trials report delayed time to linkage and low rates of linkage to care.[11,13] These results highlight the importance of addressing linkage to care where HIV "test-and-treat" is part of the strategy to improve health and control the HIV epidemic.

We sought to evaluate a multi-component, patient-centered linkage strategy implemented within the context of the SEARCH (Sustainable East Africa Research in Community Health) study, a population-based, community-wide test-and-treat trial in Kenya and Uganda.[14] The multi-component linkage strategy consisted of a patient-centered approach tailored to the setting based on the social cognitive theory,[15] targeting the documented structural, health system and behavioral barriers that hinder care engagement .[16-18] In this analysis, we evaluated linkage to HIV care among individuals newly

diagnosed with HIV and those previously diagnosed but not currently in care, and evaluated factors associated with failure to link.

METHODS

Study Setting and Population

The linkage to care intervention was nested in the intervention communities of the SEARCH Study (NCT01864603), a community-based cluster randomized trial in rural Kenya and Uganda that evaluated a multi-disease, patient-centered approach to reducing HIV incidence and improving community health and productivity. To achieve high uptake of community-wide testing, mobile, multi-disease Community Health Campaigns (CHC) lasting approximately 2 weeks per community were combined with home-based HIV testing (HBT) for those residents who were enumerated in a baseline census but who did not attend the CHC in their community.[19]

Identification of the Linkage Cohort

Census-enumerated individuals aged ≥15 years in the 16 SEARCH study intervention communities (10 in Uganda and 6 in Kenya) who tested positive for HIV by rapid HIV antibody tests between June 2013 and June 2014 and were in need of linkage to HIV care were eligible for inclusion in this analysis. Individuals were defined as in need of linkage if they were: 1) were newly diagnosed with HIV by rapid HIV antibody tests or 2) self-reported a prior diagnosis of HIV, but stated that they were not currently in HIV care and had no evidence of being in HIV care following review of medical and laboratory records.

Linkage to care intervention

Our linkage to care intervention strategy was comprised of a patient-centered, multi-component approach with the goal of linking patients to care and starting ART as soon as possible. Prior to testing campaigns, research and clinic staff completed a formal staff-training program to facilitate rapid antiretroviral initiation. The training program included didactic materials on the rationale for accelerated linkage and role playing activities to practice delivery of the linkage intervention. The accelerated linkage intervention

included multiple components, each designed to address a previously identified barrier to linkage. First, at the time of HIV testing, participants were immediately introduced to clinic staff either in person for participants who tested at a health campaign, or using a study-provided phone for participants who tested at home or other location. These personal introductions: i) established personal rapport between participant and clinic staff; ii) addressed any participant questions about HIV or the care provided in clinic; iii) assured participants of a patient-centered warm friendly environment with flexible clinic hours; and, iv) provided patients with a telephone "hot-line". The "hot-line" consisted of a number that patients could call or text message at any time to ask questions or request support, such as rescheduling clinic appointments without having to attend the clinic in person. Second, patients were provided a one-time reimbursement for transportation upon linkage (2-12.5 US dollars depending on distance from home to clinic). Third, patients received an appointment reminder phone call the day prior to the clinic appointment. Finally, patients who missed their linkage appointment were called to reschedule their clinic visit; home visits to reschedule clinic visit were done if the phone call intervention was not successful.

Linkage Outcome Measures

We defined date of linkage to care as date of a first HIV clinic visit made at any health facility within or adjacent to the SEARCH community following the community-based HIV test. "Accelerated linkage" was defined as linking to care within 7 days of HIV diagnosis. At time of the first visit, individuals and their medical records (paper or electronic) were identified at SEARCH trial-affiliated ART clinics by fingerprint-biometric matching and name. At non-SEARCH trial-affiliated clinics, unique identifiers (clinic ID numbers) and demographics were used to identify medical records.

Independent variables

Participant gender, age, marital status, education, occupation, region, stable residence (defined as residing in the community for ≥6 months in the

previous year), access to a mobile phone, and self-reported prior HIV testing data were collected at baseline census and at time of HIV testing at CHC or HBT. Socio-economic status was assessed using an asset score derived from a principal components analysis of presence of electricity in the home and ownership of clock, radio, television, phone, refrigerator, bicycle, motorcycle.[20] Baseline CD4+ T cell count and plasma HIV RNA level was measured at time of HIV testing. High HIV-risk occupation was defined as employment in an occupation reported to be associated with higher HIV prevalence in the literature for East Africa,[21-23] and included fishermen, bar owners, bar workers, tourism personnel, and drivers of trucks, taxis, motorcycles, bikes or boats. HIV testing location was classified as CHC versus home-based testing.

Statistical Analysis

The Kaplan Meier estimator was used to estimate cumulative linkage over the 365 days following baseline HIV testing at CHC or tracking, censoring at death. We calculated estimates of cumulative linkage by 1, 3, 7, 30, 90, 182 and 365 days post HIV testing.[24] To assess factors associated with linkage to care, univariate and multivariate logistic regression were used to assess predictors of linkage within 7 days, 30 days and 1 year, treating death before linkage as failure to link. Community of residence was included as a fixed effect. Variables to be included in the adjusted model were selected *a priori* based on factors identified in literature as predictive of linkage to care, and included age, sex, marital status, occupation, education, point of testing, wealth index, baseline CD4+ T cells, prior knowledge of HIV status and having a phone contact .[6,25] Subjects with missing data for asset score measurement were assigned the population mean asset score. Missing baseline laboratory CD4+ T cell count was treated as its own informative category.

Ethics

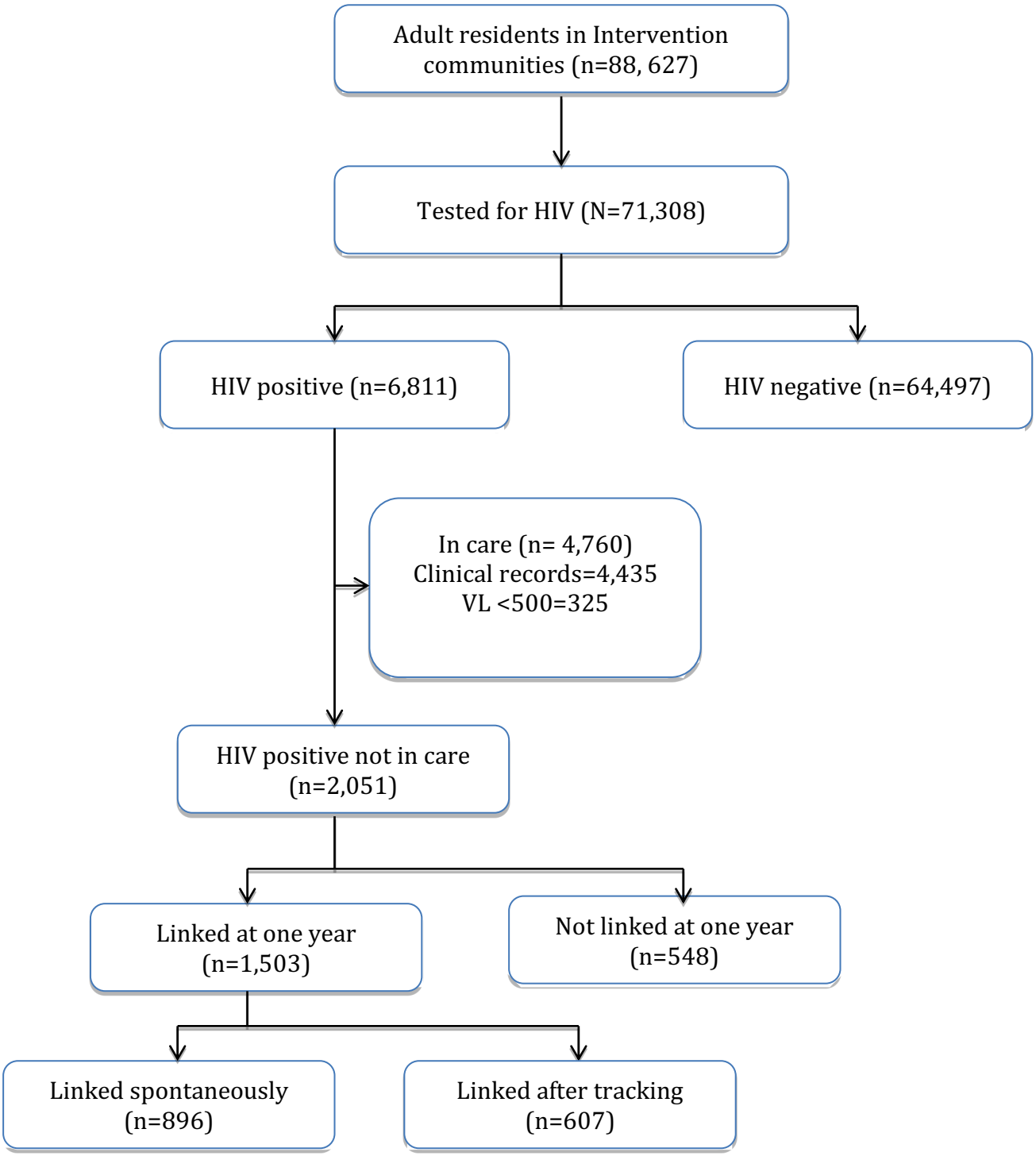
The Kenya Medical Research Institute Ethical Review Committee (Kenya), Ugandan National Council on Science and Technology (Uganda), Makerere University School of Medicine Research and Ethics Committee (Uganda), and University of California San Francisco Committee on Human Research (USA) approved the study. All participants provided verbal consent in their preferred language.

RESULTS

Linkage to care cohort

A total of 88,627 household-census enumerated individuals aged ≥15 years were approached for HIV testing in the 16 SEARCH intervention communities. Through mobile community and home-based HIV testing, HIV status was determined in 80.5% (n=71,308) of potentially eligible subjects (Fig 1). Of these, 6,811 individuals had positive HIV rapid antibody tests, corresponding to an HIV prevalence of 9.6%. Of these 6,811 HIV-positive cases, 4,760 (69.9%) had a medical record or laboratory evidence of engagement in HIV care at time of HIV antibody testing. The remaining 2,051 people living with HIV were identified as in need of engagement in care and were thus included in the linkage cohort analysis. Among these, 1,624 (79.2%) were newly diagnosed with HIV, and 427 (20.8%) reported a prior HIV diagnosis but were not currently engaged in care.

Figure 1: Study profile of residents in 16 SEARCH intervention communities in Kenya and Uganda, July 2013 to June 2015.



Linkage Cohort Characteristics.

Demographic and clinical characteristics of the linkage cohort are presented in Table 1. The majority (58%) were female, median age was 32 years (IQR 26-40) and 19.3% were under 25 years of age. Geographically, 61.4 % resided in Kenya, 27%, in Southwest Uganda and 12%, in East Uganda. The majority (70.5%) tested at a mobile CHC; 29.5% through home-based testing. Most individuals (72.2%) had access to a mobile phone, and 61.3% had received secondary or tertiary education. At the time of HIV testing, 49% had a CD4 count of ≥500 cells/μL; 28% had a CD4+ T cell count below 350 cells/μL. The median plasma HIV RNA level was 34,004 copies/μL.

Linkage to Care.

Of the 2,051 adults in the linkage cohort, 1,503 (73.4%, 95% CI: 71.5%-75.3%) were linked to care within one year of HIV testing. Among those who linked, 60% (n=896) self-linked to care, with the remaining 40% (n=607) linking after outreach tracking. Cumulative linkage in days from HIV testing is depicted in Figure 2 and Figure 3. Overall, 42.9%(95% CI 40.8, 45.0) individuals linked on the same day of HIV testing, 46.2% (95% CI 44.1, 48.4), within 3 days, 49.7% (95% CI: 47.5, 51.9), within 7 days, 56.6% (95% CI 47.5,58.7), within 30 days, and 61.3%(95% CI 52.9,63.4), within 3 months of testing. Among the 1,019 subjects who linked within the "accelerated" linkage period of 7 days, 86% linked on the same day as HIV testing (n=879), 7% between 0 and 3 days and 7% between 3 and 7 days. During the first year following HIV testing, 11 subjects died prior to linkage – 4 from medical causes including 1 with tuberculosis, 1 from traffic accident and 6 from unknown cause.

Table 1: Baseline characteristics of a cohort of 2051 individuals newly diagnosed with HIV (N=1,624) or previously diagnosed with HIV but out of care (N=429), resident in one of 16 SEARCH intervention communities in Kenya and Uganda, July 2013 to June 2015.

		All		Linked by 1 year		Not Linked by 1 year	
		N	%	N	%	N	%
All		2051		1503		548	
Sex	Male	869	42.4	654	75.3	215	24.7
	Female	1,182	57.6	849	71.8	333	28.2
Age	15-24	395	19.3	260	65.8	135	24.2
	25-34	807	39.3	573	71.0	234	29.0
	35-49	654	31.9	504	77.1	150	22.9
	≥50	195	9.5	166	85.1	29	14.9
Marital status	Married	1,494	72.9	1094	73.4	397	26.6
	Single	236	11.5	156	65.3	83	34.7
	Widowed divorced, separated	321	15.7	253	78.8	68	21.2
Education	None	166	8.09	142	85.5	24	14.5
	Primary	1,575	76.79	1,141	72.4	434	27.6
	Secondary	228	11.12	115	72.8	62	27.2
	Tertiary	82	4	54	65.9	28	34.1
Occupation	High HIV risk	223	10.9	134	61	87	39
	Low HIV risk	1,828	89.1	1,367	78	461	25.2
Testing site	CHC	1,445	70.5	1,094	75.8	349	24.2
	HBT	606	29.5	409	62.3	199	32.7
Region	Kenya	1,254	61.14	829	66.1	425	33.9
	South West Uganda	550	26.82	461	66.1	89	16.2
	East Uganda	247	12.04	213	86.2	34	13.8
Residence	Stable	1,986	96.8	1,436	72.3	550	27.7
Stable	Non stable	65	3.2	43	66.1	22	33.9
Phone	Have phone	1,482	72.2	896	72.4	341	27.6
Have phones	No phone	569	27.8	607	74.6	207	25.4
Asset score	Median (IQR)	2.78(0.57,5.86)		2.40(0.55,5.67)		2.86(0.61,6.73)	
	1st Quartile (lowest)	515	25	393	76.3	122	23.7
	2nd Quartile	513	25	373	72.7	140	27.3
	3rd Quartile	511	25	387	72.7	124	24.3
	4th Quartile	512	25	350	68.4	162	31.6

		(Highest)						
Know result	HIV	Negative	932	45.4	650	44.0	282	49.3
		Positive	427	20.8	295	20.0	132	23.1
		Do not know/No response	692	33.7	534	36.1	158	27.6
Baseline CD4		Mean (SD)	531.71(282.46)		517.8(278.2)		552.0(288.3)	
		0-349	503	27.8	312	62.0	191	38.0
		350-499	419	23.1	231	55.1	188	44.9
		=>500	889	49.1	449	50.5	440	49.5

Figure 2: Cumulative Linkage-to-Care by Time from HIV Diagnosis (Kaplan-Meier Estimates) in a cohort of 2051 individuals newly diagnosed with HIV (N=1,624) or previously diagnosed with HIV but out of care (N=429), resident in one of 16 SEARCH intervention communities in Kenya and Uganda, July 2013 to June 2015.

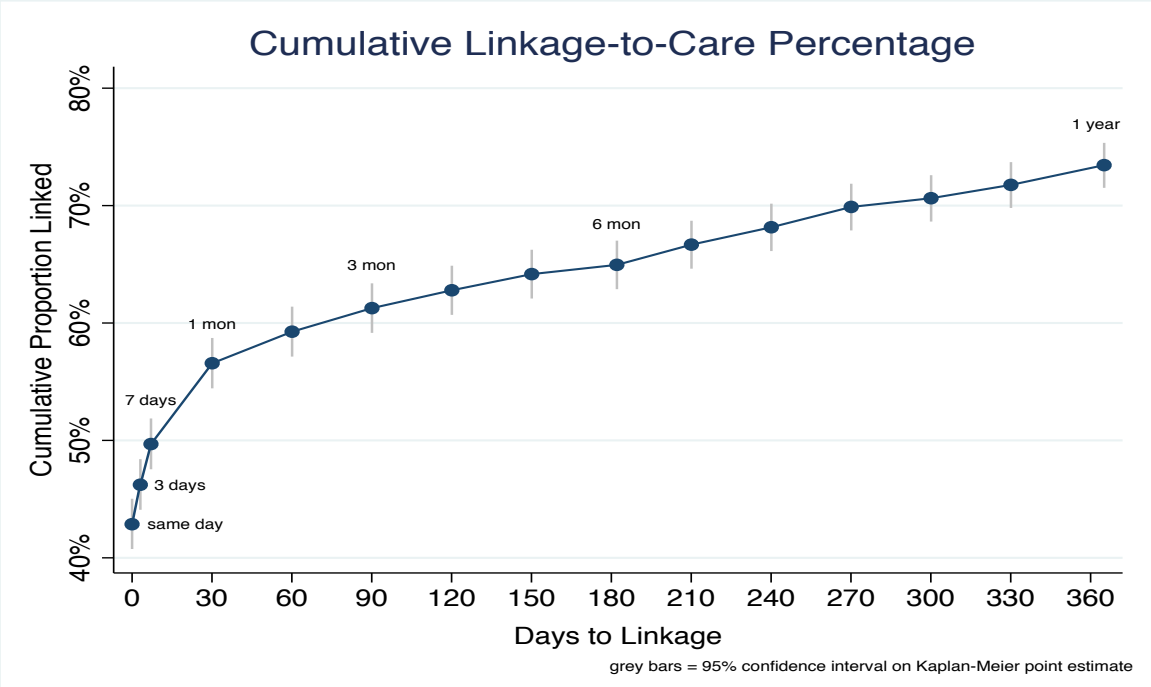
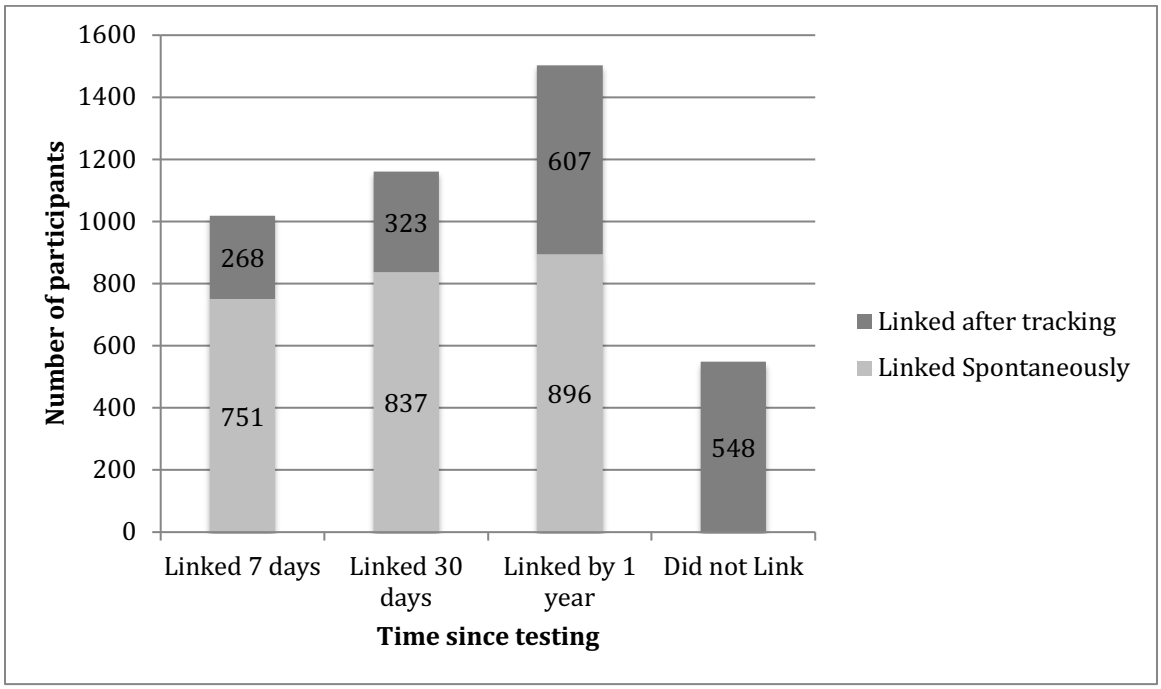


Figure 3: Bar graph of cumulative number linking over time since baseline testing a cohort of 2051 individuals newly diagnosed with HIV (N=1,624) or previously diagnosed with HIV but out of care (N=429), resident in one of 16 SEARCH intervention communities in Kenya and Uganda, July 2013 to June 2015.



Predictors of linkage to care

Univariate and multivariate estimates of the strength of association between socio-demographic and clinical characteristics and linkage to care by 7, 30 and 365 days are shown in Table 2. Educational level, having a phone contact and being a stable community resident were not associated with linkage to care by 7, 30 or 365 days. Age and occupation were associated with linkage to care. There was a 3% increase in odds of linkage with each additional year increase in age (aOR 1.03 95% CI 1.02-1.04). Compared to people with a low HIV-risk occupation, those in a high-risk occupation were less likely to link to care: aOR 0.55 (95% CI 0.45-0.67) for linkage by 7 days, aOR 0.60 (95% CI0.48-0.76) for linkage by 30 days and aOR 0.51 (95% CI 0.40-0.65) for linkage by 365 days.

Table 2: Factors associated with Linkage to care at 7 days, 30 days and 1 year in a cohort of 2051 individuals newly diagnosed with HIV (N=1,624) or previously diagnosed with HIV but out of care (N=429), resident in one of 16 SEARCH intervention communities in Kenya and Uganda, July 2013 to June 2015.

Variable		7 days				30 days				1 year			
		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
		OR(95% CI)	p-value	aOR(95%CI)	p-value	OR(95% CI)	p-value	aOR(95%CI)	p-value	OR(95% CI)	p-value	aOR(95%CI)	p-value
Sex	Male	Ref		ref		ref		ref		ref		ref	
	Female	0.78(0.65-0.93)	**0.006**	0.79(0.64-0.96)	**0.020**	0.87(0.73-1.04)	0.114	0.86(0.71-1.06)	0.170	0.91(0.75-1.11)	0.351	0.85(0.68-1.06)	0.158
Age	15-24	Ref		ref		ref		ref		ref		ref	
	25-34	1.22(0.95-1.55)	0.115	1.31(1.00-1.72)	**0.048**	1.12(0.88-1.42)	0.365	1.21(0.93-1.59)	0.155	1.25(0.96-1.61)	0.09	1.21(0.91-1.61)	0.182
	35-49	1.60(1.24-2.05)	**<0.001**	1.67(1.24-2.24)	**0.001**	1.57(1.22-2.02)	**<0.001**	1.68(1.25-2.27)	**0.001**	1.70(1.30-2.24)	**<0.001**	1.52(1.11-2.11)	**0.009**
	≥50 years	1.66(1.18-2.35)	**0.004**	1.64(1.09-2.45)	**0.016**	1.97(1.38-2.82)	**<0.001**	1.98(1.31-2.99)	**0.001**	2.99(1.92-4.64)	**<0.001**	2.37(1.45-8.87)	**0.001**
Marital status	Married	Ref		ref		ref		ref		ref		ref	
	Single	0.85(0.64-1.12)	0.236	0.98(0.72-1.33)	0.902	0.95(0.72-1.26)	0.738	1.14(0.84-1.56)	0.385	0.63(0.48-0.84)	**0.002**	0.76(0.56-1.05)	**0.096**
	D/Wid/Sep†	0.99(0.78-1.27)	0.96	0.88(0.67-1.16)	0.366	1.26(0.98-1.61)	0.069	1.01(0.77-1.34)	0.929	1.40(1.05-1.87)	**0.023**	1.14(0.83-1.57)	0.422
Education	None	Ref		ref		ref		ref		ref 1		ref	
	Primary	0.57(0.41-0.80)	**0.001**	0.82(0.57-1.17)	0.272	0.45(0.32-0.65)	<0.001	0.69(0.47-1.01)	0.059	0.46(0.30-0.71)	<0.001	0.72(0.45-1.13)	0.154
	Above Primary	0.62(0.42-0.91)	**0.014**	0.95(0.63-1.46)	0.830	0.48(0.32-0.72)	**<0.001**	0.77(0.49-1.20)	0.242	0.42(0.26-0.68)	**<0.001**	0.70(0.42-1.18)	0.180
Occupation	Low HIV risk	Ref		ref		ref				ref		ref	
	High HIV risk	0.56(0.45-0.70)	**<0.001**	0.55(0.44-0.70)	**<0.001**	0.59(0.47-0.73)	**<0.001**	0.60(0.48-0.76)	**<0.001**	0.49(0.39-0.62)	**<0.001**	0.51(0.40-0.65)	**<0.001**
Point tested	CHC‡	Ref		ref		ref		ref		ref			
	HBT§	0.52(0.42-0.63)	**<0.001**	0.55(0.45-0.67)	**<0.001**	0.53(0.43-0.64)	**<0.001**	0.56(0.46-0.70)	**<0.001**	0.58(0.47-0.71)	**<0.001**	0.61(0.49-0.76)	**<0.001**
Have Phone	Yes	1											
	No	0.89(0.74-1.08)	0.249	0.92(0.74-1.14)	0.451	0.85(0.701.04)	0.104	0.87(0.70-1.07)	0.193	0.89(0.71-1.10)	0.287	0.90(0.71-1.13)	0.359

Prior knowledge of HIV status	Negative	ref		ref		ref		ref		ref		ref	
	Positive	0.69(0.54-0.87)	**0.002**	0.67(0.52-0.85)	**0.001**	0.84(0.67-1.06)	0.144	0.82(0.66-1.04)	0.108	1.00(0.76-1.24)	0.807	0.92(0.71-1.19)	0.530
	DK¶/declined to respond	1.68(1.37-2.05)	**<0.001**	1.45(1.18-1.80)	**0.001**	1.69(1.38-2.07	**<0.001**	1.40(1.13-1.74)	**0.002**	1.47(1.17-1.84)	**0.001**	1.23(0.97-1.57)	0.083
Residence	Stable	ref		ref		ref		ref		ref			
	Non stable	1.04(0.63-1.70)	0.887	1.06(0.63-1.79)	0.837	0.98(0.60-1.62)	0.952	0.98(0.58-1.66)	0.943	1.34(0.79-2.25)	0.278	1.18(0.69-2.04)	0.548
Asset score	1st Quartile	ref		ref		ref		ref		ref		ref	
	2nd Quartile	1.04(0.81-1.33)	0.775	1.01(0.78-1.32)	0.914	0.86(0.67-1.11)	0.242	0.88(0.80-1.40)	0.326	0.90(0.68-1.19)	0.441	0.84(0.63-1.13)	0241
	3rd Quartile	0.96(0.75-1.23)	0.726	1.08(0.83-1.40)	0.590	0.84(0.65-1.08)	0.173	0.99(1.01-1.79)	0.957	0.89(0.67-1.18)	0.43	0.95(0.71-1.29)	0.762
	4th Quartile	0.63(0.49-0.81)	**<0.001**	0.63(0.48-0.82)	**0.001**	0.51(0.40-0.66)	**<0.001**	0.51(0.55-0.99)	**<0.001**	0.68(0.52-0.90)	**0.007**	0.66(0.49-0.88)	**0.005**
Baseline CD4*	0-349	ref				ref		ref		ref		ref	
	350-499	0.80(0.61-1.03)	0.088	0.76(0.58-1.00)	0.05	0.79(0.60-1.04)	0.093	0.76(0.58-1.01)	0.065	0.90(0.66-1.23)	0.502	0.91(0.661.29)	0.573
	≥500	0.46(0.37-0.57)	**<0.001**	0.65(0.51-0.82)	**<0.001**	0.47(0.38-0.59)	**<0.001**	0.71(0.56-0.91)	**0.007**	0.55(0.43-0.70)	**<0.001**	0.80(0.61-1.05)	0.114
	Missing	0.08(0.05-0.13)	**<0.001**	0.08(0.05-0.13)	**<0.001**	0.08(0.05-0.12)	**<0.001**	0.08(0.05-0.13)	**<0.001**	0.20(0.14-0.28)	**<0.001**	0.21(0.15-0.30)	**<0.001**

D/Wid/Sep†-Divorced /Widowed/ Separated CHC‡-Community Health Campaign HBT§-Home-based Testing DK¶-Did not Know * Due to collinearity of missing CD4+ T cell count and home-based point of testing, multivariate associations between linkage and all independent variables except CD4 adjusted for point-of-testing but not CD4; multivariate associations between linkage and CD4 adjusted for all variables except point of testing.

In a multivariate model adjusting for all other variables except point of testing (excluded due to collinearity with baseline CD 4), those with higher CD4+ T cell count (≥500 cells/μL. vs. <350 cells/μL.) were less likely to link within one month of testing: aOR 0.65(95% CI 0.51-0.82) for linkage by 7 days, OR 0.71 (95% CI 0.56-0.91) for linkage by 30 days.

HIV testing characteristics were also associated with linkage to care at each time point. Individuals diagnosed by home-based testing compared to those tested through CHC were about 40% less likely to link to care: aOR 0.55 (95% CI 0.45-0.67) for linkage by 7 days, aOR 0.56 (95% CI 0.46-0.70) for linkage by 30 days, and aOR 0.61 (95% CI 0.49-0.76) for linkage by 1 year. Report of prior knowledge of HIV diagnosis was associated with poorer linkage to care at earlier time points, but not at 1 year. Compared to those who previously tested HIV negative, individuals who had previously tested positive but were not currently in care were about 30% less likely to link within 7 days following their current HIV test: aOR 0.67 (95% CI 0.52-0.85). On the contrary, those who reported not knowing their HIV status were about 40% more likely to link to care within one month of testing: aOR 1.45 (95% CI 1.18-1.80), for linkage by 7 days, and aOR 1.40 (95% CI 1.13-1.74) for linkage by 30 days.

Discussion

Following population-based, community-wide HIV testing of over 70,000 adults in rural Kenya and Uganda, a patient-centered, multi-component strategy linked half of all HIV-positive persons who were not in care to HIV care within one week of testing; by one year, three quarters had linked. These linkage rates are substantially higher than linkage reported under standard-of-care in Kenya (42% by four months) and Uganda (45% by six months).[8,9] Linkage rates reported among studies offering interventions to improve linkage are higher,[25-27] but none report as high linkage rates within seven days as observed with our intervention.

As countries move towards universal treatment, a population-based approach that achieves rapid linkage to HIV care for all individuals not currently in care is required to realize the full health and prevention benefits of ART. Early data on challenges likely to be faced with universal treatment can be found from the first reports of population level HIV test and treat studies.[11,13] In the PopART study conducted in Zambia and South Africa; 53% of HIV-positive individuals not in care linked and initiated ART by 12 months.[13] In the TasP study conducted in South Africa, 29.7% linked by 6 months .[11] Some of the barriers identified by one of these trials included inconvenient clinic hours, overcrowded clinics, health providers' poor attitude, stigma and shame.[28] Our intervention aimed to address some of these structural, behavioral and health system barriers. A patient-centered approach where, for example, the clinic staff is welcoming and interacting with the client from the time of diagnosis, flexible clinical hours, appointment reminders and provider access to make enquiries via phone may have contributed to the high proportion of patients linking within a week of testing. In addition, we scheduled linkage appointments very soon after diagnosis deliberately in order to accelerate linkage.

After one month, the linkage rate slowed, suggesting that a group of more difficult to engage in care patients was reached. Our multi-disease population-based HIV testing approach achieved high HIV testing coverage across all segments of the population,[19] and would be expected to result in a population in need of linkage enriched for "hard-to-reach" subgroups such as young adults, men and people at early stages of disease, as well as providing a new opportunity to link for previously diagnosed individuals currently out of HIV care.[29] These hard to reach individuals may be less motivated to seek care,[30-32] or may face additional barriers to linkage, and may thus require additional interventions for effective linkage. Interestingly, we found that both previously diagnosed individuals not currently in care and those reporting a new diagnosis after an earlier negative HIV test were at higher

risk of failing to link than individuals with no prior HIV test, as were individuals with high CD4+ T cell count. These individuals may be experiencing other barriers to linkage such as protracted phases of grief following their diagnosis, stigma, disclosure challenges, or failure to see the need for care when not feeling ill.[25,29,30]

Despite the successful implementation of our multiple-component strategy, a quarter of individuals in need of care engagement were not linked to care by one year. Our analysis of factors associated with failure to link to care bring to the fore some of the most difficult to engage subgroups including young adults. In agreement with other studies ,[6,25,26] being young was associated with a lower likelihood of linking to care at all three time points evaluated. Individuals working in high-HIV-risk occupations such as fishing and transportation were also less likely to link, possibly due to the mobile nature of these occupations, rigid work-time-schedules and the high levels of HIV-associated stigma within these subgroups. The young and those in high HIV-risk occupations may also have an elevated risk of transmitting HIV.[29] For both their own health and to optimize prevention impacts, innovative approaches are needed to engage them in care.

We also observed lower linkage rates among people identified through home-based testing compared to individuals diagnosed through the mobile community health campaigns as well as among people who had been previously diagnosed with HIV but were not in care. This is consistent with findings of other studies .[29,33] Home-based testing following community health fairs likely taps into a different, more difficult to engage population and may reach individuals with different health seeking behaviors, possibly because of higher anticipated HIV stigma.[29,34]

After adjustment for other risk factors, individuals with the highest household wealth appeared less likely to link, in contrast to findings by other studies.[6] This association may be due to wealthier individuals accessing care

at private clinics located distant from the study community due to stigma. While we confirmed linkage at clinics outside the study communities, we were unable to confirm linkage to care for individuals seen at such clinics.

We did not find a difference in linkage based on gender, education level, or access to a phone. Lack of association with gender confirms findings of others [33,35] whereas lack of association with formal education level is in contrast to findings by other studies.[6] This may be because of many years of widespread HIV sensitization programs in Uganda and Kenya, which have increased overall knowledge and awareness about HIV to all regardless of educational level.

Our study had several strengths. In contrast to most linkage to care studies that are health facility-based, our study's population level testing allows us assess linkage inclusive of difficult to reach patients that may not get tested at a health facility. Additionally, this is one of the first studies to examine linkage to care under an implementation of universal HIV treatment and a comprehensive test-and-treat strategy in a rural area. Furthermore, linkage was verified by and based on medical records thus overcoming a social desirability bias that would be introduced by using patient self-report. Our study was also subject to limitations. We were only able to verify linkage in health facilities that we could access within and around our study communities. It is possible that some participants linked to more distant health facilities, indicating we are reporting conservative estimates of true linkage rate. Secondly, we are not able to tell which specific component in our multi-component strategy made the biggest difference in linkage.

In conclusion, timely linkage to care remains critical in treatment and prevention of HIV. Combining a mobile hybrid community-based testing strategy with a novel patient-centered, multi-component linkage strategy resulted in high linkage rates, with half of all individuals in need of HIV care linked within one week of HIV testing and three-quarters linked within a year. Our findings present a feasible and effective linkage approach for

adoption by programs in different countries as we move towards universal treatment in similar settings. In addition, our findings draw attention to specific groups that require special attention; young, individuals in informal-high-risk occupation sector, home testers and those with a high CD4+ T cell count at diagnosis still pose a challenge and require innovative interventions to improve linkage further. Concerted efforts are thus required to continue to refine and develop linkage strategies to help achieve the maximal benefits of treatment-as-prevention.

Authorship

J.A., M.L.P., E.D.C., A.V.R. and D.H. contributed to the design of the study, conduct of the study, analysis of the data, drafting of the manuscript and editing/review. L.B.B contributed to conduct of the study, analysis of data and editing/review. D.K., M.R.K., E.B. and C.R.C. contributed to the conduct of the study and editing/review.

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Chapter 3

Effect of a patient-centered phone call by a clinical officer at time of HIV testing on linkage to care in rural Kenya

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Abstract

In a randomized controlled trial, we tested whether a structured, patient-centered phone call from a clinical officer following HIV testing improved linkage to/re-engagement in HIV care. Among 130 HIV-positive persons, those randomized to the phone call were significantly more likely to link to care by 7 and 30 days ($p<0.043$).

Key words: Linkage to HIV care, re-engagement in care, phone call, randomized controlled trial, test-and-treat

Introduction

Timely linkage to HIV care is key to successful antiretroviral treatment (ART) and for effective treatment as prevention.[1] Poor linkage rates are well documented with large proportions of HIV positive persons not getting into care in a timely fashion.[2] There is need for simple, effective interventions to boost linkage to care for both the newly HIV-diagnosed and prior diagnosed persons who have fallen out of care or never linked to care.

In an ongoing test-and-treat trial where the UNAIDS "90-90-90" targets were achieved in the intervention arm by 2 years,[3] we had the opportunity to test a simple phone-call based linkage strategy that was based on social cognitive theory,[4] observations that patients who had fallen out of care often re-engaged after a personal phone call from a clinical officer, and data on phone technology that has shown promise in improving treatment outcomes.[5,6]

Methods

Study design and participants

We conducted a two-arm randomized controlled trial (RCT) nested within the SEARCH trial (NCT01864683) in East Africa between August and December 2016. The RCT involved a subset of five Kenyan communities

comprising approximately 5000 adults each from a region with an HIV prevalence of 20.1% [3]. HIV testing was done through a hybrid mobile HIV testing approach combining mobile, multi-disease community health campaigns (CHC) lasting two weeks per community with home-based HIV testing for those residents who did not attend CHC.[7] All participants $\geq$ 15 years of age, HIV-positive, and self-reported they had either never linked to HIV care or had dropped out of care for >6 months were eligible for the nested RCT. Self report of prior diagnosis and details of last clinic visit (or lack thereof) were confirmed by medical record review.

Study Procedures

All participants received standard HIV counseling and a transport voucher redeemable at linkage, irrespective of study arm. In addition, participants in the intervention arm received one structured call from a clinical officer, a holder of diploma in medicine, within an hour of post-test counseling. The clinical officers had received training on principles of patient-centered care, problem-solving by role-play of different scenarios reflecting the cultural context of the region.

A study staff made the call to the clinical officer using a study phone that was then handed to the participant. The content of the call included introductions, relationship initiation, and a brief assessment of participants' state of mind. The participant was provided with information about HIV disease, as well as the benefits of early linkage and immediate treatment. The

clinical officer assessed readiness to link, explored barriers to linkage, and sought solutions to overcome participant-specific barriers in order to ensure immediate linkage and treatment. The phone call conversation also included a description of a streamlined, patient-centered care model that would allow for spaced out clinic visits, reduced waiting times, flexibility in visiting hours and appointment reminders. Clinic options were provided for the participant to choose from; clinic staff details, including names were also shared to ensure personalized service. A phone call checklist was used to ensure consistency and fidelity to the intervention.

Outcome

The primary endpoint was linkage to care at any ART clinic within 30 days of testing; linkage within 7 days was a secondary outcome. Time to linkage was defined as time between date of study enrolment and the first ART clinic visit. If a participant opted to link to a clinic outside the study community, linkage was verified by assessment of medical records. Absence of a linkage record was treated as failure to link.

Statistical analysis

We conducted an intention-to-treat analysis. The proportion linking by 7 and 30 days between intervention and control arms was compared using Pearson chi-square tests without continuity correction.

Cumulative linkage over time was estimated using Kaplan-Meier estimation. Cox proportional hazards models, adjusted for age and sex strata, were used to compare time to linkage between arms. We also used logistic regression models to explore factors associated with not linking to care.

Sample size

Based on prior data within SEARCH study, we assumed a 56% linkage within 30 days in the control arm. A calculated sample size of 116 subjects (58 per arm) was based on simple unadjusted comparison of proportions, a two-sided alpha level of 0.05, and 80% power to detect an absolute effect size of 24% (80% linking in the intervention arm).

Ethical approval

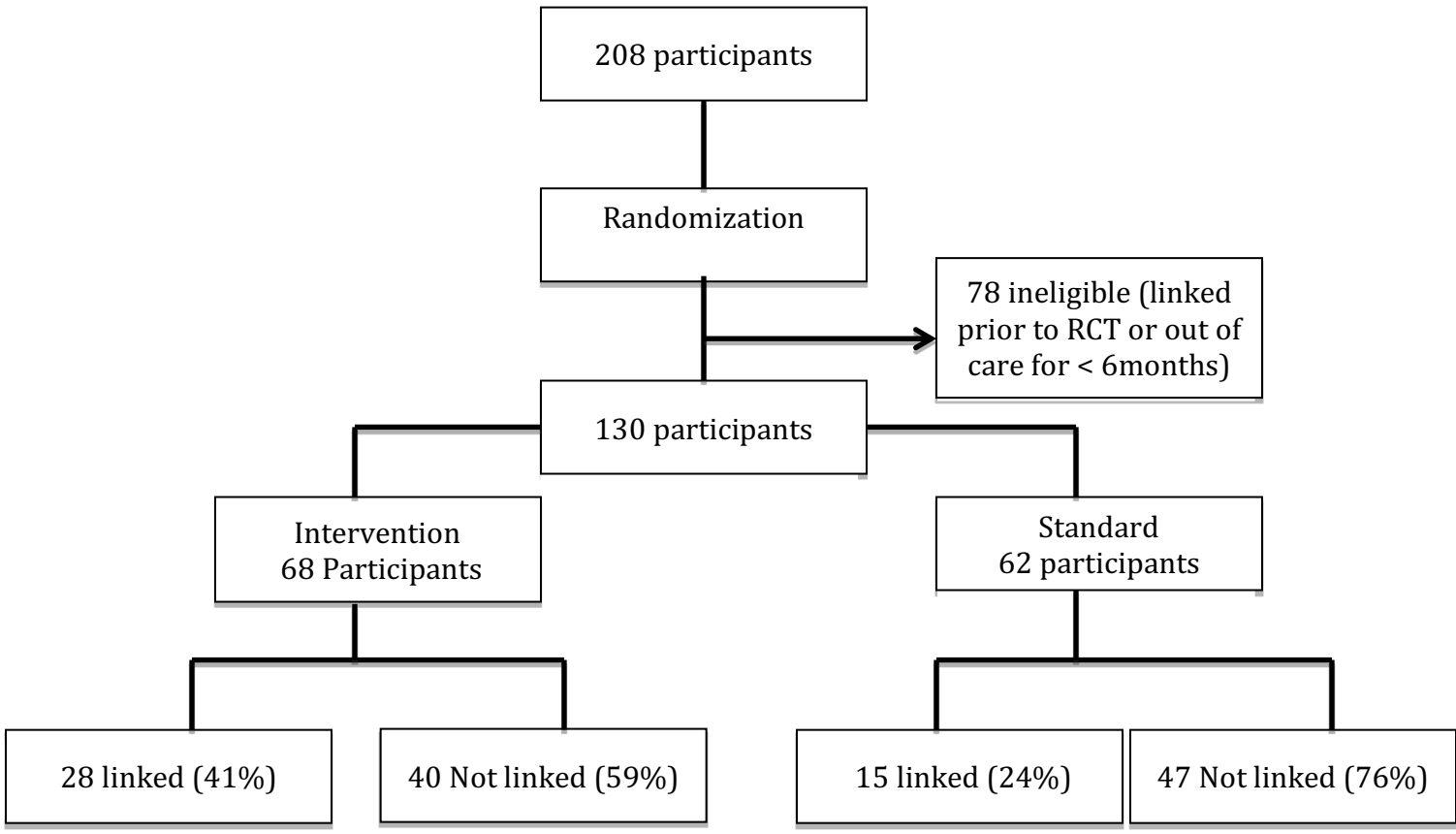
The Kenya Medical Research Institute Ethical Review Committee (Kenya), and University of California San Francisco Committee on Human Research (USA) approved the study and participants provided consent.

Results

Between August and December 2016, 223 participants were identified to be eligible to participate in the study, 15(6.7%) declined participation, 208 were enrolled and randomized (Fig. 1). The most common reason reported for decline was lack of time to participate in the study. Of the 208 enrolled, 78 were excluded from the analysis after establishing that they were ineligible

by way of their medical records (had linked prior to study or had not been out of care for >6 months).

Figure 1: Study profile of 208 participants recruited into the study with the final linkage outcomes by 30 days of the interventions.



A total of 130 participants were included in the analysis (68 intervention, 62 control). Of these, 88(68%) were newly diagnosed with HIV and 42 (32%) had a prior diagnosis but had never engaged in care or had dropped out of care >6 months prior to study enrollment, 109(84%) of the participants were tested at the CHC. The median age was 31(IQR 27-40) years, 88(64%) were

<34 years old, 27% were male, 72% were married, 75% had primary level of education or higher and 20% were unemployed. The median length of the calls was 17 minutes (Range 7-33 minutes). Baseline characteristics between the intervention and control groups were similar. Overall, 53/130(41%) participants linked to care, with 43/130 (33%) linking within 30 days. The majority of the linkage 36/53(68%) occurred within the first 7 days. During the follow-up period, no deaths were reported.

Participants in the intervention group were more likely to link to care within 7 days compared to those in the control group (24/68 (35%) vs. 12/62 (19%), p=0.043). The effect of the intervention was maintained at 30 days (28/68 (41%) vs. 15/62 (24%), p=0.040).

In Cox proportional hazards modeling, the relative hazard of linking to care at 30 days was higher in the intervention arm, before and after adjusting for age (< vs. >35 years) and sex (HR:1.82; 95%CI 0.97-3.41; p=0.061; aHR=1.86; 95%CI: 0.99-3.48; p=0.054) but the estimates were imprecise.

In logistic regression models adjusted for community, younger people (<35years vs. >35 years) (aOR 0.32; 95%CI 0.12-0.88; p 0.027) and individuals from households that did not have anyone else in HIV care, (aOR 0.33; 95%CI 0.11-0.97; p 0.045) were less likely to link within 30 days of testing.

The most common barriers to linkage revealed were disclosure to spouses, anticipated stigma, work-related mobility and travel, feeling healthy and not seeing the need for treatment. Approaches to overcome these barriers were matched to context and included facilitated disclosure, linkage to other community clinics, provision of information and personal reassurances.

Discussion

A personalized structured phone call by a health provider at the time of HIV testing significantly improved linkage to and re-engagement in care. Prior studies demonstrate that messages focused on patients' concerns, when delivered effectively, can be used to improve care engagement.[8,9] Having a clinical officer rather than a lower skilled worker perform the call, establishing rapport, health information empowerment, and addressing barriers to linkage while assuring personalized care within a patient-centered context, likely contributed to the success of the intervention.

In our setting, younger individuals and those from households without any members in HIV care were less likely to link. This is consistent with previous findings reporting lower linkage rates among the young and those lacking social support.[2,10,11] These findings suggest that interventions aimed at improving disclosure, stigma reduction, family/couple testing and counseling could improve linkage to care for these groups.

The low overall linkage rates in this study compared to prior studies[12] may in part, be explained by our study's population-wide approach which included a significant proportion were "hard-to-engage" individuals; persons who may have been diagnosed earlier and were still experiencing barriers to linkage already and individuals who had engaged in care previously but had subsequently dropped out of care.

Our study had limitations. Our sample size was insufficient to assess effectiveness of the intervention in specific subgroups of interest, such as those out of care versus the newly diagnosed. Secondly, reliance on self-report of newly diagnosed versus previously diagnosed may have resulted in some misclassification. Finally, linkage verification at clinics far removed from our study communities was not possible, and may have led to an underestimation of linkage.

In conclusion, a structured patient-centered phone call from a clinical officer at time of HIV testing or re-engagement significantly improved the proportion of individuals linked to care. The proportion of individuals linked remained low, suggesting that more innovative interventions are needed to facilitate linkage to care, especially among hard-to-engage individuals such as youth and those living with HIV who have never linked to or dropped out of care.

Conflict of interests

The authors declare that they have no competing interests.

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Supplemental On-Line Materials (appendices)

S1- Parent Study Description and Embedded Phone Call RCT.

The phone call RCT was nested within the large cluster randomized SEARCH trial whose study design has been described by Perriat et al.[7] The SEARCH study employed a community-wide mobile hybrid HIV testing model comprising a community health campaign (CHC) followed by home based testing for campaign non-attendees. This was done annually for the first four years. Despite achieving high linkage rates in SEARCH, concerns over those still not linked needed to be addressed. The phone call RCT was conducted during the fourth year of the SEARCH study to assess whether this simple intervention would improve linkage among HIV positive SEARCH study participants not engaged in care, specifically:

a) Newly diagnosed HIV positive participants
b) HIV positive participants who had not been engaged in care for >6 months as at the time of the study.

The hypothesis of the phone call RCT was thata clinical officer phone call following a receipt of a positive HIV test result in this population-based multi-disease testing context would increase probability of linking to HIV care within 30 days of testing among HIV-positive individuals not currently in care.

Study population:
Inclusion criteria:
- Resident of following SEARCH communities: Kisegi, Kitare, Magunga, Nyamrisra , Ogongo
    - Enumerated at baseline census or re-census or seen at year 4 CHC or home based testing
- Test HIV+ at year 4 CHC or home based testing
- Adult: >= 15 years at time of year 4 HIV test

Exclusion criteria
- Clinic record showing linkage prior to year 4 HIV+ test and self-report of clinic visit within the last 6 months (at linkage station or tracking)

Participant flow during CHC and HBT

Community Health Campaign (CHC)

Participants were welcomed and offered health education and pretest HIV counseling at the welcome station. They then move to the vitals station where their blood pressure, pulse rate, weight and height are measured. At this station their records were confirmed in the study database by

fingerprinting. Once this was completed, the participants went to the lab station where HIV test, sugar level and other tests are performed. Everyone then proceeded to individual HIV post-test counseling at the counseling station. Those who were HIV positive are referred to the linkage station where they were screened for eligibility to participate in the study. Eligible participants who consented to participate were randomized by the study staff at the linkage station to receive the phone call or not. The study staff at the linkage station used the study phone to call the clinical officer for the intervention.

Home-based testing (HBT)

The study staff fingerprinted the participants to confirm their details in the study database, measured the participants blood pressure and conducted pre-test counseling and offered the HIV test. Post-test counseling followed. Those who were HIV positive were screened for eligibility to participate in the study. Eligible participants who consented to participate were randomized by the staff to receive the phone call or not. The study staff then proceeded to make the call to the clinical officer for the intervention.

Intervention:

The intervention comprised a single phone call after testing within one hour of post-test counseling offered by the counselor. The phone call was made to a clinical officer, a cadre of health care workers who hold a diploma in medicine.
The call had two parts:

1. Clinical officer talking to the study staff at the linkage station (average length 3-5 minutes)
2. Clinical officer talking to the study participant (average length 7-15 minutes)

In the first part of the call the study staff making the call to the clinical officer shared information on the patient's name, age, sex and linkage to care status. The clinical officer also asked the staff a few questions to ensure the participant was truly eligible for the intervention.

In the second part, the clinical officer engaged in a structured phone call conversation with the participant. The following were the components of the call:

Step 1: Introduction
Introduction of the clinical officer to the participant.

Step 2: Engagement and relationship initiation

The clinical officer set the mood for an open conversation by asking about current matters such as weather and farming, politics, sports etc. The goal was to make the participant feel comfortable with the clinical officer while identifying anything the participant shares in common with the clinical officer as a way of enhancing the relationship or gaining access to talk freely about HIV and care engagement.
The Clinical officer then conveyed what he knew about the participant as he tried to clarify any unclear details.

The clinical officer asked the last HIV test date and how the participant felt about the new diagnosis.

Step 3: Assessment of state of mind
While engaging the participant through the second step, the clinical officer tried to assess the participant's mood and state of mind, he checked whether the participant sounds sad, shocked, anxious, already knew his status, had accepted the result, was expecting the positive result and so on.

If the participant is sad, shocked, anxious, about the HIV diagnosis the clinical officer made attempts to reassure the participant.

> "Currently we have treatment available and unlike in olden days, the condition is now a chronic disease that can be managed. We are willing to walk with you if you accept our help with this."

If the participant was calm and appears to already have known and accepted his/ her status before our testing, or was expecting such a result and is ready for further discussions, the clinical officer moved to the next step.

Step 4: Viral load counseling
The clinical officer provides viral load counseling using clear and simple examples that the participant could relate to.

> "You have heard about HIV before. HIV is a disease caused by a virus. The virus starts replicating once it enters the body and can lead to death by attacking the body defenses. The good news is that we have treatment that contains the disease. The drug stops the multiplication of the viruses and that way you can lead a normal life.
>
> When you scoop a teaspoonful of blood from a person living with HIV who is not on treatment, there will be millions of viruses due to multiplication. However, if the person takes his treatment well, the number of viruses will be so small that the machine will not be able to detect them."

Step 5: Questions from participant and exploring barriers

The clinical officer allowed for any questions about the disease from the participant by posing the question.

> "Do you have any question or concerns about this disease you would want us to talk about?"

The clinical officer then tried to evaluate the reasons that would hinder the participant from accessing care as part of exploring the participant's barriers to engagement:

> " Mr. X, can you think of anything that would make it difficult to get on treatment?"

> "Do you have any worries getting treatment for HIV Mr. X? "

Based on the participant response the clinical officer discussed with the participant potential ways of overcoming the barriers.

Examples

Case 1
Participant 1: "I work during the day and I may not be able to make it for clinic appointments?"

Clinical Officer: "At what time do you leave work?"

Participant 1: "4 pm"

Clinical Officer: "We can set appointments to review you after work"

Case 2:
Participant 2:" I hear that the medications make one feel tired."

Clinical officer: "We will be available to review you whenever you have any complaint. Please keep my phone number so that you can reach me in case of any challenges once we start the treatment".

Case 3
Participant 3: "You have told me to link at clinic X, I just don't like that clinic, they do not keep patient details confidential"

Clinical Officer: "How do you feel about clinic Y? We can link you to Nurse R who will handle you well."

Step 6: Description of streamlined care, clinic options and any other questions

A brief description of patient centered care offered at the clinics was shared with the participant highlighting flexibility, warm-friendly environment and short clinic throughput.
The participant was told about clinic options available for him/her. Upon choosing, details of staff names and phone contacts were shared with the participant.

S2. Intervention Fidelity Checklist

The following checklist filled by the clinical officer at the time of the call was used to ensure fidelity and consistency during the calls:

Date:	*SEARCH ID:*	*Clinical Officer Initials:*
Fill the spaces on the right column		
Part 1: Conversation between Clinical officer and study staff at the linkage station		
1	Name	
2	Age	
3	Sex	
4	Category (*New/LTFU*)	
5	Testing site	
Part 2: Conversation between Clinical officer and the participant		
1	Introduction	
2	Engagement, rapport building	
3	Last test date How do you feel about this result?	
4	State of mind-(from your conversation so far and the previous question what would you say is the participants state of mind.) *a) Sad* *b) Shocked* *c) Anxious* *d) Already knew, is calm and accepted* *e) Already knew, defensive and in denial* *f) Was expecting the result, calm and ready to link* *g) Was expecting the result, angry and feeling betrayed.*	
5	Viral load counseling	

6	Questions from participant	
7	Streamlined care description	
8	Barriers to linkage *(Tailor solutions based on case)*	
9	Offer clinic options	
10	Share clinic staff details	

S3 Study Participant Characteristics.

	Total n=130(100%)	Intervention n=68(52.6%)	Standard n=62(47.4%)	p-value
Sex				
Male	35(26.9%)	18(26.5%)	17(27.4%)	0.903
Female	95(73.1%)	50(73.5%)	45(72.6%)	
Age				
Median (IQR)	31 (27, 40)	30(26-41)	31(27-38)	
15-24	26(21.5%)	15(23.9%)	11(18.8%)	0.577
25-34	62(42.3%)	30(42.3%)	32(51.6%)	
35-49	28(21.5%)	17(25.4%)	11(17.2%)	
>=50	14(10.4%)	6(8.5%)	8(12.5%)	
Marital status				
Married	94(72.3%)	53(77.9%)	41(66.1%)	0.284
Single	15(11.5%)	7(10.3%)	8(12.9%)	
Widowed, Divorced, Sep	21(16.2%)	8(11.8%)	13(21.0%)	
Phone Contact*				
No	27(20.8%)	15(22.1%)	12(19.5%)	0.704
Yes	103(79.2%)	53(77.9%)	50(80.5%)	
Education				
None	8(6.2%)	4(5.9%%)	4(6.5%)	0.806
Primary	98(75.3%)	50(73.5%)	48(77.4%)	
Secondary and above	24(18.5%)	14(20.6%)	10(16.1%)	
HH Member in care				
Yes	37(24.6%)	20(29.4%)	17(27.4%)	0.801
No	93(75.4%)	48(70.6%)	45(72.6%)	
Occupation				
No Job	24(20%)	14(21.1%)	10(18.8%)	0.746
Informal-High risk	38(28.2%)	20(28.2%)	18(28.1%)	
Informal-Low risk	62(47.4%)	32(47.9%)	30(46.9%)	
Formal	6(4.4%)	2(2.8%)	4(6.3%)	

*Phone contact-refers to the number of participants who gave a phone contact at study enumeration or community health campaign

Chapter 4

High levels of retention in care with streamlined care and universal test-and-treat in East Africa

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Abstract

Objective

We sought to measure retention in care and identify predictors of non-retention among patients receiving ART with streamlined delivery during the first year of the ongoing SEARCH "test-and-treat" trial (NCT 01864603) in rural Uganda and Kenya.

Design

Prospective cohort of patients in the intervention arm of the SEARCH Study.

Methods

We measured retention in care at 12 months among HIV-infected adults who linked to care and were offered ART regardless of CD4 cell count, following community-wide HIV-testing. Kaplan-Meier estimates and Cox proportional hazards modeling were used to calculate the probability of retention at one year and identify predictors of non-retention.

Results

Among 5,683 adults (age ≥ 15) who linked to care, 95.5% (95% CI: 92.9 – 98.1%) were retained in care at 12 months. The overall probability of retention at one year was 89.3% (95% CI: 87.6 – 90.7%) among patients newly linking to care and 96.4% (95% CI: 95.8 – 97.0%) among patients previously in care. Younger age and pre-ART CD4 below country treatment initiation guidelines were predictors of non-retention among all patients. Among those newly linking, taking more than 30 days to link to care after HIV diagnosis was additionally associated with non-retention at one year. HIV viral load suppression at 12 months was observed in 4,227/4736 (89%) of patients retained with valid viral load results.

Conclusion

High retention in care and viral suppression after 1 year were achieved in a streamlined HIV care delivery system in the context of a universal test-and-treat intervention.

Key Words: HIV;Africa;Antiretroviral therapy; Healthcare; Retention in care

Introduction

Antiretroviral therapy (ART) reduces morbidity and mortality in patients with all CD4+ Tcell count levels[1, 2] and decreases the probability of HIV transmission to uninfected partners[3]. In order to realize these individual and public health benefits, in 2015 the WHO guidelines were updated to recommend ART for all HIV infected individuals, regardless of CD4 count[4] (universal treatment). Retention in care will be critical to the success of universal test-and-treat strategies, and treatment programs will be challenged to extend ART treatment to the newly eligible patients while supporting retention in care in an expanded patient population. Retention in care will also be essential to realizing the UNAIDS target of 90-90-90, particularly the final goal that 90% of the population on ART is virally suppressed.

Significant questions remain about whether high retention in a universal test-and-treat system is possible in the setting of increasing patient volumes, an increasing proportion of asymptomatic patients, and known barriers to retention. Current estimates of retention in sub-Saharan Africa are widely variable and the estimated regional average 12-month retention of 76% (range 65% - 89%) is insufficient to achieve these targets [5]. In addition, current retention estimates are likely biased due to incomplete ascertainment of outcomes and do not reflect retention under universal treatment. Individual factors including younger age[6-13], male gender[8-18], lower education[16], occupation[11, 17], and mobility[19] have all been associated with lower levels of retention in ART care and could affect retention under the test-and-treat paradigm. Additionally, clinic factors contributing to

disengagement in care, including long wait times, negative staff attitudes and frequent visits[9, 20-22] could be exacerbated as ART access is expanded.

With the advent of large scale efficacy trials of the universal test-and-treat strategy being conducted in sub-Saharan Africa[23, 24], new research is needed to bridge existing clinical and implementation science knowledge gaps around retention in care in these ambitious universal treatment strategies. The intervention arm of the ongoing Sustainable East Africa Research on Community Health (SEARCH) test-and-treat trial (NCT01864603) provides ART within a streamlined care delivery system, which was designed to offer patient-centered and efficiently delivered care to minimize many of the traditional barriers to retention. We sought to characterize predictors and barriers to retention in care in the intervention arm of the SEARCH trial during the first year of implementation of universal testing and treatment utilizing a streamlined model of ART care.

Methods

SEARCH Study Design

The SEARCH HIV test-and-treat study is a community cluster-randomized controlled trial in 32 communities in three regions: western Kenya, southwestern Uganda, and eastern Uganda. All communities received a community census and population-wide HIV testing at baseline in 2013 - 2014. These are rural communities composed of geopolitical units just above the village level (termed a 'parish' in Uganda and a 'sublocation' in Kenya) with a population of about 10,000 people each, within the catchment area of a government supported ART clinic(s). Using a hybrid mobile HIV testing approach in which 2-week multi-disease community health campaigns (CHCs) are followed by home-based testing (HBT) of CHC non-participants, 89% of the population was tested at baseline[25]. In the 16 SEARCH intervention

communities, all HIV-infected individuals were referred immediately upon HIV diagnosis to HIV care and then offered immediate ART initiation or continuation of ART therapy at the clinic within a streamlined model of care.

Streamlined care

The streamlined care model was developed using the PRECEDE framework[26] and was designed to reduce patient barriers to care. It featured ART start at first linkage to clinic, visits with reduced wait time [27], quarterly (as opposed to monthly) follow-up visits for stable patients, a patient-centered approach to care in which staff were trained to provide care in a welcoming and empathetic environment, a telephone hotline for patients with medical questions and appointment scheduling concerns, appointment reminders by phone or SMS, and provision of viral load results through a structured viral load counseling protocol [28, 29]. Patients who missed a clinic visit were tracked using a "tiered" approach performed by nurses in Uganda and community health workers in Kenya. Under the "tiered" tracking approach the patient was called after the first missed visit to determine the reason for the missed visit and reschedule the appointment. If the patient also missed the rescheduled appointment, or the patient was not reached by phone, a tracker visited the patient at home or an alternative location of their choice. In some communities the patient was offered ART in an alternative location of the patient's choosing. All patients initiating ART at CD4 T- cell counts above country-treatment guidelines who missed a clinic visit were tracked from the beginning of the study; retention tracking was expanded to include all patients starting in March 2014 in Uganda and in June 2014 in Kenya. No financial incentives for retention in care were provided.

Measures

Patient demographics were obtained during a baseline home-to-home census

enumeration. Patients with a Ministry of Health HIV medical record at the time of the baseline CHC were considered previously linked to care, and those with an ART start date indicated on their medical record were classified as prescribed ART at baseline. A viral load was obtained at least 6 months after the start of streamlined care, either during follow-up year 1 hybrid mobile testing (CHC or HBT one year after baseline testing) or in clinic. Plasma HIV-1 RNA viral load was measured from finger-prick capillary[30] or venous blood collection by commercial real-time PCR assays at multiple reference laboratories.

Retention in care was defined as not more than 90 days late to a scheduled 12-month follow-up. Patients were considered out of care (non-retention) if they were found alive, in the community and not enrolled in HIV care, moved out of the community without a documented transfer, or were lost to follow-up. Patients with a documented transfer and patients who died were censored in time-to-event analysis. Patients were considered virally suppressed if their HIV viral load was < 500 copies/ml at the time of follow-up year 1 hybrid testing or, if none available, clinic viral load performed closest in time to 12 months.

Gender, age, education, occupation, mobility, access to a mobile phone, and HIV testing location (CHC versus home-based testing) were obtained during the baseline year. Education was categorized as no school, any primary or completed primary school, and any secondary or further education. The 13 individuals who answered "don't know/refused" on the baseline census were considered to have attended no school in the analysis. The 20 occupational categories at baseline were further classified as formal (student, teacher, government worker, military worker, health worker, factory worker), informal-high risk (fisherman, bar owner, bar worker,

truck/taxi/motorcycle/bike/boat driver, or tourism), informal-low risk (farmer, shopkeeper, market vendor, hotel worker, household worker, construction worker), no job (unemployed, disabled), or other. Individuals were considered a stable resident if they reported having resided within the community for at least 6 months out of the 12 months prior to census enumeration.

Statistical Analysis

The objective of this analysis was to describe 12-month retention in care and predictors of non-retention among adults who linked to care in a SEARCH intervention community during the first year of the intervention. The analysis was thus restricted to adults (≥ 15 years) who had at least one clinic visit after baseline hybrid testing. Individuals whose first clinic visit occurred <12 months before database closure date were also excluded. For the time-to-event analysis, patients entered the risk group (T_0) at their first clinic visit after baseline hybrid testing. Time to attrition was calculated as the time between T_0 and a patient's last scheduled clinic visit. Kaplan Meier survival estimates were used to calculate probability of retention at one year. Hazard ratios for non-retention were also computed using Cox proportional hazards modeling. Follow up continued until attrition, censoring due to death or transfer, or 365 days after linkage. A secondary analysis in which death was treated as a competing risk was also performed. The proportional hazards assumption was assessed graphically and with Schoenfeld residuals. To evaluate predictors of requiring enhanced retention support in order to stay in care, we used logistic regression to evaluate adjusted predictors of the need for retention tracking after the date all patients became eligible for retention tracking (i.e. after March 1, 2014 in Uganda and after June 1, 2014 in Kenya). Multivariate models included region, sex, and age based on *a priori* determination.

Covariates that were significant in univariate analysis were added in stepwise progression and included in the model if they contributed significantly to the fit of the model using a likelihood ratio test with $p<0.1$. In the proportional hazards model, age was stratified into three categories: 15-24, 25-29, and >30 years (because retention was homogenous within these categories and did not violate the proportional hazards assumption). Community was included as a fixed effect in all models and cluster-robust standard errors with household as the unit of independence were used to control for clustering by community and household. All analyses were stratified by care status at the time of baseline hybrid testing (previously in care vs. newly linking). Stata v14 (College Station, Texas) was used for analysis.

Ethics

The Makerere University School of Medicine Research and Ethics Committee (Uganda), the Ugandan National Council on Science and Technology (Uganda), the Kenya Medical Research Institute Ethical Review Committee (Kenya), and the University of California San Francisco Committee on Human Research (USA) approved the study protocol including the consent procedures. All participants provided verbal informed consent in their preferred language with fingerprint biometric confirmation of agreement.

Results

Study population

Between April 2, 2013 and June 8, 2014, 89,431 adults (≥ 15 years) were enumerated in the 16 intervention communities[25]. Among the 7,132 (8%) who were found to be HIV-infected at the time of baseline hybrid mobile testing, 6,128 (86%) had at least one clinic visit after the baseline CHC and before follow-up year

one CHC. An additional 448 (6%) were excluded because their first visit occurred <12 months before database closure date resulting in 5,683 (80%) included in analysis. At baseline, 4,082 (72%) had a history of HIV care and 3,458 (61%) had ever been prescribed ART, while 1602 (28%) were linking to care for the first time [Figure 1].

Demographics

Of the 5,683 patients who linked to HIV care, 3,703 (65.2%) were from Kenya, 1,306 (23.0%) were from western Uganda, and 674 (11.9%) were from eastern Uganda; 3,820 (67.2%) were female; 603 (10.6%) were between 15-24 years of age and 1,494 (26.3%) were under age 30; and almost all were stable residents (5,544, 97.5%). One thousand two hundred fifty seven (22.1%) had a pre-ART CD4 above country treatment guidelines at the time of ART start. Four thousand three hundred eight two (77.1%) had tested at the CHC vs. 23.9% at HBT. Regional differences were seen; Kenyan participants were more likely to be younger, have lower levels of education, work in the fishing industry, and to have tested during home-based testing (vs. at CHCs). Kenyans were also more likely to have a history of previous HIV care and ART [Table 1].

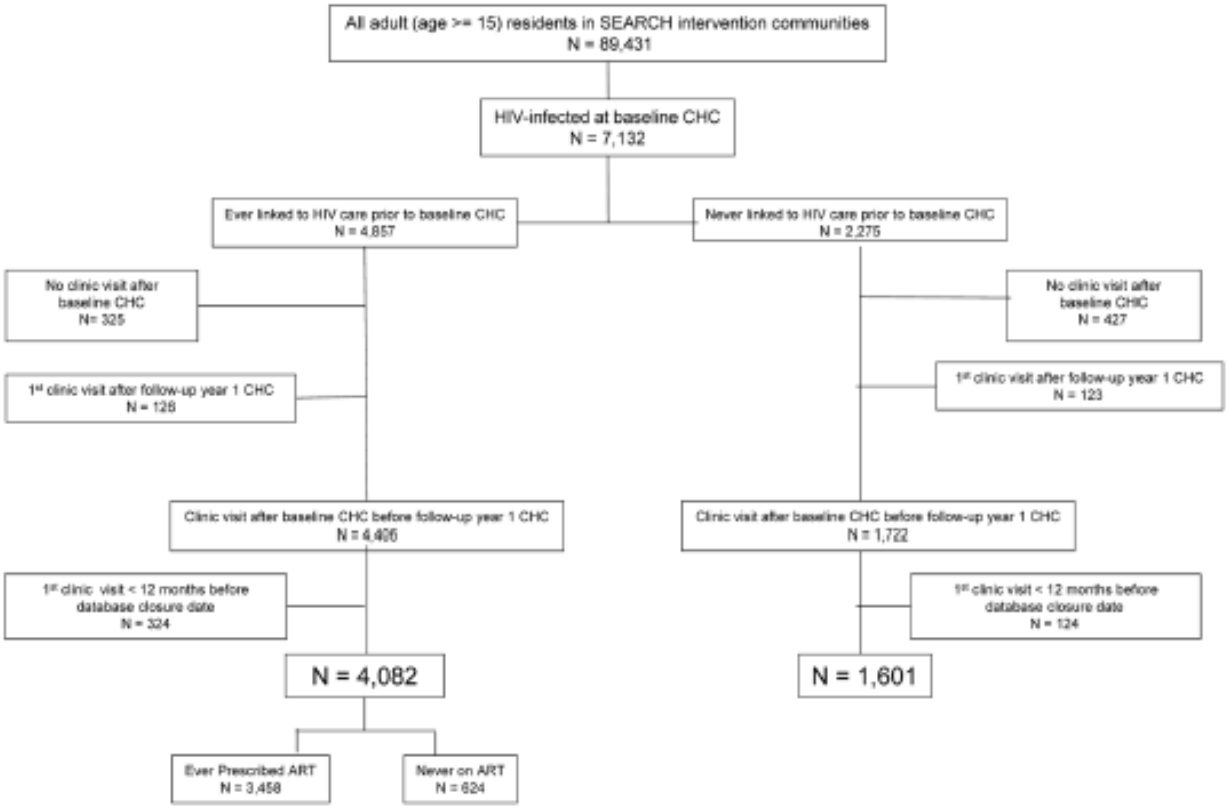

Figure 1.
Study population

Table 1: Baseline characteristics among adult (age ≥ 15 years) residents of SEARCH intervention communities who linked to care after baseline CHC and before follow-up year 1 CHC (N = 5683)

	Uganda-West (N = 1306)	**Uganda-East (N = 674)**	**Kenya (N = 3703)**	**Total (N = 5683)**
Sex				
Male [n (%)]	219 (32.5%)	219 (32.5%)	1163 (31.4%)	1863 (32.8%)
Female [n (%)]	455 (67.5%)	455 (67.5%)	2540 (68.6%)	3820 (67.2%)
Age [years, median (IQR)]	36 (29-44)	39 (31-46)	37 (29-46)	
15-19 years	42 (3.2%)	20 (3.0%)	75 (2.0%)	137 (2.4%)
20-24 years	130 (10.0%)	43 (6.4%)	293 (7.9%)	466 (8.2%)
25-29 years	189 (14.5%)	83 (12.3%)	619 (16.7%)	891 (15.7%)
30-34 years	232 (17.8%)	91 (13.5%)	604 (16.3%)	927 (16.3%)
35-39 years	207 (15.9%)	118 (17.5%)	617 (16.7%)	942 (16.6%)
40-44 years	187 (14.3%)	125 (18.6%)	447 (12.1%)	759 (13.4%)
> 45 years	319 (24.4%)	194 (28.8%)	1048 (28.3%)	1561 (27.5%)
Education				
No School	230 (17.6%)	123 (18.3%)	184 (5%)	537 (9.5%)
Primary or less	794 (60.8%)	405 (60.1%)	3214 (86.8%)	4413 (77.7%)
Any Secondary or further	282 (21.6%)	144 (21.4%)	293 (7.9%)	313 (5.5%)
Don't know/refused to answer	0	1 (0.2%)	12 (0.3%)	13 (0.2%)
Occupation				
Farming	858 (65.7%)	485 (72.0%)	2118 (57.2%)	3461 (65.7%)
Fishing	1 (0.1%)	3 (0.5%)	417 (11.3%)	421 (7.4%)
Shopkeeper/Vendor	103 (7.9%)	30 (4.5%)	425 (11.5%)	558 (9.8%)
Household worker	50 (3.8%)	30 (4.5%)	175 (4.7%)	255 (4.5%)
Transport worker	26 (2.0%)	13 (1.9%)	33 (0.9%)	72 (1.3%)
Student	18 (1.4%)	12 (1.8%)	42 (1.1%)	72 (1.3%)
Other	194 (14.9%)	78 (11.6%)	299 (8.1%)	571 (10.1%)
No Job	56 (4.3%)	23 (3.4%)	194 (5.2%)	273 (4.8%)
Mobility status				
Stable n(%)	1258 (96.3%)	658 (97.6%)	3628 (98%)	5544 (97.5%)

Mobile n(%)	48 (3.7%)	16 (2.4%)	75 (2.0%)	139 (2.5%)
Access to mobile phone [n (%)]	758 (58.0%)	306 (45.4%)	2657 (71.8%)	3721 (65.5%)
CD4 at baseline CHC				
<50 cells/mm^3	10 (0.8%)	8 (1.2%)	24 (0.7%)	42 (0.7%)
50-200 cells/mm^3	93 (7.1%)	59 (8.8%)	188 (5.1%)	340 (6.0%)
200-350 cells/mm^3	231 (17.7%)	127 (18.8%)	543 (14.4%)	892 (15.7%)
350-500 cells/mm^3	326 (25.0%)	166 (24.6%)	783 (21.1%)	1275 (22.4%)
>500 cells/mm^3	588 (45.0%)	281 (41.7%)	1827 (49.3%)	2696 (47.4%)
Missing baseline CD4	58 (4.4%)	33 (4.9%)	347 (9.4%)	438 (7.7%)
Pre-ART CD4 above country treatment guidelines§	408 (31.2%)	196 (29.1%)	653 (17.6%)	1257 (22.1%)
HIV RNA < 500 copies/ml	431 (33.0%)	190 (28.2%)	1656 (44.7%)	2277 (40.1%)
Missing baseline viral load	381 (29.2%)	193 (28.6%)	873 (23.6%)	1245 (21.9%)
Previous linkage to care [n (%)]	743 (56.9%)	396 (58.8%)	2943 (79.5%)	4082 (71.8%)
On ART before baseline CHC [n (%)]	585 (44.8%)	318 (47.2%)	2359 (63.7%)	3262 (57.4%)
HIV Testing Location				
CHC*	1075 (82.3%)	606 (89.9%)	2701 (72.9%)	4382 (77.1%)
HBT**	228 (17.5%)	60 (8.9%)	998 (26.7%)	1286 (22.6%)
Missing	3 (0.2%)	8 (1.2%)	4 (0.1%)	15 (0.3%)

* CHC = Community Health Campaign

** HBT = Home Based Testing

§ Country guidelines for treatment were to initiate ART at CD4 < 350 cells/ml until December 2013 in Uganda and until June 2014 in Kenya, after which country treatment guidelines were changed to reflect the 2013 WHO guidelines of ART initiation at CD4 < 500 cells/m

Retention in care outcomes

Of the 5,683 adults who linked to care during the eligible period, 5,058 (88.6%) were retained at their original clinic and 260 (4.6%) had a documented transfer to an alternative site. Sixty (1.1%) patients died, 108 (1.9%) were known to be alive and in the community, and 64 (1.1%) moved out of the community without a documented transfer. Of the 60 deaths, 15 were due to illness, 1 was due to an accident, and 44 were unknown. The overall probability of retention at one year, adjusted for out-transfers and deaths, was 95.5% (95% CI: 92.9 – 98.1%). The probability of retention at one year was 89.3% (95% confidence interval (CI) 87.6 – 90.7%) among patients newly linking to care and 96.4% (95% CI 95.8 – 97.0%) among patients previously in care. Probability of retention at one year was higher among those previously in care compared to those newly linking across all subgroups. The lowest observed retention (76.3%; 95% CI 70.9 – 81.7%) was among adults age 15-24 linking to care for the first time [Figure 2].

Virologic Outcomes

Overall, at follow-up viral load testing 4,455/5,683 (78.5%) had a suppressed viral load, 621/5,683 (10.9%) had a viral load > 500 copies/ml, and 610/5,683 (10.7%) did not have viral load results. Patients with viral load results available were more likely to be retained in care ($p<0.001$), live in East Uganda ($p = 0.002$), be age 30 years or older ($p < 0.001$), and have a pre-ART CD4 count above country treatment guidelines ($p<0.001$). Among the 5,058 retained in care, follow-up viral load data were available for 4,736 (93.6%); of these, 4,227 (89%) were suppressed.

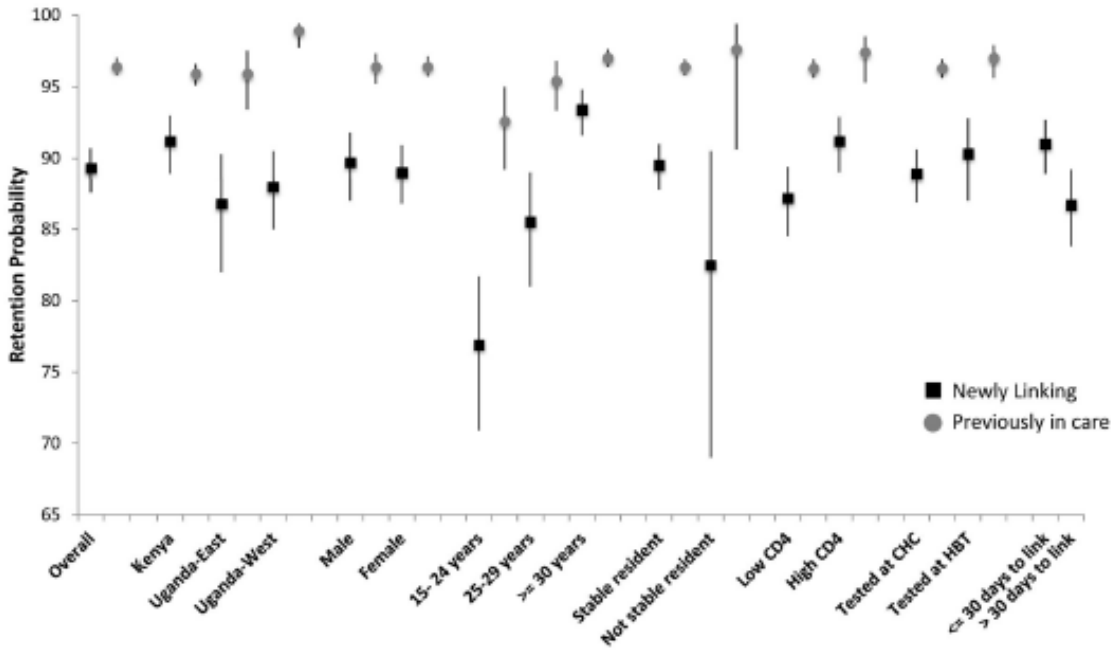

Figure 2.
Probability and 95% confidence intervals of being retained in care at one year among patients previously in care and newly linking to care in SEARCH intervention communities, overall and by subgroup
Low CD4 = pre-ART CD4 less than country treatment guidelines
High CD4 = pre-ART CD4 above country treatment guidelines
CHC = Community Health Campaign
HBT = Home-based testing

Predictors of retention

Among both those newly linking to care and those previously in care, there was no significant association between non-retention and sex, education level, occupation, mobility, or whether HIV testing was completed at the CHC or in HBT. Non-retention was significantly more likely among younger patients, with those age 15-24 years being the least likely to be retained in care at 12 months among those newly linking

to care (aHR 3.78, 95% CI 2.48 – 5.76) and those previously in care (aHR 2.70, 95% CI 1.70 – 4.29). Additionally, among patients newly linking to care, non-retention was more likely among residents of eastern Uganda (aHR 2.52, 95% CI 1.04 – 6.12) and those who took more than 30 days to link to care (aHR 1.41, 95% CI 1.03 - 1.95). In addition to young age, not having access to a mobile phone (aHR 1.94, 95% CI 1.36 – 2.77) was the only other predictor associated with increased risk of non-retention in multivariate analysis among patients who had a history of HIV care [Table 2]. Results were similar when death was treated as a competing risk rather than censoring event .

Predictors of retention tracking

Patients newly linking to care were more likely to require retention tracking to stay in care compared to those previously in care (31.1% vs. 9.3%, $p<0.001$). Patients who lived in Uganda, younger patients, men, and those with a pre-ART CD4 count above country treatment guidelines were more likely to require retention tracking to stay in care. Testing site (CHC vs. HBT) and time to link were not associated with retention tracking [Table 3].

Table 2. Predictors of non-retention at 12 months in adult residents of SEARCH intervention communities who linked to HIV care after baseline CHC and before follow-up year 1 CHC (N =5683)

	Newly Linking to care (N = 1601)				Previously in Care (N = 4082)			
Predictor	**Hazard Ratio**	**95% CI**	**Adj Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**	**Adj Hazard Ratio**	**95% CI**
Region								
Kenya	ref		ref		ref		ref	
Uganda-East	1.90	0.82-4.43	2.52	1.04-6.12	0.64	0.15-2.79	0.53	0.12-2.32
Uganda-West	0.95	0.36-2.51	0.88	0.32-2.42	0.28	0.13-0.60	0.25	0.12-0.52
Sex								
Male	ref		ref		ref		ref	
Female	1.08	0.80-1.47	0.76	0.54-1.06	1.01	0.71-1.43	0.84	0.59-1.21
Age								
15- 24	3.94	2.72-5.70	3.78	2.48-5.76	2.48	1.57-3.90	2.70	1.70-4.29
25-29	2.39	1.61-3.55	2.51	1.67-3.77	1.48	0.95-2.32	1.59	1.01-2.51
>= 30	ref		ref		ref		ref	
Education								
No School	0.53	0.30-0.94	0.78	0.44 – 1.40	0.83	0.43-1.60		
Primary	ref		ref		ref			
Any secondary or further	0.78	0.50-1.23	0.76	0.48 – 1.21	0.88	0.48-1.61		
Occupation								
Formal	ref		ref		ref			
Informal – high risk	1.71	0.37-7.86	1.37	0.28 – 6.73	1.01	0.29-3.49		
Informal – low risk	2.16	0.67-7.01	1.79	0.51 – 6.28	1.10	0.44-2.80		
No job	4.61	1.30-16.4	2.79	0.72 – 10.7	2.41	0.83-6.94		
Other	2.32	0.59-9.2	1.79	0.42 – 7.58	0.68	0.18-2.59		
Access to a mobile phone								
Yes	ref				ref		ref	
No	1.27	0.92-1.76			1.94	1.35-2.77	1.94	1.36 – 2.77
Mobility								
Stable resident	ref				ref			

Not stable resident	1.77	0.87-3.60			0.82	0.20-3.39		
Pre-ART CD4								
Below country treatment guidelines	ref		ref		ref		ref	
Above country treatment guidelines	0.68	0.50-0.93	0.62	0.45-0.84	0.75	0.40-1.38	0.63	0.34-1.17
Site of testing								
CHC	ref				ref			
HBT	0.93	0.61-1.40			0.90	0.56-1.42		
Time to link								
<= 30 days	ref		ref					
> 30 days	1.52	1.11-2.10	1.41	1.03-1.95				

Abbreviations: CI = Confidence Interval; CHC = Community Health Campaign; HBT = Home-based Testing

Country guidelines for treatment were to initiate ART at CD4 < 350 cells/ml until December 2013 in Uganda and until June 2014 in Kenya, after which country treatment guidelines were changed to reflect the 2013 WHO guidelines of ART initiation at CD4 < 500 cells/ml

Table 3. Predictors of requiring tracking for retention support among patients retained in care at one year (N = 5318)

	Newly Linking to care (N = 1412)				Previously in Care (N = 3906)			
Predictor	**OR**	**95% CI**	**Adj OR**	**95% CI**	**OR**	**95% CI**	**Adj OR**	**95% CI**
Region								
Kenya	ref		ref		ref		ref	
Uganda-East	4.76	2.89 – 7.85	12.0	4.80 – 30.1	8.15	3.39 – 19.6	6.85	2.82 – 16.7
Uganda-West	1.51	0.84 – 2.71	1.25	0.50 – 3.15	2.0	1.51 – 2.66	0.75	0.30 – 1.85
Sex								
Male	ref		ref		ref		ref	
Female	0.85	0.66 – 1.08	0.68	0.52 – 0.89	0.98	0.76 – 1.27	0.70	0.52 – 0.95
Age								
15-24 years	1.97	1.27 – 3.03	2.55	1.59 – 4.10	2.76	1.77 – 4.31	2.39	1.46 – 3.91
25-29 years	1.84	1.24 – 2.75	2.00	1.30 – 3.07	2.05	1.38 – 3.07	1.90	1.21 – 2.99
30-34 years	1.28	0.85 – 1.92	1.40	0.90 – 2.16	1.88	1.28 – 2.77	1.85	1.22 – 2.81
35-39 years	1.35	0.90 – 2.05	1.44	0.93 – 2.24	1.28	0.87 – 1.89	1.25	0.81 – 1.92
40-44 years	0.96	0.61 – 1.52	1.09	0.67 – 1.78	1.08	0.71 – 1.64	1.06	0.67 – 1.66
> 45 years	ref		ref		ref		ref	
Education								
No School	0.87	0.60 – 1.28	1.18	0.76 – 1.82	1.02	0.69 – 1.49	1.24	0.80 – 1.92
Primary	ref		ref		ref		ref	
Any secondary or further	0.92	0.65 – 1.32	0.97	0.65 – 1.42	0.84	0.58 – 1.22	0.99	0.66 – 1.47
Occupation								
Formal	ref				ref			
Informal – high risk	1.22	0.54 – 2.75			1.64	0.75 – 3.58		
Informal – low risk	0.96	0.50 – 1.84			1.43	0.73 – 2.82		
No job	1.27	0.58 – 2.78			1.70	0.75 – 3.87		
Other	0.58	0.22 – 1.55			1.64	0.63 – 4.27		
Own a mobile phone								
Yes	ref		ref		ref		ref	
No	1.26	0.97 – 1.63	1.17	0.89 – 1.55	1.25	0.97 – 1.62	1.30	0.98 – 1.73

Mobility								
Stable resident	ref		ref		ref		ref	
Not stable resident	0.34	0.12 – 0.93	0.33	0.13 – 0.84	0.76	0.29 – 1.97	0.83	0.26 – 2.63
Pre-ART CD4								
Below country treatment guidelines	ref		ref		ref		ref	
Above country treatment guidelines	3.19	2.43 – 4.19	3.16	2.39 – 4.18	10.1	7.49 – 13.6	9.52	7.00 – 12.9
Site of testing								
CHC	ref		ref		ref		ref	
HBT	0.85	0.63 – 1.15	0.87	0.62 – 1.20	1.13	0.82 – 1.55	1.08	0.77 – 1.53
Time to link								
<= 30 days	ref		ref					
> 30 days	1.28	0.99 – 1.66	1.25	0.95 – 1.64				

Abbreviations: CI = Confidence Interval; CHC = Community Health Campaign; HBT = Home-based Testing

Country guidelines for treatment were to initiate ART at CD4 < 350 cells/ml until December 2013 in Uganda and until June 2014 in Kenya, after which country treatment guidelines were changed to reflect the 2013 WHO guidelines of ART initiation at CD4 < 500 cells/m

Discussion

In one of the first evaluations of retention in HIV care in the setting of a universal test-and-treat program, we found 95% of patients who linked to care were still in care one year after introducing universal ART delivered via streamlined care in two country public health systems. This included demographic groups who have historically demonstrated lower retention, such as men, those with lower educational levels, and persons who work in high-risk occupations (e.g. fisherfolk). In contrast to concerns about retention among those with high CD4 counts (patients who will increasingly beinitiating ART under new universal ART guidelines), these patients demonstrated high retention with 91% of patients newly linking patients and 97% of those previously in care retained in care at one year.

The streamlined model of care employed in the SEARCH-supported clinics might have contributed to the high levels of observed retention, as it addresses many of the traditional barriers to retention, such as negative staff attitudes, frequent clinic visits, and long waiting times. Staff were trained to deliver care in a warm and welcoming environment and to support adherence and retention in an empathetic manner with patients[29]. Decreased wait times and decreased frequency of visits from monthly to every three months increases the clinic capacity to see more patients, which will be critical for treatment programs to scale-up under universal test-and-treat[28]. Reducing wait times may mitigate stigma associated with queuing outside HIV clinics for some patients. Also, the provision of viral load results and structured viral load counseling provided a tool for adherence assessment and retention support.

Active outreach, especially immediately after or within one week of missed appointments, is known to improve retention[31-33]. Retention tracking that was initiated immediately following a missed visit was part of the streamlined care package, and used a tiered approach to adapt to the resources and needs of the communities as well as the individual patients. Patients in Uganda, men, younger patients, and those newly linking to care were more likely to require retention tracking to stay in care, possibly reflecting a higher risk of attrition among these groups. Although mobility has been associated with lower retention[19], unstable residents who were retained in care had a lower probability of requiring retention tracking. It may be that the unstable residents who successfully link to care are highly motivated to stay in care. While patients with high CD4 were also more likely to have been tracked, early during the study follow up period only high CD4 patients were eligible for tracking and may have continued to be prioritized throughout the follow-up period even after all patients became eligible.

In contrast to other settings in sub-Saharan Africa in which men have lower retention rates than women[7-10, 12, 13, 17, 18, 34], we did not observe any significant gender disparity. The streamlined care system employed by the clinics, which decreased the frequency and improved the efficiency of visits, could have particularly benefited men by reducing any disruption to employment or other work. In these communities in rural East Africa a large proportion of the men work as farmers or fishermen, which requires them to be away from their communities for extended periods, and has been a demonstrated to deter men from to facility-

based testing[35]. Men did require additional effort through retention tracking to stay in care, and may have benefited from this individualized outreach.

These data also highlight the challenges adolescents and young adults face in remaining in care. Younger adults not only required more effort through retention tracking to stay in care, but those under age 30 also had significantly lower retention than older age groups. This age group faces high levels of stigma in their home environment and at school, which negatively affects retention[36]. In addition, younger adults are more likely to be mobile, traveling for education or employment. In our population, 5% of the youth (age 15-24) are mobile compared to 2.5% of the overall population. These mobile youth demonstrated the lowest overall retention, with only 81% still in care at 12 months. Retention support that addresses this vulnerable population will be required as our streamlined care model evolves. Alternative treatment sites, such as school-based treatment, longer intervals between refills to accommodate those who attend school outside of the community, and alternative methods of antiretroviral therapy, including long-acting methods, may be needed to support this population.

This analysis is subject to several limitations. These high retention rates should be interpreted in the context of the 86% who linked to care within one year. Those with delayed linkage may experience higher rates of non-retention, and those with the greatest challenges to linkage are those who are also likely to experience challenges staying in care. While the majority of patient outcomes at one year were ascertained, there were likely silent transfers that were not accounted for among those who moved out of the study community without a documented transfer or

among those with missing outcomes[9, 37]. In addition, the care outcomes of the patients with an official transfer are unknown. However, data on patients transferring care in the region indicates almost all patients with an official transfer are linked to care at their destination facility within 3 months[38]. Only retention in the first year is captured so longer follow-up will be necessary to evaluate durability of retention in care. Finally, the viral suppression in this population could be underestimated, as almost 10% patients were missing viral load data at 12 months. We anticipate the completeness of viral load results will increase as viral load monitoring is expanded in East Africa.

To our knowledge, these are the first data on retention in care in a universal test-and-treat setting and demonstrate that high levels of retention in care are achievable when some of the known barriers to retention have been targeted. As universal test-and-treat is expanded, these barriers will need to be continually addressed to ensure durable retention, especially as patients' ages, and life factors change. Specific targeted interventions to retain young adults will also be crucial to the success of test-and-treat programs, as will strengthening timely linkage to care and retention for new diagnoses, and supporting those accessing care for the first time.

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Chapter 5

Association of implementation of a universal testing and treatment intervention with HIV diagnosis, receipt of antiretroviral therapy, and HIV viral suppression among adults in East Africa

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Key Points

Question: Was implementation of an HIV "Test and Treat" intervention in rural East Africa associated with increases in diagnosis, treatment, and viral suppression among adults with HIV infection?

Findings: In this descriptive study that included 77,774 adult residents of the intervention communities of an ongoing cluster randomized trial, the proportion of HIV-positive adults with viral suppression increased from 44.7% at baseline to 80.2% after two years, along with increases in HIV diagnosis and initiation of antiretroviral therapy.

Meaning: Implementation of a community-based testing and treatment intervention in East Africa was associated with an increased proportion of HIV-positive adults who achieved viral suppression, along with increased HIV diagnosis and initiation of antiretroviral therapy.

Abstract

Importance: Antiretroviral treatment (ART) is now recommended for all HIV-positive persons. The United Nations Programme on HIV/AIDS (UNAIDS) has set global targets to diagnose 90% of HIV-positive individuals, treat 90% of diagnosed individuals with ART, and suppress viral replication among 90% of treated individuals, for a population-level target of 73% of all HIV-positive persons with HIV viral suppression.

Objective: To describe changes in the proportions of HIV-positive adults diagnosed with HIV, treated with ART, and with HIV viral suppression following implementation of a community-based testing and treatment program in rural East Africa.

Design, Setting, and Participants: Observational analysis based on interim data from sixteen rural Kenyan (N=6) and Ugandan (N=10) intervention communities in the SEARCH Study, an ongoing cluster-randomized trial. Community residents who were age ≥15 years (N=77,774) and were community residents for ≥6 months/past year were followed up to two years (2013-2014 to 2015-2016).

Intervention: HIV serostatus and plasma HIV RNA level were measured annually at multi-disease health campaigns followed by home-based testing for non-attendees. All HIV-positive individuals were offered ART using a streamlined delivery model designed to reduce structural barriers, improve

patient-clinician relationships, and enhance patient knowledge and attitudes about HIV.

Main outcomes and measures: Primary outcome was viral suppression (plasma HIV RNA<500 copies/ml) among all HIV-positive adults, assessed at baseline and after one and two years. Secondary outcomes included HIV diagnosis, ART among previously diagnosed adults (i.e., diagnosed prior to baseline and during the 2 year program), and viral suppression among adults who had initiated ART.

Results: Among 77,774 adult residents (45.3% men, 35.1% age 15-24 years), baseline HIV prevalence was 10.3% (7,108/69,283). The proportion of HIV-positive adults with HIV viral suppression was 44.7% (3,464/7,745;95%CI:43.5%, 45.9%) at baseline and 80.2% (5,666/7,068;95%CI:79.1%, 81.2%) after two years of intervention, a 35.5 percentage point increase (95%CI:34.4%-36.6%). After two years, 95.9% (6,780/7,068; 95%CI:95.3%, 96.5%) of HIV-positive adults were diagnosed; 93.4% (6,334/6,780; 95%CI:92.8%, 94.0%) of those diagnosed had received ART; and, 89.5% (5,666/6,334;95%CI:88.6%, 90.3%) of those treated had achieved HIV viral suppression.

Conclusions: Among HIV-positive adults in rural Kenya and Uganda, implementation of community-based testing and treatment was associated with an increased proportion of HIV-positive adults who achieved viral

suppression, along with increased HIV diagnosis and initiation of antiretroviral therapy.

In these communities, the UNAIDS population-level viral suppression target was exceeded within 2 years after program implementation.

TrialRegistration:NCT01864683

Introduction

Early antiretroviral therapy (ART) improves the health of HIV-positive individuals and reduces HIV transmission.[1-3] Mathematical models and observational analyses suggest that an intensive global investment to expand ART coverage could alter the epidemic trajectory and improve longevity, health, and economic productivity.[4-7] However, realizing this potential requires diagnosing HIV, initiating ART, and suppressing viral replication in most HIV-positive persons, a progression referred to as the HIV "care cascade".

The global health community has responded with a mandate for action. In 2014, UNAIDS issued an ambitious worldwide target: by 2020, at least 90% of HIV-positive individuals will be diagnosed, at least 90% of those diagnosed will be receiving ART, and at least 90% of those receiving ART will have suppressed viral replication, for an overall target of 73% of all HIV-positive individuals with HIV viral suppression.[8] In 2015, the World Health Organization (WHO) recommended that all HIV-positive adults initiate ART, irrespective of CD4 count.[9]

Apart from Botswana,[10] most nations in Sub-Saharan Africa remain substantially below the UNAIDS target.[8,11-13] Further, many non-suppressed HIV-positive individuals are asymptomatic with high CD4 counts.[13] Such individuals may prove challenging to test, engage in care, and virally

suppress.[14,15] Scalable strategies to effectively diagnose, treat, and achieve viral suppression among HIV-positive individuals in Sub-Saharan Africa are needed.

The Sustainable East Africa Research in Community Health Study (SEARCH, **NCT01864683**) is an ongoing cluster-randomized trial in rural Kenya and Uganda evaluating the effect of a cascade-wide "test and treat" strategy, compared to country-specific standard-of-care, on HIV, health, and economic outcomes. The trial intervention integrates community-based multi-disease testing, universal eligibility for ART for all HIV-positive individuals, and streamlined patient-centered ART delivery. In this descriptive study, interim data from the trial intervention communities were used to evaluate population-level HIV viral suppression and the HIV care cascade at study baseline and after one and two years of delivering the test and treat intervention.

Methods

Study Population

The SEARCH Study is a cluster-randomized trial that enrolled 32 pair-matched rural communities, each with approximately 5,000 adult residents. Between June 2013 and June 2014, all residents in each community were enrolled during a household census.[16] The study included data from adult (≥15 years of age) residents of 10 Ugandan and 6 Kenyan intervention

communities, each followed for two years (until June 2015 to June 2016).

All participants provided verbal informed consent in their preferred language. The Makerere University School of Medicine Research and Ethics Committee (Uganda), the Ugandan National Council on Science and Technology (Uganda), the Kenya Medical Research Institute Ethical Review Committee (Kenya), and the University of California San Francisco Committee on Human Research (USA) approved the consent procedures and the study.

Intervention

Population-based HIV testing was conducted at baseline and annually thereafter using a hybrid model that combined multi-disease community health campaigns (including diabetes and hypertension screening) with home-based testing for residents who did not attend the campaign.[16] All HIV-positive individuals were eligible for ART with efavirenz plus tenofovir disoproxil fumarate, co-formulated either with emtricitabine (Truvada) or with lamivudine, and were offered facilitated linkage to care consisting of: 1) immediate appointments at government clinics; 2) personal introductions to clinic staff; 3) clinician phone number; 4) one-time transport voucher; and, 5) tracking of individuals who did not link to care.[17] Streamlined ART delivery included: 1) 3-month follow-up schedule for clinically stable patients; 2) flexible hours and a welcoming environment; 3) clinician phone

number; 4) text or telephone-based appointment reminders; and, 5) HIV RNA measures, with structured discussion of results with patients to support visit and medication adherence.[18]

Measures

Demographic data were collected at the baseline census. Stable and non-stable residence was defined as living in the community ≥6 and <6 months/past year, respectively. At baseline and after one and two years, HIV serostatus was measured at community health campaigns; adults who did not attend were subsequently tracked and offered home-based testing.[16] After baseline, individuals newly identified as community residents were classified as migrants into the community. Prior residents who were reported to no longer live in the community were classified as migrants out of the community.

Participants with a positive antibody test, detectable HIV RNA, or a Ministry of Health record of prior HIV care were considered HIV-positive. Plasma HIV RNA was measured on all HIV-positive individuals annually during hybrid mobile testing (at the health campaign or subsequent tracking).[19] Viral suppression at baseline and after one and two years was defined as HIV RNA<500 copies/ml, measured during that year's hybrid mobile testing. Prior diagnosis was defined as a prior positive HIV test or Ministry of Health record of HIV care; baseline self-reported diagnosis was included in

sensitivity analysis. ART use was assessed with Ministry of Health records; HIV-positive individuals with suppressed HIV RNA were considered receiving ART.

Statistical Analyses

Power calculations and sample size were calculated for the primary randomized trial; this descriptive study was nested within the larger trial. The analysis was pre-specified (as described in the on-line supplement).[20] The primary outcome was population-level viral suppression (plasma HIV RNA<500 copies/ml) among all HIV-positive adult residents. The secondary outcomes were: HIV diagnosis; ART use among those diagnosed with HIV, and HIV viral suppression among those treated with ART.

Primary and secondary outcomes were evaluated in an open cohort of HIV-positive community residents at three time points, corresponding to the dates of annual community-wide testing at baseline and after one and two years. Individuals entered the cohort at the first time-point they were HIV-infected, ≥15 years old, and community residents. Individuals left the cohort when they died or migrated out of the community.

In this open cohort, we estimated the following proportions: 1) number of HIV-positive individuals with HIV viral suppression/number of all HIV-positive individuals (population-level viral suppression), 2) number of

individuals diagnosed with HIV prior to time of annual testing/number of all HIV-positive individuals, 3) number of individuals treated with ART at or before time of annual testing/number of individuals diagnosed with HIV prior to time of annual testing, and, 4) number of individuals with HIV viral suppression/number of individuals treated with ART at or before time of annual testing. Primary analysis was restricted to baseline stable residents (i.e., those living in the community ≥6 months during the past year). Secondary analyses 1) stratified on gender, age, and country; and, 2) included non-stable residents (i.e., those living in the community <6 months during the past year) and residents identified during annual testing as migrants into the community.

Because diagnosis, ART coverage and HIV viral suppression in the open cohort of HIV-positive adults depend not only on effective testing, treatment and suppression, but also on HIV incidence, population migration, and mortality, we also conducted longitudinal closed cohort analyses. First, we estimated the proportion of adult stable residents diagnosed with HIV at or before study baseline who, after one and two years, had 1) never initiated ART, 2) initiated ART and had plasma HIV RNA≥500 copies/ml, 3) initiated ART and had plasma HIV RNA<500 copies/ml, 4) died, and 5) out-migrated. Second, follow-up was censored at death or out-migration and the risk of and demographic factors associated with 1) never testing for HIV by two years (among adults without an HIV diagnosis prior to baseline), 2) never initiating

ART by two years (among baseline HIV-positive adults) and 3) having HIV RNA>500 copies/ml at two years (among baseline HIV-positive adults) were evaluated. Third, HIV viral suppression at one and two years was evaluated in the following subgroups of baseline HIV-positive adults, censoring at death or out-migration: 1) newly diagnosed at baseline, 2) previously diagnosed but ART naïve at baseline, and 3) currently or previously treated with ART at baseline (overall, and within baseline HIV viral suppression strata).

In primary analyses, targeted maximum likelihood estimation (TMLE)[21,22] was used to estimate 1) the number of HIV-positive individuals, adjusting for differences in baseline demographics and testing history between individuals with measured versus missing HIV serostatus (to account for possible over- or under- representation of HIV-positive individuals among those tested), and 2) the number of HIV-positive individuals with HIV viral suppression, adjusting for differences in baseline demographics, testing, ART, and suppression history between individuals with measured versus missing HIV RNA (to account for possible over- or under- representation of individuals with HIV viral suppression among those with HIV RNA measured at annual testing). Unadjusted estimates were calculated as proportions among individuals seen at annual testing with known HIV serostatus and HIV RNA levels.

In secondary analyses, TMLE was also used to adjust for censoring by death

or out-migration and, in exploratory analysis, to evaluate demographic variables associated with failure to test, use ART, and suppress HIV replication. To minimize model misspecification bias, propensity score and outcome models were estimated using Super Learning,[22] a machine-learning method that used 5-fold cross validation to combine general additive models, stepwise regression, and logistic regression. Analyses adjusted for community and used household as the independent unit in cross-validation and when calculating influence curve and non-parametric bootstrap-based standard errors.[24] Statistical significance was assessed based on 2-sided P value <0.05. Analyses were conducted in R version 3.3.2 using packages ltmle_0.9-8-4 and SuperLearner_2.0-21.[23-25]

Results

Study population and testing coverage

There were 77,774 adult stable residents in the 16 intervention communities at baseline, of whom 45.3% were men and 35.1% were 15-24 years old (Table 1). Baseline HIV prevalence was 10.3% (Southwest Uganda: 6.5%, 1,462/22,410; East Uganda: 3.5%, 785/22,681; Kenya: 20.1%, 4,861/24,192). During two years of follow-up, 907 individuals died, 13,257 migrated out of a study community, and 9,020 turned 15 years old (eFigure 1). Secondary analyses included an additional 11,851 non-stable residents and 6,437 migrants into a study community (eFigure2).

Annual HIV serostatus testing and RNA testing levels were high.[16] At baseline, year one, and year two, respectively, 89.1% (69,283/77,774), 89.4% (64,999/72,744), and 86.8% (63,045/72,630) of adult stable residents had known HIV status (tested at that year's annual campaign or had previously tested positive), and 70.1% (4,983/7,108), 85.9% (6,016/7,003) and 83.6% (5,786/6,925) of those known to be HIV-positive had HIV RNA measured during hybrid mobile testing. Missing HIV RNA levels were more common at baseline due to assay failures at early campaigns.[26]

Diagnosis, ART use, and suppression in an open cohort of HIV-positive adults

At baseline, 44.7% (3,464/7,745; 95%CI:43.5%, 45.9%) of HIV-positive adults had achieved HIV viral suppression. Population-level suppression was 75.2% (5,399/7,182; 95%CI:74.1%, 76.3%) after one year and 80.2% (5,666/7,068; 95%CI:79.1%, 81.2%) after two years of intervention (Figure 1a; eTables 1-2). Over two years, population-level HIV viral suppression increased 35.5 percentage points

Table 1. Characteristics of baseline adult (≥15 years old) stable (≥6 months of prior year in community) residents of 16 SEARCH intervention communities (10 in Uganda and 6 in Kenya).

	Southwest Uganda (N=25,014)	**EastUganda (N=25,120)**	**Kenya (N=27,640)**	**Total (N=77,774)**
Known HIV status[1]	22,410(89.6%)	22,681(90.3%)	24,192 (87.5%)	69,283 (89.1%)
HIV Positive	1,462 (6.5%)	785(3.5%)	4,861 (20.1%)	7,108 (10.3%)
Male	11,687(46.7%)	11,394(45.4%)	12,165 (44.0%)	35,246 (45.3%)
Age in Years				
15-24	8,478 (33.9%)	9,582 (38.1%)	9,253 (33.5%)	27,313 (35.1%)
25-34	5,732 (22.9%)	5,315 (21.2%)	6,688 (24.2%)	17,735 (22.8%)
35-44	4,398 (17.6%)	4,007 (16.0%)	4,251 (15.4%)	12,656 (16.3%)
>44	6,406 (25.6%)	6,216 (24.7%)	7,448 (26.9%)	20,070 (25.8%)
Never Married[2]	7,440 (29.7%)	6,924 (27.6%)	7,541 (27.3%)	21,905 (28.2%)
Education				
Less than primary[3]	4,438 (17.7%)	3,871 (15.4%)	2,138 (7.7%)	10,447 (13.4%)
Primary	14,020 (56.0%)	15,297 (60.9%)	22,358 (80.9%)	51,675 (66.4%)
Secondary or higher	6,556 (26.2%)	5,952 (23.7%)	3,144 (11.4%)	15,652 (20.1%)
Occupation				
Formal Sector[4]	5,280 (21.1%)	5,836 (23.2%)	6,626 (24.0%)	17,742 (22.8%)
High Risk Informal Sector[5]	657 (2.6%)	399 (1.6%)	2,334 (8.4%)	3,390 (4.4%)
Low Risk Informal Sector[6]	16,389 (65.5%)	17,250 (68.7%)	15,397 (55.7%)	49,036 (63.0%)
Other[7]	1,550 (6.2%)	880 (3.5%)	1,215 (4.4%)	3,645 (4.7%)
No Job or Disabled	1,138 (4.5%)	755 (3.0%)	2,068 (7.5%)	3,961 (5.1%)
Household Wealth Index[8]				

[1]Tested at baseline or with Ministry of Health record indicating prior diagnosis.
[2] N=246 (0.3%) missing
[3] N=159 (0.2%) missing
[4] Formal Sector:teacher, student, government worker, military worker, health worker, factory worker
[5] Informal Sector High Risk: fishmonger, fisherman, bar owner, bar worker, transport, tourism
[6] Informal Sector Low Risk: farmer, shopkeeper, market vendor, hotel worker, housewife, household worker, construction worker, mining
[7] N=249 (0.3%) missing
[8] Quintiles, based on principle components analysis of household wealth survey.

1st (least wealth)[9]	5,301 (21.2%)	4,836 (19.3%)	3,041 (11.0%)	13,178 (16.9%)
2nd	5,218 (20.9%)	5,387 (21.4%)	4,492 (16.3%)	15,097 (19.4%)
3rd	4,740 (18.9%)	5,550 (22.1%)	6,557 (23.7%)	16,847 (21.7%)
4th	4,442 (17.8%)	5,067 (20.2%)	10,959 (39.6%)	20,468 (26.3%)
5th (most wealth)	5,313 (21.2%)	4,280 (17.0%)	2,591 (9.4%)	12,184 (15.7%)
≥1 month/past year away from community[10]	3,333 (13.3%)	3,045 (12.1%)	1,969 (7.1%)	8,347 (10.7%)

[9] N=249 (0.3%) missing
[10]N=4 (0.005%) missing

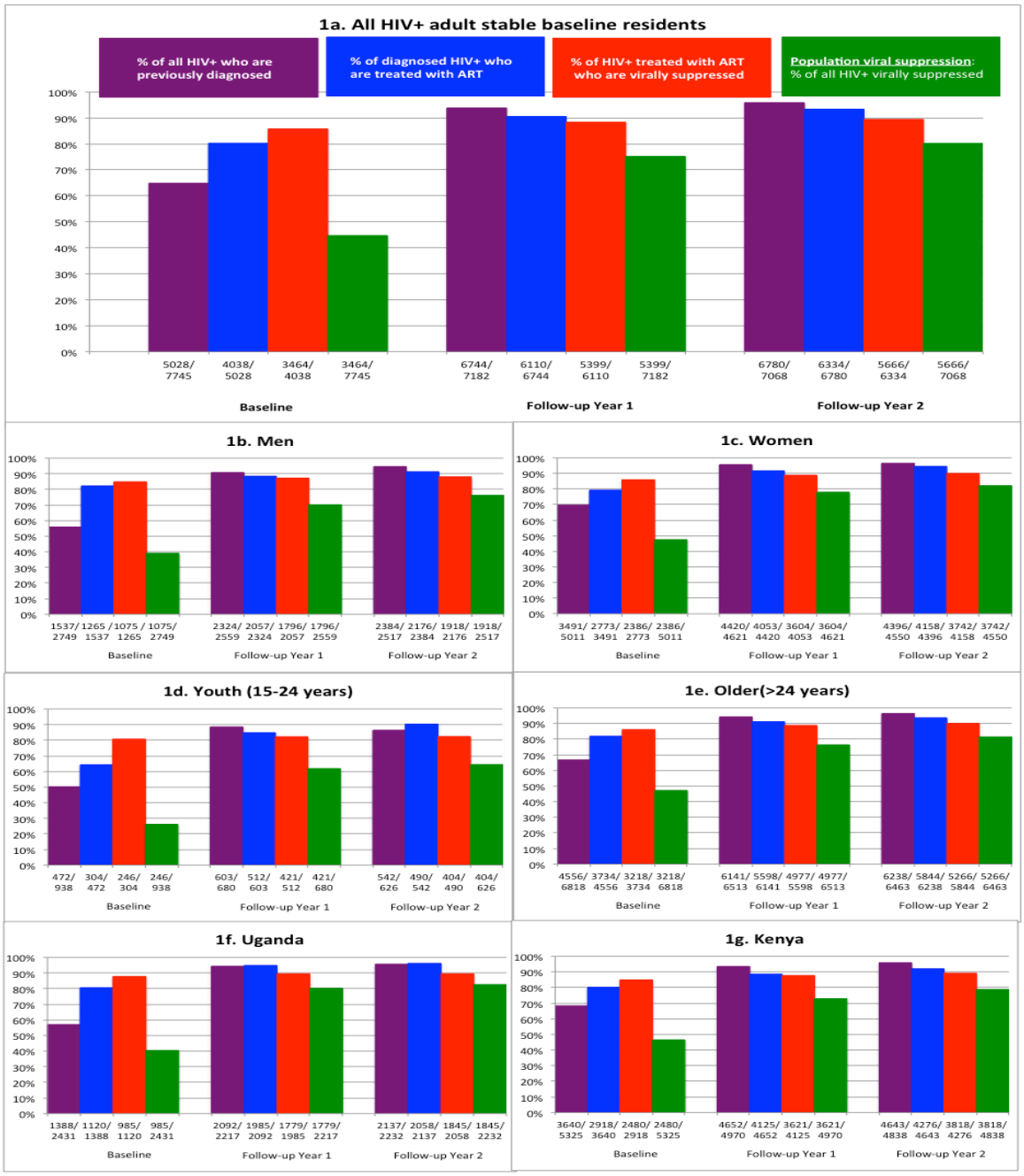

Figure 1. Prior diagnosis, ART, and viral suppression among HIV-positive adult stable residents. Bars show, among an open cohort of HIV-positive adults evaluated at baseline and one and two years: 1) proportion of HIV-positive residents who were previously diagnosed; 2) proportion of previously diagnosed HIV-positive residents who were previously or currently receiving ART; 3) proportion of HIV-positive residents previously or currently receiving ART who had HIV RNA<500 copies/ml; and, 4) proportion of all HIV-positive residents who had HIV RNA<500 copies/ml. Numbers show estimated numerators and denominators of each proportion, adjusted for incomplete HIV serostatus and HIV RNA measurement (eTables 1-2)

(95%CI: 34.4%, 36.6%, p<0.001). At baseline, 64.9% (5,028/7,745; 95%CI:63.8%, 66.0%) of HIV-positive adults were previously diagnosed (70.4% incorporating self-report, 5,454/7,745; 95%CI:69.4%, 71.5%), 80.3% (4,038/5,028; 95%CI:79.2%, 81.4%) of those previously diagnosed had initiated ART, and 85.8% (3,464/4,038; 95%CI:84.6%, 87.0%) of those with prior ART initiation had achieved HIV viral suppression. After two years, 95.9% (6,780/7,068; 95%CI:95.3%, 96.5%) of HIV-positive adults were previously diagnosed, 93.4% (6,334/6,780; 95%CI:92.8%, 94.0%) of those diagnosed had initiated ART, and 89.5% (5,666/6,334; 95%CI:88.6%, 90.3%) of those with prior ART initiation had achieved HIV viral suppression. Population-level HIV viral suppression at two years was similar when migrants into the community and non-stable residents were included (6,157/7,792;79.0%; 95%CI:78.0%, 80.0%, eTable3)and was higher in unadjusted analyses (4,951/5,786; 85.6%, 95%CI:84.6%, 86.5%, eTable2).

Among subgroups of the open cohort (Figure 1b-g, eTable 2), at baseline a smaller proportion of HIV-positive men (55.9%) compared to women (69.7%) were previously diagnosed (13.8 percentage point difference; 95%CI:12.1%,15.5%), and men were less likely to have achieved HIV viral suppression (39.1% versus 47.6% among women, 8.5 percentage point difference, 95%CI:6.8%,10.2%). At baseline, youth (15-24 years) were less likely than older adults to have been previously diagnosed, treated once diagnosed, and suppressed once treated, and a lower proportion of HIV-

positive youth (26.2%) compared to older adults (47.2%) had achieved HIV viral suppression (21.0 percentage point difference,

95%CI:18.5%,23.5%). Age and sex disparities, although smaller, remained after two years. After two years, 76.2% of men versus 82.2% of women (6.0 percentage point difference, 95%CI:4.3%,7.7%), and 64.5% of youth versus 81.5% of older adults (17.0 percentage point difference, 95%CI:13.6%,20.4%) had achieved HIV viral suppression.

ART use and HIV viral suppression in a closed cohort of baseline HIV-positive adults

Among a closed cohort of 7,108 stable adult residents diagnosed with HIV at or before study baseline (Figure 2, eTable 4), at baseline, 29.3% (N=2,080) were newly diagnosed and 13.9% (N=990) were previously diagnosed but ART naïve. Adjusting for missing HIV RNA, an estimated 8.1% (N=575) had initiated ART but had HIV RNA≥500 copies/ml, and 48.7% (N=3,463) had HIV RNA<500 copies/ml. In contrast, after two years, the estimated proportion with HIV viral suppression was 73.4% (N=5,218), 1.9% (N=136) had died, and 11.9% (N=849) had migrated out of the community. While initial disparities in suppression between countries, ages and genders declined over time (Figures 2b-g), by two years 28.5% (246/864) of youth had migrated out of the community and only 54.7% (473/864) of youth were resident in the community with HIV viral suppression (versus 76.0%,

4,748/6,244, for ages >24 years).

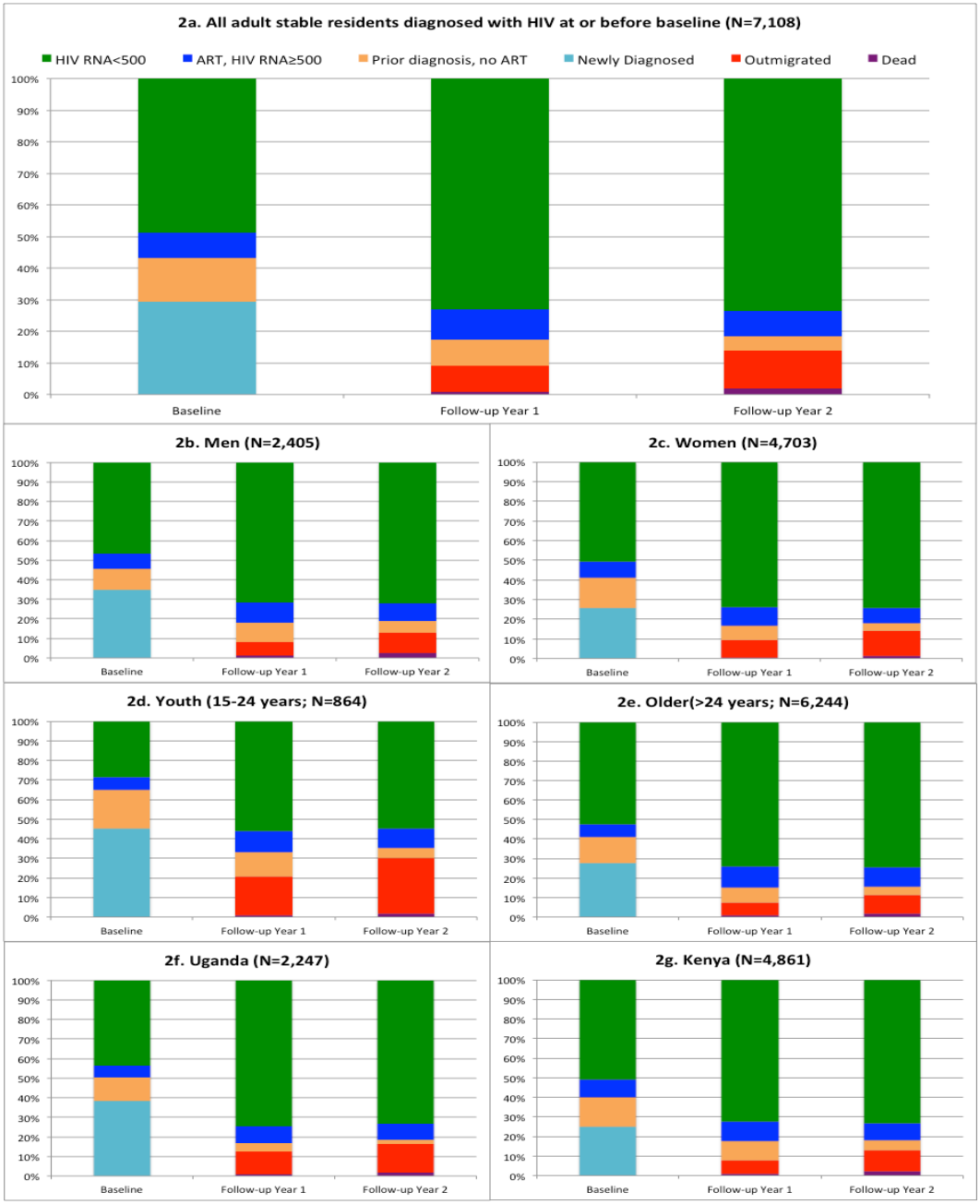

Figure 2. Prior diagnosis, ART, viral suppression, out-migration, and death among HIV-positive adults diagnosed at or before baseline. Segmented bars show the proportion of the closed cohort of baseline HIV-positive adults who, at baseline and after one and two years, had: 1) no prior diagnosis; 2) prior diagnosis but no prior or current ART; 3) prior or current ART and HIV RNA≥500 copies/ml; 4) prior or current ART and HIV RNA<500 copies/ml; 5) death; and, 6) out-migration. Adjusted to account for incomplete plasma HIV RNA measurement (eTable 4).

In longitudinal analysis in which follow-up was censored at death or migration out of the community, with adjustment for potentially informative censoring and missing HIV RNA, after one year, 79.7% (95%CI:78.7%, 80.8%) of the baseline HIV-positive cohort (N=7,108) had achieved HIV viral suppression, increasing to 83.8% (95%CI:82.8%, 84.9%) after two years (Table 2), compared with 48.7% (47.4%, 50.0%) who had viral suppression at baseline (eTable 4). In the subgroup of individuals newly diagnosed at baseline, (N=2,080) 62.8% (95%CI:60.4%, 65.2%) had achieved HIV viral suppression after one year, increasing to 68.8% (95%CI:66.4%, 71.2%) after two years. Individuals previously diagnosed but ART-naïve at baseline (N=990) were more likely to have achieved HIV viral suppression (78.1%; 95%CI:75.3%, 80.8% and 86.5%; 95%CI:84.2%, 88.8% at one and two years), while ART-experienced individuals with a baseline HIV RNA level≥500 copies/ml (N=426) were less likely to have achieved HIV viral suppression(49.5%; 95%CI:44.2%, 54.7% and 62.2%; 95%CI:57.2%, 67.2% at one and two years). Almost all individuals with a suppressed HIV RNA level measured at baseline (N=2,549) maintained a suppressed HIV RNA level one and two years later (96.3%; 95%CI:95.6%, 97.1% and 96.8%; 95%CI:96.0%, 97.6% at one and two years).

Table 2.Post-baseline viral suppression (HIV RNA<500 copies/ml) in a closed cohort of HIV-positive adults diagnosed at or before study baseline (N=7,108). Overall, and within subgroups defined by diagnosis prior to baseline, ART initiation prior to baseline, and viral suppression at baseline. Longitudinal analysis, follow-up censored at death or out-migration.

		Follow-up Year 1		Follow-up Year 2	
Baseline diagnosis, treatment, and suppression status	**N (%[1])**	**No. with viral suppression/ Total No. with measured HIV RNA[2] (%)**	**Adjusted proportion [3] (95% CI)**	**No. with viral suppression/ Total No. with measured HIV RNA[4]**	**Adjusted proportion[3] (95% CI)**
All	7,108 (100.0%)	4,682/5,578 (83.9%)	79.7% (78.7%, 80.8%)	4,602/5,215 (88.2%)	83.8% (82.8%, 84.9%)
Newly Diagnosed (HIV RNA≥500 copies/ml)	2,080 (29.3%)	963/1,321 (72.9%)	62.8% (60.4%, 65.2%)	965/1,205 (80.1%)	68.8% (66.4%, 71.2%)
Previously Diagnosed, no ART (HIV RNA≥500 copies/ml)	990 (13.9%)	649/812 (79.9%)	78.1% (75.3%, 80.8%)	685/778 (88.0%)	86.5% (84.2%, 88.8%)
Previous or Current ART	4,038 (56.8%)	3,070/3,445 (89.1%)	88.8% (87.7%, 89.9%)	2,952/3,232 (91.3%)	90.5% (89.4%, 91.6%)
HIV RNA not measured	1063 (15.0%)	732/846 (86.5%)	86.6% (84.3%, 88.9%)	685/779 (87.9%)	87.2% (84.9%, 89.5%)
HIV RNA≥500 copies/ml	426 (6.0%)	175/355 (49.3%)	49.5% (44.2%, 54.7%)	204/325 (62.8%)	62.2% (57.2%, 67.2%)
HIV RNA<500 copies/ml	2,549 (35.9%)	2,163/2,244 (96.4%)	96.3% (95.6%, 97.1%)	2,063/2,128 (96.9%)	96.8% (96.0%, 97.6%)

[1]N in subgroup/ 7,108 baseline stable adult HIV-positive participants

[2]Among N= 6,460 baseline HIV-positive individuals alive and not out-migrated by follow-up year 1

[3]Among N=7,108 baseline stable adult HIV-positive participants.Estimated probability of viral suppression at time of that year's annual testing, adjusted for censoring by death/out-migration and for missing HIV RNA. Baseline adjustment variables: community, age, sex, occupation, mobility (≥1 mo./past year away from community), wealth, marital status, and education. Time-varying adjustment variables: prior health campaign or home-based contact, prior ART initiation (for subgroups not already initiated ART use at baseline), and prior HIV RNA testing and suppression history.

[4]Among N=6,123 baseline HIV-positive individuals alive and not out-migratedby follow-up year 2

Demographic variables associated with testing, ART, and suppression

Associations between baseline demographics and failure to test for HIV, initiate ART, and virally suppress were explored in closed cohort analyses, adjusting for censoring at death or out-migration. Among 72,746 baseline adult stable residents not diagnosed with HIV before baseline, the probability of testing for HIV at least once over two years of follow-up was 96.8% (95%CI:96.6%, 97.0%,eTable 5). In multivariable analyses, residents who were male, never married, mobile (≥1 month/past year away from community), age 25-44 years (versus >44 years), and had less than primary education (versus primary) were at higher risk of never testing for HIV (eTable 6).

Among 7,108 HIV-positive adults diagnosed at or before baseline, an estimated 93.8% (95%CI:93.2%, 94.4%, eTable 5) had ever used ART and 83.8% (95%CI:82.8%, 84.9%, Table 2) had achieved HIV viral suppression at two years. In multivariable analyses, residents who were male, younger, and had intermediate wealth were at higher risk of never initiating ART (eTable 7), while those who were male, younger, and not employed in the formal sector were at higher risk of non-suppression (Table 3).

Table 3. Association between baseline demographic variables and viral non-suppression (plasma HIV RNA>500 copies/ml) at follow-up year 2 in a closed cohort of HIV-positive adults diagnosed at or before study baseline (N=7,108)). Longitudinal analysis, follow-up censored at death or out-migration

	No. without viral suppression/ Total No. residents with HIV RNA measured (%)[1]	Unadjusted Risk Difference (95% CI)	P value	Adjusted Risk Difference [2] (95% CI)	P value
Sex					
Male	228/1691 (13.5%)	2.6% (0.7%, 4.4%)	0.006	6.0% (3.5%, 8.5%)	<0.001
Female	385/3524 (10.9%)	Ref	Ref	Ref	Ref
Age(Years)					
15-24	87/469 (18.6%)	9.2% (3.6%, 14.9%)	0.001	15.3% (9.8%, 20.9%)	<0.001
25-34	224/1650 (13.6%)	4.3% (1.5%, 7.0%)	0.002	8.8% (6.2%, 11.4%)	<0.001
35-44	163/1604 (10.2%)	0.8% (-2.0%, 3.7%)	0.56	2.2% (-0.2%, 4.5%)	0.07
>44	139/1492 (9.3%)	Ref	Ref	Ref	Ref
Marital Status					
Married, Widowed, Divorced, Separated	576/5003 (11.5%)	Ref	Ref	Ref	Ref
Never married	37/212 (17.5%)	5.9% (2.7%, 9.1%)	<0.001	5.5% (-2.2%, 13.1%)	0.17
Education					
Less than Primary	63/484 (13.0%)	Ref	Ref	Ref	Ref
Primary	484/4141 (11.7%)	-1.3% (-3.2%, 0.5%)	0.16	-1.5% (-6.2%, 3.2%)	0.54
Secondary or higher	66/590 (11.2%)	-1.8% (-12.1%, 8.5%)	0.73	-3.3% (-8.8%, 2.2%)	0.24

[1]Of the 7,108 baseline HIV-positive individuals, 985 died or out-migrated by year 2. Of the remaining 6,123 individuals, 5,215 (85.2%) had HIV RNA measured at year 2 and contributed to the unadjusted analyses

[2]All 7,108 adults contributed to the adjusted analyses, which controlled for right-censoring by death and out-migration.Baseline adjustment variables: community, age, sex, occupation, mobility, wealth, marital status, education. Time-varying adjustment variables (used in addition to baseline variables to adjust for censoring by death/out-migration and missing HIV RNA measures): prior health campaign and home-based contact, prior ART initiation, prior HIV RNA testing and suppression history.

Occupation					
Formal Sector[3]	18/211 (8.5%)	Ref	Ref	Ref	Ref
High Risk Informal Sector[4]	66/496 (13.3%)	4.8% (-7.7%, 17.3%)	0.45	8.3% (3.3%, 13.4%)	0.001
Low Risk Informal Sector[5]	474/4087 (11.6%)	3.1% (1.6%, 4.6%)	<0.001	6.3% (2.4%, 10.3%)	0.002
Other	28/197 (14.2%)	5.7% (-7.9%, 19.3%)	0.41	10.2% (2.5%, 17.9%)	0.009
No Job or Disabled	27/224 (12.1%)	3.5% (-10.0%, 17.0%)	0.61	11.4% (4.7%, 18.1%)	<0.001
Household Wealth Index[6]					
1st (least wealth)	88/813 (10.8%)	-0.9% (-5.3%, 3.6%)	0.70	0.6% (-2.7%, 3.9%)	0.73
2nd	129/989 (13.0%)	1.4% (-3.6%, 6.3%)	0.59	2.1% (-1.2%, 5.4%)	0.21
3rd	147/1177 (12.5%)	0.8% (-3.3%, 4.9%)	0.70	2.8% (-0.3%, 6.0%)	0.08
4th	157/1449 (10.8%)	-0.9% (-4.2%, 2.5%)	0.62	2.9% (-0.2%, 6.1%)	0.06
5th (most wealth)	92/787 (11.7%)	Ref	Ref	Ref	Ref
Mobility					
< 1 Month/past year away from community	562/4856 (11.6%)	Ref	Ref	Ref	Ref
≥1 Month/past year away from community	51/359 (14.2%)	2.6% (-0.6%, 5.9%)	0.11	2.5% (-1.2%, 6.2%)	0.19

[3] Formal Sector:teacher, student, government worker, military worker, health worker, factory worker

[4] Informal Sector High Risk: fishmonger, fisherman, bar owner, bar worker, transport, tourism

[5] Informal Sector Low Risk: farmer, shopkeeper, market vendor, hotel worker, housewife, household worker, construction worker, mining

[6] Quintiles, based on principle components analysis of household wealth survey

Discussion

At study baseline, 44.7% of HIV-positive adults had suppressed HIV viral replication. After two years of a community-based HIV test and treat intervention, 95.9% of HIV-positive adults were previously diagnosed (prior to baseline or during the 2 year program), 93.4% of those had received ART, and 89.5% of those had achieved HIV viral suppression; overall, 80.2% of HIV-positive adults had suppressed HIV viral replication.

The WHO global public health mandate to identify and offer ART to the 37 million persons living with HIV is a challenging goal– skepticism regarding the feasibility of reaching the UNAIDS 90-90-90 target by 2020 is legitimate. Globally, approximately half of persons living with HIV know their diagnosis,[8] many diagnosed persons do not link to care or drop out after starting ART,[27,28] HIV funding has not increased over the past 5 years, [29] and stigma remains a barrier, particularly in vulnerable populations.[30,31] The two most important findings of these analyses are: 1) the 2015 WHO guidelines to treat persons regardless of CD4 count can be successfully implemented, and 2) the UNAIDS 90-90-90 target of 73% of HIV-positive persons with HIV viral suppression can be achieved and exceeded within a two year period in rural East Africa.

Few studies in Sub-Saharan Africa have directly evaluated population-level HIV testing, treatment, and suppression of HIV viral replication to

<500copies/ml,[10,11,13,32-37] and even fewer have data after starting an HIV test and treat intervention.[38] Botswana– an upper-middle income country with a population of two million– is closest to achieving the UNAIDS 90-90-90 target.[10] Despite Botswana's policy to initiate ART at CD4 counts <350 cells/mm^3, an estimated 70% of HIV-positive persons resident in Botswana have achieved HIV viral suppression, an achievement attributed to Botswana's political leadership, early adoption of HIV opt-out testing and ART, decentralization of HIV care, and access to HIV RNA monitoring.

This study demonstrates progress towards achieving the UNAIDS targets in rural Uganda and Kenya in regions with baseline HIV prevalence ranging from 3.5% to 20.1%. Further, among populations in which less than half of HIV-positive adults had achieved HIV viral suppression at study baseline, an intervention that included treatment of adults with >350 CD4 cells/mm^3 using a streamlined HIV care delivery model integrated into government health clinics exceeded the UNAIDS overall population-level viral suppression target after one year.

HIV testing is one of the most challenging obstacles to achieving universal ART coverage. Before the testing intervention, 64.9% of HIV-positive community residents knew their status, less than the 83% with known status in Botswana,[10] but substantially more than the regional UNAIDS estimate of 56%.[8] Using an "out of facility" mobile testing strategy that combined multi-

disease testing at community health campaigns with home testing for non-attendees, the proportion of HIV-positive persons aware of their status increased to 95.9% after two years. Community engagement contributed to this success. Participation of men, whose knowledge of HIV status lagged that of women at study baseline, was enhanced by targeted outreach that included competitive sporting events, conveniently located testing services with evening hours, and non-HIV services including diabetes and hypertension screening and sexual health consultation.[16]

Poor retention in HIV care and adherence to ART, particularly among persons starting therapy with high CD4 count, is a potential barrier to achieving the new WHO treatment guidelines.[9] A streamlined delivery model was used to enhance retention among patients initiating ART at all CD4 counts. This patient-centered model of care was designed to reduce structural barriers, improve patient-clinician relationships, and enhance patient knowledge and attitudes about HIV. It is an example of what is now called "differentiated" HIV care– a client-centered approach that adapts HIV services to reflect the preferences and expectations of people living with HIV.[39] There is increasing global consensus that successfully treating all persons living with HIV, as well as generating more efficient health systems, will require differentiated care approaches.

This study provides insight into four groups— youth, men, and those newly

diagnosed or failing ART — who are falling short of achieving the UNAIDS 90-90-90 target. At baseline, only 50.3% of HIV-positive youth (15-24 years) were aware of their status. This increased to 86.5% after two years, suggesting that the testing strategy was reaching most youth. However, population-level HIV viral suppression at two years remained 64.5% in youth compared to 81.5% in older populations, due in part to the lower proportion of viral suppression (82.4%) among youth who had started therapy. Barriers faced by youth included stigma and logistics of HIV care for those in boarding school. More research is needed to design age-specific solutions.

Among men at baseline, HIV testing and linkage for ART start were major barriers in the HIV care cascade. The testing intervention closed much of the gender gap in knowledge of HIV status over two years. However, after two years, HIV-positive men remained less likely to be diagnosed, treated, and virally suppressed on treatment, resulting in a persistent disparity in population-level suppression (82.2% among women vs. 76.2% among men).

HIV-positive individuals who were newly diagnosed at baseline failed to achieve targets for ART initiation and viral suppression. In a closed cohort analysis, only 68.8% had achieved HIV viral suppression after two years. This group will require new approaches to enhance linkage and adherence. Adults with HIV RNA>500 copies/ml at baseline despite prior ART initiation also was short of target— only 62.2% had achieved HIV viral suppression

after two years. Non-adherence, HIV drug resistance, and unmet structural barriers to care all likely contribute to poor suppression in this often vulnerable and difficult-to-reach population. Additional approaches, including improved implementation of 2nd and 3rd line ART treatment and possibly HIV resistance testing, should be evaluated.

This analysis did not address if HIV incidence decreased with the improvements observed in the care cascade. UNAIDS has already set a new target of 95-95-95 by 2030, recognizing that the current target alone is unlikely to eliminate the HIV epidemic.[40] Reaching the HIV-positive individuals who remain without HIV viral suppression is a priority, both for their own health and because of their potential contribution to ongoing HIV transmission.

This analysis has several limitations. First, prior to trial completion, which will allow for comparison with the standard-of-care, progress towards the UNAIDS target cannot be attributed to the intervention. Second, primary analysis focused on baseline stable community residents due to their full exposure to the intervention; however, these individuals may be easier to test, treat and suppress than more mobile populations. Although sensitivity analyses including non-stable residents and migrants into the community yielded similar estimates, ascertainment of migrants into the community was not comprehensive. Cascade outcomes among individuals who left the

community are also unknown, as is the contribution of migrant individuals to ongoing HIV transmission.[38]

Conclusion

Among HIV-positive adults in rural Kenya and Uganda, implementation of a community-based testing and treatment intervention was associated with an increased proportion of HIV-positive adults who achieved viral suppression, along with increased HIV diagnosis and initiation of antiretroviral therapy. In these communities, the UNAIDS population-level viral suppression target was exceeded within 2 years after program implementation.

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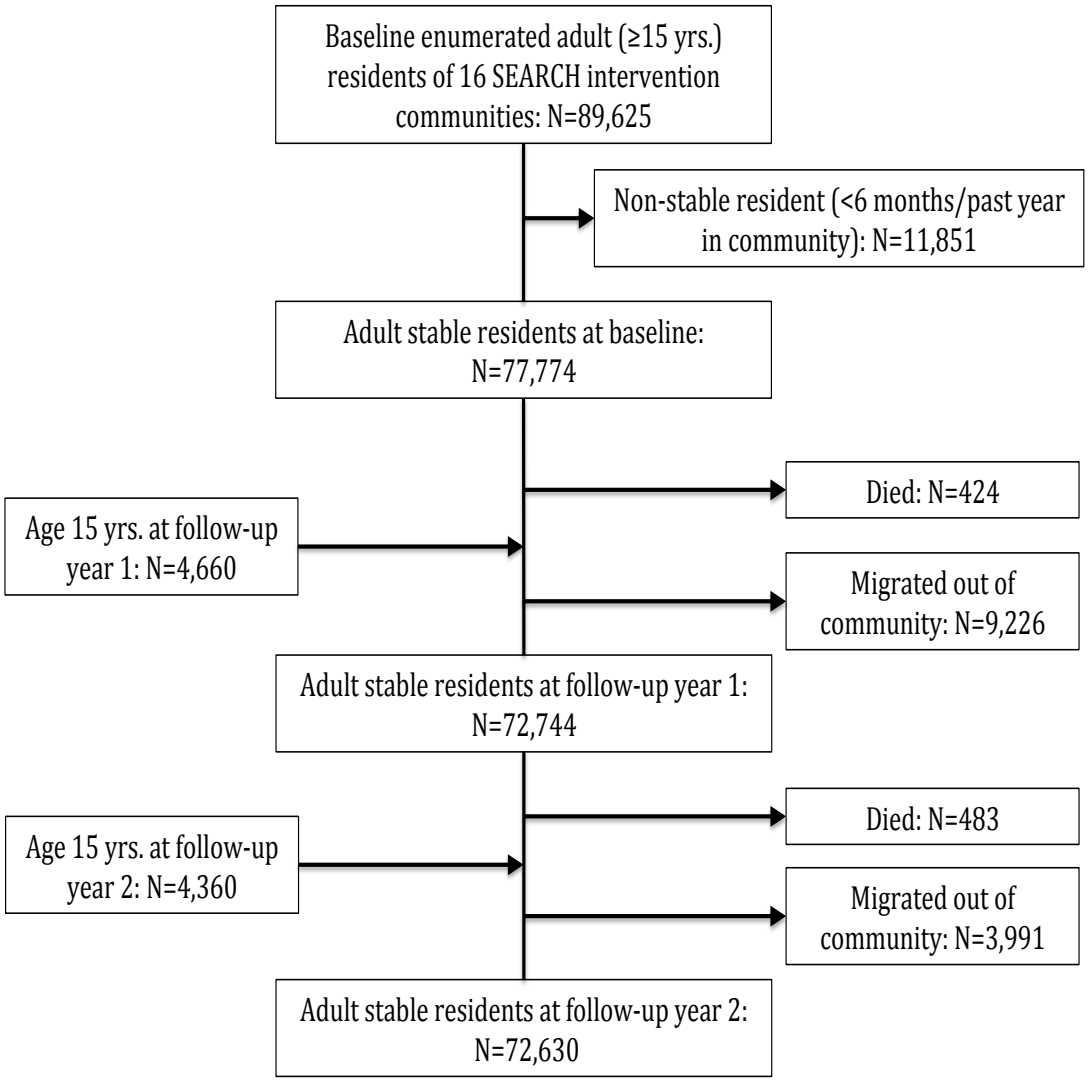
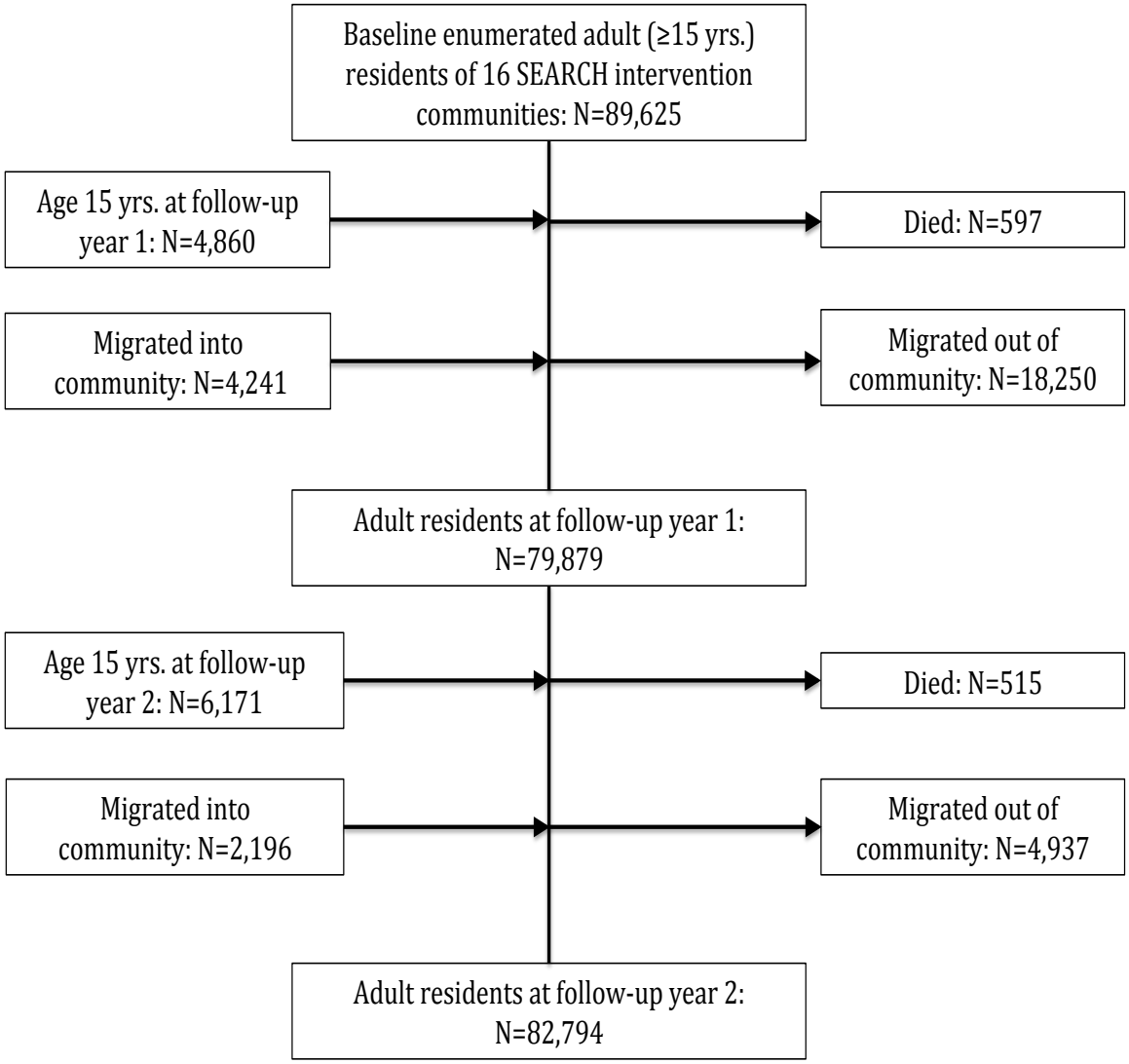
eFigure 1. Study population for primary analysis. Adult (≥15 years) stable residents (≥6 months of past year in community) enumerated in the baseline household census in 16 intervention communities of the SEARCH Study.



eFigure 2. Study population for sensitivity analysis. Adult (≥15 years) residents of 16 intervention communities of the SEARCH Study, including baseline non-stable residents and migrants into the community.



eTable 1. Prior diagnosis, ART use, and viral suppression (HIV RNA<500 copies/ml) at baseline and at one and two years of follow-up in the open cohort of HIV-positive adult stable residents. Table provides detail on numerators and denominators used for unadjusted and adjusted (primary) analysis in open cohort.

	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
No. baseline enumerated adult stable residents	77774	72744	72630
Among individuals seen at annual testing[1](used for unadjusted estimates)			
No. individuals with known HIV status[2]	69083	64302	62241
No. HIV+ individuals	6908	6307	6121
No. HIV+ individuals with prior HIV diagnosis	4829	6049	5978
No. HIV+ individuals with prior or current ART	3881	5666	5748
No. HIV+ individuals with measured HIV RNA[3]	4983	6016	5786
No. HIV+ individuals with prior or current ART and measured HIV RNA	2975	5485	5504
No. HIV+ individuals with prior or current ART and HIV RNA<500 cps/ml	2549	4851	4951
Estimated total number of individuals (used for adjusted estimates)			
No. HIV+ individuals[4]	7745	7182	7068
No. HIV+ individuals with prior HIV diagnosis[5]	5028	6744	6780
No. HIV+ individuals with prior or current ART[5]	4038	6110	6334
No. HIV+ individuals with HIV RNA<500 cps/ml[6]	3464	5399	5666

[1]Resident in community (not dead or migrated out of the community) and contacted at that year's annual testing (community health campaign or subsequent home-based testing)
[2]Tested for HIV at that year's annual testing or with record of prior positive HIV test
[3]PlasmaHIV RNA measured at that year's annual testing
[4]Adjusted for differences in community, baseline demographics (age, sex, occupation, ≥1 mo./past year away from community, wealth, marital status, education), prior health campaign and home-based contact, and prior HIV testing between individuals with measured vs. missing HIV serostatus
[5] Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)
[6]Adjusted for differences in community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression between individuals with measured vs. missing HIV RNA level

eTable 2. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents. Adjusted and unadjusted estimates for the full open cohort and within subgroups defined by sex, age, and country. Numerator/Denominator: Percentage (95% Confidence Interval)

	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Full cohort			
% HIV+ with a prior HIV diagnosis			
Unadjusted	4829/6908: 69.9% (68.8%, 71.1%)	6049/6307: 95.9% (95.4%, 96.4%)	5978/6121: 97.7% (97.3%, 98.0%)
Adjusted[1]	5028/7745: 64.9% (63.8%, 66.0%)	6744/7182: 93.9% (93.3%, 94.5%)	6780/7068: 95.9% (95.3%, 96.5%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	3881/4829: 80.4% (79.2%, 81.5%)	5666/6049: 93.7% (93.0%, 94.3%)	5748/5978: 96.2% (95.6%, 96.7%)
Adjusted[2]	4038/5028: 80.3% (79.2%, 81.4%)	6110/6744: 90.6% (89.9%, 91.3%)	6334/6780: 93.4% (92.8%, 94.0%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	2549/2975: 85.7% (84.4%, 87.0%)	4851/5485: 88.4% (87.6%, 89.3%)	4951/5504: 90.0% (89.1%, 90.8%)
Adjusted[3]	3464/4038: 85.8% (84.6%, 87.0%)	5399/6110: 88.4% (87.5%, 89.3%)	5666/6334: 89.5% (88.6%, 90.3%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	2549/4983: 51.2% (49.7%, 52.6%)	4851/6016: 80.6% (79.6%, 81.7%)	4951/5786: 85.6% (84.6%, 86.5%)
Adjusted[4]	3464/7745: 44.7% (43.5%, 45.9%)	5399/7182: 75.2% (74.1%, 76.3%)	5666/7068: 80.2% (79.1%, 81.2%)

[1]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior HIV testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 2. Continued. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents. Adjusted and unadjusted estimates for the full open cohort and within subgroups defined by sex, age, and country. Numerator/Denominator: Percentage (95% Confidence Interval)

	Baseline	Follow-up Year 1	Follow-up Year 2
Men			
% HIV+ with a prior HIV diagnosis			
Unadjusted	1442/2309: 62.5% (60.5%, 64.5%)	2010/2126: 94.5% (93.6%, 95.5%)	2005/2063: 97.2% (96.5%, 97.9%)
Adjusted[1]	1537/2749: 55.9% (54.1%, 57.8%)	2324/2559: 90.8% (89.6%, 92.1%)	2384/2517: 94.7% (93.6%, 95.8%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	1187/1442: 82.3% (80.4%, 84.3%)	1859/2010: 92.5% (91.3%, 93.6%)	1909/2005: 95.2% (94.3%, 96.2%)
Adjusted[2]	1265/1537: 82.3% (80.4%, 84.2%)	2057/2324: 88.5% (87.2%, 89.8%)	2176/2384: 91.3% (90.1%, 92.4%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	762/895: 85.1% (82.8%, 87.5%)	1568/1795: 87.4% (85.8%, 88.9%)	1621/1827: 88.7% (87.3%, 90.2%)
Adjusted[3]	1075/1265: 84.9% (82.7%, 87.2%)	1796/2057: 87.3% (85.8%, 88.9%)	1918/2176: 88.1% (86.7%, 89.6%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	762/1624: 46.9% (44.5%, 49.3%)	1568/2008: 78.1% (76.3%, 79.9%)	1621/1939: 83.6% (81.9%, 85.3%)
Adjusted[4]	1075/2749: 39.1% (37.2%, 41.0%)	1796/2559: 70.2% (68.3%, 72.1%)	1918/2517: 76.2% (74.4%, 78.1%)

[1]Adjusted for community, baseline demographics (age, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (age, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (age, occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 2. Continued. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents. Adjusted and unadjusted estimates for the full open cohort and within subgroups defined by sex, age, and country. Numerator/Denominator: Percentage (95% Confidence Interval)

	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
<u>Women</u>			
% HIV+ with a prior HIV diagnosis			
Unadjusted	3387/4599: 73.6% (72.4%, 74.9%)	4039/4181: 96.6% (96.1%, 97.2%)	3973/4058: 97.9% (97.5%, 98.3%)
Adjusted[1]	3491/5011: 69.7% (68.4%, 70.9%)	4420/4621: 95.7% (95.0%, 96.3%)	4396/4550: 96.6% (95.9%, 97.3%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	2694/3387: 79.5% (78.2%, 80.9%)	3807/4039: 94.3% (93.5%, 95.0%)	3839/3973: 96.6% (96.1%, 97.2%)
Adjusted[2]	2773/3491: 79.4% (78.1%, 80.8%)	4053/4420: 91.7% (90.9%, 92.5%)	4158/4396: 94.6% (93.9%, 95.3%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	1787/2080: 85.9% (84.4%, 87.4%)	3283/3690: 89.0% (88.0%, 90.0%)	3330/3677: 90.6% (89.6%, 91.5%)
Adjusted[3]	2386/2773: 86.0% (84.6%, 87.5%)	3604/4053: 88.9% (87.9%, 89.9%)	3742/4158: 90.0% (89.0%, 91.0%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	1787/3359: 53.2% (51.5%, 54.9%)	3283/4008: 81.9% (80.7%, 83.1%)	3330/3847: 86.6% (85.5%, 87.6%)
Adjusted[4]	2386/5011: 47.6% (46.2%, 49.0%)	3604/4621: 78.0% (76.8%, 79.2%)	3742/4550: 82.2% (81.0%, 83.5%)

[1]Adjusted for community, baseline demographics (age, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (age,occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (age,occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 2. Continued. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents.

	Baseline	Follow-up Year 1	Follow-up Year 2
<u>Youth (15-24 years)</u>			
% HIV+ with a prior HIV diagnosis			
Unadjusted	460/851: 54.1% (50.8%, 57.6%)	513/571: 89.8% (87.4%, 92.4%)	452/503: 89.9% (87.3%, 92.5%)
Adjusted[1]	472/938: 50.3% (47.2%, 53.6%)	603/680: 88.6% (86.0%, 91.3%)	542/626: 86.5% (83.3%, 89.9%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	297/460: 64.6% (60.3%, 69.1%)	458/513: 89.3% (86.6%, 92.0%)	419/452: 92.7% (90.3%, 95.1%)
Adjusted[2]	304/472: 64.4% (60.2%, 68.9%)	512/603: 84.9% (82.1%, 87.9%)	490/542: 90.4% (88.0%, 92.9%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	177/220: 80.5% (75.2%, 85.7%)	358/435: 82.3% (78.7%, 85.9%)	319/389: 82.0% (78.2%, 85.8%)
Adjusted[3]	246/304: 80.8% (76.0%, 85.8%)	421/512: 82.3% (78.9%, 85.9%)	404/490: 82.4% (78.8%, 86.2%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	177/596: 29.7% (26.0%, 33.4%)	358/537: 66.7% (62.7%, 70.7%)	319/449: 71.0% (66.8%, 75.3%)
Adjusted[4]	246/938: 26.2% (23.4%, 29.3%)	421/680: 61.9% (58.2%, 65.9%)	404/626: 64.5% (60.4%, 68.8%)

[1]Adjusted for community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 2. Continued. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents.)

	Baseline	Follow-up Year 1	Follow-up Year 2
Older (>24 years)			
% HIV+ with a prior HIV diagnosis			
Unadjusted	4369/6057: 72.1% (71.0%, 73.3%)	5536/5736: 96.5% (96.0%, 97.0%)	5526/5618: 98.4% (98.0%, 98.7%)
Adjusted[1]	4556/6818: 66.8% (65.7%, 68.0%)	6141/6513: 94.3% (93.6%, 95.0%)	6238/6463: 96.5% (95.9%, 97.2%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	3584/4369: 82.0% (80.9%, 83.2%)	5208/5536: 94.1% (93.4%, 94.7%)	5329/5526: 96.4% (95.9%, 96.9%)
Adjusted[2]	3734/4556: 82.0% (80.8%, 83.1%)	5598/6141: 91.2% (90.4%, 91.9%)	5844/6238: 93.7% (93.1%, 94.3%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	2372/2755: 86.1% (84.8%, 87.4%)	4493/5050: 89.0% (88.1%, 89.9%)	4632/5115: 90.6% (89.7%, 91.4%)
Adjusted[3]	3218/3734: 86.2% (84.9%, 87.4%)	4977/5598: 88.9% (88.0%, 89.8%)	5266/5844: 90.1% (89.3%, 91.0%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	2372/4387: 54.1% (52.5%, 55.6%)	4493/5479: 82.0% (81.0%, 83.1%)	4632/5337: 86.8% (85.9%, 87.7%)
Adjusted[4]	3218/6818: 47.2% (45.9%, 48.5%)	4977/6513: 76.4% (75.3%, 77.6%)	5266/6463: 81.5% (80.4%, 82.6%)

[1]Adjusted for community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 2. Continued. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents.

	Baseline	Follow-up Year 1	Follow-up Year 2
<u>Uganda</u>			
% HIV+ with a prior HIV diagnosis			
Unadjusted	1330/2189: 60.8% (58.6%, 63%)	1834/1914: 95.8% (94.9%, 96.7%)	1768/1814: 97.5% (96.7%, 98.2%)
Adjusted[1]	1388/2431: 57.1% (55%, 59.2%)	2092/2217: 94.4% (93.3%, 95.4%)	2137/2232: 95.8% (94.5%, 97.0%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	1077/1330: 81.0% (78.8%, 83.2%)	1779/1834: 97.0% (96.2%, 97.8%)	1738/1768:98.3% (97.7%, 98.9%)
Adjusted[2]	1120/1388: 80.7% (78.6%, 82.9%)	1985/2092: 94.9% (93.9%, 95.9%)	2058/2137: 96.3% (95.5%, 97.1%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	643/735: 87.5% (85.0%, 89.9%)	1536/1715: 89.6% (88.1%, 91.0%)	1456/1608: 90.5% (89.1%, 92.0%)
Adjusted[3]	985/1120: 87.9% (86.0%, 89.9%)	1779/1985: 89.6% (88.2%, 91.1%)	1845/2058: 89.6% (88.1%, 91.2%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	643/1377: 46.7% (43.9%, 49.5%)	1536/1832: 83.8% (82.1%, 85.6%)	1456/1669: 87.2% (85.6%, 88.9%)
Adjusted[4]	985/2431: 40.5% (38.5%, 42.6%)	1779/2217: 80.3% (78.5%, 82.1%)	1845/2232: 82.7% (80.7%, 84.7%)

[1]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 2. Continued. Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult stable residents.

	Baseline	Follow-up Year 1	Follow-up Year 2
Kenya			
% HIV+ with a prior HIV diagnosis			
Unadjusted	3499/4719: 74.1% (72.8%, 75.5%)	4215/4393: 95.9% (95.4%, 96.5%)	4210/4307: 97.7% (97.3%, 98.2%)
Adjusted[1]	3640/5325: 68.4% (67.1%, 69.7%)	4652/4970: 93.6% (92.8%, 94.4%)	4643/4838: 96.0% (95.3%, 96.6%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	2804/3499: 80.1% (78.8%, 81.5%)	3887/4215: 92.2% (91.4%, 93.1%)	4010/4210: 95.2% (94.6%, 95.9%)
Adjusted[2]	2918/3640: 80.2% (78.8%, 81.5%)	4125/4652: 88.7% (87.7%, 89.6%)	4276/4643: 92.1% (91.3%, 92.9%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	1906/2240: 85.1% (83.6%, 86.6%)	3315/3770: 87.9% (86.8%, 89.0%)	3495/3896: 89.7% (88.7%, 90.7%)
Adjusted[3]	2480/2918: 85.0% (83.5%, 86.5%)	3621/4125: 87.8% (86.7%, 88.9%)	3818/4276: 89.3% (88.3%, 90.3%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	1906/3606: 52.9% (51.2%, 54.6%)	3315/4184: 79.2% (78.0%, 80.5%)	3495/4117: 84.9% (83.8%, 86.0%)
Adjusted[4]	2480/5325: 46.6% (45.1%, 48.1%)	3621/4970: 72.9% (71.5%, 74.2%)	3818/4838: 78.9% (77.7%, 80.2%)

[1]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 3. Sensitivity analysis: Prior diagnosis, ART use, and viral suppression at baseline and at one and two years of follow-up in an open cohort of HIV-positive adult residents, including non-stable baseline residents and migrants into the community.

	Baseline	Follow-up Year 1	Follow-up Year 2
Full cohort			
% HIV+ with a prior HIV diagnosis			
Unadjusted	4893/7040: 69.5% (68.4%, 70.7%)	6402/6813: 94.0% (93.4%, 94.5%)	6463/6702: 96.4% (96.0%, 96.9%)
Adjusted[1]	5195/8580: 60.6% (59.5%, 61.7%)	7130/7745: 92.1% (91.4%, 92.7%)	7383/7792: 94.8% (94.2%, 95.4%)
% HIV+ and previously diagnosed with prior or current ART use			
Unadjusted	3935/4893: 80.4% (79.3%, 81.6%)	5982/6402: 93.4% (92.8%, 94.1%)	6204/6463: 96.0% (95.5%, 96.5%)
Adjusted[2]	4168/5195: 80.2% (79.1%, 81.4%)	6453/7130: 90.5% (89.8%, 91.2%)	6886/7383: 93.3% (92.7%, 93.9%)
% HIV+ and previously or currently on ART with HIV RNA<500 copies/ml			
Unadjusted	2578/3011: 85.6% (84.3%, 86.9%)	5107/5786: 88.3% (87.4%, 89.1%)	5334/5935: 89.9% (89.1%, 90.7%)
Adjusted[3]	3569/4168: 85.6% (84.4%, 86.9%)	5692/6453: 88.2% (87.4%, 89.1%)	6157/6886: 89.4% (88.6%, 90.2%)
% HIV+ with HIV RNA<500 copies/ml			
Unadjusted	2578/5062: 50.9% (49.5%, 52.4%)	5107/6483: 78.8% (77.7%, 79.8%)	5334/6330: 84.3% (83.3%, 85.2%)
Adjusted[4]	3569/8580: 41.6% (40.5%, 42.8%)	5692/7745: 73.5% (72.4%, 74.6%)	6157/7792: 79.0% (78.0%, 80.0%)

[1]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education, stable residence), prior health campaign andhome-based contact, and prior testing

[2]Assuming complete ascertainment of prior diagnosis and ART use for all HIV-positive (missing=fail)

[3]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education, stable residence), prior health campaign andhome-based contact, and prior testing, diagnosis, ART use, and suppression

[4]Adjusted for community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education, stable residence) prior health campaign and home-based contact, and prior testing, diagnosis, ART use, and suppression

eTable 4. Proportion of a closed cohort of HIV-positive adults diagnosed at or before study baseline who are dead, migrated out of the community, newly diagnosed, previously diagnosed but ART naïve, ART experienced but not virally suppressed, and virally suppressed at baseline and at one and two years of follow-up (N=7,108). Adjusted and unadjusted estimates for the full closed cohort and within subgroups defined by sex, age, and country. Numerator/Denominator: Percentage (95% Confidence Interval)

	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Baseline HIV+ adult residents (N=7108)			
Died	0/7108: 0.0% (0.0%, 0.0%)	59/7108: 0.8% (0.6%, 1%)	136/7108: 1.9% (1.6%, 2.2%)
Out-migrated	0/7108: 0.0% (0.0%, 0.0%)	589/7108: 8.3% (7.6%, 9.0%)	849/7108: 11.9% (11.2%, 12.7%)
Newly diagnosed	2080/7108: 29.3% (28.1%, 30.4%)	0/7108: 0.0% (0.0%, 0.0%)	0/7108: 0.0% (0.0%, 0.0%)
No prior or current ART	990/7108: 13.9% (13.1%, 14.8%)	591/7108: 8.3% (7.6%, 9.0%)	320/7108: 4.5% (4.0%, 5.0%)
HIV RNA (unadjusted)			
HIV RNA not measured	1063/7108: 15.0% (14.1%, 15.8%)	580/7108: 8.2% (7.5%, 8.8%)	712/7108: 10.0% (9.3%, 10.8%)
Measured HIV RNA ≥500 copies/ml	426/7108: 6.0% (5.4%, 6.6%)	607/7108: 8.5% (7.9%, 9.2%)	489/7108: 6.9% (6.3%, 7.5%)
Measured HIV RNA <500 copies/ml	2549/7108: 35.9% (34.7%, 37.0%)	4682/7108: 65.9% (64.7%, 67.0%)	4602/7108: 64.7% (63.6%, 65.9%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	575/7108: 8.1% (7.4%, 8.8%)	677/7108: 9.5% (8.8%, 10.3%)	585/7108: 8.2% (7.5%, 8.9%)
HIV RNA <500 c/ml	3463/7108: 48.7% (47.4%, 50.0%)	5192/7108: 73.0% (71.9%, 74.1%)	5218/7108: 73.4% (72.3%, 74.5%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

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	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Men (N=2405)			
Died	0/2405: 0.0% (0.0%, 0.0%)	32/2405: 1.3% (0.9%, 1.8%)	66/2405: 2.7% (2.1%, 3.4%)
Out-migrated	0/2405: 0.0% (0.0%, 0.0%)	165/2405: 6.9% (5.9%, 7.9%)	248/2405: 10.3% (9.1%, 11.5%)
Newly diagnosed	868/2405: 36.1% (34.2%, 38%)	0/2405: 0.0% (0.0%, 0.0%)	0/2405: 0.0% (0.0%, 0.0%)
No prior or current ART	272/2405: 11.3% (10.0%, 12.6%)	247/2405: 10.3% (9.0%, 11.5%)	146/2405: 6.1% (5.1%, 7.0%)
HIV RNA (unadjusted)			
HIV RNA not measured	370/2405: 15.4% (13.9%, 16.8%)	244/2405: 10.1% (8.9%, 11.4%)	302/2405: 12.6% (11.2%, 13.9%)
Measured HIV RNA ≥500 copies/ml	133/2405: 5.5% (4.6%, 6.4%)	217/2405: 9.0% (7.9%, 10.2%)	180/2405: 7.5% (6.4%, 8.5%)
Measured HIV RNA <500 copies/ml	762/2405: 31.7% (29.8%, 33.5%)	1500/2405: 62.4% (60.4%, 64.3%)	1463/2405: 60.8% (58.9%, 62.8%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	190/2405: 7.9% (6.7%, 9.1%)	249/2405: 10.3% (9.0%, 11.6%)	222/2405: 9.2% (8.0%, 10.4%)
HIV RNA <500 copies/ml	1075/2405: 44.7% (42.6%, 46.8%)	1712/2405: 71.2% (69.3%, 73.1%)	1723/2405: 71.7% (69.8%, 73.5%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (age,occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

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	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Women (N=4703)			
Died	0/4703: 0.0% (0.0%, 0.0%)	27/4703: 0.6% (0.4%, 0.8%)	70/4703: 1.5% (1.1%, 1.8%)
Out-migrated	0/4703: 0.0% (0.0%, 0.0%)	424/4703: 9.0% (8.2%, 9.8%)	601/4703: 12.8% (11.8%, 13.7%)
Newly diagnosed	1212/4703: 25.8% (24.5%, 27%)	0/4703: 0% (0.0%, 0.0%)	0/4703: 0.0% (0.0%, 0.0%)
No prior or current ART	718/4703: 15.3% (14.2%, 16.3%)	344/4703: 7.3% (6.6%, 8.1%)	174/4703: 3.7% (3.2%, 4.2%)
HIV RNA (unadjusted)			
HIV RNA not measured	693/4703: 14.7% (13.7%, 15.8%)	336/4703: 7.1% (6.4%, 7.9%)	410/4703: 8.7% (7.9%, 9.5%)
Measured HIV RNA ≥500 copies/ml	293/4703: 6.2% (5.5%, 6.9%)	390/4703: 8.3% (7.5%, 9.1%)	309/4703: 6.6% (5.9%, 7.3%)
Measured HIV RNA <500 copies/ml	1787/4703: 38.0% (36.6%, 39.4%)	3182/4703: 67.7% (66.3%, 69%)	3139/4703: 66.7% (65.4%, 68.1%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	388/4703: 8.3% (7.4%, 9.1%)	428/4703: 9.1% (8.2%, 10.0%)	367/4703: 7.8% (7.0%, 8.7%)
HIV RNA <500 copies/ml	2385/4703: 50.7% (49.2%, 52.2%)	3480/4703: 74% (72.7%, 75.3%)	3491/4703: 74.2% (72.9%, 75.5%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (age, occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

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	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Youth age 15-24 years (N=864)			
Died	0/864: 0.0% (0.0%, 0.0%)	6/864: 0.7% (0.1%, 1.2%)	13/864: 1.5% (0.7%, 2.3%)
Out-migrated	0/864: 0.0% (0.0%, 0.0%)	173/864: 20.0% (17.3%, 22.7%)	246/864: 28.5% (25.4%, 31.5%)
Newly diagnosed	392/864: 45.4% (42%, 48.8%)	0/864: 0.0% (0.0%, 0.0%)	0/864: 0.0% (0.0%, 0.0%)
No prior or current ART	168/864: 19.4% (16.8%, 22.1%)	106/864: 12.3% (10%, 14.5%)	47/864: 5.4% (3.9%, 7.0%)
HIV RNA (unadjusted)			
HIV RNA not measured	84/864: 9.7% (7.7%, 11.7%)	83/864: 9.6% (7.6%, 11.6%)	107/864: 12.4% (10.1%, 14.6%)
Measured HIV RNA ≥500 copies/ml	43/864: 5.0% (3.5%, 6.4%)	81/864: 9.4% (7.4%, 11.4%)	69/864: 8.0% (6.2%, 9.8%)
Measured HIV RNA <500 copies/ml	177/864: 20.5% (17.8%, 23.2%)	415/864: 48.0% (44.6%, 51.4%)	382/864: 44.2% (40.9%, 47.6%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	59/864: 6.8% (4.9%, 8.6%)	95/864: 10.9% (8.7%, 13.2%)	85/864: 9.9% (7.7%, 12.1%)
HIV RNA <500 copies/ml	245/864: 28.4% (25.3%, 31.5%)	484/864: 56.1% (52.6%, 59.5%)	473/864: 54.7% (51.2%, 58.2%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

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	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Older age >24 years (N=6244)			
Died	0/6244: 0.0% (0.0%, 0.0%)	53/6244: 0.8% (0.6%, 1.1%)	123/6244: 2.0% (1.6%, 2.3%)
Out-migrated	0/6244: 0.0% (0.0%, 0.0%)	416/6244: 6.7% (6%, 7.3%)	603/6244: 9.7% (8.9%, 10.4%)
Newly diagnosed	1688/6244: 27.0% (25.9%, 28.2%)	0/6244: 0.0% (0.0%, 0.0%)	0/6244: 0.0% (0.0%, 0.0%)
No prior or current ART	822/6244: 13.2% (12.3%, 14%)	485/6244: 7.8% (7.1%, 8.4%)	273/6244: 4.4% (3.9%, 4.9%)
HIV RNA (unadjusted)			
HIV RNA not measured	979/6244: 15.7% (14.7%, 16.6%)	497/6244: 8.0% (7.3%, 8.7%)	605/6244: 9.7% (8.9%, 10.5%)
Measured HIV RNA ≥500 copies/ml	383/6244: 6.1% (5.5%, 6.7%)	526/6244: 8.4% (7.7%, 9.1%)	420/6244: 6.7% (6.1%, 7.4%)
Measured HIV RNA <500 copies/ml	2372/6244: 38.0% (36.7%, 39.3%)	4267/6244: 68.3% (67.1%, 69.5%)	4220/6244: 67.6% (66.4%, 68.8%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	523/6244: 8.4% (7.6%, 9.1%)	585/6244: 9.4% (8.6%, 10.1%)	497/6244: 8.0% (7.2%, 8.7%)
HIV RNA <500 c/ml	3211/6244: 51.4% (50.1%, 52.8%)	4705/6244: 75.4% (74.2%, 76.5%)	4748/6244: 76.0% (74.9%, 77.2%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

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	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Uganda (N=2247)			
Died	0/2247: 0.0% (0.0%, 0.0%)	20/2247: 0.9% (0.5%, 1.3%)	42/2247: 1.9% (1.3%, 2.4%)
Out-migrated	0/2247: 0.0% (0.0%, 0.0%)	257/2247: 11.4% (10.1%, 12.8%)	326/2247: 14.5% (13%, 16%)
Newly diagnosed	859/2247: 38.2% (36.1%, 40.3%)	0/2247: 0.0% (0.0%, 0.0%)	0/2247: 0.0% (0.0%, 0.0%)
No prior or current ART	268/2247: 11.9% (10.6%, 13.3%)	98/2247: 4.4% (3.5%, 5.2%)	51/2247: 2.3% (1.6%, 2.9%)
HIV RNA (unadjusted)			
HIV RNA not measured	385/2247: 17.1% (15.5%, 18.8%)	252/2247: 11.2% (9.9%, 12.6%)	387/2247: 17.2% (15.5%, 18.9%)
Measured HIV RNA ≥500 copies/ml	92/2247: 4.1% (3.2%, 4.9%)	169/2247: 7.5% (6.4%, 8.6%)	129/2247: 5.7% (4.7%, 6.7%)
Measured HIV RNA <500 copies/ml	643/2247: 28.6% (26.6%, 30.6%)	1451/2247: 64.6% (62.5%, 66.6%)	1312/2247: 58.4% (56.3%, 60.5%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	135/2247: 6.0% (5.0%, 7.0%)	193/2247: 8.6% (7.3%, 9.9%)	179/2247: 8.0% (6.7%, 9.3%)
HIV RNA <500 copies/ml	985/2247: 43.8% (41.7%, 46%)	1679/2247: 74.7% (72.8%, 76.6%)	1649/2247: 73.4% (71.4%, 75.4%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

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	Baseline	**Follow-up Year 1**	**Follow-up Year 2**
Kenya (N=4861)			
Died	0/4861: 0.0% (0.0%, 0.0%)	39/4861: 0.8% (0.6%, 1.1%)	94/4861: 1.9% (1.5%, 2.3%)
Out-migrated	0/4861: 0.0% (0.0%, 0.0%)	332/4861: 6.8% (6.1%, 7.6%)	523/4861: 10.8% (9.8%, 11.7%)
Newly diagnosed	1221/4861: 25.1% (23.8%, 26.4%)	0/4861: 0.0% (0.0%, 0.0%)	0/4861: 0.0% (0.0%, 0.0%)
No prior or current ART	722/4861: 14.9% (13.8%, 15.9%)	493/4861: 10.1% (9.3%, 11%)	269/4861: 5.5% (4.9%, 6.2%)
HIV RNA (unadjusted)			
HIV RNA not measured	678/4861: 13.9% (12.9%, 15%)	328/4861: 6.7% (6.0%, 7.5%)	325/4861: 6.7% (6.0%, 7.4%)
Measured HIV RNA ≥500 copies/ml	334/4861: 6.9% (6.2%, 7.6%)	438/4861: 9.0% (8.2%, 9.8%)	360/4861: 7.4% (6.6%, 8.2%)
Measured HIV RNA <500 copies/ml	1906/4861: 39.2% (37.8%, 40.6%)	3231/4861: 66.5% (65.1%, 67.9%)	3290/4861: 67.7% (66.3%, 69.1%)
HIV RNA (adjusted[1])			
HIV RNA ≥500 copies/ml	438/4861: 9.0% (8.1%, 9.9%)	484/4861: 9.9% (9.0%, 10.9%)	407/4861: 8.4% (7.5%, 9.2%)
HIV RNA <500 copies/ml	2480/4861: 51.0% (49.5%, 52.6%)	3513/4861: 72.3% (70.9%, 73.6%)	3568/4861: 73.4% (72.1%, 74.7%)

[1]Numerators are estimated number of baseline HIV-positive individuals suppressed or not suppressed, adjusted for differences in community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), baseline prior testing and diagnosis, prior health campaign andhome-based contact, prior ART use, and prior suppression between individuals with measured versus missing HIV RNA level.

eTable 5. Probability of ever testing for HIV (in a closed cohort of individuals without a prior HIV diagnosis at study baseline, N=72,746) and ever initiating ART (in a closed cohort of HIV-positive adults diagnosed at or before study baseline, N=7,108) one and two years after study baseline. Longitudinal analysis, follow-up censored at death or migration out of the community.

		Follow-up Year 1		**Follow-up Year 2**	
Probability of testing for HIV at least once at close of annual testing					
	N	No. tested ≥1 time/ No. Alive and uncensored (%)	Estimated probability of ever testing[1] (95% CI)	No. tested ≥1 time/ No. Alive and uncensored (%)	Estimated probability of ever testing[1] (95% CI)
Without HIV diagnosis prior to baseline testing	72746	61194/63382 (96.5%)	95.5% (95.3%, 95.7%)	58245/59472 (97.9%)	96.8% (96.6%, 97.0%)
Probability of having ever initiated ART by time of annual testing					
	N	No. with prior ART initiation/ No. Alive and uncensored (%)	Estimated probability of ever initiating ART[2] (95% CI)	No. with prior ART initiation/ No. Alive and uncensored (%)	Estimated probability of ever initiating ART[2] (95% CI)
Diagnosed with HIV at or before baseline testing	7108	5869/6460 (90.9%)	90.3% (89.5%, 91.1%)	5803/6123 (94.8%)	93.8% (93.2%, 94.4%)

[1]Estimated probability of testing at least once by close of that year's annual testing, adjusted for potentially informative censoring by community and baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education).

[2]Estimated probability of having ever initiated ART by close of that year's annual testing, adjusted for potentially informative censoring by community, baseline demographics (age, sex, occupation, ≥1mo./past year away from community, wealth, marital status, education), prior health campaign and home-based contact, and prior HIV RNA testing history.

eTable 6. Association between baseline demographic variables and failure to test for HIV at least once by follow-up year 2 in a closed cohort of adult stable residents without a record of prior HIV diagnosis at baseline (N=72,746). Longitudinal analysis, follow-up censored at death or migration out of the community.

	No. never tested/Total No. residents (%)[1]	Unadjusted Risk Difference (95% CI)	P value	Adjusted Risk Difference[2] (95% CI)	P value
Sex					
Male	809/26842 (3.0%)	1.7% (1.5%, 2.0%)	<0.001	1.7% (1.3%, 2.1%)	<0.001
Female	418/32630 (1.3%)	Ref	Ref	Ref	Ref
Age in Years					
15-24	311/19527 (1.6%)	-0.4% (-0.6%, -0.1%)	0.02	-0.5% (-1.2%, 0.2%)	0.18
25-34	331/13257 (2.5%)	0.5% (0.0%, 1.1%)	0.04	1.7% (0.9%, 2.4%)	<0.001
35-44	256/9821 (2.6%)	0.7% (-0.1%, 1.4%)	0.07	1.5% (0.6%, 2.4%)	<0.001
>44	329/16867 (2.0%)	Ref	Ref	Ref	Ref
Marital Status					
Married, Widowed, Divorced, or Separated	910/44503 (2.0%)	Ref	Ref	Ref	Ref
Never married	317/14969 (2.1%)	0.1% (-0.2%, 0.3%)	0.57	2.0% (0.7%, 3.2%)	0.002

[1]Residentswithout an HIV diagnosis prior to baseline and not dead or migrated out of the community by follow-up year 2, N=59,472. Differs from 72,746 due to 13,274 individuals who died or migrated out of the community by year 2.

[2]Adjusted for community and baseline demographics (age, sex, occupation, mobility, wealth, marital status, education).

Education					
< Primary	130/8804 (1.5%)	Ref	Ref	Ref	Ref
Primary	717/39525 (1.8%)	0.3% (0.1%, 0.6%)	0.003	-1.7% (-2.8%, -0.7%)	0.001
≥ Secondary	380/11143 (3.4%)	1.9% (1.0%, 2.9%)	<0.001	0.2% (-0.9%, 1.4%)	0.69

eTable 6. Continued. Association between baseline demographic variables and failure to test for HIV at least once by follow-up year 2 in a closed cohort of adult stable residents without a record of prior HIV diagnosis at baseline (N=72,746). Longitudinal analysis, follow-up censored at death or migration out of the community.

	No. never tested/Total No. residents (%)[1]	**Unadjusted Risk Difference (95% CI)**	**P value**	**Adjusted Risk Difference[2] (95% CI)**	**P value**
Occupation					
Formal Sector[3]	262/12788 (2.0%)	Ref	Ref	Ref	Ref
High Risk Informal Sector[4]	103/2298 (4.5%)	2.4% (0.0%, 4.8%)	0.05	0.8% (-0.3%, 1.9%)	0.17
Low Risk Informal Sector[5]	668/39163 (1.7%)	-0.3% (-0.6%, -0.1%)	0.003	-1.1% (-1.9%, -0.4%)	0.003
Other	120/2480 (4.8%)	2.8% (0.5%, 5.0%)	0.01	2.8% (1.4%, 4.2%)	<0.001
No Job or Disabled	74/2743 (2.7%)	0.6% (-1.0%, 2.2%)	0.43	0.9% (-0.5%, 2.4%)	0.22
Household Wealth Index[6]					

[1]Residentswithout an HIV diagnosis prior to baseline not dead or migrated out of the community by follow-up year 2, N=59,472. Differs from 72,746 due to 13,274 individuals who died or migrated out of the community by year 2.
[2]Adjusted for community and baseline demographics (age, sex, occupation, mobility, wealth, marital status, education).
[3] Formal Sector:teacher, student, government worker, military worker, health worker, factory worker
[4] Informal Sector High Risk: fishmonger, fisherman, bar owner, bar worker, transport, tourism
[5] Informal Sector Low Risk: farmer, shopkeeper, market vendor, hotel worker, housewife, household worker, construction worker, mining
[6] Quintiles, based on principle components analysis of household wealth survey

1st (least wealth)	216/10047 (2.1%)	0.3% (-0.4%, 1.0%)	0.39	0.5% (-0.2%, 1.1%)	0.17
2nd	203/11843 (1.7%)	-0.1% (-0.7%, 0.4%)	0.63	0.0% (-0.6%, 0.7%)	0.89
3rd	242/13124 (1.8%)	-0.0% (-0.5%, 0.5%)	0.97	-0.2% (-0.8%, 0.4%)	0.56
4th	400/15508 (2.6%)	0.7% (0.2%, 1.3%)	0.01	0.7% (0.1%, 1.3%)	0.02
5th (most wealth)	166/8950 (1.9%)	Ref	Ref	Ref	Ref
Mobility					
< 1 Month/past year away from community	1044/54155 (1.9%)	Ref	Ref	Ref	Ref
≥1 Month/past year away from community	183/5317 (3.4%)	1.5% (1.1%, 1.9%)	<0.001	3.2% (2.5%, 4.0%)	<0.001

eTable 7. Association between baseline demographic variables and never using ART by follow up year 2 in a closed cohort of HIV-positive adults diagnosed at or before study baseline (N=7,108). Longitudinal analysis,

	No. never treated/Total No. residents (%)[1]	Unadjusted Risk Difference(95% CI)	P value	Adjusted Risk Difference[2] (95% CI)	P value
Sex					
Male	146/2091 (7.0%)	2.7% (1.4%, 3.9%)	<0.001	3.5% (1.9%, 5.2%)	<0.001
Female	174/4032 (4.3%)	Ref	Ref	Ref	Ref
Age in Years					
15-24	47/605 (7.8%)	4.6% (0.8%, 8.4%)	0.02	6.5% (2.8%, 10.3%)	<0.001
25-34	145/1970 (7.4%)	4.2% (2.3%, 6.1%)	<0.001	4.8% (3.0%, 6.5%)	<0.001
35-44	74/1851 (4.0%)	0.8% (-0.9%, 2.5%)	0.34	0.6% (-0.9%, 2.1%)	0.45
>44	54/1697 (3.2%)	Ref	Ref	Ref	Ref
Marital Status					
Married, Widowed, Divorced, or Separated	289/5813 (5.0%)	Ref	Ref	Ref	Ref
Never married	31/310 (10.0%)	5.0% (2.4%, 7.7%)	<0.001	3.3% (-1.8%, 8.5%)	0.21
Education					
< Primary	22/571 (3.9%)	Ref	Ref	Ref	Ref
Primary	257/4792 (5.4%)	1.5% (0.4%, 2.6%)	0.006	1.9% (-0.5%, 4.3%)	0.11
≥ Secondary	41/760 (5.4%)	1.5% (-5.4%, 8.5%)	0.66	1.6% (-1.4%, 4.7%)	0.29

[1]Among baseline HIV+ residents not dead or migrated out of the community by follow-up year 2, N=6123. Differs from 7,108 due to 985 baseline HIV-positive individuals who died or migrated out of the community by year 2.

[2]Baseline adjustment variables: community, age, sex, occupation, mobility, wealth, marital status, education. Time-varying adjustment variables (used in addition to baseline variables to adjust for censoring by death/out-migration): prior health campaign and home-based contact, prior ART initiation, prior HIV RNA testing history.

eTable 7. Continued. Association between baseline demographic variables and never using ART by follow up year 2 in a closed cohort of HIV-positive adults diagnosed at or before study baseline (N=7,108). Longitudinal analysis, follow-up censored at death or migration out of the community.

	No. never treated/Total No. residents (%)[78]	**Unadjusted Risk Difference (95% CI)**	**P value**	**Adjusted Risk Difference[79] (95% CI)**	**P value**
Occupation					
Formal Sector[80]	18/286 (6.3%)	Ref	Ref	Ref	Ref
High Risk Informal Sector[81]	48/604 (7.9%)	1.7%(-8.0%, 11.3%)	0.74	0.7% (-3.8%, 5.1%)	0.77
Low Risk Informal Sector[82]	216/4704 (4.6%)	-1.7%(-2.7%, -0.7%)	<0.001	-2.1% (-5.8%, 1.7%)	0.28
Other	21/256 (8.2%)	1.9%(-10.2%, 14.0%)	0.76	0.3% (-5.6%, 6.2%)	0.92
No Job or Disabled	17/273 (6.2%)	-0.1% (-11.0%, 10.9%)	0.99	1.4% (-3.9%, 6.7%)	0.60
Household Wealth Index[83]					
1st (least wealth)	51/990 (5.2%)	1.5% (-1.5%, 4.5%)	0.32	0.9% (-1.0%, 2.8%)	0.36
2nd	51/1110 (4.6%)	0.9% (-1.7%, 3.6%)	0.48	0.9% (-1.0%, 2.8%)	0.34
3rd	70/1364 (5.1%)	1.5% (-1.1%, 4.0%)	0.26	1.6% (-0.3%, 3.5%)	0.10
4th	112/1672 (6.7%)	3.1% (0.6%, 5.5%)	0.01	3.9% (2.0%, 5.8%)	<0.001
5th (most wealth)	36/987 (3.6%)	Ref	Ref	Ref	Ref
Mobility					

[78]Among baseline HIV+ residents not dead or migrated out of the community by follow-up year 2, N=6123.Differs from 7,108 due to 985 baseline HIV-positive individuals who died or migrated out of the community by year 2.

[79]Baseline adjustment variables: community, age, sex, occupation, mobility, wealth, marital status, education. Time-varying adjustment variables (used in addition to baseline variables to adjust for censoring by death/out-migration): prior health campaign and home-based contact, prior ART initiation, prior HIV RNA testing history.

[80] Formal Sector:teacher, student, government worker, military worker, health worker, factory worker

[81]Informal Sector High Risk: fishmonger, fisherman, bar owner, bar worker, transport, tourism

[82]Informal Sector Low Risk: farmer, shopkeeper, market vendor, hotel worker, housewife, household worker, construction worker, mining

[83]Quintiles, based on principle components analysis of household wealth survey

< 1 Month/past year away from community	295/5663 (5.2%)	Ref	Ref	Ref	Ref
≥1 Month/past year away from community	25/460 (5.4%)	0.2% (-1.8%, 2.2%)	0.83	0.3% (-2.1%, 2.7%); 0.79	0.79

Chapter 6

Discussion

The therapeutic and preventive benefits of ART currently hold the promise to control the HIV epidemic. The benefits of treatment as prevention lead to the latest WHO guidelines recommending a test and treat strategy, where all people with HIV are eligible for ART [1]. This highlights the need and urgency to identify all PLWH early, link them to care, and initiate them on ART, with a goal of sustained viral suppression [2]. The progress towards achieving this has been evaluated using the care cascade, which unfortunately demonstrated massive drop-offs along the cascade in almost all care settings [3]. For test and treat to achieve its goal, each step of the cascade must be optimized. The first large trial evaluating the test and treat approach failed to show an impact on HIV incidence, a finding attributed to poor linkage to care among study participants [4]. To address this challenge, the losses from the cascade in the test and treat era need to be quantified, the steps suffering the largest dropouts identified, the reasons for these dropouts analysed, and interventions designed to address the challenges identified.

In this thesis we conducted a qualitative analysis to explore the barriers to care engagement within a test and treat environment and discovered an array of barriers affecting different steps along the cascade. The barriers identified were behavioral (treatment fatigue and forgetting to take medications, stigma), structural (distance to clinics, poverty), health system

(poor health provider attitudes, patient-unfriendly clinic set-up), social (work interference, lack of social support), and drug related (drug side effects, pill burden). Stigma remained a major barrier to care engagement across multiple steps of the care cascade. With such a broad spectrum of barriers, the most effective approach was a combination intervention strategy (CIS) with multiple interventions targeting different barriers and different phases on the cascade simultaneously to improve outcomes among PLWH. We therefore designed and applied a streamlined patient centered multi-component strategy along the care cascade to improve patient outcomes with adaptations to suit the respective steps of the care cascade.

Our patient centered approach made a difference. After two years, our intervention had exceeded the UNAIDS 90-90-90 targets of testing, ART initiation and viral suppression. The study achieved a community-wide viral suppression of 80.2%, exceeding the 73% target set by UNAIDS [5]. Viral suppression rates were however not uniform across the population, with lower viral suppression among the youth compared to adults and slightly lower suppression among males as compared to females. Innovative interventions need to be developed to achieve better outcomes in these population groups.

Because linkage to care is known to be an important bottleneck, we focused several of our patient-friendly intervention components on linkage to care,

including building rapport with patients at diagnosis, sharing clinic contact details, phone call reminders a day prior to the linkage appointment date and physical tracing if the appointment was missed. We achieved 73% linkage by one year among those who had never engaged in care, which was markedly higher than the 30% linkage rate at six months observed in the TasP test and treat trial [4]. Half of the participants receiving the intervention linked to care within 7 days of testing. This is of significance as early engagement and ART initiation portends better outcomes for patients and the community [2]. Rapid linkage and ART initiation has been highlighted as an important goal, if the therapeutic and preventive benefits of ART are to be leveraged upon for HIV epidemic control [6].

Even though we achieved high linkage rates, not everyone linked to care. Our randomized controlled trial targeted the "difficult to engage" patients using a patient centered intervention that explored individual barriers to care engagement and involved patients in developing solutions on how to overcome their barriers to engage in care via a clinical officer led phone call. Despite the overall low linkage rate (41%) observed in this trial, twice as many individual who received the intervention linked to care as compared to those who did not [7]. These results demonstrate the value of individualized and personalized approaches in complement to a public health approach, with the goal of reaching all people living with HIV, including those that are difficult to engage in care.

Based on the literature, we further anticipated challenges with retention and thus focused on delivering an intervention that would optimize retention in care. Our intervention achieved 95.5 % retention at 12 months among all our participants and 89.3% among those newly linked [8], a markedly higher retention rate compared to the estimates of 63.3% and 66.6% in recent population-wide data reviews [9,10]. Even though our period of evaluation was short, past studies have shown that the highest attrition occurs within the first year of care with stabilization thereafter [11].

Strengths and Limitations

The studies were population-wide analyses and thus respond to progressive thinking in care cascade research with an aim of improving outcomes at the population level. They also reflect the contributions of a patient-centered intervention within the context of the UNAIDS 90-90-90 targets framework that aims for population-wide outcomes. Furthermore, the intervention presented in this thesis were comprehensive, focusing on the entire cascade and thus able to evaluate the full impact (i.e. from HIV testing to viral suppression) of the intervention and compare the outcomes achieved to the UNAIDS 90-90-90 targets.

The thesis used an implementation research approach, evaluating a patient-centered intervention implemented of in real life rural sub-Saharan Africa

setting. The findings would thus be largely generalizable to similar settings. Furthermore, I used a mixed methods approach, a methodology of research that employs the integration of quantitative and qualitative data within a single investigation or sustained program of inquiry [12]. I employed qualitative, observational and randomized controlled trial methods, generating a broad array of data that compliment each other and allows both the quantification of effects and exploration of the reasons underlying the observed results.

The studies included were not without limitations. The analyses were limited to the intervention arm of the trial and therefore largely consisted of descriptive analysis. However, in assessing the impact of our intervention, we compared our outcomes to the UNAIDS 90-90-90 targets as the "yard stick" of desired outcomes, as well as the baseline parameters measured in the study population. Secondly, given the comprehensive, multi-component design of our intervention, we were unable to identify which component of the patient centered streamlined care model had the greatest impact. Finally, there may be a limit to the generalizability of our findings based on cultural or contextual differences between communities.

Next Steps

While our patient centered streamlined care intervention improved outcomes and, narrowed gaps, drop-offs along the cascade continued highlighting the need for further innovative approaches to seal the cascade leaks and assist in efforts towards control of the HIV epidemic.

To guide our thinking and development of novel intervention, we propose a further revision of the care cascade. As viral suppression remains the ultimate goal of HIV treatment, viral suppression should be explicitly factored into the cascade. Currently, the care cascade described the process from testing to ART initiation, early and life-long retention on ART [11]. We propose to include viral suppression as the endpoint of the HIV care cascade, with an intermediate phase marked by initial viral suppression within 6-12 months of treatment, referred to as early treatment success (Figure 1). The final step in the cascadeproposed is the life-long viral suppression, this we refer to as life-longtreatment success on Figure 1.

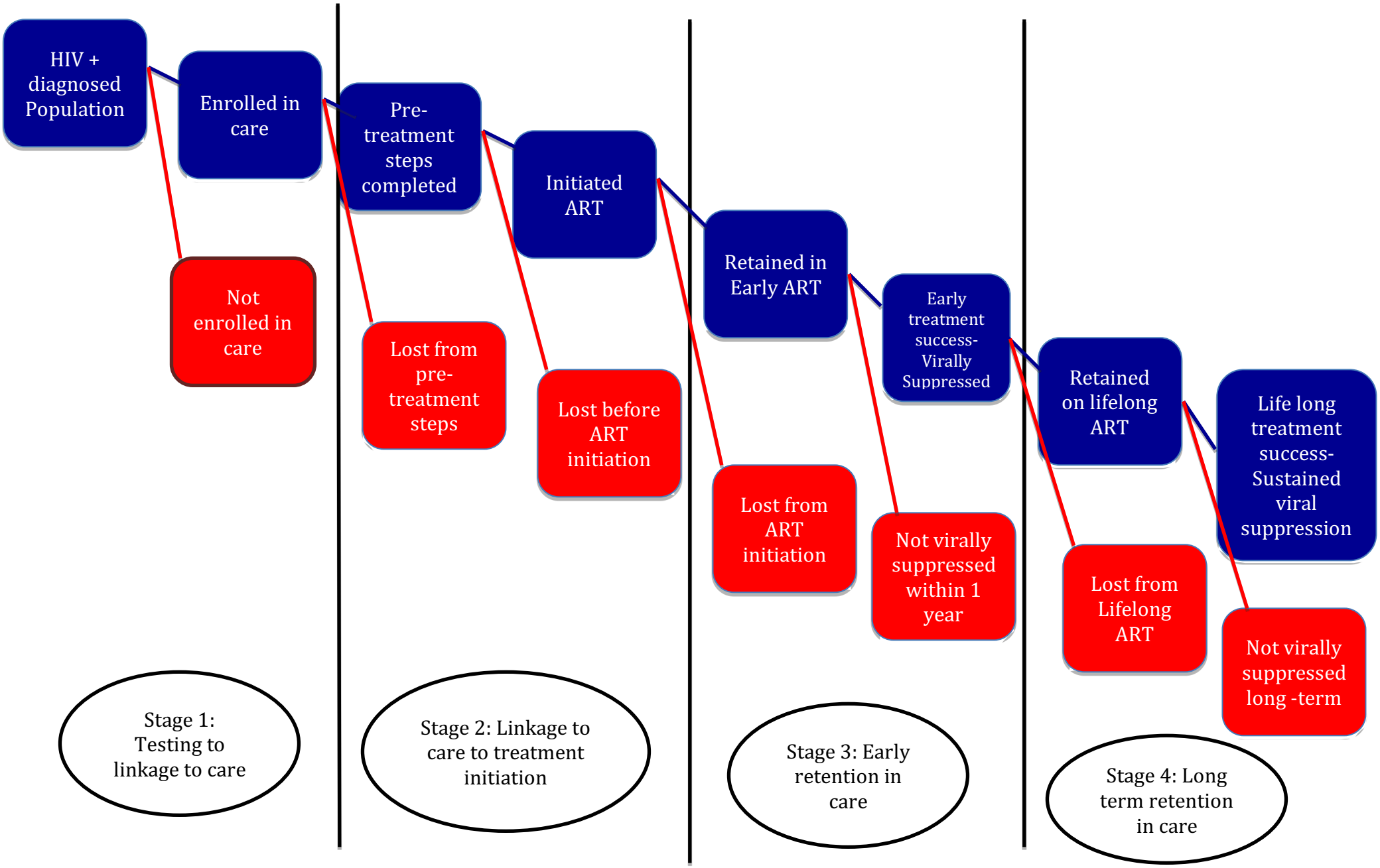

Figure 1: Proposed new HIV care cascade incorporating patient viral suppression outcomes

Based on the findings represented in this thesis and the experiences I gained in the field, I would like to suggest several themes that should be addressed when designing novel interventions to further improve outcomes along the HIV care cascade. First, a population–wide approach that detects new infection early and engages all PLWH in care is likely to make the greatest impact in addressing the HIV epidemic. Cascade care research needs to shift focus and target interventions to entire populations as opposed to sub-populations such as those coming for testing at a health clinic. Second, populations are, have been, and will continue to be mobile. The health system needs to adapt to patient mobility. Health information systems must change to accommodate mobile patients and enable health agencies to account for patients who transfer from one health facility to another. Greater efforts should be made to ensure that health data is linked and shared between health facilities to ensure continued high quality of patient care as well as accountability for the patients in terms of successful referrals by health agencies. Simple approaches, such as, a transfer form and a follow–up phone call by health care providers to the recipient health facility soon after referral are a good starting point for rural settings in sub-Saharan Africa. Future research should address innovative interventions, including e-Health approaches aimed at improving outcomes along the HIV care cascade. Third, stigma continues to be a major barrier to care engagement along the entire cascade of HIV care in rural sub-Saharan Africa. If interventions are to work, cascade care researchers cannot ignore stigma. In designing interventions in

these settings, it will be prudent to combine these with stigma reduction strategies for better outcomes to be observed. Fourth, HIV care cascade research needs to standardize terms such as linkage to care, retention in care, ART adherence and viral suppression. Lack of uniformity in applying these terms portends different outcomes and thus makes meaningful comparison difficult across different populations. Finally, the biggest challenge in improving the HIV care cascade is "the remaining 10 %"or "difficult to engage" groups at the different steps along the cascade. While the public health approach has achieved major milestones in dealing with the HIV menace, these groups need special emphasis. We must acknowledge that there is a proportion of PLWH for whom the public health approach has not worked. These individuals need a different approach that may be individualized or distinctly different from the rest. Their unique circumstances and barriers need to be explored and interventions defined to address these hindrances to ensure they are engaged in care. A balance between the public health approach and individualized approach must be struck so that the "difficult to engage" patients are not left behind in the efforts to control HIV.

Progress has been made in dealing with HIV. Within the context of no vaccine or a functional cure for the disease, innovative interventions that will ensure all PLWH are engaged in care and virally suppressed will mark the next huge

leap in HIV control. Much work and effort needs to be directed in sealing the leakages in the cascade to achieve this desired control of the epidemic.

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Curriculum Vitae

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Educational Background

PhD Student, University of Antwerp, Belgium.

2012- 2013 University of California, Berkeley (UCB), Masters of Public Health in Epidemiology

2008- 2002 Moi University, School of Medicine, Bachelor of Medicine and Bachelor of Surgery (MB.Ch.B)

Teaching Experience

2017- current
Teaching Epidemiology at the School of Public Health, Jaramogi Oginga Odinga University of Science and Technology to second year Bachelor of Science(Public Health) Class

Peer review

2014-current Reviewer in the following Journals:

World Journal of Paediatrics,
World Journal of Virology
World Journal of Gastroenterology
PLoS ONE

Conferences/Abstracts/Presentations

June 2012 PACE Conference, University of Nairobi, Kenya
Ayieko J., Lisa D., Jeremy P et al. Cost per call analysis of Uliza! A health care provider hotline service.- Oral presentation.

May 2012 Future Virology Conference, Mombasa, Kenya
Ayieko J., Lisa D., Jeremy P et al. Cost per call analysis of Uliza! A health care provider hotline service.-Poster presentation.

Feb 2016 CROI conference, Boston, USA

Ayieko J, Gabriel Chamie, Craig Cohen, Tamara Clark, Edwin Charlebois, Maya Petersen, Moses Kamya, Diane Havlir, Theodore Ruel and the SEARCH team
Hybrid HIV testing achieves high coverage of rural East African children.-Poster presentation

July 2016 AIDS 2016-IAS conference, Durban, South Africa
Ayieko J , Annelies Van Rie, Asiphas Owaraganise, Florence Mwangwa,Vivek Jain,Lillian Brown, Theodore Ruel, Tamara Clark,Douglas Black, Alexia Exarchos, Dalsone Kwarisiima, Elizabeth A Bukusi, Craig R Cohen,Moses Kamya, Elvin Geng, Maya Petersen, Diane Havlir, Edwin Charlebois and the SEARCH team, A Novel Strategy for Accelerated Linkage to Care Following Community-Wide HIV Testing.-Poster presentation

Feb 2017 CROI conference, Seattle, Washington, USA - Poster presentation

July 2017 AIDS 2017 IAS Conference Paris, France - Oral abstract presentation

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July 2018 AIDS 2018 – Amsterdam, Netherlands

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