Effect of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing on linkage to HIV care in south-western Uganda

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Abstract

Background: Home-based HIV counselling and testing (HBHCT) is highly acceptable and may be an effective strategy for HIV prevention and population-based test-and-treat programmes in sub-Saharan Africa (SSA). However, few data are available on linkage to care or on the effectiveness of strategies to increase linkage to care among HIV-positive persons identified through HBHCT in SSA. The aims of this PhD were to (i) systematically review the literature on linkage to care among HIV-positive adults diagnosed through HBHCT in SSA; and (ii) to conduct a cluster-randomised controlled trial to measure the effectiveness of a counselling intervention after HIV diagnosis through HBHCT in increasing linkage to care in rural Masaka district, Uganda.

Methods: (i) Five databases (Medline, Embase, Global Health, Web of Science, and Africa-Wide information) were systematically searched for studies published between 1st January 2000 and 19th August 2016. Authors of studies for which some required information was missing were requested to provide additional data. (ii) For the trial, 28 rural communities were randomly allocated (1:1) to the intervention (HBHCT, referral, and brief home-based counselling sessions one and two months after HBHCT) or control group (HBHCT and referral only). HIV-positive adults (≥18 years) not yet in care were enrolled. Primary outcomes were linkage (registration with an HIV clinic) at 6 months after HBHCT, and time to linkage. Analyses were by intention-to-treat using random effects logistic regression and Cox regression with shared frailty.

Results: (i) 19 eligible studies were identified; one had all the required data. Additional data were obtained for 13 studies; thus, 14 studies were included in the review. Linkage to care was generally lower (<33%) if HBHCT was followed by referral only, and

higher (>80%) if some strategy was used to facilitate uptake of referral. Only one study was a randomised trial and most were susceptible to outcome ascertainment bias. (ii) In the trial, 551 individuals tested HIV-positive; 205 (37.2%) were already in care and thus ineligible. 302 (87.3% of those eligible) were enrolled (intervention, n=149). Retention was similar across trial arms (92% overall). Overall linkage to care was 42.1%. Counselling was associated with a 2.18-fold [95% confidence interval (CI)=1.26-3.78] increase in the odds of linkage. There was no evidence of a difference between arms in the rate of linkage in the first two months, but subsequently the rate of linkage was higher in the intervention arm (hazard ratio=4.87, 95% CI=1.79-13.27).

Conclusion: Counselling substantially increases linkage to care among HIV-positive adults identified through HBHCT and can increase antiretroviral therapy coverage in SSA.

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Table of Contents

List of figures

Chapter 2: General methods

Chapter 3 (manuscript 1): Linkage to HIV care after home-based HIV counselling and testing in sub-Saharan Africa: A systematic review

List of tables

List of abbreviations and acronyms

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
CAB	Community Advisory Board
CD4	CD4 cell count
CTX	Cotrimoxazole
CTXp	Cotrimoxazole prophylaxis
DFID	UK Department for International Development
EDCTP	European and Developing Countries Clinical Trials Partnership
HBHCT	Home-based HIV counselling and testing
HCT	HIV counselling and testing
HIV	Human immunodeficiency virus
IAVI	International AIDS Vaccine Initiative
k	Coeffient of variation
MoH	Ministry of Health
MRC	Medical Research Council
PITC	Provider initiated testing and counselling
PNFP	Private not-for-profit
POC	Point of care
REC	Research ethics committee
SMS	Short message service
SSA	sub-Saharan Africa
TASO	The AIDS Support Organisation
UNAIDS	Joint United Nations Programme on HIV/AIDS

UNCST	Uganda National Council for Science and Technology
UVRI	Uganda Virus Research Institute
VCT	Voluntary counselling and testing
VMMC	Voluntary medical male circumcision
WHO	World Health Organisation

Chapter 1: Background to the study

1.1 Introduction

Access to anti-retroviral therapy (ART) in sub-Saharan Africa (SSA) has expanded considerably but AIDS-related mortality remains high [1]. This is mostly due to the late presentation of patients for treatment. Most HIV-positive persons in the region initiate ART at CD4 counts <200 cells/mm [2], the ART eligibility threshold in earlier treatment guidelines [3]. The World Health Organisation (WHO) currently recommends ART initiation for all adults living with HIV at any CD4 count [4]. This recommendation is based on evidence showing that earlier initiation of ART reduces HIV-related mortality and morbidity [5-9] and sexual transmission of HIV [10]. Also, a growing body of evidence suggests that earlier initiation of ART may reduce the development of non-AIDS defining conditions such as cardiovascular disease, kidney disease, liver disease, and cancer [11, 12].

Early ART initiation is dependent on early HIV diagnosis through HIV counselling and testing (HCT) and prompt linkage to care [13]. HCT is essential in expanding HIV prevention and treatment services [14] but its uptake in SSA remains low [15]. For instance, the proportion of HIV-positive adults who are aware of their HIV status is estimated to be only 60% [16]. In order to expand access to HIV testing in generalised epidemic settings, WHO recommends community-based HCT with linkage to prevention, care and treatment services, in addition to facility-based HCT [4].

1.2 HCT models

HCT approaches may be categorised as facility- and community-based strategies [17, 18]. The former can be client- or provider-initiated [14, 17]. The client-initiated approach was

the primary HCT model in SSA before ART became widely available [14, 15]. This model requires availability of facilities, public awareness of that availability, and an individual's decision to actively seek HCT [14]. Its uptake depends on an individual's perception of his/her risk of HIV infection, availability of transport, service quality [14], and level of stigma [14, 19-22]. Increased ART availability led to the adoption of provider-initiated HCT in many SSA countries [23-25], in which HCT is routinely recommended by health workers to anybody attending health facilities [14, 23, 26, 27]. Provider-initiated HCT can identify many new HIV-positive individuals [26-29]. However, it is limited to people attending health facilities [26], may be associated with coercion [23, 24], and may not be a priority to health-care staff in busy clinics [26].

In the community-based approach, services are delivered through mobile, workplace-, school-, and home-based models [14]. Community-based HCT may also be delivered as part of multi-disease campaigns (campaign HCT) [30]. Mobile HCT achieves higher testing uptake compared to facility-based HCT [31], reaches many individuals who are unaware of their HIV status [32], facilitates access for remote populations [31, 33], and is cost-effective for expanding HCT coverage and identifying previously undiagnosed HIV-positive persons compared to facility-based HCT [34]. The disadvantages of mobile HCT include high workload [14], high cost [14], and insufficient linkage to care [30, 35]. Workplace-based HCT provides employees with confidential voluntary HCT at work [17, 36]. It can increase HIV testing [37], especially among men [18], and those who are young, single, and do manual work [37]. School-based testing targets sexually active youth and initiates access to care for HIV-positive adolescents and prevention services for HIV-negatives [38, 39]. Concerns with workplace- and school-based HCT relate to lack of confidentiality [18, 38, 40, 41], potential coercion [38, 42], and weaknesses in linking persons who test HIV-positive to HIV care services [38, 39, 42].

Home-based HCT (HBHCT) is provided to everyone in a community through a door-to-door approach or may be targeted at the household members of known tuberculosis or HIV-positive persons. HBHCT is highly acceptable [43, 44] and increases testing uptake [45, 46], is cost-effective at reaching previously untested persons compared with other HCT models [47], promotes equitable access of services [48] and may help to promote HCT for couples [49, 50] and prevention of mother-to-child HIV transmission [50]. HBHCT facilitates early HIV diagnosis and may promote early linkage to care [50]. Its disadvantages include concerns about confidentiality, privacy, potential coercion, domestic conflicts and fear of stigma [49]. Campaign HCT involves intensive community mobilization lasting 1-2 weeks followed by mobile HIV testing, often coupled with other preventive medical services [44] such as childhood immunisations, antenatal consultations, and screening for communicable and non-communicable diseases [51, 52]. A major advantage of this HCT delivery model is the normalisation of HIV testing as a part of a broader healthcare package, thus reducing stigma [51, 52].

1.3 HCT in Uganda

In Uganda HCT began in 1990 with the client-initiated HCT model. Following increased access to ART, provider-initiated HCT and HBHCT models were introduced in 2005 to identify individuals that need care [53]. Nevertheless, HCT uptake is still low. A national AIDS indicator survey conducted in 2011 found that only 57% of adults (15-49 years) had undergone HCT and received the results [54]. Also, about 60% of HIV-positive adults were unaware of their HIV status [54]. In order to increase access to HCT, the Uganda Ministry of Health (MoH) recommends the use of a mix of facility- and community-based HCT models [55, 56].

1.4 Linkage to HIV care in SSA

Since 2011, four systematic reviews [44, 57-59] have investigated linkage to care after HIV testing in SSA. The first review found eight studies [facility-based HCT (5), HBHCT (1), mobile HCT (1), and mobile- and facility-based HCT (1)] that reported the proportion of patients who enrolled in care after HIV diagnosis [57]. The median proportion of patients who enrolled in care after testing HIV-positive was 44% (range: 31%–68%). The review also found ten studies [facility-based HCT (9) and mobile HCT (1)] that reported the proportion of patients who were assessed for ART eligibility i.e. patients who provided samples for CD4 count testing and/or returned for the results following HIV diagnosis. The median proportion of patients that completed one or both of these steps was 59% (range: 35%-88%). The second review found 19 studies [facility-based HCT (16), HBHCT (2), mobile- and facility-based HCT (1)] that had data on the period between HIV diagnosis and ART eligibility assessment (WHO clinical staging or CD4 count testing) [58]. The pooled proportion of patients who completed ART eligibility assessment was 57% [95% Confidence Interval (CI), 48%-66%]. The third review found six studies (all used facility HCT) that covered the period between HIV diagnosis and initiation of ART [59]. The pooled proportion of patients who had a CD4 count measured was 72% (95% CI, 60%-84%).

In the fourth review, linkage to care was reported separately for each HCT strategy [44]. Facility HCT was divided into: patient-initiated testing i.e. voluntary counselling and testing (VCT) and routine HCT that is initiated by a provider i.e. provider-initiated HCT. Linkage to care was defined as visiting a clinic for community-based HCT, and returning to the clinic to obtain CD4 count results (or enrolling in pre-ART care) for facility HCT. Linkage was reported for 31 studies [HBHCT (10), mobile HCT (6), campaign HCT (2), facility VCT (8), and facility provider-initiated HCT (5)]: 4 of these studies had been

included in the previous reviews. Linkage to care was reported separately for home and campaign HCT interventions with facilitated linkage (e.g. follow-up counselling to encourage referral uptake) and those where no such strategies were used. Linkage to care was highest for home and campaign HCT with facilitated linkage [95%, 95% CI (87–98%)] and lowest for home and campaign HCT without facilitated linkage [26%, 95% CI (18%–36%)]. Linkage to care was low for mobile HCT [37%, 95% CI (24%–51%)] but fairly high for facility VCT [61%, 95% CI (48%–72%)] and facility provider-initiated HCT [55%, 95% CI (39%–71%)].

In summary, these reviews show that linkage to HIV care in SSA is generally low, that facility-based HCT achieves higher linkage to HIV care than community-based HCT, and that interventions to facilitate referral uptake could increase linkage to HIV care for HIV-positive persons identified through community-based HCT.

1.5 Barriers for linkage to HIV care

Barriers for linkage to care may be at the individual, socio-cultural, programme/health-facility, and structural levels [60]. Individual-level barriers include fear of stigma [61-65], non-disclosure of HIV-positive status [35, 61, 65-67], denial of HIV diagnosis [62, 64, 65, 67], absence of physical symptoms [65, 68], misconceptions about ARVs [64, 65, 69], and fear of their side effects [65, 69], lack of partner [64, 65, 68] and other social support [61, 66, 67, 70], perceived disrespect for patients by HIV care staff [65] and fear of possible breach of patient confidentiality [64, 70]. Socio-cultural barriers include poverty [60, 64], lack of formal community support networks [60, 64], presence and use of alternative medicines [61, 62, 64, 68, 70] and traditional/spiritual healers [64, 71]. Program/health facility-level barriers include: high transport costs [57, 61, 65, 68], long distance [61, 65, 68, 72] to and waiting times at [65, 68] the HIV clinics, inappropriate

ART eligibility screening tests [60], and inadequate supply of ARVs [64, 70]. Structural barriers include unintegrated HCT and ART services, absence of robust referral tracking mechanisms, and human resource limitations such as shortage of staff, lack of incentives, inadequate training, and supervision [60].

1.6 Interventions to improve linkage to HIV care

A few, mostly observational studies, have evaluated interventions aimed at improving linkage to HIV care in SSA [73]. These interventions include: provision of immediate or point-of-care (POC) CD4 count testing to decrease time to ART eligibility assessment [51, 52, 66, 74-77], home-based ART initiation [78], integration of ART care into antenatal services [79], assisted partner notification for index patients with HIV infection (this involves elicitation of information about sex partners and contacting them to ensure that they test for HIV and link to care) [80], use of peer navigators [66], community escorts [62], or lay counsellors [77] to help with the linkage process, provision of funds for transportation to the HIV clinic [52, 62, 81], and follow-up counselling to encourage referral uptake [74, 75, 77, 82, 83].

1.7 Rationale for the research

HBHCT has the potential to increase HIV testing uptake in SSA [18] and may be an effective platform for HIV prevention and population-based test-and-treat strategies [84]. However, few data are available on linkage to HIV care after HBHCT or on the effectiveness of strategies to increase linkage to HIV care for HIV-positive persons identified through HBHCT in SSA [73]. Overall, the available evidence shows that HBHCT without additional strategies to facilitate referral achieves inadequate linkage to HIV care [44, 85-89]; and that such strategies could substantially increase linkage [44, 74, 75, 77, 90]. However, most of this evidence comes from uncontrolled observational studies, not trials. Hence, it is difficult to exclude the possibility of confounding due to

differences in levels of stigma, healthcare seeking behaviour, familiarity with the health care services, and other factors. Moreover, linkage to care in most of these studies was not separately estimated for newly and previously diagnosed HIV-positive individuals, or children/adolescents and adults. Linkage outcomes for individuals who have previously tested HIV-positive and those that are newly identified through HBHCT have been shown to vary substantially [84, 85]. Similarly, linkage to HIV care among children/adolescents may be influenced by factors that are unique to this population [91, 92] and has been shown to differ from that in adult patients [88]. A further issue is that in some of the studies [74, 75, 90], two or more linkage interventions were used concurrently, making it difficult to estimate the individual effects of each intervention on linkage to care.

The aim of my PhD was to summarise available data on linkage to HIV care among adults (≥18 years) newly identified with HIV through HBHCT in SSA, and to evaluate the impact of home-based follow-up counselling on linkage to HIV care among HIV-positive adults identified through HBHCT in Uganda. Counselling is an essential component of HIV prevention and treatment and may reduce psychosocial barriers of linkage to care [65]. For instance, counselling facilitates disclosure of HIV positive status to sexual partners [93, 94], friends [94] and family members [73]. In turn, disclosure makes it possible for the HIV-positive individual to receive psychosocial support, a key facilitator of linkage to HIV care [60]. Follow-up counselling may also be used to provide information about ART, locally available HIV care services and encourage linkage to care [82]. Moreover, it is a relatively simple strategy that may be delivered through non-medical personnel [69, 95], an attribute that makes its adoption in low resource settings feasible.

1.8 Research questions

- What is the rate of linkage to HIV care achieved by HBHCT in SSA?
- Does home-based follow-up counselling after HIV diagnosis through HBHCT increase linkage to HIV care in Uganda?
- Does home-based follow-up counselling after HIV diagnosis through HBHCT reduce time between HIV diagnosis and linkage to HIV care in Uganda?
- Does home-based follow-up counselling after HIV diagnosis through HBHCT reduce time between HIV diagnosis and receipt of CD4 count results in Uganda?
- Does home-based follow-up counselling after HIV diagnosis through HBHCT reduce time between HIV diagnosis and ART initiation in Uganda?
- Does home-based follow-up counselling after HIV diagnosis through HBHCT increase adherence to cotrimoxazole prophylaxis (CTXp) in Uganda?
- What are the facilitating factors for and barriers to linkage to HIV care after HBHCT in Uganda?
- Does home-based follow-up counselling increase uptake of repeat HIV testing among individuals who test HIV negative through HBHCT?

1.9 Overall aims

- To document the currently available information on linkage to HIV care in SSA among individuals diagnosed as HIV positive through HBHCT.
- To evaluate the impact of home-based follow-up counselling after HIV diagnosis through HBHCT on linkage to HIV care in Uganda.

1.10 Overall objectives

(i) Using a systematic review;

- To review the literature on linkage to HIV care after HBHCT in SSA.

(ii) Using an open-label cluster-randomised trial in Masaka, south-western Uganda;

- To determine the effect of follow-up counselling on the proportion of individuals linking to HIV care within 6 months of HIV diagnosis through HBHCT.
- To determine the effect of follow-up counselling on the time to linkage to HIV care after HIV diagnosis through HBHCT.
- To investigate the effect of follow-up counselling on time to obtaining CD4 counts after HIV diagnosis through HBHTC.
- To investigate the effect of follow-up counselling on time to ART initiation after HIV diagnosis through HBHTC.
- To determine the effect of follow-up counselling on adherence to CTXp six months after HIV diagnosis through HBHTC.
- To determine the facilitating factors and barriers associated with linkage to HIV care.
- To determine the effect of follow-up counselling on the uptake of repeat HIV testing among HIV negative individuals six months after HBHTC.

1.11 Thesis structure

This thesis follows the 'research paper' style format. Chapter 1 provides background information, chapter 2 describes the general methods, and chapters 3-6 comprise manuscripts that have been published in or submitted to peer-reviewed journals. The manuscripts are:

- Linkage to HIV care after home-based HIV counselling and testing in SSA: A systematic review (submitted; received reviewers' comments and preparing a response)

- An open-label cluster randomised trial to evaluate the effectiveness of a counselling intervention on linkage to care among HIV-infected patients in Uganda: Study design (published)
- Brief counselling after home-based HIV counselling and testing strongly increases linkage to care: a cluster-randomised trial in Uganda (submitted)
- Factors associated with uptake of home-based HIV counselling and testing and access to HIV care services among identified HIV-positive persons in Masaka, Uganda (submitted)

Chapter 7 gives a summary of the main findings, methodological strengths and challenges of this research, other ongoing and planned studies that are related to this work, and concluding remarks. The analysis plan, data collection tools, study monitor's report, and ethics approvals are provided in the appendices.

1.12 Role of the candidate

I developed the systematic review protocol under the guidance of Ms Kathy Baisley (KB) and Professor Heiner Grosskurth (HG). I performed the database search, screened the abstracts, and extracted data from the eligible studies. Dr. Samuel Biraro, a clinical epidemiologist and staff member of the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI) Uganda research Unit on AIDS with experience in HIV epidemiology and HIV intervention research; and experience with systematic reviews, was the second independent reviewer. For papers that suggested that unpublished data relevant to the review may be available, I corresponded with the authors of the original papers, incorporated additional data in the review and obtained final approval from authors (who all agreed to become part of a 'working group' that I coordinated).

I developed the research concept for the trial. I wrote the study protocol and revised it after receiving input from KB, HG, and Dr. Anatoli Kamali (AK). I obtained the necessary ethical approvals, recruited and trained study staff, secured the collaboration of HIV care providers and community leaders, supervised mapping of the study area and defined the study clusters, and organised and supervised randomisation of the clusters. I developed the study tools, supervised data collection and entry, and was responsible for data management. I requested and obtained co-funding from the international AIDS Vaccine Initiative (IAVI) and the London School of Hygiene & Tropical Medicine (LSHTM) for HIV and CD4 count test expenditures.

I developed the data analysis plan (Appendix 1) with input from KB, HG, and Professor Richard Hayes. I performed the analyses under KB's and HG's supervision. I wrote the manuscripts arising from the above work, incorporated feedback from my supervisors and other co-authors, and submitted the final drafts for publication as corresponding author. For the papers that have already been published or reviewed at the time of thesis submission, I revised the manuscripts and responded to reviewers' comments.

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1.14 References

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Chapter 2: General methods

2.1 Introduction

Two studies were conducted in order to achieve the objectives of this PhD:

1) A systematic review
    - To document the currently available information on linkage to HIV care in SSA among adult (≥18 years) individuals newly diagnosed with HIV infection through HBHCT

2) An open-label cluster randomised controlled trial
    - To evaluate the impact of home-based follow-up counselling after HIV diagnosis through HBHCT on linkage to HIV care in Masaka south-western Uganda

The studies are described briefly in this chapter, and in detail in subsequent chapters.

2.2 Systematic review

Five databases (Medline, Embase, Global Health, Web of Science, and Africa-Wide information) were searched for studies published between 1st January 2000 and 19th August 2016 using combined terms for "HIV", "voluntary counselling and testing", "home-based", "mobile", "community", "door-to-door", "survey", "linkage", "pre-ART" and "Africa or individual names of countries in SSA". Abstracts were screened and all potentially eligible papers subjected to full text screening. Studies were included if they were conducted in SSA and had original data on linkage to care among adults (≥18 years) newly identified with HIV infection through HBHCT. Data from eligible papers were extracted using a data extraction form. Studies for which the required information was not published but might have been collected were identified and

corresponding authors asked to share these data, if available. Risk of bias in the included studies was assessed on three items i.e. selection bias, outcome ascertainment, and attrition, based on the recommendations of the Cochrane Collaboration [1]. The results were summarised using the PRISMA guidelines [2]. A meta-analysis was not performed because the studies identified varied widely with regard to design, setting, and definitions of, time points for assessing, method used to ascertain, and strategies to facilitate linkage to care.

2.3 Open-label cluster randomised controlled trial

The primary objectives of the trial were:

1) To determine the effect of home-based follow-up counselling on the proportion of individuals linking to HIV care within 6 months of HIV diagnosis through HBHCT.
2) To determine the effect of home-based follow-up counselling on the time to linkage to HIV care after HIV diagnosis through HBHCT.

2.3.1 Study design

The study was a cluster randomised controlled trial of referral to HIV care and follow-up counselling (14 clusters) compared to referral to HIV care only (14 clusters), for participants diagnosed as HIV-positive through HBHCT (Table 1) .

Table 1: Study design

	Enrolment	**Month 1**	**Month 2**	**Month 6**
Intervention (14 clusters)	HBHCT + referral for care	Home-based follow-up counselling	Home-based follow-up counselling	Outcome assessments: • Linkage to HIV care • Adherence to CTXp • Receipt of CD4 count results • ART initiation • Uptake of repeat HCT
Control (14 clusters)	HBHCT + referral for care			Outcome assessments: • Linkage to HIV care • Adherence to CTXp • Receipt of CD4 count results • ART initiation • Uptake of repeat HCT

At enrolment, participants in the control arm received HBHCT (pre-test counseling, rapid HIV testing, post-test counselling and HIV test results) and a written referral for HIV care. Participants in the intervention arm received home-based follow-up counselling at 1 and 2 months after enrolment in addition to HBHCT and written referral. Study outcomes were assessed 6 months after enrolment in both study arms.

2.3.2 Study setting

The study was conducted in 3 rural subcounties of Masaka, a district in south-western Uganda (Figure 1). The district has 6 rural (Mukungwe, Bukakata, Buwunga, Kyanamukaaka, Kabonera, Kyesiiga) and 3 urban (Nyendo-Ssenyange, Katwe-Butego, Kimanya-Kyabakuza) sub-counties (Figure 2). The sub-counties are further divided into 39 parishes and 352 villages [3]. The urban sub-counties together constitute the municipaility of Masaka, a town located approximately 140 kilometres to the southwest of Kampala, Uganda's capital. The district has a total population of 297,004 [4].

HIV prevalence

Surveys in Masaka district have consistently reported a high adult HIV prevalence. General population surveys conducted in 1994 [5] and 2004 [6] found a HIV prevalence of 10% and 11% respectively. In a 2011 national AIDS indicator survey, the district was surveyed jointly with 10 other districts that have similar language and cultural characteristics; this regional group had the highest HIV prevalence in the country at 11% [7]. HIV prevalence is higher in some sub-populations. For instance, a 2009 survey among persons aged ≥13 years in fishing communities found an HIV prevalence of 24% [8].

HIV care services

The major ART care providers in the district are Uganda Cares, a partnership between the AIDS Healthcare Foundation (USA) and the Uganda MoH; and The AIDS Support organisation (TASO), a private not-for-profit (PNFP) organisation; both are located within Masaka Regional Referral Hospital in Masaka municipality. Other providers include Kitovu hospital, a PNFP facility also located in the municipality and eight lower level government (6) and PNFP (2) health centres located in four of the six rural sub-counties.

The minimum care package for HIV-positive persons in Uganda includes: clinical evaluation and monitoring of HIV disease; ART; daily CTXp for life; screening, prevention, and management of HIV-related co-infections and comorbidities; sexual and reproductive health services; nutritional services; and psychosocial support and palliative care [9, 10]. At the time of the study, ART was recommended for all HIV-positive individuals with CD4 <500 cells/mm^3; and those who were co-infected with tuberculosis or hepatitis B, pregnant, breastfeeding, categorised as most-at-risk persons,

and partners in sero-discordant couples irrespective of WHO clinical stage or CD4 count [11].

Figure 1: Map of Uganda showing location of Masaka district[1]

[1] Source: MRC/UVRI Uganda Research Unit on AIDS

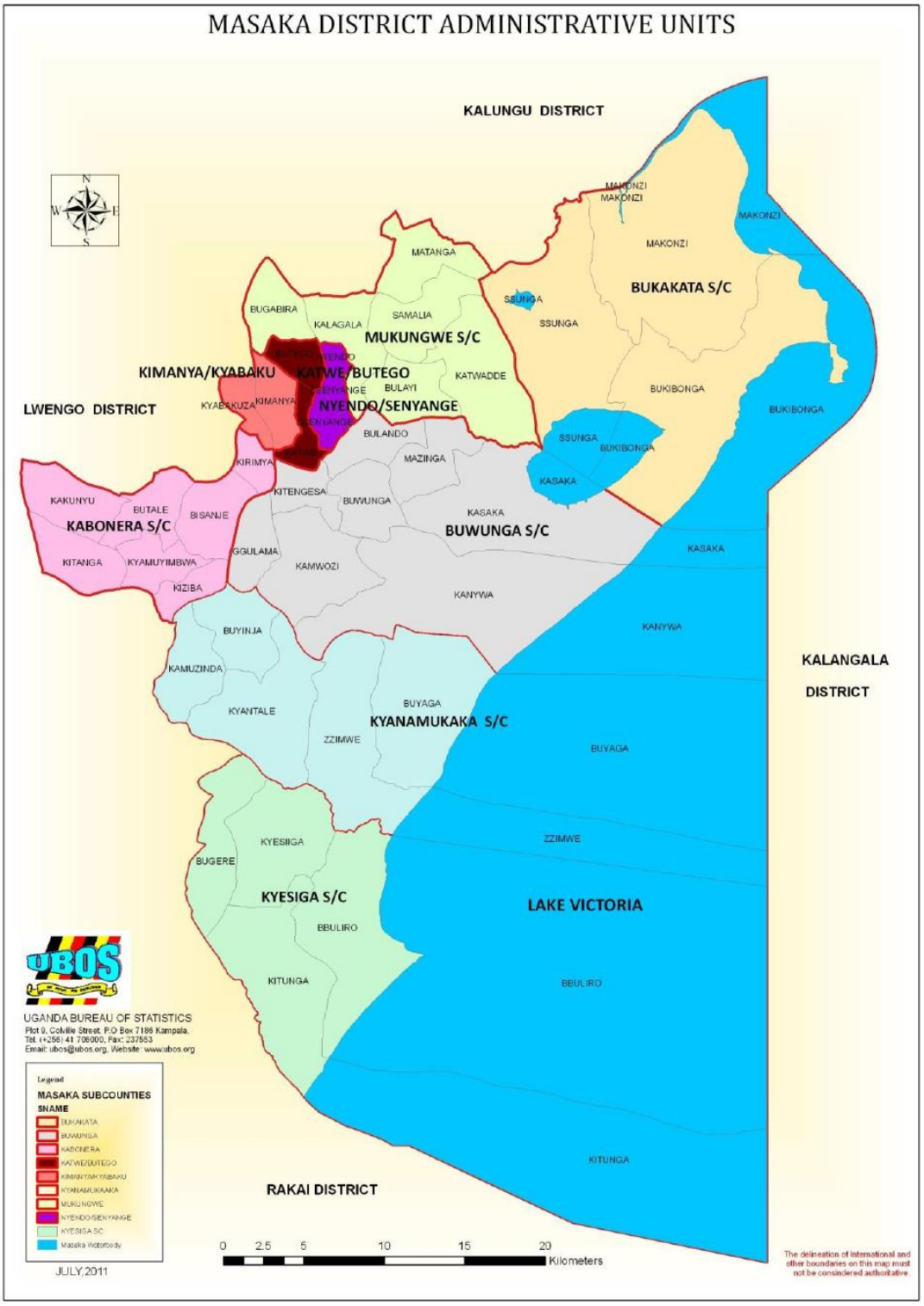

Figure 2: Masaka district map showing the subcounties and parishes[2]

[2]Source: Uganda Bureau of Statistics

Research facilities and staff

The study was based at the MRC/UVRI Unit's clinical research site in Masaka municipality (Figure 3). The site has administrative, clinical, counselling, community liaison, laboratory, and data management staff and facilities. The study team comprised 13 counsellors, 3 community mobilisers, 1 driver, 3 data entry staff, 1 community liaisons officer, and myself. I coordinated all the study activities.

Figure 3: A clinic facility at MRC/UVRI Masaka

2.3.3 Study population

The study population comprised HIV-positive adults identified through HBHCT in Mukungwe, Buwunga, and Kyanamukaka, 3 of the 6 rural sub-counties in the district. These sub-counties were selected because of their proximity to the MRC/UVRI research facility.

HIV-negative individuals were also recruited from each randomised community primarily to reduce the possibility of revealing the sero-status of HIV-positive (main study) participants. However, this opportunity was used to investigate whether follow-up counselling increases the uptake of repeat testing among HIV-negative individuals.

Participant eligibility criteria

HIV-positive participants

Inclusion criteria

1. HIV-positive adult (≥18 years)
2. Willing to provide informed consent
3. Willing to receive follow-up counselling at home

Exclusion criteria

1. Previous or current receipt of HIV care
2. On-going participation in other health-related research
3. Planning to change residence within the next 6 months
4. Inability to give informed consent e.g. due to an on-going psychiatric illness

HIV-negative participants

Inclusion criteria

1. HIV negative adult (≥18 years)
2. Willing to provide informed consent
3. Willing to receive follow-up counselling at home

Exclusion criteria

1. Planning to change residence in the next 6 months
2. Inability to give informed consent e.g. due to on-going psychiatric illness

2.3.4 Identification of clusters

All villages (n=158) in the study area were mapped (Figure 2) and all resident adults (≥18 years) in each village enumerated. To ensure a reasonable number of eligible participants in each cluster, I combined small (<400 adults) villages with adjacent villages into larger clusters of at least 400 adults. The number of villages combined to form larger clusters ranged from 2 to 4. Therefore, a cluster was defined as a village or a set of villages with at least 400 adults. Clusters were separated by a buffer zone of at least one non-participating village to minimise the risk of contamination.

2.3.5 Sample size assumptions

The sample size was calculated to ensure adequate power to address the hypothesis that follow-up counselling would increase the proportion of individuals that link to care. Based on previous studies in the area [6, 7], I assumed an adult HIV prevalence of 10%. The 2011 Uganda national HIV sero-prevalence survey (in which Masaka district participated) found that 60% of HIV-positive adults were unaware of their HIV status and therefore not in care [7]. However, anticipating an increase in HCT coverage since the survey, I adjusted this figure to 40%. Based on these figures and the population estimates from the mapping data, the estimated harmonic mean number of available study participants in a cluster was 21. Assuming that 10% of the potential participants would be ineligible or refuse to participate, and that a further 10% would be lost to follow-up, the harmonic mean number of individuals that was expected to be available for enrolment and completion of the study in each cluster was 17.

Across clusters, I assumed a coefficient of variation, *k*, of 0.25. This was based on past studies of linkage to HIV care [12-14] that were conducted in settings similar to Masaka in which *k* ranged from 0.12 to 0.33 (Table 2).

Table 2: Coefficient of variation values for settings similar to Masaka[3]

Study	Country, setting	Type of study	Outcome	Time of evaluation (months)	*k*
Study 1 [12]	Kenya, 6 rural communities	Community-based HCT	Clinic attendance	3	0.33
				10	0.18
Study 2 [13]	Uganda, 15 peri-urban villages	HBHCT	Clinic attendance	3	0.13
Study 3 [14]	Uganda, 25 rural villages	HIV sero-survey	Screening for ART	24	0.12

Table 3 shows estimates for the power of the study at the 5% significance level for different sample sizes, *k* values, and levels of linkage. From the different possible scenarios in Table 3, I chose the scenario with a linkage of 35% in the control arm based on findings from studies in which no additional strategies had been used to facilitate linkage to care after HBHCT [15-18]. The estimated intervention effect was based on findings from observational studies that had used follow-up counselling to facilitate linkage to care after HBHCT [13, 19-21]. With a sample of 22 clusters (11 per arm) and a harmonic mean of 17 participants expected to complete the study in each cluster, the study was assumed to have 90% power to detect an increase in linkage to care from 35% in the control arm to 60% in the intervention arm at a significance level of 0.05. This sample size would also give 95% power to detect a hazard ratio of 1.7 for the effect of the intervention on time to linkage, or 80% power to detect a hazard ratio of 1.5.

[3]Data for estimation of *k* was kindly provided by Abigail M. Hatcher (study 1), Connie Celum (study 2), and Kathy Baisley (study 3).

After completing enrolment in the first seven clusters, I observed that 12% (419/3546) of registered resident adults from the mapping exercise were not found at home and could not be contacted in spite of repeated attempts. Of those found at home, 11% (358/3127) declined to have HBHCT. Furthermore, among HIV positive persons, there was a higher than expected level of engagement in HIV care: only 26% (75/294) of those who tested positive in HBHCT were not in care. As a result, the number of participants enrolled per cluster was much lower (harmonic mean <10) than anticipated. Based on these preliminary findings, the number of clusters was increased to 28 (14 per arm) with an expected harmonic mean of 7 participants completing the study in each cluster; this would allow for detection of the same difference in proportions with a power of 83%, or a hazard ratio of 1.7 with a power of 85%.

Table 3: Power estimates at the 5% significance level for different sample sizes, coefficient of variation values, and levels of linkage

Number of clusters per arm	Harmonic mean of potential participants per cluster	Proportion of potential participants ineligible/ refusing to enrol (%)	Harmonic mean of participants enrolled per cluster	Proportion of participants lost to follow-up after 6 months (%)	Harmonic mean of participants per cluster at 6 months	*k*	Linkage in the control arm (%)	Linkage in the intervention arm (%)	Power (%)	Number of participants completing 6 months of follow-up in each study arm‡
10	21	10	19	10	17	0.12	30	51.5	95	170
11	**21**	10	**19**	10	**17**	**0.12**	**35**	**60.0**	**99**	**187**
12	21	10	19	10	17	0.12	40	68.6	100	204
13	21	10	19	10	17	0.12	45	77.2	100	221
10	21	10	19	10	17	0.13	30	51.5	94	170
11	**21**	10	**19**	10	**17**	**0.13**	**35**	**60.0**	**99**	**187**
12	21	10	19	10	17	0.13	40	68.6	100	204
13	21	10	19	10	17	0.13	45	77.2	100	221
10	21	10	19	10	17	0.18	30	51.5	91	170
11	**21**	10	**19**	10	**17**	**0.18**	**35**	**60.0**	**97**	**187**
12	21	10	19	10	17	0.18	40	68.6	99	204
13	21	10	19	10	17	0.18	45	77.2	100	221
10	21	10	19	10	17	0.25	30	51.5	83	170
11	**21**	10	**19**	10	**17**	**0.25**	**35**	**60.0**	**91**	**187**

Number of clusters per arm	Harmonic mean of potential participants per cluster	Proportion of potential participants ineligible/ refusing to enrol (%)	Harmonic mean of participants enrolled per cluster	Proportion of participants lost to follow-up after 6 months (%)	Harmonic mean of participants per cluster at 6 months	*k*	Linkage in the control arm (%)	Linkage in the intervention arm (%)	Power (%)	Number of participants completing 6 months of follow-up in each study arm‡
12	21	10	19	10	17	0.25	40	68.6	96	204
13	21	10	19	10	17	0.25	45	77.2	98	221
10	21	10	19	10	17	0.33	30	51.5	71	170
11	**21**	10	**19**	10	**17**	**0.33**	**35**	60.0	**80**	**187**
12	21	10	19	10	17	0.33	40	68.6	87	204
13	21	10	19	10	17	0.33	45	77.2	92	221

‡Power calculations are based on number of participants after loss to follow-up

2.3.6 Preparatory activities

Preparatory activities included mapping of the study area, community mobilisation, discussion of the study with the MRC/UVRI Masaka site community advisory board (CAB) (Figure 4), staff recruitment and training, and meetings with HIV care providers to establish procedures for tracking of study participants and verification of reported linkage.

Figure 4: Discussing the study with the MRC/UVRI Masaka CAB members

2.3.7 Randomisation

Randomisation was stratified on distance (≤10 km or >10 km) and on cluster make-up, i.e. whether the cluster was composed of a single large village or several small villages. Restricted randomisation was then used to achieve balance on the following cluster-level characteristics: cluster size; presence of a trading centre; location along a major road; lakeshore location; and presence of an HIV clinic within 5 km. The tolerance thresholds for balance were defined through an iterative process in which different

thresholds were tried and the number and the validity of all acceptable allocations examined. Of the 70,560 possible allocations under the stratified design, 28,932 (41%) were found to satisfy the additional balance criteria. Of these, a list of 1000 allocations was randomly generated from which one allocation was selected at a public randomisation ceremony. Each allocation had a unique running number.

Public randomisation ceremony

The randomisation ceremony was held on 13th March 2015 and attended by 1-2 leaders from each of the villages. Three sacks each containing 10 balls labelled 0 to 9 were prepared, representing allocations 001 to 999, and 000 representing 1000. The principles underlying the random selection procedure were carefully explained in simple words (Figure 5). Three community leaders, selected by their peers, were then invited and one after the other asked to draw one ball from one sack (3 balls total) thus generating a 3-digit number (Figure 6). This number corresponded to a running number on the list and thus indicated the selected allocation.

The six clusters added later were treated as a separate stratum. Possible allocations for these clusters were generated using the same procedure described above and one allocation selected at a second public randomization ceremony on 30th June 2015.

Figure 5: Explaining the randomisation procedure to community leaders

Figure 6: Three community leaders display the selected allocation at a randomisation ceremony

2.3.8 Follow-up counselling intervention

Development of the intervention

Development of the intervention was based on: i) published evidence indicating that psychosocial factors are common barriers of linkage to HIV care in SSA [12, 18, 22-30], that counselling can reduce the effects of these barriers [26, 31-35] and may increase linkage to care [13, 20, 21]; ii) anecdotal evidence from the same population – obtained through discussions with counsellors at the MRC/UVRI-Masaka research site – suggesting that psychosocial factors such as fear of stigma, denial of HIV-positive status, and lack of information about HIV and HIV care services were common reasons for not linking to care among HIV-positive persons identified through previous HCT programmes in Masaka.

In keeping with previous studies that have used counselling to promote linkage to care [13, 20, 21, 36], intervention counselling sessions in this study were conducted at one and two months after HBHCT and referral for care. The sessions were conducted at participants' homes; each lasted approximately 45 minutes.

Barriers targeted by the intervention

The intervention targeted previously identified individual psychosocial barriers of linkage to care such as fear of stigma [22-26], non-disclosure of HIV-positive status [12, 18, 22, 26, 27], denial of HIV diagnosis [18, 23, 25, 26], absence of physical symptoms [26, 28], misconceptions about ARVs [25, 26, 29] and fear of their side effects [26, 29], belief in spiritual healing [26] and/or use of alternative medicines [22, 23, 25, 28, 30], lack of partner [25, 26, 28] and other social support [12, 18, 22, 30], perceived disrespect for patients by HIV care staff [26] and fear of possible breach of

patient confidentiality [25, 30]. The intervention did not target barriers related to program-level factors such as access to care [22, 26, 28, 37], availability of care services, and quality of care [26, 28]; socio-cultural factors such as social norms, poverty, and lack of formal community support networks [25, 31]; or structural factors such as HIV care policies [31], health systems [31], and socio-economic environment [31].

Content of the intervention

The counselling sessions covered the following general issues: acceptance of HIV diagnosis, fear of or experience of stigma, plans to seek HIV care and support services, importance of HIV status disclosure and availability of psychosocial support for linkage to and retention in care; and information about decentralised locally available HIV care services, ARV medication, and the rationale for early linkage to and retention in care. The sessions were also used to address specific issues e.g. family or marital discord arising after disclosure of HIV status, occurrence of adverse effects following initiation of CTXp and/or ART etc. Any issues identified in the first session were followed up in the second session.

Staff training

The intervention was delivered by counsellors who did not have medical training but were trained in HCT. The counsellors comprised existing MRC/UVRI staff with experience working in Masaka district as well as new staff that were specifically recruited to work on the study; all had at least one year's experience in conducting community-based HCT including HBHCT. Specific training on the intervention was conducted in the 4 weeks prior to study initiation. Prior to the training, study counsellors were asked to read the study protocol in order to get a basic understanding

of the study background, rationale, and objectives. The training was conducted using two approaches: i) one group seminar attended by all counsellors that comprised a didactic 30-minute presentation and 60-minute session to discuss any issues that weren't clear in the protocol or the presentation; ii) a single 30-minute one-on-one session with each of the counsellors. The one-on-one sessions were conducted within 1-2 weeks of the group seminar. These sessions were used to go over the main points in the group presentation and discuss any remaining concerns that the individual counsellors may have had.

Maintaining fidelity of the intervention

To ensure that the intervention was delivered as intended and as consistently as possible, counsellors were provided with a list of the counselling content that they could refer to during the counselling sessions. In addition, counsellors made written notes summarising the issues discussed in each counselling session. I reviewed the counselling notes at least twice every week during the trial and followed up any omissions or deviations with the individual counsellors.

Choice of time point for assessing intervention effect

The effect of the intervention on linkage to care was assessed 4 months after the second counselling visit (6 months after HBHCT and referral). This time point was chosen because: i) funding was limited and could not allow for a longer period of follow-up; ii) it would allow for the assessment of the intervention effect on post-linkage outcomes i.e. ART initiation and adherence to CTXp; and iii) it would enable comparisons with other studies that used the 6 month time point to assess linkage.

2.3.9 Study procedures

Screening and enrolment procedures

HCT

HCT was the first step in the screening process. Counsellors visited households in the randomised villages, enumerated all residents aged ≥18 years using a household data collection form (Appendix 2), and offered HBHCT to those present. Households where some or all adults were not at home at the initial counsellor visit were revisited two more times. HCT was conducted in accordance with the national guidelines [38]. Pre-test counselling covered the following: benefits of HCT, the testing process, possible results, HIV risk assessment, HIV prevention, importance of disclosure, referral, and linkage to care. Participants were given an opportunity to ask questions and discuss any issues of concern before testing. Finger-prick blood specimens were obtained and screened using the Alere Determine HIV-1/HIV-2 rapid test kit (Alere Medical, Japan). Individuals whose samples tested negative on the screening test were given HIV negative results. Samples that tested positive were subjected to confirmatory testing using Stat-Pak HIV 1/2 (Chembio Diagnostic systems, USA). Individuals whose samples tested positive on the confirmatory test were given HIV positive results. Samples with discordant screening and confirmatory test results were further tested with Uni-Gold HIV 1/2 (Trinity Biotech, Ireland) as tie-breaker. The Uni-Gold HIV 1/2 test result was issued as the final result. Post-test counselling included assessment of readiness to receive test result, communication of result, assessment of the individual's understanding of the result, a discussion on risk reduction strategies, partner notification and testing, disclosure plans, available HIV care services, and referral plans. HCT was conducted separately for each individual. However, married/cohabiting individuals had

the option of receiving HCT as a couple. On average, 30 minutes were required for each HCT session and an extra 15 minutes for completion of study procedures. Details of persons accepting HCT including the results were recorded on a HCT worksheet (Appendix 3).

Informed consent and participant recruitment

Individuals who tested HIV-positive were provided detailed information about the study using an informed consent document (see Appendices 4-7 for English and Luganda versions of the informed documents used in the study). If an individual was illiterate, the counsellor read the document to them in the presence of a literate impartial witness. An opportunity was given for the individual to consider the information, ask questions, and discuss any issues before consenting to participate. Individuals indicated their consent to participate by signing/marking the consent form. Consenting individuals were assessed for eligibility using the eligibility assessment form (Appendix 8) and those meeting the eligibility criteria assigned a study number and enrolled. HIV-positive persons who were excluded from the study for any reason were documented and referred for care as necessary.

Recruitment of HIV-negative participants

Once 3 HIV-positive participants were enrolled, the next person that tested HIV negative was also invited to join the study after consenting and satisfying the study eligibility criteria. This procedure was repeated until all households in the randomised villages were visited.

Collection of sociodemographic data

A counsellor-administered questionnaire (Appendix 9) was used to collect data on sex, age, marital status, occupation, education, religion, house-hold characteristics including ownership of specified items by household members, travel time to the nearest HIV clinic, HCT history, knowledge of own, and partner's HIV status. A locator form (Appendix 10) was used to collect detailed locator information from each enrolled participant.

Referral for HIV care

All individuals identified as HIV-positive and not in care were referred to their preferred HIV clinic for care. Two referral forms (Appendix 11) were completed for each referral; one was provided to the participant to take to the HIV clinic and the other kept in a central file at the MRC/UVRI Masaka site.

Follow-up procedures

Home-based follow-up counselling (intervention)

At 1 and 2 months after HIV diagnosis, counsellors visited all participants in the intervention arm to conduct follow-up counselling. Participants not found at home were revisited at least two more times.

Content of counselling (HIV-positive participants)

- Developments since HIV diagnosis including the individual's acceptance of HIV-positive status, experience of stigmatisation, plans to seek HIV care and support services.

- The significance of disclosing ones HIV status to friends and/or family and the importance of obtaining psychosocial support for linkage to and retention in HIV care.
- Information about local HIV care services, ARVs, pre-ART and ART care
- The importance of regular HIV clinic attendance following linkage to HIV care

Content of counselling (HIV-negative participants)

- Information on HIV risk reduction strategies
- The importance of regular HIV HCT

Each follow-up counselling session lasted approximately 45 minutes.

Collection of linkage to HIV care data

The linkage status questionnaire (Appendix 12) was administered at the month-6 visit. Data was collected on whether or not the participant had linked to care, HIV clinic name and address, participant's clinic registration number, and dates of linkage, obtaining CD4 counts and ART initiation. Data was also collected on participants' knowledge of: HIV-positive status prior to enrolment to confirm responses obtained at the enrolment visit; any fellow participants in neighboring villages they may have heard of, and if they had discussed the study with these individuals. This information was used to assess the possibility and extent of contamination between trial arms. Approximately 30 minutes was required to administer the questionnaire.

Measurement of adherence to CTXp

At month 6, participants were also asked if they had initiated CTXp and if so, if they had missed any doses, reasons for missed doses, and number of doses missed in the past

month. Participants were categorised as ‘adherers’ and ‘non-adherers’, using an intake of >80% of prescribed pills as threshold.

CD4 count testing

CD4 count test results for participants that linked to care were obtained from the HIV clinics. Participants who had not undergone a CD4 count test despite linking to care as well as those that had not linked to care were offered CD4 count testing by study staff at the month 6 visit. In this case, about 5ml of venous blood was collected at participants’ homes and transported to the MRC/UVRI-Masaka laboratory for testing. Results were recorded on the CD4 count & repeat HIV test form (Appendix 13) and delivered to participants’ homes within one week.

Repeat HIV testing

Repeat HIV testing was offered to HIV-negative participants in both trial arms at the month-6 visit. Venous samples were obtained and transported to the MRC/UVRI-Masaka laboratory where repeat HIV testing was conducted. The results were recorded on the CD4 count & repeat HIV test form (Appendix 13) and the results delivered to participants’ homes within one week. At this occasion, laboratory HIV testing was preferred over rapid testing in participants’ homes in order to avoid unmasking the HIV-positive status of participants who provided venous samples for CD4 count testing at this visit.

Status of participants during follow-up

At each visit following enrolment, a follow-up visit form (Appendix 14) was completed to document if the participant had completed the visit and if not, whether they had refused follow-up, were not contacted, or had died.

Referral tracking and confirmation of linkage to care

Referrals were tracked for all participants who self-reported linking to care. A counsellor visited the HIV clinic that the participant had reported attending at the month 6 visit, and with the help of the staff at the HIV clinic used information provided by the participant (e.g. names, unique clinic-assigned registration numbers) and referral forms to identify participant's clinic records. Once the participant's clinic records were positively identified, clinic documents e.g. pre-ART, ART registers, and individual files were examined and the following data recorded on a medical records questionnaire (Appendix 15): details (including dates) of initial registration with and subsequent visits to the provider, clinical staging, CD4 count testing history and results, CTXp and ART initiation.

Figures 7-12 depict a follow-up meeting between a participant and the counselor to establish whether the participant linked to care and the documentation examined by the counselor at the participant's home, and at the HIV clinic to confirm linkage. Participants for whom linkage was not confirmed were revisited and interviewed about any discrepancies.

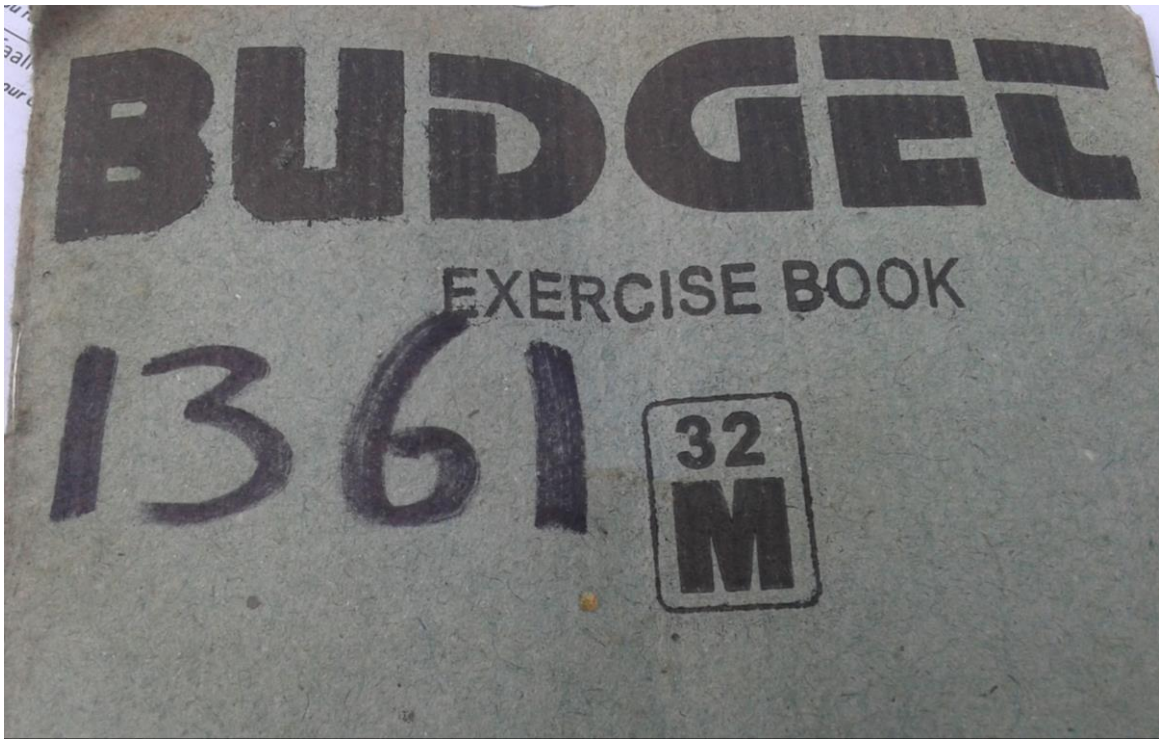

Figure 7: A notebook retrieved from a participant at a follow-up visit with documentation of the care that he is receiving from an HIV clinic (note the unique patient registration number)

Figure 8: A study counsellor examines a participant's HIV care documentation during a home follow-up visit

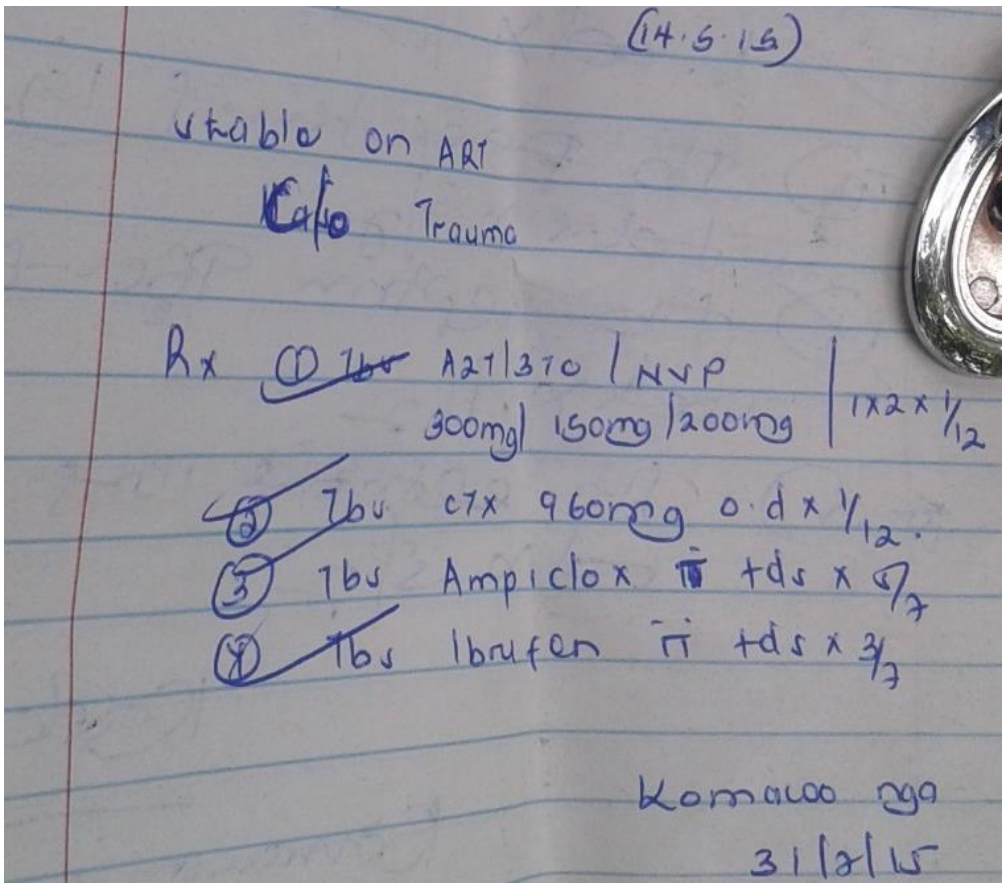

Figure 9: Prescription for ARVs, cotrimoxazole (CTX) and other drugs as recorded in the participant's notebook

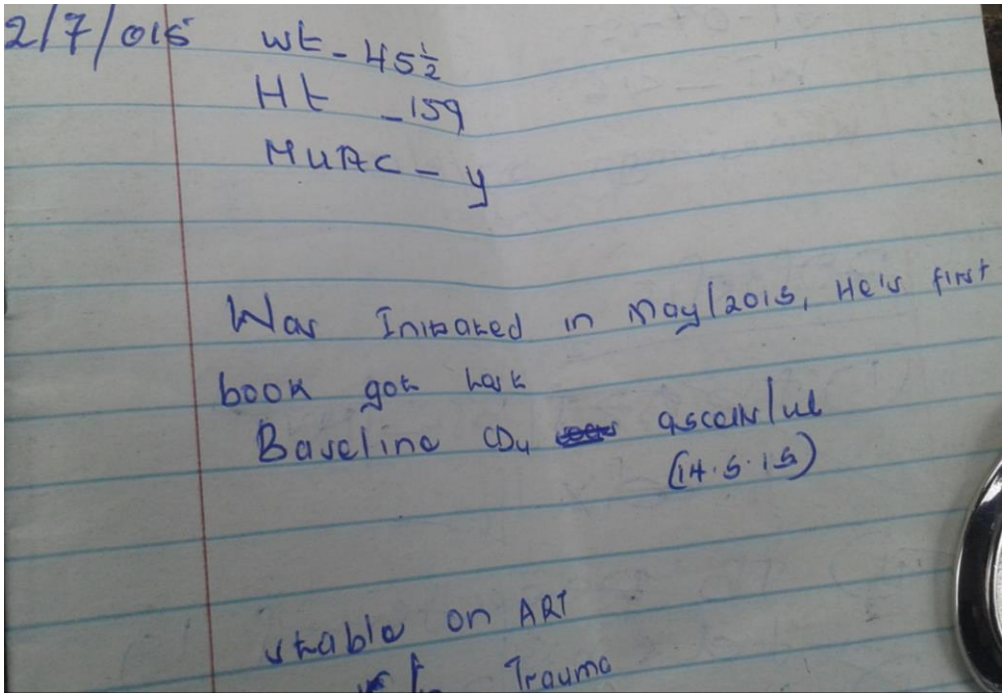

Figure 10: Baseline CD4 count and other clinical observations as recorded in the participant's notebook.

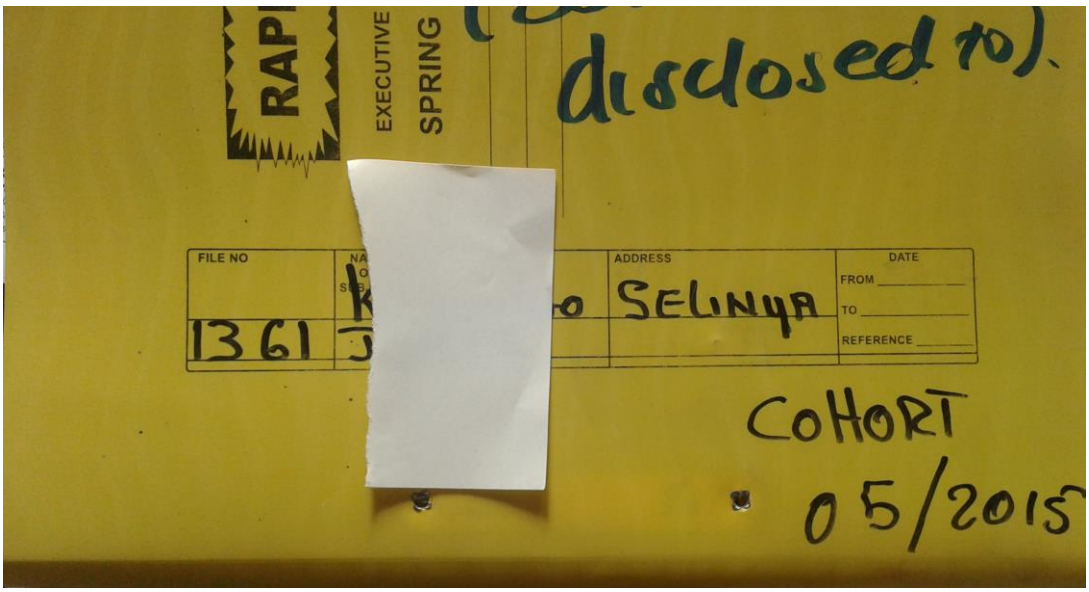

Figure 11: Participant's HIV clinic file (note the unique patient registration number)

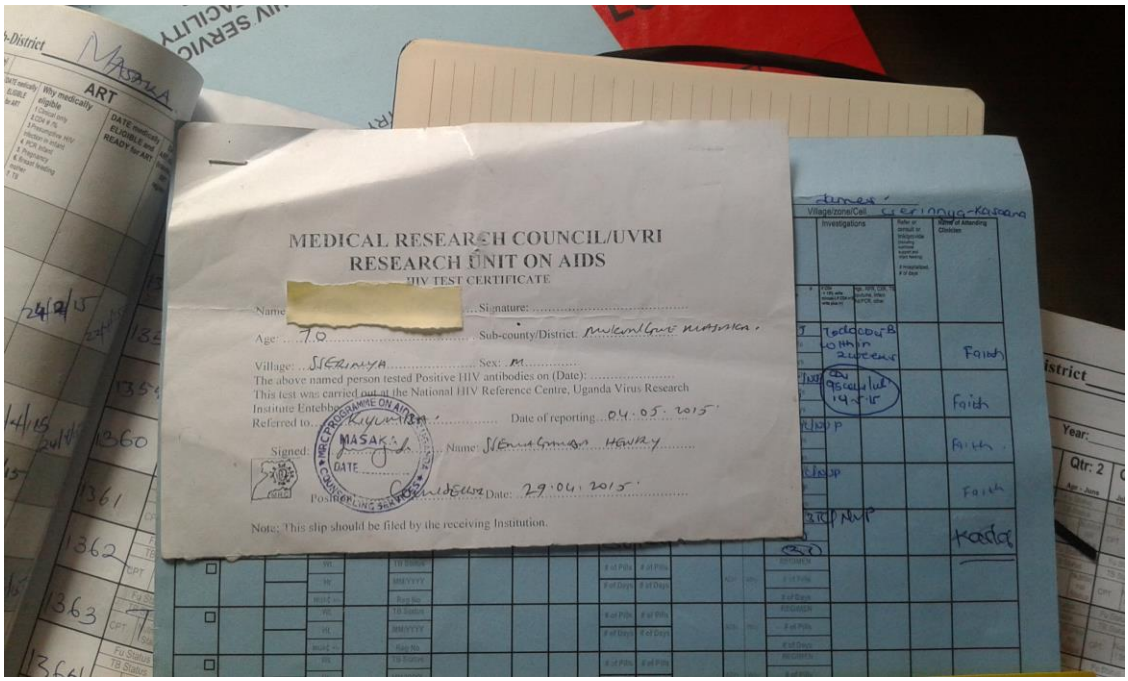

Figure 12: A study referral form retrieved from a participant's file at one of the HIV clinics

2.3.10 Data management and analysis

Data were collected using paper-based questionnaires. Before data entry, questionnaires were checked for completeness, logical consistency, and entry. Data were double-entered and validated in Microsoft Access. Checks were run on the entered data every fortnight and queries sent to the study field team for resolution. Data corrections arising

from these queries were submitted for entry and the process repeated until no more queries were generated. A detailed description of the methods used for analysis is provided in the analysis plan (Appendix 1) and the manuscript addressing the main trial objectives (chapter 5).

2.3.11 Study management

I was responsible for the overall conduct of the trial. A study working group comprising of the lead counsellor, community liaisons officer, and myself met weekly to review the progress of the trial, plan community mobilisation activities, and address study related issues. The trial was monitored by an internal MRC/UVRI study monitor. The monitor's report is included in appendix 16. Dr. Anatoli Kamali, the MRC/UVRI based associate supervisor provided additional oversight for the trial.

2.3.12 Ethical considerations

The trial was approved by the Ethics Committee of UVRI (reference number GC/127/14/12/491) (Appendix 17), the Ethics Committee of LSHTM (reference number 8833) (Appendices 18 & 19), and the Uganda National Council for Science and Technology (reference number HS 1732) (Appendix 20). Written informed consent (including consent to track referrals and review medical records for persons who link to care) was obtained from each participant prior to conduct of study procedures. The trial was registered at ClinicalTrials.gov (NCT02497456).

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Chapter 3 (manuscript 1): Linkage to HIV care after home-based HIV counselling and testing in sub-Saharan Africa: A systematic review

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SECTION A – Student Details

Student	Eugene Ruzagira
Principal Supervisor	Heiner Grosskurth
Thesis Title	Effect of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing on linkage to HIV care in south-western Uganda

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Tropical Medicine and International Health
Please list the paper's authors in the intended authorship order:	Eugene Ruzagira, Kathy Baisley, Anatoli Kamali, Samuel Biraro, Heiner Grosskurth
Stage of publication	**Undergoing revision** – 'REVIEWERS' COMMENTS RECEIVED, PREPARING A RESPONSE'

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the systematic review under the guidance of Kathy Baisley (KB) and Heiner Grosskurth (HG). I performed the search for the relevant articles. Samuel Biraro: a clinical epidemiologist and staff member of the MRC/UVRI Uganda Research Unit on AIDS, and I independently screened the identified

	articles and reached a consensus on their eligibility. For articles that suggested that unpublished data relevant to the review may be available, I contacted the authors to request additional data which I incorporated in the review. I prepared the manuscript, incorporated feedback from KB, HG, and other co-authors, and submitted it for publication. Currently, I am preparing responses to reviewers' comments.

Student Signature: _____ Date: 02/03/2017

Supervisor Signature: _____ Date: 3/3/2017

Linkage to HIV care after home-based HIV counselling and testing in sub-Saharan Africa: A systematic review

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Abstract

Objective: To systematically review the literature on linkage to care among adults newly identified with HIV infection through home-based HIV counselling and testing (HBHCT) in sub-Saharan Africa (SSA).

Methods: Five databases were searched for studies published between 1st January 2000 and 19th August 2016. Eligible studies were reviewed, assessed for risk of bias and findings summarised using the PRISMA guidelines.

Results: Fourteen studies from six countries met the eligibility criteria. Nine studies used specific strategies (point-of-care CD4 count testing, follow-up counselling, provision of transport funds to clinic, and counsellor-facilitated clinic linkage) in addition to routine referral to facilitate linkage to care. Time intervals for ascertaining linkage ranged from one week to twelve months post-HBHCT. Linkage to care ranged from 8.2% (95% CI,

6.8%-8.8%) to 99.1% (95% CI, 96.9%-99.9%). Linkage to care was generally lower (<33%) if HBHCT was followed by referral only, and higher (>80%) if additional strategies were used. Only one study assessed linkage to care by means of a randomised trial. Five studies had data on cotrimoxazole (CTX) prophylaxis and twelve on ART eligibility and initiation. CTX uptake among those eligible ranged from 0% to 100%. The proportion of persons eligible for ART ranged from 16.5% (95% CI, 12.1-21.8) to 77.8% (95% CI, 40.0-97.2). ART initiation among those eligible ranged from 14.3% (95% CI, 0.36%-57.9%) to 94.9% (95% CI, 91.3%-97.4%). Additional linkage strategies, whilst seeming to increase linkage to care, were not associated with higher uptake of CTX and/or ART. Most of the studies were susceptible to risk of outcome ascertainment bias. A pooled analysis was not performed because of heterogeneity across studies with regard to design, setting, and the key variable definitions.

Conclusion: Only few studies from SSA investigated the proportion of patients linking to HIV care among adults newly diagnosed with HIV through HBHCT. Linkage to care was often low after routine referral but higher if additional interventions were used to facilitate it. The effectiveness of promising linkage strategies should be confirmed through randomised controlled trials.

Introduction

Access to antiretroviral therapy (ART) in sub-Saharan Africa (SSA) has expanded considerably but AIDS-related mortality remains high[1]. A major cause of this mortality is the late presentation of patients for treatment[2]. Early ART initiation is dependent on early HIV diagnosis, and prompt linkage to and retention in care[3]. HIV counselling and testing (HCT) is essential in expanding HIV prevention and treatment services[4]. However, HCT uptake in SSA remains low[5]. For instance, the proportion of HIV-positive adults in SSA who are aware of their HIV status has been estimated to be only 60%[6]. In order to expand access to HIV testing in settings with generalised HIV epidemics, WHO recommends community-based HCT with linkage to prevention, care and treatment services, in addition to facility-initiated HCT[7].

Home-based HIV counselling and testing (HBHCT) is highly acceptable and has the potential to substantially increase HIV testing uptake in SSA[8]. It is cost-effective at reaching previously untested persons compared with other HCT models[9], promotes equitable access of services[10] and may help to promote HCT among couples[11] and prevention of mother-to-child HIV transmission[12]. Importantly, HBHCT facilitates early HIV diagnosis and therefore provides an opportunity for early linkage to care[12]. These attributes highlight the potential of HBHCT as an effective platform for HIV prevention and population-based test-and-treat strategies. Despite these advantages, few data are available on linkage to care after HBHCT particularly among newly identified HIV-positive persons or on the effectiveness of strategies to increase linkage after HCT[13]. In order to identify effective linkage strategies, data are specifically required on linkage to care soon (e.g. within a year) after HBHCT. The reasons for this include the current WHO recommendation to initiate ART among all HIV-positive adults regardless of WHO clinical stage and at any CD4 count; increasing use of HBHCT in Africa; and growing

importance of early treatment for improved clinical outcomes and HIV prevention. A recent systematic review on linkage to care following community- and facility-based HCT[14] included ten HBHCT studies, but did not distinguish linkage outcomes between newly and previously diagnosed HIV-positive individuals, or between children/adolescents and adults. Individuals who previously tested HIV-positive and have not yet linked to care are likely to differ from newly identified patients with regard to barriers that may prevent service uptake[15]. Similarly linkage to care among children/adolescents may be influenced by factors that are unique to this population[16,17].

The specific objectives of our review were to: estimate the proportion of individuals in SSA linking to care [i.e. the people who registered (reported or confirmed) with an HIV care provider] within 12 months among those who were newly diagnosed with HIV; the proportion initiating daily cotrimoxazole (CTX) prophylaxis (i.e. the people who initiated daily CTX prophylaxis among those who linked to care and were eligible for CTX); and the proportion initiating ART (i.e. the people who initiated ART among those who linked to care and were eligible for ART); and to summarise data on the strategies that have been used to increase linkage to care after HBHCT.

Methods

Search strategy

We searched five databases (Medline, Embase, Global Health, Web of Science, and Africa-Wide information) for studies published between 1st January 2000 (time at which roll-out of ART programmes began in SSA[8]) and 19th August 2016. The following key terms were used: (HIV diagnosis OR HIV voluntary counselling and testing OR HIV testing and counselling OR HIV counselling and testing) AND (home based OR mobile OR community OR household OR door-to-door OR survey) AND (linkage OR access

OR uptake OR enrolment OR non-enrolment OR retention OR loss to follow-up OR loss to care OR care OR treatment OR pre- antiretroviral therapy) AND (Africa OR individual names of countries in SSA). No language restriction was applied to the literature search. Identified articles were exported using Endnote reference management software and duplicates removed. Two authors (ER and SB) independently screened titles and abstracts of articles to identify eligible publications, discussed inconsistencies, and reached a consensus on their eligibility. Studies were eligible if they were conducted in SSA, and had original data on linkage to care among adults (≥18 years) newly identified with HIV infection through HBHCT. Studies whose study populations included persons <18 years were eligible but only data for participants aged ≥18 years were utilised for this review. Studies for which the required information was not published but might have been collected were identified and the corresponding authors approached with requests for additional data. Where two or more eligible articles reported on similar or overlapping populations, the article with the most complete data was included. Review articles were excluded but their bibliographies as well as those of the identified articles were manually checked to identify any additional studies. Conference abstracts were excluded. All potentially eligible papers were then subjected to full text screening.

Data extraction and synthesis

A data extraction form was used to collect the following information from each eligible article: first author's name, publication year, country and setting where study was conducted, study population, sample size, study design, definition of linkage to care, strategies used to promote and time for evaluation of linkage to care. We also obtained the number of HIV-positive adults who were newly diagnosed, and, among those, the numbers who linked to care, were eligible for, and initiated CTX prophylaxis and ART. Risk of bias in the included studies was assessed using a component approach, similar to

the Cochrane Collaboration's[18], and based on three items: selection bias, outcome ascertainment, and attrition. The results were summarised using the PRISMA guidelines[19].

We used the reported data to calculate the proportions (and their 95% confidence intervals, using the Clopper–Pearson method) who linked to care, initiated CTX prophylaxis, were eligible for and initiated ART. The denominator for linkage was all newly diagnosed HIV-positive adults (≥18 years) who had a potential minimum follow-up period corresponding to the time point when linkage was assessed (i.e. including those who out-migrated, died, or were lost to follow-up, but excluding those who entered the study at a later date so had a shorter potential follow-up period). The denominator for ART eligibility was all individuals who linked within the specified time period and those for initiation of CTX prophylaxis and ART were all individuals who linked and were eligible for CTX and ART respectively. We did not perform a meta-analysis because the identified studies varied widely with regard to design, setting, definition of linkage to care, the time points of and method for ascertaining linkage, and with regard to the strategies used to facilitate linkage.

Results

Summary of search results

The search identified 5,905 articles of which 61 were subjected to full text screening. Of those screened, 21 were eligible for detailed review; two were excluded on the basis of reporting on overlapping study populations[20,21]. Of the remaining 19 articles, one[22] had all the required data. Additional data were obtained for 13[15,23-34] of the remaining 18 articles after contacting the respective corresponding authors. Thus, 14 studies were included in the review (Figure 1). A summary description of the included studies is

presented in Table 1. The studies were conducted in six countries i.e. Uganda[23,24,28,29], South Africa[26,28-30,33,34], Kenya[15,22], Malawi[27,31], Lesotho[32], and Swaziland[25] between 2005 and 2015. Most (92%) studies were based in rural[15,23,25,26,28-32,34] or semirural settings[24,27]; two were conducted in both rural and urban[22,33] populations. The number of newly identified HIV-positive adults varied widely across studies (range: 15–1637).

Risk of bias

Only two[28,30] studies had a low risk of bias for all assessed items (Table 2). Risk of selection bias was low (≥80% HBHCT coverage) in four[22,24,28,30] studies. Risk of attrition bias was low (≥80% participant retention) in eight[24,26-30,33,34] of ten studies in which participants were followed. Self-reported linkage to care was confirmed by tracking referrals and review of records at the referral clinic in only two studies[23,26]. In the first study[23], no information was reported on the proportion of participants for whom clinic records were not found. In the second study[26], clinic records were found for only 71% of the tracked referrals and self-reported data was used to ascertain linkage for the rest of the participants. Self-reported linkage to care was confirmed by review of documentation issued to patients by HIV clinics (e.g. clinic cards) in three studies[28-30]; linkage was not verified with the HIV clinics. In five studies[15,25,31,32,34], ascertainment of linkage to care was based on data from HIV clinics in the areas where the studies were conducted; participants who may have linked to HIV clinics outside of the study areas were not tracked. Self-reported data was used to ascertain linkage to care in the rest of the studies[22,24,27,33].

Summary of study objectives and populations

Genberg *et al.*[15] conducted a retrospective analysis using HBHCT data from Bunyala, a rural sub-county in western Kenya and HIV care provider clinical data to assess linkage

to and engagement in care in previously and newly diagnosed individuals. HBHCT was offered to all resident persons aged ≥13 years as part of a standard HIV care service in the area. 3,482 persons tested HIV-positive; 1329 (38%) were newly identified HIV-positive adults (≥18 years) and hence eligible for the review.

Dalal *et al.*[22] conducted an HBHCT study among participants in a population-based disease surveillance program in two areas in Kenya: Lwak, a rural area in the west of the country and Kibera, an informal urban settlement in Nairobi. The aim of the study was to assess HBHCT acceptance, HIV prevalence, and linkage to care. HBHCT was offered to persons aged ≥13 years and children (≤12 years) whose biologic mother was HIV-positive or deceased. 2759 persons tested HIV-positive; 1637 (59%) were eligible for the review.

Nakigozi *et al.*[23] conducted a retrospective study to assess the frequency and determinants of non-enrolment into HIV care services among all 15-49 year old persons testing HIV-positive through HBHCT in a rural population-based survey in Rakai, Uganda. 1451 persons tested HIV-positive; 1137 (78.4%) were eligible for the review.

Tumwebaze *et al.*[24] conducted an uncontrolled prospective intervention study of HBHCT with CD4 count laboratory testing (results were returned to participants a week later), referral for care, and follow-up counselling in Kabwohe, a mixed rural and peri-urban area in southwest Uganda to evaluate this strategy as a platform for delivery of combination HIV prevention services. All residents aged ≥18 years were eligible to participate. 152 persons tested HIV-positive; 77 (51%) were eligible for the review.

Parker *et al.*[25] evaluated HBHCT and mobile HCT programmes with regard to uptake, costs, HIV positivity rates and linkage to care in Shiselweni, Swaziland. HBHCT was

offered as part of routine HIV care services to persons aged ≥18 months in three rural communities in the region. 170 persons tested HIV-positive through HBHCT; 142 (84%) were eligible for the review.

Naik *et al.*[26] conducted a prospective cohort analysis to determine linkage to care and factors that influence the rate of linkage to care among clients who tested HIV-positive through HBHCT in Umzimkhulu, a rural area in Kwazulu-Natal, South Africa. HBHCT was offered to individuals aged ≥14 years in 19 communities as a standard HIV care service (11 communities) and in the context of a cluster randomised trial comparing HBHCT to standard-of-care (mainly facility-based) HCT with regard to HIV testing rates (eight communities) [21]. 492 persons tested HIV-positive; 410 (83%) were eligible for the review.

Becker *et al.*[27] conducted a prospective study to estimate the uptake of HBHCT and testing and family planning services among couples in three villages in Mpemba, a peri-urban area of Blantyre, Malawi. HBHCT was offered as part of a research study. Couples were eligible if the woman was aged 15-49 years and the man aged ≥15 years. 46 individuals tested HIV-positive of whom 15 (33%) were eligible for the review.

Barnabas *et al.*[28] conducted an uncontrolled prospective intervention study of HBHCT with point-of-care (POC) CD4 count testing, referral for care, and follow-up counselling in two rural communities in KwaZulu-Natal, South Africa, and in Mbarara, southwest Uganda to assess the effects of this strategy on linkage to care, ART initiation, and viral suppression at 12 months. Eligible participants were HIV-positive adults aged ≥18 years. 635 persons tested HIV-positive; 229 (36%) were eligible for the review.

Barnabas *et al.*[29] conducted a multisite, open-label, household randomised controlled trial to assess the effectiveness of community-based HCT and linkage strategies compared with standard referral for linking HIV-positive persons to ART and HIV-negative uncircumcised men to voluntary medical male circumcision (VMMC) in two rural settings in uMgungundlovu District, KwaZulu-Natal, South Africa, and Sheema District, southwest Uganda. HIV-positive ART naïve individuals aged ≥16 years identified through home-based or mobile HCT were randomly assigned in a factorial design to receive lay counsellor clinic linkage facilitation, lay counsellor follow-up home visits, or standard-of-care referral, and then either to POC CD4 count testing or referral for clinic CD4 count testing. 1325 HIV positive individuals were randomised; 511 (39%) were eligible for the review.

van Rooyen *et al.*[30] conducted an uncontrolled pilot study of a HBHCT intervention combined with POC CD4 count testing, referral for care, and follow-up visits in the rural Vulindlela sub district of KwaZulu-Natal, South Africa among persons aged ≥18 years to assess the effect of this strategy on HIV testing coverage, identification of HIV infected persons who are unaware of their HIV serostatus, linkage to care, and reduced HIV infectiousness through high uptake of and adherence to ART. 201 persons tested HIV-positive; 73 (36%) were eligible for the review.

Wringe *et al.*[31] conducted a retrospective analysis to examine HIV testing and ART uptake in four community based HIV cohort studies in Africa. HBHCT was offered as part of a research study in one of the cohorts located in Karonga, a rural district in Northern Malawi. The cohort comprised all residents aged ≥15 years. 473 HIV-positive, ART naïve persons were included in the analysis; 431 (91%) were eligible for the review.

Labhardt *et al.*[32] conducted a cluster randomized trial to compare HBHCT and mobile HCT with regard to HCT uptake in Butha-Buthe and Thaba-Tseka, two rural districts with high HIV prevalence in Lesotho. HCT was provided in the context of a multi-disease campaign that included provision of other health care services. The target population included persons of all ages who were not known to be HIV-positive. 39 individuals were newly diagnosed with HIV in the HBHCT clusters; 37 (95%) were eligible for the review.

Velen *et al.*[33] evaluated the uptake of HCT among household contacts (≥14 years) of index TB patients and linkage to care among those newly diagnosed with HIV. The study was part a cluster randomized trial designed to determine the effectiveness of adding isoniazid preventative therapy and point-of-care CD4 count testing in a TB contact tracing program based in rural and urban regions of South Africa. The study was limited to trial participants in the standard of care arm (TB contact tracing only). 26 persons were newly identified with HIV; 25 (96%) were eligible for the review.

Iwuji *et al.*[34] reported the uptake of home-based HIV testing, linkage to care, uptake of ART, and community attitudes about ART from the first phase of the ANRS 12249 TasP cluster-randomised trial conducted in rural KwaZulu-Natal, South Africa. The trial compared the effect of early ART, initiated irrespective of CD4 count, to that of ART initiated according to national guidelines (CD4 count ≤350 cells/μL, WHO stage 3 or 4 until December 2014, ≤500 cells/μL from January 2015) on HIV incidence in the general population. HBHCT was provided to all persons aged ≥16 years who were resident in participating communities. A total of 2,569 persons were ascertained as HIV-positive in the first phase of the trial [942 tested HIV-positive (including 539 previously undiagnosed individuals aged ≥18 years) and 1,627 reported a known HIV-positive status]; 358 (14%) were eligible for the review.

Linkage to HIV care

In all studies, persons who tested HIV positive were referred for care. Additional strategies to facilitate linkage to care were used in nine (64%)[23,24,26-30,32,34] of the studies. These strategies included: provision of funds for transport to the HIV clinic[27]; follow-up counselling[23,24,26,28-30,34]; lay counsellor facilitation of the initial HIV clinic visits (the counsellor met the HIV-positive participant at the clinic and explained the clinic processes and the benefits of ART)[29]; POC CD4 count[28-30,32] and home-based collection of samples for viral load[28] testing and provision of results. Linkage to care was ascertained within 3 months of HBHCT in 50% of studies[15,22,24,26,27,32,33]. Ascertainment of linkage in the remaining studies was done >3 to 6[23,25,30] and >6 to 12[28,29,31,34] months after HBHCT.

Linkage to care ranged from 8.2% (95% CI, 6.8%-8.8%)[15] to 85.4% (95% CI, 75.8%-92.2%)[29] when only referral was offered, and 24.3% (95% CI, 11.8%-41.2%)[32] to 99.1% (95% CI, 96.9%-99.9%)[28] when referral plus additional interventions to facilitate linkage were offered. In general, linkage to care was lower (<33%) in the studies that offered referral only[15,22,25,31,33] and higher (>80%) in those that used a combination of additional linkage strategies[24,28-30].

Uptake of CTX prophylaxis and ART

Five studies conducted in Kenya[22], Uganda[23,24], and Uganda and South Africa[28,29] had data on initiation of CTX prophylaxis among eligible individuals who linked to care. CTX prophylaxis is only recommended for patients with CD4 count ≤200 cells/μL, WHO stage 3 or 4 or HIV/TB co-infection in South Africa[35] but is routinely provided to all HIV-positive persons irrespective of CD4 count or WHO disease stage in Uganda[36] and Kenya[37]. Of the studies conducted in Uganda and Kenya, additional interventions to facilitate referral uptake were offered in all except one. CTX uptake in these studies

ranged from 78.2% (95% CI, 69.3-85.5%)[28] to 100%[23,24,29]. CTX uptake was also high [90.6% (95% CI, 87.3%-93.2%)] in the study that offered referral only[22]. Interventions to facilitate linkage were offered in the two studies that were conducted in South Africa. Uptake of CTX among patients with CD4 count ≤200 cells/μL in these studies ranged from 0%[29] to 33.3% (95% CI, 4.3-77.7)[29].

Twelve studies[15,22-26,28-32,34] had data on ART eligibility and ART initiation among patients who linked to care. The proportion of individuals eligible for ART initiation ranged from 16.5% (95% CI, 12.1-21.8)[26] to 77.8% (95% CI, 40.0-97.2)[32]. ART uptake among those who linked to care ranged from 33% (95% CI, 24.2%-41.7%)[22] to 94.0% (95% CI, 85.4%-98.3%)[31] in the studies that provided referral only. A similar range i.e. 14.3% (95% CI, 0.36%-57.9%)[32] to 94.9% (95% CI, 91.3%-97.4%)[23] was observed in the studies that provided referral plus additional linkage interventions. ART initiation rates were highest (≥90%) in the two studies in which HIV care services were provided through community-based research clinics[23,31].

Discussion

Home based HIV counselling and testing is increasingly being used in SSA, and an effectively conducted HBHCT strategy would be a key precondition for HIV control programmes that propagate a test-and-treat approach for HIV prevention[26]. The success of such programmes will partly depend on their capacity to achieve high levels of linkage to care following HIV diagnosis[38]. Hence, it is necessary to identify and set up strategies that will effectively link persons identified with HIV through HBHCT to care and treatment. As observed in this review however, only a few studies have investigated linkage to care among adults newly identified with HIV through HBHCT in SSA. Linkage to care was below 33% in five of six studies where participants were only referred for

care with no further interventions to facilitate referral[15,22,25,31,33]. With the exception of two studies[32,34], studies that used additional linkage strategies recorded moderate (>50% to <80%)[23,27] to high (>80%)[24,28-30] levels of linkage. In general, linkage to care was highest when participants were offered POC CD4 count testing and follow-up counselling[24,28-30]. These findings suggest that interventions that facilitate referral uptake could enhance linkage to care among adults newly identified with HIV through HBHCT.

Only a small number of studies included in this review investigated the uptake of CTX. In Kenya and Uganda where routine CTX prophylaxis is recommended irrespective of CD4 count or clinical stage[36,37], uptake was high (>70%) irrespective of whether or not additional interventions were applied. This may be because CTX is widely available, inexpensive, and simple to use[39]. In contrast and in spite of facilitated linkage, uptake of CTX prophylaxis among those eligible (CD4 count ≤200 cells/μL[35]) in South Africa was low (≤33%). The reasons for this are not clear. However previous studies have found irregular supply and lack of stocks of CTX, lack of awareness among health care workers, and perceived low priority of CTX prophylaxis due to the absence of a reporting requirement, to be some of the barriers to implementation of CTX prophylaxis policies[40].

Consistent with previous findings[8], significant proportions of HIV-positive persons identified through HBHCT were still ineligible for ART (based on national guidelines that were in use at the time of the respective studies). The finding that ART uptake was highest in the studies where services were provided through community-based research clinics may be attributed to such clinics being more accessible and less prone to limitations that characterise many public sector ART care programmes in SSA, including the requirement for several visits to prepare patients for ART[29], crowded, busy and unwelcoming clinics[41], non-functioning laboratories[41], and inadequate supply or lack of

antiretroviral drugs[42]. Additionally, some research clinics are likely to have close and long standing relationships with communities in which they are located.

HBHCT studies with facilitated linkage have been shown to achieve higher ART initiation rates among participants who link to care compared to those without facilitated linkage[14]. However, ART initiation rates were high in some but not all studies with facilitated linkage described in this review. Additionally, some studies without facilitated linkage achieved higher ART initiation rates than some of those with facilitated linkage. For instance although participants in the study by van Rooyen *et al.*[30] received POC CD4 count testing and follow-up counselling following HBHCT and referral, only 54% of eligible linkers initiated ART compared to 94% in the Wringe *et al.*[31] study where participants were only given referrals for HIV care. It is likely that clinic level factors such as those mentioned above may be more important in influencing events after linkage to care. Also, people who link to care in the absence of facilitated linkage may be more motivated to receive care.

This review has some limitations. First, the number of relevant studies found is small and represents only six countries in particular areas. This may limit the generalizability of the findings. Second, the methodologies used in these studies varied widely, making it impractical to combine findings from individual studies into a pooled analysis. Third, outcome assessments in most of the included studies were based solely on self-reports or records in HIV clinics within the respective study areas; hence linkage to care may have been overestimated in the case of self-reports or underestimated if some individuals linked to clinics outside of their communities. Findings from our own trial[43] show that about 5% of patients reporting that they have linked to care after HBHCT, have actually not done so, probably due to social desirability bias. Because participants in our trial are

informed early on that self-reported linkage will be verified, we believe that this figure may be substantially higher in other studies. Also, 6% of linkers in our trial have been confirmed to have reported to HIV clinics outside of the study area.

Importantly, most of the linkage intervention studies reported were observational, determining intervention effects without control groups. Randomised trials represent the gold-standard methodology in the evaluation of an intervention including its likely effect size[44]. It is therefore desirable to confirm the impact and establish the cost effectiveness of these strategies in randomised controlled trials. Apart from the trial included in this review[29], we are aware of five other trials to investigate the effectiveness of a variety of strategies on linkage to care following HIV diagnosis through HBHCT. None of these other trials have been reported yet. They include: i) a recently completed individually randomised trial aiming to assess the accuracy, feasibility and acceptability of POC CD4 testing for persons found HIV positive through HBHCT, and to determine the (cost-) effectiveness of this intervention in improving linkage to care and time to ART initiation in rural Western Kenya[45]; ii) our own soon to be completed cluster randomised trial to evaluate the impact of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing (HBHCT), on linkage to care in Uganda[43]; iii) an ongoing cluster randomised trial that will evaluate the effectiveness of a linkage to care counselling intervention at achieving HIV viral suppression and intermediate outcomes of linkage/time to care, time to/receipt of opportunistic infection prophylaxis, and antiretroviral therapy (ART) among people testing HIV positive during (HBHCT) in rural Uganda[46]; iv) an ongoing household randomised trial in rural Lesotho to evaluate the effectiveness of same day home-based ART initiation after HIV diagnosis coupled with a reduced frequency of clinic follow-up visits in improving linkage to care, retention in care, and viral suppression[47]; and v) a planned individually randomised trial that will

compare home and other community recruitment strategies, HIV testing strategies (self-testing, HCT in a home/mobile setting, and facility-based HCT), and different linkage strategies (referral only, text message reminder, and financial incentive) among young at-risk women, 15-24 years old, in Homa Bay County, western Kenya[48].

In conclusion, we found that only few published studies investigated linkage to HIV care among adults newly diagnosed with HIV through HBHCT in SSA. In general, HBHCT without additional intervention strategies to increase service uptake achieved inadequate linkage while HBHCT combined with some kind of additional strategy seemed to achieve higher linkage. There is a need to confirm the impact of the most promising linkage strategies through randomised controlled trials before they can be recommended for large scale adoption.

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Figure 1: Systematic search flow diagram

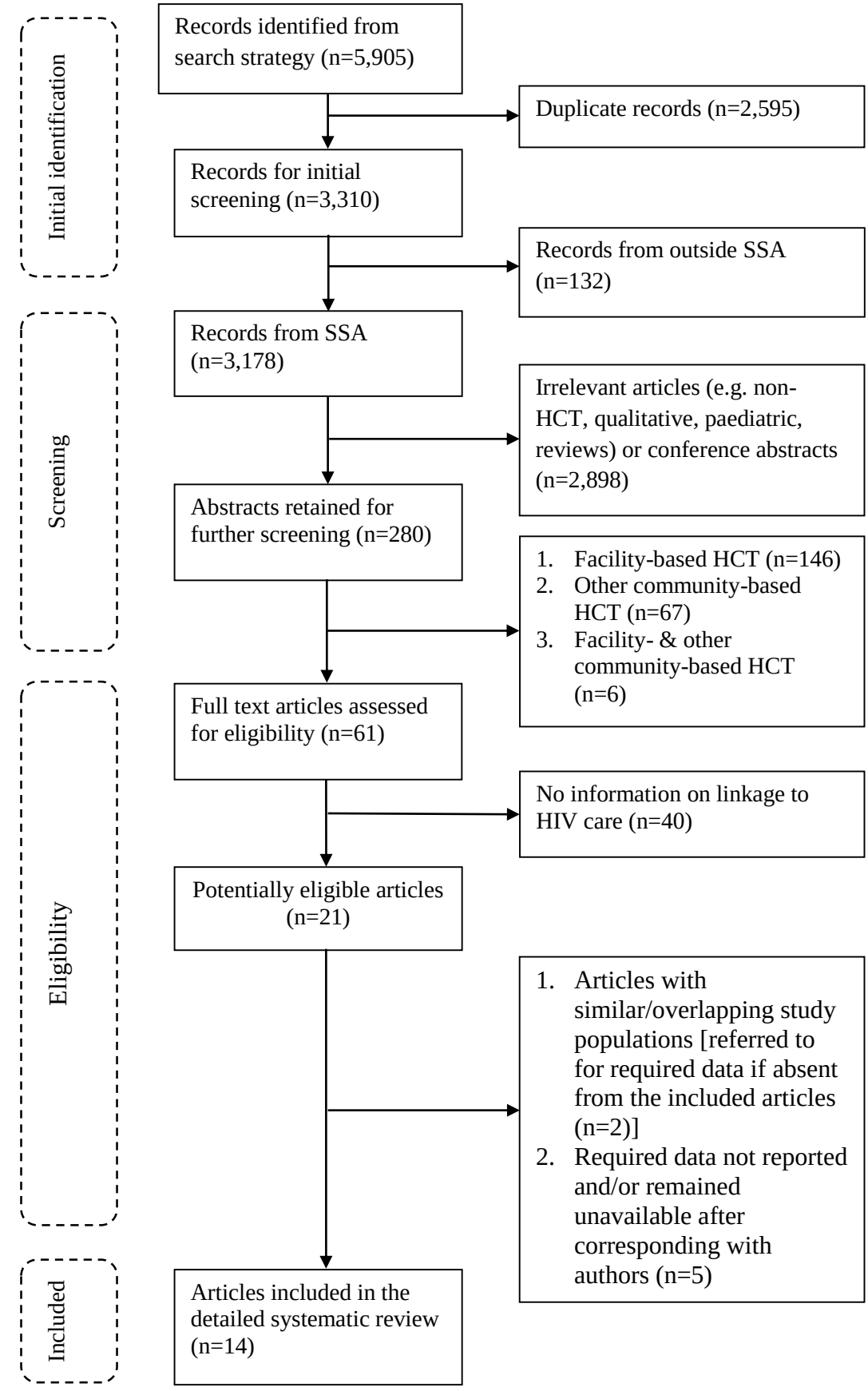

Table 1: Description of studies included in the systematic review

Author, year	Country, setting	Study period	Study design	HIV care provider	Linkage to care definition	Linkage strategies	CD4 ART eligibility threshold (cells/µL)	Linkage assessment time (months)	Number in analysis (Number of HIV-positive persons in study)	Linked	Initiated CTX[a]	Eligible for ART[b]	Initiated ART
										n (%, 95% CI)	n/N (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
Genberg, 2015[15]	Kenya, rural	2009-2011	Retrospective population-based cohort	Public clinic	Registration at clinic	Referral only	≤250	3	1329 (3482)	109 (8.2, 6.8-9.8)	Not reported	41 (37.6, 28.5-47.4)	23 (56.1, 39.7-71.5)
Dalal, 2013[22]	Kenya, rural & urban	2008	Prospective population-based cohort	Public clinic	Registration at clinic	Referral only	≤250	1	1637 (2759)	414 (25.3, 23.2-27.5)	375/414 (90.6, 87.3-93.2)	120 (29.0, 24.7-33.6)	39 (33.0, 24.2-41.7)
Wringe, 2012[31]	Malawi, rural	2008-2010	Retrospective population-based cohort	Research clinic	Screening for ART eligibility	Referral only	≤250	12	431 (473)	126 (29.2, 24.9-33.8)	Not reported	67 (53.2, 44.1-62.1)	63 (94.0, 85.4-98.3)
Parker, 2015[25]	Swaziland, rural	2013	Prospective population-based cohort	Public clinic	Registration at clinic	Referral only	≤350	6	142 (170)	45 (31.7, 24.1-40.0)	Not reported	17 (37.8, 23.8-53.5)	9 (52.9, 27.8-77.0)
Velen, 2016[33]	South Africa, rural & urban	2013-2014	Prospective cohort of participants in a TB contact tracing trial.	Public clinic	Registration at clinic	Referral only	≤350	3	25 (26)	8 (32.0, 14.9-53.5)	Not reported	Not reported	Not reported
Iwuji, 2016[34]	South Africa, rural	2012-2014	Prospective cohort of participants in	Public & research clinics	Registration at clinic	Referral & follow-up counselling[c]	≤350	12	358 (2569)	162 (45.3, 40.0-50.6)	Not reported	101 (71.6, 63.4-78.9)[d]	81 (80.2, 71.1-87.5)

Author, year	Country, setting	Study period	Study design	HIV care provider	Linkage to care definition	Linkage strategies	CD4 ART eligibility threshold (cells/μL)	Linkage assessment time (months)	Number in analysis (Number of HIV-positive persons in study)	Linked	Initiated CTX[a]	Eligible for ART[b]	Initiated ART
										n (%, 95% CI)	n/N (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
			a population-based trial.										
Naik, 2015[26]	South Africa, rural	2009-2011	Prospective cohort of participants in population-based trial and non-trial HBHCT interventions	Public clinic	Obtaining a CD4 count	Referral & at least 3 follow-up counselling visits[e]	≤200	3	410 (492)	248 (60.5, 55.6-65.3)	Not reported	41 (16.5, 12.1-21.8)	33 (80.5, 65.1-91.2)
Labhardt, 2014[32]	Lesotho, rural	2011	Prospective cohort of participants in a population-based trial.	Public clinic	Registration at clinic	Referral & POC CD4 count testing	≤350	1	37 (39)	9 (24.3, 11.8-41.2)	Not reported	7 (77.8, 40.0-97.2)	1 (14.3, 0.36-57.9)
Becker, 2014[27]	Malawi, peri-urban	2009	Population-based uncontrolled intervention study	Public clinic	Registration at clinic	Referral & provision of funds for transport to clinic to participants who	≤250	1 week	15 (46)	8 (53.3, 26.6-78.7)	Not reported	Not reported	Not reported

Author, year	Country, setting	Study period	Study design	HIV care provider	Linkage to care definition	Linkage strategies	CD4 ART eligibility threshold (cells/μL)	Linkage assessment time (months)	Number in analysis (Number of HIV-positive persons in study)	Linked	Initiated CTX[a]	Eligible for ART[b]	Initiated ART
										n (%, 95% CI)	n/N (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
						disclosed their HIV status to their partners[f]							
Nakigozi, 2011[23]	Uganda, rural	2005-2008	Retrospective population-based cohort	Research clinic	Registration at clinic	Referral & follow-up counselling[g]	≤250	6	1137 (1451)	781 (68.7, 65.9-71.4)	781/781 (100.0)	237 (30.3, 27.1-33.7)	225 (94.9, 91.3-97.4)
Tumwebaze, 2012[24]	Uganda, rural & peri-urban	2010-2011	Population-based uncontrolled intervention study	Public clinic	Registration at clinic	Referral, CD4 count laboratory testing (results returned to participant a week later), & follow-up counselling (1, 2 & 3 months)	≤250	3	77 (152)	63 (81.8, 71.4-89.7)	63/63 (100.0)	13 (20.6, 11.5-32.7)	8 (61.5, 31.6-86.1)
Barnabas, 2014[28]	South Africa &	2011-2013	Population-based	Public clinic	Registration at clinic	Referral, POC CD4	≤350	12	229 (635)	227 (99.1, 96.9-99.9)	2/12 (16.7, 2.1-48.4)	74 (32.6, 26.5-39.1)	59 (79.7, 68.8-88.2)

Author, year	Country, setting	Study period	Study design	HIV care provider	Linkage to care definition	Linkage strategies	CD4 ART eligibility threshold (cells/μL)	Linkage assessment time (months)	Number in analysis (Number of HIV-positive persons in study)	Linked	Initiated CTX[a]	Eligible for ART[b]	Initiated ART
										n (%, 95% CI)	n/N (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
	Uganda, rural		uncontrolled intervention study			count testing, follow-up counselling (1, 3, 6, 9, & 12 months), & viral load testing (0 & 6 months)					SA; 86/110 (78.2, 69.3-85.5) UG		
van Rooyen, 2013[30]	South Africa, rural	2011-2012	Population-based uncontrolled intervention study	Public clinic	Registration at clinic	Referral, POC CD4 count testing, & follow-up counselling (1, 3, & 6 months)	≤200	6	73 (201)	70 (95.9, 88.5-99.1)	Not reported	35 (50.0, 37.8-62.2)	19 (54.3, 36.6-71.2)
Barnabas, 2016[29]	South Africa &	2013-2015	Household randomised controlled	Public clinic	Registration at clinic	Referral only	≤350	9	82 (226)	70 (85.4, 75.8-92.2)	2/6 (33.0, 4.3-77.7) SA; 20/25	37 (52.9, 40.6-64.9)	28 (75.7, 58.8-88.2)

Author, year	Country, setting	Study period	Study design	HIV care provider	Linkage to care definition	Linkage strategies	CD4 ART eligibility threshold (cells/μL)	Linkage assessment time (months)	Number in analysis (Number of HIV-positive persons in study)	Linked	Initiated CTX[a]	Eligible for ART[b]	Initiated ART
										n (%, 95% CI)	n/N (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
	Uganda, rural		trial of HIV-positive persons identified through HBHCT or mobile HCT (6 groups)[h]								(80.0, 59.3-93.2) UG		
						Referral & POC CD4 count testing	≤350	9	81 (213)	73 (90.1, 81.5-95.6)	1/4 (25.0, 0.63-80.6) SA; 37/38 (97.4, 86.2-99.9) UG	43 (58.9, 46.8-70.3)	25 (58.1, 42.1-73.0)
						Referral & counsellor clinic linkage facilitation	≤350	9	104 (231)	102 (98.1, 93.2-99.8)	1/3 (33.3, 0.84-90.6) SA; 18/21 (85.7, 63.7-97.0) UG	51 (50.0, 39.9-60.1)	39 (76.5, 62.5-87.2)
						Referral, POC CD4 count testing, & counsellor clinic linkage facilitation	≤350	9	72 (206)	69 (95.8, 88.3-99.1)	0/3 (0.0) SA; 23/27 (85.2, 66.3-95.8) UG	43 (62.3, 49.8-73.7)	23 (53.5, 37.7-68.8)

Author, year	Country, setting	Study period	Study design	HIV care provider	Linkage to care definition	Linkage strategies	CD4 ART eligibility threshold (cells/μL)	Linkage assessment time (months)	Number in analysis (Number of HIV-positive persons in study)	Linked	Initiated CTX[a]	Eligible for ART[b]	Initiated ART
										n (%, 95% CI)	n/N (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
						Referral & follow-up counselling (1, 3, & 6 months)	≤350	9	87 (229)	80 (92.0, 84.1-96.7)	0/12 (0.0) SA; 30/30 (100.0) UG	41 (51.3, 39.8-62.6)	31 (75.6, 59.7-87.6)
						Referral, POC CD4 count testing & follow-up counselling (1, 3, & 6 months)	≤350	9	85 (220)	81 (95.3, 88.4-98.7)	1/5 (20.0, 0.51-71.6) SA; 28/28 (100.0) UG	46 (56.8, 45.3-67.8)	36 (78.3, 63.6-89.1)

[a]Uptake of CTX prophylaxis is shown separately for South Africa (SA) and Uganda (UG) because eligibility criteria are different in each country.

[b]Based on locally recommended CD4 count eligibility threshold during the study period.

[c]Follow-up counselling was offered to individuals who did not link to care within 3 months of referral; number and timing of follow-up visits were not specified.

[d]Information on ART eligibility and initiation was not available for persons who linked to the public health facilities. Hence, the denominator used for ART eligibility (n=141) is the number of persons who linked to the TasP trial research clinics.

[e]Timing of follow-up visits was not specified.

[f]The number of participants who disclosed their HIV status to their partners was not reported.

[g]Number and timing of follow-up visits were not specified.

[h]Results for linkage to care and other outcomes are presented separately for each of the six groups in the trial.

Table 2: Risk of bias within studies

Author, year	Selection of participants[a]	Outcome ascertainment[b]	Loss to follow-up[c]
Genberg, 2015[15]	Participants comprised persons aged ≥13 years who tested HIV-positive in a population-based study. HBHCT coverage could not be estimated because the size of the target population was not reported. *Unclear risk*	Clinic-verified data. No information on persons who may have linked to clinics outside the study area. *Unclear risk*	No participant follow-up
Dalal, 2013[22]	Participants comprised HIV-positive persons aged ≥13 years and children aged ≤12 years whose biologic mother was HIV-positive or deceased who were enrolled in a population-based disease surveillance program. HBHCT coverage was 82%. *Low risk*	Self-report for all participants. *High risk*	48% (881/1839) loss to follow-up. *High risk*[d]
Wringe, 2012[31]	Participants comprised persons aged ≥15 years who tested HIV-positive in a population-based cohort. HBHCT coverage could not be estimated because the total number of persons in the target population was not reported. *Unclear risk*	Clinic-verified data. No information on persons who may have linked to clinics outside the study area. *Unclear risk*	No participant follow-up
Parker, 2015[25]	Participants comprised persons who tested HIV-positive in a house-to-house HBHCT program. HBHCT was conducted in only 26% of households in the target area due to time constraints. It is not clear how these households were selected. *High risk*	Clinic-verified data. Participants who were referred health facilities outside the study area were excluded from analysis. *Unclear risk*	No participant follow-up
Velen, 2016[33]	Participants comprised household contacts of TB patients in a TB contact tracing trial. HBHCT was offered to household contacts of TB patients selected through convenience sampling. *High risk*	Self-report for all participants. *High risk*	12% (3/26) loss to follow-up. *Low risk*
Iwuji, 2016[34]	Participants comprised persons aged ≥16 years who tested HIV-positive or self-reported being HIV-positive in a community-randomised trial. HBHCT coverage was 64%. *High risk*	Clinic verified data. No information on persons who may have linked to clinics outside the study area. *Unclear risk*	16% (58/358) loss to follow-up. *Low risk*[e]
Naik,2015[26]	Participants comprised all persons aged ≥14 years who tested HIV-positive in 19 communities. HBHCT coverage could not be estimated because the size of the population targeted for testing in the participating communities was not reported. *Unclear risk*	Self-report & clinic-verified data or self-report only (29% of participants). *High risk*	18% (79/438) loss to follow-up. *Low risk*[f]

Author, year	Selection of participants[a]	Outcome ascertainment[b]	Loss to follow-up[c]
Labhardt, 2014[32]	Participants comprised newly identified HIV-positive persons all of ages from communities randomised to receive HBHCT in a cluster-randomised trial. HBHCT coverage could not be estimated because the total number of persons in the target population was not reported. *Unclear risk*	Clinic-verified data. No information on persons who may have linked to clinics outside the study area. *Unclear risk*	No participant follow-up
Becker, 2014[27]	Participants were married individuals (Female, 15-49 years; Male, ≥15 years) who tested HIV-positive through house-to-house couple HBHCT in three villages. HBHCT was offered to all eligible participants in one village and approximately one-third in the other two villages (no information on how participants in these two villages were selected). *High risk*	Self-report for all participants. *High risk*	2% (1/46) loss to follow-up. *Low risk*
Nakigozi, 2011[23]	Participants comprised 15-49 year old persons who tested HIV-positive in a population-based cohort. Annual HIV testing coverage in the cohort is >90%. However, 21% of the persons who tested HIV-positive were excluded from the analysis because they had either refused to learn their HIV results (3%) or received their HIV result less than six months before data-set closure (18%). *High risk*	Self-report & clinic-verified data. No information on whether self-reported linkage was confirmed with clinic records for all participants. *Unclear risk*	Loss to follow-up not reported. *Unclear risk*
Tumwebaze, 2012[24]	Participants comprised all adults (≥18 years) who tested HIV-positive in a house-to-house HBHCT study. HBHCT coverage was 80%. *Low risk*	Self-report for all participants. *High risk*	2% (3/152) loss to follow-up. *Low risk*
Barnabas, 2014[28]	Participants comprised adults (≥18 years) persons who tested HIV-positive in a house-to-house HBHCT study. HBHCT coverage was 96%. *Low risk*	Self-report & review of documentation issued to patient by the HIV clinic. *Low risk*	10% (62/635) loss to follow-up. *Low risk*
van Rooyen, 2013[30]	Participants comprised adults (aged ≥18 years) who tested HIV-positive in house-to-house HBHCT study. HBHCT coverage was 91%. *Low risk*	Self-report & review of documentation issued to patient by the HIV clinic. *Low risk*	2% (5/201) loss to follow-up. *Low risk*
Barnabas, 2016	Participants comprised HIV-positive ART naïve individuals aged ≥16 years identified through community-based HCT (HBHCT & mobile HCT). HBHCT coverage could not be estimated	Self-report & review of documentation issued to patient by the HIV clinic. *Low risk*	3% (40/1325) loss to follow-up. *Low risk*

Author, year	Selection of participants[a]	Outcome ascertainment[b]	Loss to follow-up[c]
	because the size of the population targeted for testing in the participating communities was not reported. *Unclear risk*		

[a]In population-based studies, there was low risk of bias if HBHCT coverage (defined as the number of persons accessing HBHCT out of the total resident population) was ≥80%, high risk if HBHCT coverage was <80% and unclear risk if there was no information on coverage. In non-population based cohort studies, there was low risk if participants were randomly selected, high risk if the selection was non-random and unclear risk if there was insufficient information on participant selection.

[b]There was low risk of bias if ascertainment of linkage to care was by both self-report & examination of HIV clinic records or documentation issued to patients by the HIV clinic for ≥80% of the participants, high risk if ascertainment was by self-report only and unclear risk if there was insufficient information on ascertainment of linkage outcomes for some study participants.

[c]There was low risk if retention of HIV-positive persons identified through HBHCT was ≥80%, high risk if retention was <80% and unclear risk if information was not available.

[d]Only applicable to HIV-positive individuals who were newly identified through HBHCT.

[e]Only applicable to newly identified HIV-positive persons who were referred to care at least 12 months before the end of the first phase of the trial i.e. May 2014.

[f]Only applicable to HIV-positive individuals who were not engaged in care at baseline.

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Chapter 4 (manuscript 2): An open-label cluster randomised trial to evaluate the effectiveness of a counselling intervention on linkage to care among HIV-infected patients in Uganda: Study design

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Principal Supervisor	Heiner Grosskurth
Thesis Title	Effect of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing on linkage to HIV care in south-western Uganda

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An open-label cluster randomised trial to evaluate the effectiveness of a counselling intervention on linkage to care among HIV-infected patients in Uganda: Study design

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ABSTRACT

Introduction: Home-based HIV counselling & testing (HBHCT) is highly acceptable and has the potential to increase HIV testing uptake in sub-Saharan Africa. However, data are lacking on strategies that can effectively link HIV-positive individuals identified through HBHCT to care. This trial was designed to assess the effectiveness of two brief home-based counselling sessions on linkage to care, provided subsequent to referral for care among HIV-positive patients identified through HBHCT in a rural community in Masaka district, Uganda.

Methods: 28 communities (clusters) were randomly allocated to control (referral only) and intervention (referral and follow-up counselling) arms (n = 14 clusters/arm). Randomisation was stratified on distance from the district capital (≤10 km vs > 10 km) and cluster size (larger single village vs combined small villages), and restricted to ensure balance on selected cluster characteristics. A list of possible allocations was generated and one randomly selected at a public ceremony. HBHCT is being offered to all adults (≥18 years), and HIV-positive individuals not yet in care are eligible for enrolment. The intervention is provided at one and two months post-enrolment. Primary outcomes, assessed 6 months after enrolment, are: the proportion of individuals linking to HIV care within 6 months of HIV diagnosis and time to linkage. The primary analysis will be based on individual-level data.

Discussion: This study will provide evidence on the impact of a counselling intervention on linkage to care among adults identified with HIV infection through HBHCT. Interpretation of the trial outcomes will be aided by results from an on-going qualitative sub-study.

1. Introduction

Access to anti-retroviral therapy (ART) in sub-Saharan Africa has expanded considerably but AIDS-related mortality remains high [1]. A major cause of mortality is the late presentation of patients for care [2,3]. Early ART initiation depends on early HIV diagnosis through HIV counselling and testing (HCT) and prompt linkage to care [4]. HCT is essential in expanding HIV prevention and treatment services [5,6], but its uptake in sub-Saharan Africa remains low [7]. For instance, up to 74% of men and 58% of women in the region have never been tested for HIV [8].

In sub-Saharan Africa, home-based HIV testing and counselling (HBHCT) has the potential to substantially increase people's awareness of their HIV status [9]. HBHCT is highly acceptable [10–12], cost-effective at reaching previously untested persons compared with other HCT models [13], promotes equitable access of services [14] and may promote couples HCT [15,16] and prevention of mother-to-child HIV transmission [16]. Additionally, HBHCT facilitates early HIV diagnosis and may promote early linkage to care [16]. However few studies have reported data on linkage to HIV care after HBHCT [17,18]. Unfortunately, these studies suggest that without additional strategies to facilitate linkage, less than half of HIV-positive persons identified through HBHCT link to care [18,19]. In contrast, HBHCT studies in which such linkage strategies were used showed an increase of up to 90% [20–25]. However, most of these were uncontrolled observational

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studies. There is a need for rigorous evaluation of promising linkage strategies, using randomised controlled trials in order to identify the most effective approach.

Follow-up counselling after HIV diagnosis and referral is one of the strategies that has been utilised to facilitate linkage to care [21,24,25]. Counselling may mitigate psychosocial barriers of linkage to care [26]. For instance, counselling facilitates disclosure of HIV positive status [27]. In turn, disclosure makes it possible for the patient to receive psychosocial support, a key facilitator of linkage to care [28]. Follow-up counselling may also be used to provide information about ART, other care services and encourage linkage to care [29]. It is also a relatively simple strategy that may be delivered through non-medical personnel [30,31], which makes it feasible also in low resource settings. We describe an ongoing cluster randomised controlled trial of follow-up counselling after referral to HIV care, compared to referral only, among individuals diagnosed with HIV infection through HBHCT in Masaka district, Uganda.

1.1. Study objectives and outcomes

The objective of the study is to determine the effectiveness of follow-up counselling on linkage to HIV care, defined as active registration with an HIV clinic. Primary outcomes are: the proportion of individuals linking to care within 6 months of HIV diagnosis through HBHCT, and time between HIV diagnosis and linkage to care. Secondary outcomes include time between HIV diagnosis and receipt of CD4 cell count test results, time between HIV diagnosis and ART initiation, and the proportion of participants who report adherence to daily cotrimoxazole prophylaxis 6 months after HIV diagnosis. A further secondary outcome is the proportion of HIV-negative participants who agree to repeat HIV testing 6 months after HBHCT.

2. Methods

2.1. Study design and population

2.1.1. HIV-positive participants

The study is an open-label cluster randomised controlled trial being conducted in three rural sub-counties in Masaka district, Uganda. It is based at the MRC/UVRI Unit station in Masaka. The study population consists of newly and previously diagnosed HIV-positive adults (≥18 years) identified through HBHCT who are not in care and are willing to provide informed consent and receive follow-up counselling at home. Exclusion criteria include: previous/current receipt of HIV care, on-going participation in other health-related research, planned change of residence in the next 6 months, and inability to provide informed consent.

2.1.2. HIV-negative participants

HIV-negative adults (≥18 years) who are willing to provide informed consent, receive follow-up counselling at home, and have no intention of changing residence in the next 6 months are recruited from each randomised community primarily to reduce the possibility of revealing the HIV positive status of the main trial participants. Data from these participants will also be used to investigate whether follow-up counselling increases the uptake of repeat HIV testing.

2.2. Identification and selection of clusters

Clusters comprised one or more villages i.e. the smallest administrative areas. All villages (n = 158) in the study area were mapped (Fig. 1) and the number of adults in each village obtained (range: 50–1500). To ensure a reasonable number of eligible participants in each cluster, we combined small (<400 adults) villages with adjacent villages into larger clusters of at least 400 adults. Therefore, a cluster was defined as a village or a set of villages with at least 400 adults. Clusters were separated by a buffer zone of at least one non-participating village to minimise the risk of contamination.

2.3. Sample size estimates

Sample size was calculated to ensure adequate power to address the hypothesis that follow-up counselling would increase the proportion of individuals that link to care. Based on previous studies in the area [32,33], we assumed an adult HIV prevalence of 10%. The 2011 Uganda national HIV sero-prevalence survey (Masaka district was included in the survey) found that 60% of HIV-positive adults are unaware of their HIV status and are therefore not in care [33]. However, anticipating increased HCT coverage since the survey, we adjusted this figure to 40%. Based on these figures and the population estimates from the mapping data (harmonic mean of 525 adults in each cluster), we estimated that the harmonic mean number of HIV-positive persons who would not be in care in a cluster was 21 (i.e. $525 \times 0.10 \times 0.40$). After further adjusting for persons who would be excluded due to ineligibility or refusal to participate (10%) as well as loss to follow-up (10%) after enrolment, we estimated that the harmonic mean number of individuals completing the study in each cluster would be 17.

We assumed a between cluster coefficient of variation, k, of 0.25. This was based on past studies of linkage to HIV care [22,34,35] that were conducted in settings similar to Masaka in which k ranged from 0.12 to 0.33. We assumed linkage of 35% in the control arm based on findings from earlier HBHCT studies [36–39]. The estimated intervention effect was based on findings from HBHCT studies that have used follow-up counselling to facilitate linkage to care in Uganda [21,22]. Using methods for stratified cluster randomised trials [40], and assuming a k of 0.25 and a harmonic mean of 17 participants completing the study in each cluster, we estimated that 11 clusters per arm would be required to have 90% power to detect an increase in linkage to care from 35% in the control arm to 60% in the intervention arm as statistically significant ($p < 0.05$). This sample size would also give us 95% power to detect a hazard ratio of 1.7 for the effect of the intervention on time to linkage, or 80% power to detect a hazard ratio of 1.5 [41].

After completing enrolment in the first seven clusters, we observed that 12% (419/3546) of registered resident adults from the mapping exercise were not found at home and could not be contacted in spite of repeated attempts. Of those found at home, 11% (358/3127) declined to have HBHCT. Furthermore, among HIV positive persons, there was a higher than expected level of engagement in HIV care: only 26% (75/294) of those who tested positive in HBHCT were not in care. As a result, the number of participants enrolled per cluster was much lower (harmonic mean < 10) than anticipated. Based on these preliminary findings, the number of clusters was increased to 28 (14 per arm) with an expected harmonic mean of 7 participants completing the study in each cluster; this would allow for detection of the same difference in proportions with a power of 83%, or a hazard ratio of 1.7 with a power of 85%.

2.4. Randomisation of clusters

We used a combination of stratification and restriction in order to minimise between-cluster variation and achieve overall balance between study arms with regard to key variables. First, randomisation was stratified on distance (≤10 km or >10 km) from the Masaka district capital, as this may influence accessibility to HIV

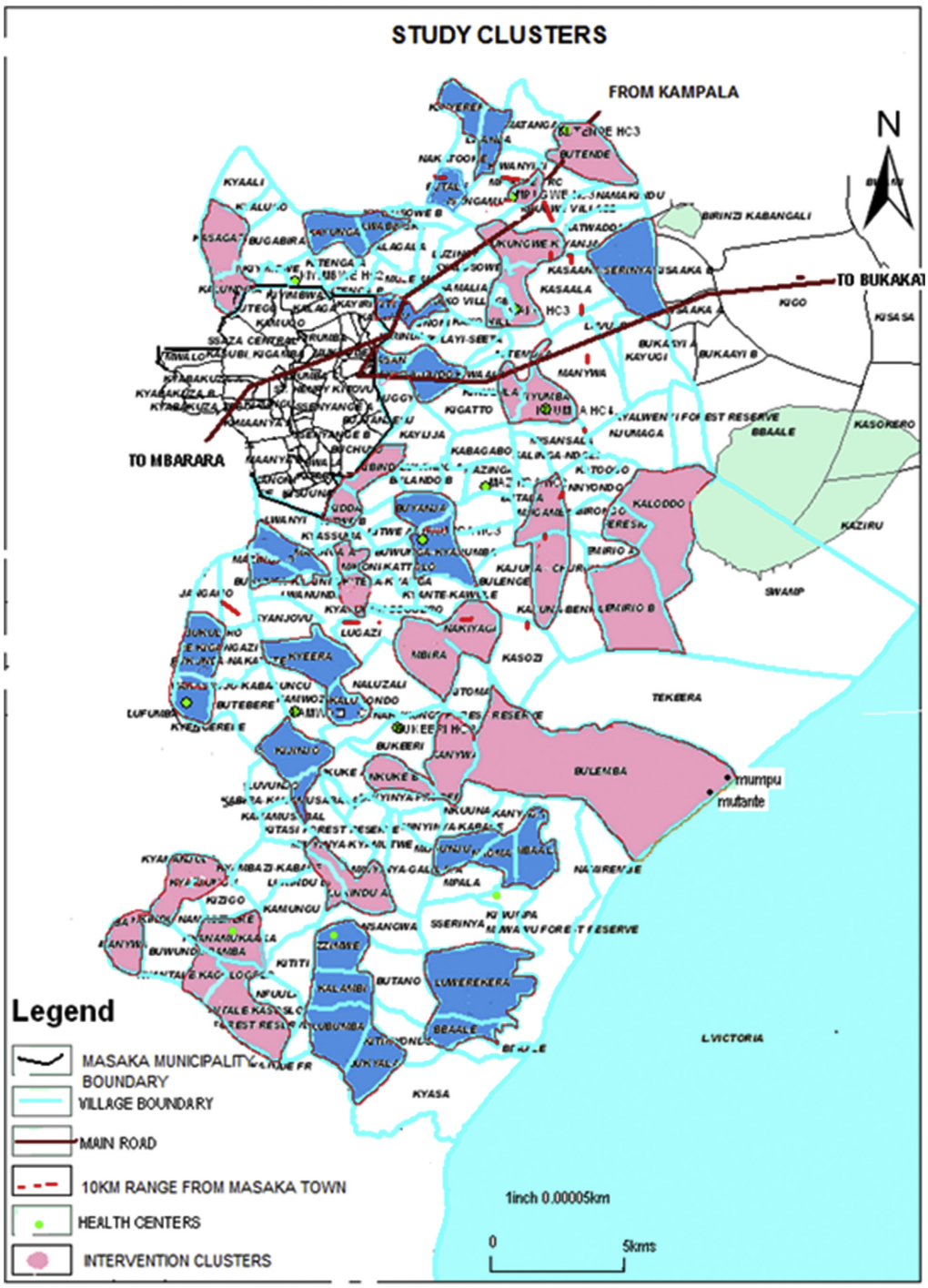

Fig. 1. Study clusters.

care, and on cluster make-up, i.e. whether the cluster was composed of a single large village or several small villages: 70,560 possible allocations (possible ways in which clusters could be randomised to intervention or control arms) were generated under the stratified design. Restricted randomisation was then applied to achieve balance on the following covariates: cluster size; presence of a trading centre; location along a major road; lakeshore location; and presence of an HIV clinic within 5 km. The tolerance thresholds for balance were defined through an iterative process in which different thresholds were tried and the number and the validity of the acceptable allocations examined. Of the possible allocations under the stratified design, 28,932 (41%) were found to satisfy the additional balance criteria after restriction. Of these, a list of 1000 acceptable allocations was randomly generated from which one was selected at public randomisation ceremony. Each allocation had a unique running number.

2.4.1. Public randomisation ceremony

The ceremony was held on 13th March 2015 and attended by 1–2 leaders from each of the villages. Three sacks each containing 10 balls labelled 0 to 9 were prepared, representing allocations 001 to 999, and 000 representing 1000. The principle underlying the random selection procedure was carefully explained in simple words. Three community leaders, selected by their peers, were then invited and one after the other each asked to draw one ball from one sack (3 balls total) thus generating a 3-digit number, corresponding to the allocation running number on the list. The six clusters added later were treated as a separate stratum. Possible allocations for these clusters were generated using the same procedure described above and one allocation selected at a second public randomisation ceremony on 30th June 2015.

2.5. Study interventions

Participants in the control and intervention clusters receive HBHCT and a written referral to an HIV care clinic of their choice if found to be HIV-positive. In addition, participants in the intervention clusters receive two follow-up counselling sessions at their home, delivered within 2 months after testing. Each session lasts about 45 min. The counselling intervention is designed to address common previously described psychosocial barriers of linkage to HIV care such as stigma [42–45], non-disclosure of HIV status [34,46,47], denial of HIV diagnosis [43,45,47], misconceptions about antiretroviral drugs (ARV) [26,30,45], and fear of their side effects [26,30], lack of partner [45,48] and other social support [34,47,49], and misconceptions about ART provider practices [45,49]. The content of the counselling intervention includes: a discussion of the individual's acceptance of HIV diagnosis, experience of stigma, plans to seek care and support services, importance of HIV status disclosure and psychosocial support for linkage to and retention in care; and provision of information about local HIV care services, ARVs, and rationale for early linkage to care. In keeping with previous observational studies of linkage to care interventions [21,22,25,29], follow-up counselling in our study is conducted at one and two months after HBHCT. HIV-negative participants in the intervention arm are offered home-based risk reduction counselling and encouraged to seek regular HIV testing.

2.6. Study procedures

A summary of the study procedures is provided in Table 1.

2.6.1. Preparatory phase

Mapping of the study area, community mobilisation meetings, staff recruitment and training, setting up of referral tracking and linkage verification procedures with HIV care providers were conducted in the three months prior to study initiation. In each cluster, additional community mobilisation is conducted one week prior to HBHCT.

2.6.2. Screening and enrolment

Accompanied by a community guide, study counsellors visit all the households in the randomised clusters, enumerate all resident adults aged ≥18 years and offer them HBHCT. HCT is conducted in accordance with national guidelines [50]. Married/cohabiting individuals are given the option of couple or individualised HCT. Identified HIV-positive individuals who are not yet in care are given a written referral letter (a copy is retained for the study file) to take to their preferred HIV care provider for initiation of cotrimoxazole prophylaxis, CD4 count testing (results available within 4 weeks), and ART initiation if eligible under national guidelines (CD4 <500 cells/μL). Additionally, they are given detailed information about the study and invited to consent and participate. After obtaining consent, the individual's eligibility for the study is assessed, he/she is enrolled if eligible, and informed of his/her cluster allocation. A questionnaire is then administered to collect data on socio-demographic characteristics and history of previous HIV testing history. Households in which some or all adults are not at home are revisited at least two more times.

Once 3–4 HIV-positive participants are enrolled, enrolment is also offered to the first consenting person that tests HIV negative in the next household. We expect to recruit at least 84 HIV-negative participants.

2.6.3. Participant follow-up

There are four post-enrolment home-based follow-up visits.

- Months 1 and 2 (intervention arm only): to provide follow-up counselling.
- Month 6: to collect data on linkage to care and other outcomes, perform CD4 cell count testing for participants who have not had a CD4 count test at an HIV clinic or are not aware of the result, and repeat HCT for HIV-negative participants. CD4 cell count and repeat rapid HIV tests are conducted at the MRC/UVRI laboratory in Masaka town. Repeat rapid HIV tests are conducted at the laboratory instead of participants' homes in order to make the procedures for HIV-positive and HIV-negative participants as similar as possible and thus minimise the risk of revealing participants' HIV status.
- Month 6 + 1 week: to provide CD4 cell count or repeat HIV test results.

Participants not found at home at any of the post-enrolment visits are revisited at least two more times.

2.6.4. Collection of outcome data

Outcome data are collected using two methods: Firstly, a questionnaire is administered by the counsellor to collect information on whether and when the participant linked to care, provided a blood sample for CD4 cell count testing and received the results, was informed of his/her ART eligibility and initiated ART, initiated cotrimoxazole prophylaxis and whether he/she adhered to cotrimoxazole prophylaxis. Good adherence to cotrimoxazole prophylaxis is defined as self-report of having taken >80% (≥25) of 30 doses in the past month. Secondly, clinic records are reviewed, looking for a participant's referral letter and medical forms, and pre-ART and/or ART register books to verify self-reported linkage and other outcomes. Participants whose records are not found at the HIV clinic are re-contacted, informed of the verification outcome, and asked to clarify if they actually registered for care or

Table 1
Study procedures.

Procedure	−3 months	−1 week	Month 0	Month 1	Month 2	Month 6	Month 6 + 1 week
Mapping & identification of clusters	X						
Community mobilisation[a]	X	X					
Recruitment and training of staff	X						
Set up of referral tracking and linkage verification procedures	X						
Census & HBHCT			X				
Study information & informed consent			X				
Eligibility screening & enrolment			X				
Collection of socio-demographic data			X				
Referral for care			X				
Follow-up counselling (Intervention arm)				X	X		
Collection of outcome data (participant interview)						X	
Collection of outcome data (review of HIV clinic records)						X	
Sample collection for CD4 cell count testing[b]						X	
Sample collection for repeat HIV testing						X	
Delivery of CD4 cell count and repeat HIV test results[c]							X

[a] Community mobilisation activities are conducted up to one week before onset of HBHCT in each cluster.
[b] CD4 count testing is done for participants who have not had a CD4 count test or are not aware of the result.
[c] Testing is conducted at the MRC/UVRI in Masaka town.

not. Except for adherence to cotrimoxazole, which is not recorded in the clinic records, only verified data will be used for the analysis of primary and secondary outcomes.

2.6.5. Data management

Data are collected using paper-based questionnaires. Before data entry, questionnaires are checked for completeness and logical consistency. Data are double-entered and validated in Microsoft Access. Queries are run on the entered data every fortnight and reports sent to the study team for resolution. Data arising from the resolved queries are resubmitted for entry and the process is repeated until no more queries are generated.

2.7. Analysis plan

Analyses will be by intention to treat and based on individual-level data, since there is a reasonable number of clusters per arm and the cluster size varies considerably [51]. Random effects logistic regression and Cox regression with shared frailty will be used to estimate the effect of the intervention on the proportion of participants linking to care and time to linkage, respectively. Likelihood ratio tests will be performed for hypothesis testing. Similar methods will be used to estimate the effect of the intervention on the proportions of participants that adhere to cotrimoxazole prophylaxis and undergo repeat HIV testing, and on the time to receipt of CD4 count results, and ART initiation. The primary analysis of the intervention effect for all outcomes will be adjusted for randomisation stratum as a fixed effect. Exploratory analyses adjusting for age and sex a priori, and other characteristics that show substantial baseline imbalance, will also be carried out. Although the primary analyses will be based on individual-level approaches, analyses based on cluster-level approaches will also be performed to check the robustness of the results. Kaplan-Meier methods will be used to calculate time to linkage, receipt of CD4 count results, and ART initiation in each arm. Median and interquartile ranges for time to these outcomes will be estimated. A detailed statistical analysis plan will be prepared prior to data analysis.

Ethical approval

The initial study protocol and subsequent amendments were approved by Uganda Virus Research Institute Research Ethics Committee (GC/127/14/12/491), the Uganda National Council for Science and Technology (HS 1732), and The London School of Hygiene and Tropical Medicine Ethics Committee (8833). Written informed consent (including consent to track referrals and review medical records for persons who link to care) is obtained from each participant before study procedures are conducted. The trial is registered at ClinicalTrials.gov (NCT02497456).

3. Discussion

This study is one of the few randomised trials from sub-Saharan Africa designed to evaluate the effect of an intervention to increase linkage to HIV care following HIV diagnosis through HBHCT. We are aware of five other such trials. The first is a recently completed individually randomised controlled trial from South Africa and Uganda that assessed whether community-based HIV testing (including HBHCT) with counsellor support (home-based follow-up counselling and accompanied referral) and POC CD4 cell count testing increases uptake of ART. In this trial, linkage to care was high (≥89%) across all linkage strategies used [20]. The second is a completed but not yet reported individually randomised trial from rural western Kenya aiming to assess the accuracy, feasibility and acceptability of point-of-care (POC) CD4 testing for persons found HIV positive through HBHCT, and to determine the (cost-) effectiveness of this intervention in improving linkage to care and time to ART initiation [52]. The third is an ongoing cluster randomised trial in rural Uganda to evaluate the effectiveness of linkage to care counselling in achieving HIV viral suppression and to determine intermediate outcomes (linkage, time to initiation of opportunistic infection prophylaxis, and time to initiation of ART among people testing HIV positive during HBHCT) [53]. The fourth is an ongoing household randomised trial in rural Lesotho to evaluate the effectiveness of same day home-based ART initiation after HIV diagnosis coupled with a reduced frequency of clinic follow-up visits in improving linkage to care, retention in care, and viral suppression [54]. The fifth is a planned individually randomised trial in western Kenya that will compare home and other community recruitment strategies, HIV testing strategies (self-testing, HCT in a home/mobile setting, and facility-based HCT), and different linkage strategies (referral only, text message reminder, and financial incentive) to an adaptive (SMART trial design) linkage to care intervention, among young at-risk women [55]. Primary outcomes for this trial include uptake of recruitment strategies, uptake of testing modalities, linkage to and retention in care.

A major strength of our trial is that referrals for care are tracked and medical records examined to verify self-reported linkage. Hence it is unlikely that the proportion of persons linking to care will be overestimated. Despite concerns about inadequate routine

record keeping at health care facilities in Uganda [56], we have so far not encountered such a problem at HIV care clinics. All information on reported linkage collected and analysed to date have either been verified by clinical records, or have been withdrawn as false when individual patients were re-interviewed in case of discrepancies. Participants who self-report not linking to care are not tracked further, as it is unlikely that individuals would link to care but choose to report otherwise.

We randomised communities instead of individuals in order to minimise the risk of contamination between trial arms e.g. through sharing of follow-up counselling information, which would result in a dilution of intervention effects. Also, individual randomisation may not have been acceptable to participants especially if they perceive one of the interventions to be inferior to the other.

The study has some limitations. First, some individuals in the study communities may have knowledge of their cluster allocation which may influence their decision to enrol in the study. Individuals may obtain prior knowledge of cluster allocation through community leaders who attended the pre-enrolment public randomisation ceremony or from those in the same community who have enrolled before them. To minimise the effect of this potentially differential enrolment, individuals are only informed of their cluster allocation after they have consented and enrolled in the study. Additionally, within each village, participants are enrolled over 2–4 days, to minimise the time available for individuals to find out their allocation from fellow village residents. Related to this is the risk of differential loss to follow-up after enrolment e.g. because different proportions of participants may withdraw from the trial after becoming aware of their allocation. To mitigate against this, part of the eligibility criteria is "availability for the entire duration of the study and willingness to be followed up at home". Participants who indicate that they will not be available for follow-up are excluded from the study. Second, despite the creation of buffer zones between clusters, there might still be a risk of contamination resulting from possible interaction between study participants from different trial arms. Data on the occurrence of such interaction is collected at the month-6 visit; the results will be reported along with the main trial findings.

We did not include a component to evaluate cost-effectiveness of the home-based follow-up intervention. Such evaluation may be necessary to inform policy if the intervention is found to be effective. However, given the fact that it is a relatively simple intervention, the costs of incorporating it into the routine HBHCT work are likely to be minimal.

Whereas quantitative methods such as those used in our trial are appropriate for investigating the effect of a health care intervention, a qualitative exploration of experiences, attitudes, beliefs and understandings is needed to find out why the intervention works or does not work [57,58]. For this reason, a qualitative substudy is being conducted in both trial arms in a sub-set of participants who linked successfully to care and others who did not in order to better understand the reasons for linkage or lack of linkage to HIV care.

This study will contribute evidence on the impact of referral plus home-based follow-up counselling on linkage to care, as compared to only referral among adults identified with HIV infection through HBHCT in Uganda. Interpretation of trial outcomes will be aided by findings from the qualitative sub-study.

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Chapter 5 (manuscript 3): Brief counselling after home-based HIV counselling and testing strongly increases linkage to care: a cluster-randomised trial in Uganda

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SECTION A – Student Details

Student	Eugene Ruzagira
Principal Supervisor	Heiner Grosskurth
Thesis Title	Effect of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing on linkage to HIV care in south-western Uganda

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of the International AIDS Society
Please list the paper's authors in the intended authorship order:	Eugene Ruzagira, Heiner Grosskurth, Anatoli Kamali, Kathy Baisley
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the research concept, and designed the study with input from Kathy Baisley (KB), Anatoli Kamali (AK), and Heiner Grosskurth (HG). I was the principal investigator and supervised all study aspects. I wrote the protocol and developed all the study tools, obtained the necessary ethical

	approvals, recruited and trained staff, secured the collaboration of HIV care providers and community leaders, organised and conducted the public randomisation ceremonies, and supervised the screening, enrolment and follow-up of study participants. I supervised data collection and entry, and was responsible for overall data management. I prepared the analysis plan with input from KB, HG, and Richard Hayes. I performed the analysis under KB's supervision. I prepared the manuscript, revised it after receiving comments from KB, AK, and HG, and submitted it for publication.

Student Signature: _____ Date: 02/03/2017

Supervisor Signature: _____ Date: 3/3/2017

Brief counselling after home-based HIV counselling and testing strongly increases linkage to care: a cluster-randomised trial in Uganda

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Key words: HIV/AIDS, home-based HIV counselling and testing, linkage to care, Uganda, Africa

Abstract

Introduction: The aim of this study was to determine whether counselling provided subsequent to HIV testing and referral for care increases linkage to care among HIV-positive persons identified through home-based HIV counselling and testing (HBHCT) in Masaka, Uganda.

Methods: The study was an open-label cluster randomised trial. 28 rural communities were randomly allocated (1:1) to intervention (HBHCT, referral, and counselling at one and two months) or control (HBHCT and referral only). HIV-positive care-naïve adults (≥18 years) were enrolled. To conceal participants' HIV status, one HIV-negative person was recruited for every 3 HIV-positive participants. Primary outcomes were linkage (registration with an HIV clinic) status at 6 months, and time to linkage. Primary analyses were intention-to-treat using random effects logistic regression or Cox regression with shared frailty, as appropriate.

Results: 302 (intervention, n=149; control, n=153) HIV-positive participants were enrolled. Except for travel time to the nearest HIV clinic, baseline participant characteristics were generally balanced between trial arms. Retention was similar across trial arms (92% overall). 127 (42.1%) participants linked to care: 76 (51.0%) in the intervention arm versus 51 (33.3%) in the control arm [odds ratio=2.18, 95% confidence interval (CI)=1.26-3.78; p=0.008)]. There was evidence of interaction between trial arm and follow-up time (p=0.009). The probability of linkage, did not differ between arms in the first two months of follow-up but was subsequently higher in the intervention arm versus the control arm [hazard ratio=4.87, 95% CI=1.79-13.27, p=0.002].

Conclusion: Follow-up counselling substantially increases linkage to care among HIV-positive adults identified through HBHCT and may enhance efforts to increase antiretroviral therapy coverage in sub-Saharan Africa.

Clinical Trial Number: NCT02497456

Introduction

Home-based HIV counselling and testing (HBHCT) is highly acceptable [1-3], cost-effective at reaching previously untested persons compared with other HIV counselling and testing (HCT) models [4], and has the potential to substantially increase knowledge of HIV status in Sub-Saharan Africa (SSA) [5]. However, linkage to care following HBHCT is often inadequate. A recent review found that in the absence of interventions to facilitate linkage, less than one-third of HIV-positive persons identified through HBHCT in SSA link to care [6].

In order for the populations targeted by HBHCT to fully benefit from HIV prevention and care services, interventions that can link them to these services need to be identified and utilised. Results from observational studies suggest that counselling provided after referral could increase linkage to care among HIV-positive persons identified through HBHCT in SSA [7-11]. A major limitation of observational studies however is that it is difficult to account for the effects of confounding factors such as stigma, healthcare seeking behaviour, and familiarity with the health care services. Moreover, counselling in some of these studies [7, 8, 10] was delivered alongside other interventions to increase linkage, making it difficult to distinguish the effects of each. Therefore, randomised trials are required to determine the potential effects of counselling and other interventions on linkage. One randomised trial conducted in South Africa and Uganda evaluated the effect of follow-up counselling after community-based HCT on linkage. In this trial, follow-up counselling had modest effects on linkage [12].

In the current study, we evaluated the effectiveness of counselling after HIV diagnosis and referral to care, compared to referral to care only, on linkage to care among HIV-

positive individuals identified through HBHCT in Masaka district, Uganda. We used a cluster randomised design in order to reduce the risk of contamination between trial arms and increase acceptability of the interventions.

Methods

Study design and participants

The study was an open-label cluster randomised controlled trial. A description of the methods has been previously reported [13]. Briefly, 28 rural communities (clusters) were randomly allocated (1:1) to intervention (HBHCT, referral and counselling at one and two months) or control (HBHCT and referral only). HBHCT was offered to all adults (≥18 years). HIV-positive persons were eligible to participate if they were able to consent, not previously or currently in care, available for follow-up, and not participating in other health-related research. To reduce the possibility of revealing participants' HIV-positive status to other community members, one HIV-negative adult (≥18 years) who was willing to be followed-up was recruited for every 3 HIV-positive participants. Participants were recruited between March and September 2015.

Intervention

The intervention comprised two 45-minute counselling sessions delivered at participants' homes one and two months after HBHCT. The content of the counselling included: a discussion of the individual's acceptance of HIV diagnosis, fear of or experience of stigma, plans to seek care, importance of HIV status disclosure and availability of psychosocial support for linkage to and retention in care; and information about local HIV care services, antiretroviral drugs, and rationale for early linkage to HIV care. HIV-

negative participants in the intervention arm received HIV risk reduction counselling and information on the importance of regular HCT.

Outcomes

Primary outcomes were linkage to care (registration with an HIV clinic), determined 6 months after HIV diagnosis, and time to linkage. Secondary outcomes were time to obtaining a CD4 count, time to antiretroviral therapy (ART) initiation, and adherence (≥80% intake) to daily cotrimoxazole prophylaxis (CTXp) at 6 months. Uptake of repeat HCT at the 6 month visit by HIV-negative participants was also defined as a secondary study outcome.

Randomisation

To ensure a reasonable number of participants in each cluster, small villages were combined with adjacent villages into larger clusters of ≥400 adults. Clusters were separated by a buffer zone of ≥1 non-participating villages to minimise the risk of contamination between trial arms. Clusters were randomly allocated to intervention and control arms. Stratification and restricted randomisation were used to minimise between-cluster variation and achieve overall balance between trial arms with regard to key variables [13]. Stratification was defined by distance (≤10 km or >10 km) from the district capital, and by cluster make-up, i.e. whether the cluster was composed of a single large village or several small villages. Restricted randomisation was then applied to achieve balance on the following cluster-level variables: size (number of adults in a cluster); presence of a trading centre; location along a major road; lakeshore location; and presence of an HIV clinic within 5 km.

Procedures

Preparatory activities: these included mapping of the study area, enumeration of all adults, community mobilisation, and setting of up referral tracking and outcome verification procedures.

HCT: HIV testing was conducted in accordance with national guidelines [14] by experienced counsellors. Married/cohabiting individuals had the option of receiving HCT as a couple. Blood obtained by finger-prick was tested using HIV rapid test kits: Alere Determine HIV-1/HIV-2 (Alere Medical, Japan) for screening, Stat-Pak HIV 1/2 (Chembio Diagnostic systems, USA) for confirmation of positive results, and Uni-Gold HIV 1/2 (Trinity Biotech, Ireland) as tie-breaker.

Enrolment: Eligible individuals were given study information, informed that their community could either be in either of the study arms, and invited to consent. Individuals were informed about which trial arm their community was allocated to after enrolment. Participants completed a counsellor-administered questionnaire on socio-demographic characteristics and HCT history.

Collection of outcome data: 6 months after HBHCT, participants were visited by a counsellor to collect information on study outcomes. To assess the potential of contamination between trial arms, participants were asked if they knew of persons from other villages who were participating in the study and if they had discussed the study with them. Self-reported linkage and other outcomes were confirmed by tracking referrals and reviewing clinic records. Participants whose records could not be found at the clinics were

informed of the verification outcome and asked to clarify if they had actually linked or not.

HIV-negative study component: similar enrolment procedures were applied to the HIV-negative participants. Study counsellors visited participants in the intervention arm at one and two months to conduct counselling, and in both arms at 6 months, to offer repeat HCT.

Ethical considerations

The trial was approved by Uganda Virus Research Institute Research Ethics Committee, the Uganda National Council for Science and Technology, and the Ethics Committee of the London School of Hygiene and Tropical Medicine. Written informed consent was obtained from each participant before study procedures were conducted. The trial is registered at ClinicalTrials.gov (NCT02497456).

Sample size

Based on findings from HBHCT studies in which only referral was provided following HIV diagnosis [15-18] and those in which counselling was provided after referral [7, 8], we assumed linkage of 35% in the control arm and that this would increase to 60% in the intervention arm. We aimed to have 80% power to detect this increase in linkage at a significance level of 5%. Based on data from settings similar to Masaka [13], we assumed that the between-cluster coefficient of variation (k) for linkage in the absence of intervention was 0.25. Based on these assumptions and an estimated harmonic mean of 7 participants per cluster, 28 clusters would be needed. This sample size would also provide

>80% power to detect a hazard ratio of 1.7 for the effect of the intervention on time to linkage [19].

Analysis

All analyses were pre-specified in an analysis plan. The primary analyses were intention-to-treat and based on individual-level data, since there was a sufficient number of clusters per arm and the cluster size varied considerably [20]. Random effects logistic regression and Cox regression with shared frailty were used to estimate the effect of the intervention on the linkage and time to linkage, respectively. Participants who were lost to follow-up were assumed not to have linked to care. Those who were reported at the 6 month follow-up visit to have permanently left the study area were censored midway between enrolment and that visit. Those who were still in the study area but did not attend the 6 month visit were censored at that visit. The primary analyses of the intervention effect were adjusted for randomisation stratum as a fixed effect. Secondary analyses were adjusted for age and sex a priori, and other characteristics that showed substantial baseline imbalance. Due to the nature of the intervention i.e. repeated counselling sessions, it was expected that the effect of the intervention might change over time. Therefore, the proportional hazards assumption was examined by splitting follow-up time into two intervals (0-2 months and >2 months) at a point corresponding with the time of the second counselling session, and testing for an interaction between trial arm and time. Similar methods were used to estimate the effect of the intervention on the proportions that adhered to CTXp, and on the time to obtaining CD4 counts, and ART initiation among HIV-positive participants, and on the proportion that accepted repeat HCT among HIV-negative participants.

Analyses based on cluster-level summaries (Additional file 1) were also performed to check the robustness of the individual-level analysis, using methods for stratified cluster randomised trials [21]. Intervention effects on binary outcomes were measured using prevalence ratios (PR), calculated as the ratio of the arithmetic mean of the cluster-specific prevalence of the outcome in each arm. The 95% confidence interval (CI) was calculated with variance estimated from the residual mean square from a two-way analysis of variance (ANOVA) of cluster-specific prevalence on stratum and trial arm. Adjusted PR were calculated as the arithmetic mean ratio of observed to expected prevalences in each cluster, with logistic regression used to estimate the expected prevalence, adjusted for age, sex, stratum, and other variables that showed baseline imbalance. CIs were obtained from an ANOVA of the observed/expected prevalences on stratum and trial arm, as described above. Intervention effects on time-to-event outcomes were measured using rate ratios (RR) by similar methods; Poisson regression was used to estimate expected number of events for the adjusted analyses.

Data from the control arm was used to estimate *k* for linkage to care. STATA version 12.0 (StataCorp, College Station, Texas) was used for all analyses.

Results

The trial profile is shown in Figure 1.

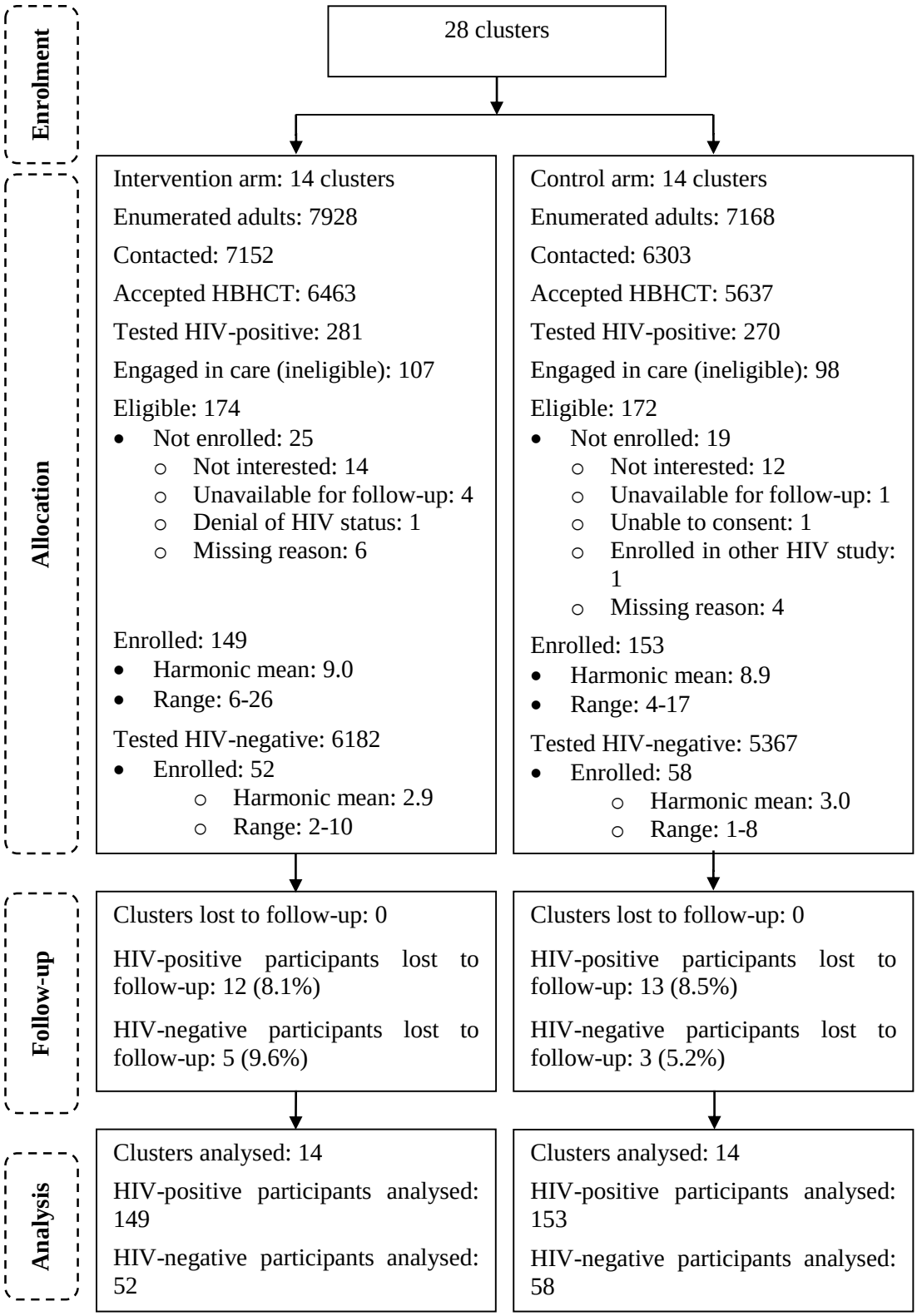

Figure 1: Flow of clusters and participants through the trial

13,455 people (89.1% of those enumerated) were contacted of which 12,100 (89.9%) accepted HBHCT. Common reasons for declining HBHCT were being HIV-positive and already engaged in care (437, 32.3%), not wanting to know one's HIV status (397, 29.3%), and having recently undergone HCT (214, 15.8%). Of those who accepted HBHCT, 551 (4.6%) tested HIV-positive, and of these 205 (37.2%) were already in care and thus ineligible. Of those eligible, 302 (87.3%) were enrolled. Baseline participant characteristics are summarized in Table 1.

Table 1: Baseline characteristics of participants

	HIV-positive participants		**HIV-negative participants**	
	Intervention	**Control**	**Intervention**	**Control**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Total enrolled	149	153	52	58
Sex				
Female	76 (51.0)	89 (58.2)	26 (50.0)	37 (63.8)
Male	73 (49.0)	64 (41.8)	26 (50.0)	21 (36.2)
Mean age in years (SD)	32.6 (11.3)	33.7 (12.0)	36.1 (11.9)	33.6 (12.5)
Age group				
18-24 years	34 (22.8)	37 (24.2)	10 (19.2)	16 (27.6)
25-34 years	63 (42.3)	58 (37.9)	15 (28.9)	18 (31.0)
35-44 years	29 (19.5)	30 (19.6)	14 (26.9)	13 (22.4)
45+ years	23 (15.4)	28 (18.3)	13 (25.0)	11 (19.0)
Marital status				
Married/cohabiting	85 (57.1)	97 (63.4)	38 (73.1)	43 (74.1)
Single	22 (14.8)	26 (17.0)	6 (11.5)	10 (17.2)
Divorced/separated/widowed	42 (28.2)	30 (19.6)	8 (15.4)	5 (8.6)
Education				
None/incomplete primary	86 (57.7)	96 (62.8)	22 (42.3)	25 (43.1)
Primary	34 (22.8)	32 (20.9)	9 (17.3)	14 (24.1)
Above primary	29 (19.5)	25 (16.3)	21 (40.4)	19 (32.8)
Occupation				
Subsistence farmer	84 (56.4)	80 (52.3)	16 (30.8)	25 (43.1)
Other	65 (43.6)	73 (47.7)	36 (69.2)	33 (56.9)
Socio-economic status*				

	HIV-positive participants		HIV-negative participants	
	Intervention	**Control**	**Intervention**	**Control**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Low	56 (37.6)	61 (39.9)	10 (19.2)	19 (32.8)
Middle	52 (34.9)	56 (36.6)	18 (34.6)	14 (24.1)
High	41 (27.5)	36 (23.5)	24 (46.2)	25 (43.1)
Travel time to nearest HIV clinic				
<30 minutes	52 (34.9)	34 (22.2)	21 (40.4)	12 (20.7)
30 minutes or more	97 (65.1)	119 (77.8)	31 (59.6)	46 (79.3)
Ever tested for HIV				
No	30 (20.1)	29 (19.0)	1 (1.9)	1 (1.7)
Yes	119 (79.9)	124 (81.0)	51 (98.1)	57 (98.3)
Tested for HIV in the last 12 months				
No	71 (47.7)	81 (52.9)	6 (11.5)	5 (8.6)
Yes	78 (52.4)	72 (47.1)	46 (88.5)	53 (91.4)
Previously aware of HIV-positive status				
No	131 (87.9)	134 (87.6)	-	-
Yes	18 (12.1)	19 (12.4)	-	-

SD = standard deviation; *Socio-economic status categories were obtained from a wealth index scale based on ownership of household and other properties using principal component analysis.

The mean age of HIV-positive participants was 33.2 years (standard deviation, 11.7); the majority were female (54.6%), married/cohabiting (60.3%), had incomplete primary school/no formal education (60.3%), and had previously undergone HCT (80.5%). 265 (87.8%) were newly diagnosed. Baseline variables were generally balanced between trial arms; however, participants in the intervention arm were more likely to report <30 minutes travel time to the nearest HIV clinic than those in the control arm (34.9% vs. 22.2%). 25 (8.3%) HIV-positive participants were lost to follow-up (12 in the intervention arm): 13 (4.3%) permanently left the study area; 8 (2.6) for unknown reasons; 2 (<1%) died; and 2 (<1%) were unwilling to continue follow-up.

110 HIV-negative individuals were enrolled (Table 1). The distribution of baseline characteristics among HIV-negative participants was similar to that of HIV-positive participants. 8 (7.3%) were lost to follow-up.

Linkage to care: 127 (42.1%) of the 302 HIV-positive participants linked to care: 76 (51.0%) in the intervention arm versus 51 (33.3%) in the control arm [odds ratio (OR)=2.18, 95% CI=1.26-3.78; Table 2].

Table 2: Effect of follow-up counselling on linkage, adherence to CTXp and uptake of repeat HCT

	Intervention arm	Control arm	OR (95% CI)	p-value	aOR (95% CI)¶	p-value
Among HIV-positive participants						
Linkage to care	76/149 (51.0)	51/153 (33.3)	2.18 (1.26-3.78)	0.008	2.14 (1.24-3.70)	0.009
Adherence to CTXp	66/149 (44.3)	43/153 (28.1)	2.15 (1.16-3.98)	0.02	2.17 (1.20-3.93)	0.01
Among HIV-negative participants						
Uptake of repeat HIV test	42/52 (80.8)	46/58 (79.3)	1.08 (0.42-2.78)	0.87	0.70 (0.24-2.03)	0.52

OR = Odds ratio; aOR = adjusted odds ratio; CI = Confidence interval; ¶Adjusted for age, sex, strata & travel time to the nearest HIV clinic

The effect of the intervention was similar after adjusting for age, sex, and travel time to the HIV clinic [adjusted (a)OR=2.14, 95% CI=1.24-3.7)]. The crude and adjusted effect estimates from the cluster-level analysis were attenuated but consistent with a higher linkage in the intervention versus the control arm [prevalence ratio (PR)=1.59, 95% C=1.09-2.33; aPR=1.58, 95% CI=1.07-2.34].

The probability of linkage was similar in both trial arms up to the first month of follow-up. Subsequently, more participants linked in the intervention arm than in the control arm with the difference becoming more marked at around the second month of follow-up (Figure 2).

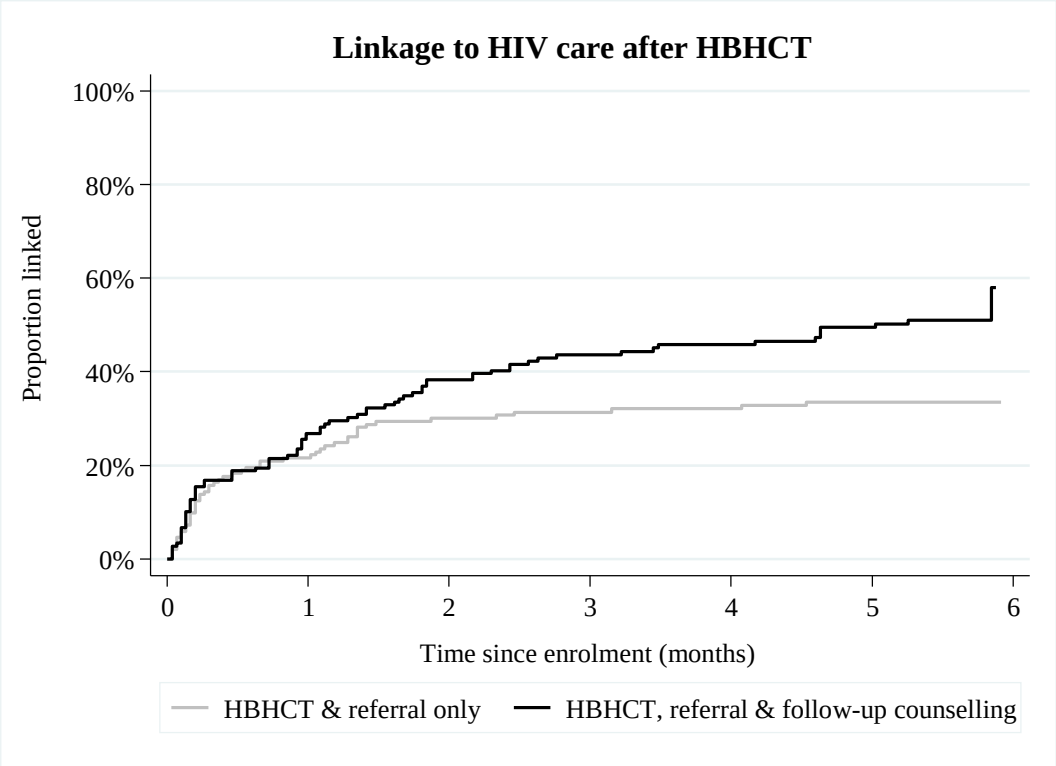

Figure 2: Kaplan-Meier estimates of linkage to care

The overall hazard ratio (HR) was 1.65 (95% CI=1.11-2.44) and was similar after adjusting for age, sex, and travel time to the HIV clinic [aHR=1.62, 95% CI=1.12 to 2.33; Table 3].

Table 3: Effect of follow-up counselling on time to linkage, obtaining CD4 counts and ART initiation

	Intervention arm			Control arm						
	N	**n**	**pm**	**N**	**n**	**pm**	**HR (95% CI)**	**p-value**	**aHR (95% CI)¶**	**p-value**
Linkage to care*										
Entire follow-up period	149	76	492	153	51	590	1.65 (1.11-2.44)	0.02	1.62 (1.12-2.33)	0.02
0 - 2 months	149	57	224	153	46	239	1.32 (0.86-2.03)	0.20	1.30 (0.87-1.94)	0.20
>2 months	92	19	268	107	5	351	4.87 (1.79-13.27)	0.002	4.78 (1.77-12.89)	0.002
Obtaining CD4 counts*										
Entire follow-up period	149	67	561	153	40	664	1.91 (1.25-2.93)	0.005	1.86 (1.23-2.80)	0.007
0 - 2 months	149	40	247	153	30	266	1.45 (0.88-2.40)	0.14	1.41 (0.87-2.28)	0.17
>2 months	109	27	313	123	10	398	3.35 (1.59-7.04)	0.001	3.27 (1.57-6.81)	0.002
ART initiation*										
Entire follow-up period	149	50	630	153	40	662	1.31 (0.85-2.04)	0.22	1.33 (0.85-2.06)	0.21
0 - 2 months	149	25	264	153	33	262	0.78 (0.46-1.34)	0.37	0.79 (0.46-1.34)	0.38
>2 months	124	25	365	120	7	399	3.90 (1.67-9.11)	0.002	3.96 (1.69-9.26)	0.002

N = sample size; n = number with outcome; pm = person-months; HR = Hazard ratio; aHR = adjusted hazard ratio; CI = Confidence interval; ¶Adjusted for age, sex, strata & travel time to nearest HIV clinic; *The respective p-values for interaction between trial arm and follow-up time for linkage to care, obtaining CD4 counts, and ART initiation were 0.009, 0.05, and 0.0007.

There was strong evidence of interaction between trial arm and follow-up time (p=0.009). In the first interval (0-2 months), 57 (38.3%) participants linked in the intervention arm versus 46 (30.1%) in the control arm [HR=1.32, 95% CI=0.86-2.03; aHR=1.30, 95% CI=0.87-1.94]. In the second interval (>2 months), 19 (20.7%) participants linked in the intervention arm versus 5 (4.7%) in the control arm [HR=4.87, 95% CI=1.79-13.27; aHR=4.78, 95% CI=1.77-12.89]. The cluster-level analysis was also consistent with an intervention effect on rate of linkage [rate ratio (RR)=1.84, 95% CI=0.99-3.42; aRR=1.92, 95% CI=0.96-3.86)].

Obtaining CD4 counts from HIV clinics: 107 (35.4%) participants obtained CD4 counts; 67 (45.0%) in the intervention arm versus 40 (26.1%) in the control arm. The overall HR was 1.91 (95% CI=1.25-2.93; Table 3) and was similar after adjusting for age, sex, and travel time to the HIV clinic [aHR=1.86, 95% CI= 1.23-2.80]. There was some evidence of interaction between trial arm and follow-up time (p=0.05). In the first follow-up interval, 40 (26.8%) participants obtained CD4 counts in the intervention arm versus 30 (19.6%) in the control arm [HR=1.45, 95% CI=0.88-2.40; aHR=1.41, 95% CI=0.87-2.28]. In the second follow-up interval, 27 (24.8%) participants obtained CD4 counts in the intervention arm versus 10 (8.1%) in the control arm [HR=3.35, 95% CI=1.59-7.04; aHR=3.27, 95% CI=1.57-6.81]. Results from the cluster-level analysis were consistent with an intervention effect on time to receiving CD4 counts [RR=2.10, 95% CI=1.14-3.84; aRR=2.12, 95% CI=1.22-3.70].

ART initiation: 90 (29.8%) participants initiated ART overall; 50 (33.6%) in the intervention arm versus 40 (26.1%) in the control arm. The overall HR was 1.31 (95% CI=0.85-2.04) and was similar after adjusting for age, sex, and travel time to the HIV

clinic [aHR=1.33, 95% CI=0.85-2.06; Table 3]. There was strong evidence of interaction between trial arm and follow-up time (p=0.0007). In the first follow-up interval, 25 (16.8%) participants initiated ART in the intervention arm versus 33 (21.6%) in the control arm [HR=0.78, 95% CI=0.46-1.34; aHR=0.79, 95% CI=0.46-1.34]. In the second follow-up interval, 25 (20.2%) participants initiated ART in the intervention arm versus 7 (5.8%) in the control arm [HR=3.90, 95% CI=1.67-9.11; aHR=3.96, 95% CI=1.69-9.26]. In the cluster-level analysis, the intervention also increased ART initiation overall, but there was no evidence of a significant difference [RR=1.21, 95% CI=0.69-2.13; aRR=1.27, 95% CI=0.77-2.12].

Adherence to CTXp: 36.1% of the participants reported adhering to CTXp; adherence was higher in the intervention arm compared to the control arm [44.3% versus 28.1%; OR=2.15, 95% CI=1.16-3.98; aOR (adjusted for age, sex, and time to the HIV clinic)=2.17, 95% CI=1.20-3.93; Table 2]. The cluster-level estimates for the effect of intervention on adherence to CTXp were attenuated compared with those from the individual-level analysis, but were consistent with significantly higher adherence in the intervention arm compared to the control arm [PR=1.69 95% CI=1.04-2.75; aPR=1.70, 95% CI=1.06-2.74].

Uptake of repeat HCT among HIV-negative participants: overall uptake of repeat HCT was 80.0%. There was no evidence of a difference in uptake between intervention and control arms [80.8% versus 79.3%; OR=1.08, 95% CI=0.42-2.78; aOR (adjusted for age, sex, and time to the HIV clinic)=0.70, 95% CI= 0.24-2.03; Table 2]. Conclusions from the cluster-level analysis were similar [PR=0.95, 95% CI=0.76-1.20; aPR=0.90, 95% CI=0.72-1.13].

Contamination: two (<1%) individuals reported that they had discussed the trial with participants from villages other than their own.

Coefficient of variation: k values for linkage and rate of linkage were 0.33 and 0.52 respectively.

Discussion

This trial showed that an intervention comprising two brief counselling sessions for adults identified with HIV through HBHCT strongly increases linkage to care. In the individual-level analysis, the intervention was associated with a twofold increase in the proportion of persons linking to care, and approximately 5-fold increase in the hazard of linkage after the second counselling visit; the estimates did not change after adjusting for age, sex, and travel time to the HIV clinic. Results from the cluster-level analysis were also consistent with an intervention effect on linkage and time to linkage. The trial also showed that follow-up counselling significantly increased the rate of obtaining CD4 counts, ART initiation, and adherence to CTXp. For all time-to-event outcomes, the intervention effect increased with follow-up time, and became apparent after the second follow-up counselling visit.

These results support reports from observational studies of enhanced linkage after follow-up counselling for persons identified with HIV through HBHCT [7, 8, 10]. The effect estimates observed in this trial were stronger than those observed in a previous trial that investigated the impact of follow-up counselling after community-based HCT (including HBHCT) on linkage [12]. Follow-up counselling in that trial increased the proportions of individuals linking and initiating ART by only 4% and 23% respectively. This was

probably due to the high (89%) level of linkage in the standard-of-care (referral only) arm of that trial and the high proportion of ART-eligible participants who did not start ART due to the requirement for repeat CD4 count testing at the clinic [participants were randomly assigned in a factorial design to counsellor clinic linkage facilitation, counsellor follow-up home visits, or standard-of-care, and then either point-of-care CD4 count testing or referral for clinic CD4 count testing] and other clinic-level barriers to ART initiation. In contrast, linkage in our standard-of-care arm was 33.3%, a figure consistent with that observed after routine referral in studies from diverse settings in SSA [15, 16, 22-25]. Additionally, all HIV care providers in our study area were aware of our trial and facilitated the verification of study outcomes for participants who sought care at their facilities. It is possible that this collaboration may have reduced the effects of clinic-level barriers on the uptake of care services for our trial participants, making it possible to detect an intervention effect beyond linkage. Although a reduction in clinic-level barriers to uptake of care would have been similar for participants in both treatment arms, those in the intervention arm would have been better prepared to take advantage of this than their counterparts in the control arm if follow-up counselling increased motivation to initiate care.

Consistent with previous studies in generalised epidemic settings [26, 27], uptake of repeat HCT among HIV-negative individuals was high. Previous HCT may reduce the psychological stress associated with testing hence making it easier to accept repeat HCT. Follow-up counselling had no measurable effect on uptake of repeat HCT. This may partly be due to the high (79.3%) uptake of HCT in the control arm, and partly due to the small sample size.

The study had a number of strengths. The trial was conducted under real-world conditions in a relatively large area. HIV-positive participants were referred for care to over ten facilities that provided standard services. Participation and retention rates were high and did not differ by treatment arm thereby reducing risk of selection bias. The cluster randomised design further minimised selection bias, and ensured that the risk of contamination between treatment arms, and consequently that of diluting the intervention effects, was low. Referrals for all participants who reported having linked to care were tracked to the clinics to verify linkage, receipt of CD4 counts, initiation of CTXp and ART. This minimised the risk of bias that would have resulted from incomplete tracking of referrals and reliance on self-reported data. Indeed, 5% of the participants who reported having linked had in fact not done so when this information was verified at the clinics, a classical example of social desirability bias.

The study also had some limitations. First, it was an open-label study: knowledge of the interventions may have influenced participants' decisions to remain in the study. However since there was no differential loss to follow-up between arms, this is unlikely to have been a major issue. Second, data on adherence to CTXp was based on self-reports and could have been prone to social desirability or recall bias. Third, we did not measure the impact of follow-up counselling on retention in care due to the short follow-up period. Fourth, the observed *k* was higher than that used in the sample size estimation implying that the trial could potentially have been slightly underpowered.

In summary, this is the second randomised trial designed to evaluate the effect of an intervention on linkage to care following HIV diagnosis through HBHCT in SSA. The findings suggest that follow-up counselling, a relatively simple intervention delivered by

non-medical personnel to HIV-positive adults identified through HBHCT, substantially increases linkage to care and uptake of other services including ART. In settings such as ours, follow-up counselling may be a useful strategy in achieving the second UNAIDS target (i.e. receipt of ART for 90% of the people who know their HIV status) [28] and should be considered for scaling up.

Competing interests

The authors have no competing interests to declare

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Authors' contributions

All authors contributed to the conception and design of the study; E.R. conducted the study; A.K. provided technical oversight; E.R., K.B. did the data analysis; E.R., H.G., K.B. developed the first draft. All authors participated in writing the manuscript and approved the final version.

Additional file 1: Cluster-level summaries

Table 4: Proportions of HIV-positive participants linking to care in each cluster

Intervention arm			Control arm		
Cluster	Number enrolled	Number linked (%)	Cluster	Number enrolled	Number linked (%)
3	6	2 (33.3)	8	15	4 (26.7)
13	7	2 (28.6)	9	12	6 (50.0)
17	17	10 (58.8)	19	4	2 (50.0)
20	12	5 (41.7)	22	6	1 (16.7)
29	8	3 (37.5)	25	10	5 (50.0)
33	8	5 (62.5)	37	11	5 (45.5)
35	9	2 (22.2)	43	6	0 (0.0)
38	6	4 (66.7)	46	6	2 (33.3)
52	7	6 (85.7)	50	15	2 (13.2)
53	13	9 (69.2)	62	17	9 (52.9)
54	26	11 (42.3)	65	17	8 (47.1)
73	7	3 (42.9)	70	9	4 (44.4)
74	13	8 (61.5)	71	17	3 (17.6)
75	10	6 (60.0)	72	8	0 (0.0)

Table 5: Cluster-level rates of linkage to care among HIV-positive participants

Intervention arm					Control arm				
Cluster	**Number enrolled**	**Number linked**	**PM**	**Rate/100 PM**	**Cluster**	**Number enrolled**	**Number linked**	**PM**	**Rate/100 PM**
3	6	2	21.5	9.3	8	15	4	64.1	6.2
13	7	2	30.7	6.5	9	12	6	36.1	16.6
17	17	10	56.2	17.8	19	4	2	9.0	22.3
20	12	5	44.4	11.3	22	6	1	26.8	3.7
29	8	3	28.8	10.4	25	10	5	29.6	16.9
33	8	5	19.2	26.0	37	11	5	37.5	13.3
35	9	2	36.1	5.5	43	6	0	32.1	0.0
38	6	4	12.4	32.4	46	6	2	23.2	8.6
52	7	6	12.8	46.8	50	15	2	74.8	2.7
53	13	9	36.4	24.7	62	17	9	47.2	19.0
54	26	11	101.9	10.8	65	17	8	58.6	13.6
73	7	3	24.9	12.0	70	9	4	36.0	11.1
74	13	8	36.2	22.1	71	17	3	70.6	4.2
75	10	6	31.0	19.3	72	8	0	44.1	0.0

PM: person-months

Table 6: Cluster-level rates of obtaining CD4 count results among HIV-positive participants

Intervention arm					Control arm				
Cluster	Number Enrolled	Number receiving CD4 counts	PM	Rate/ 100 PM	Cluster	Number Enrolled	Number receiving CD4 counts	PM	Rate/ 100 PM
3	6	2	21.5	9.3	8	15	3	73.2	4.1
13	7	1	34.5	2.9	9	12	6	38.0	15.8
17	17	8	67.4	11.9	19	4	1	14.6	6.9
20	12	5	47.8	10.5	22	6	1	29.0	3.4
29	8	3	30.1	10.0	25	10	4	37.6	10.7
33	8	5	21.6	23.2	37	11	4	42.8	9.4
35	9	2	36.1	5.5	43	6	0	32.1	0.0
38	6	4	14.1	28.3	46	6	0	33.4	0.0
52	7	4	26.1	15.3	50	15	2	77.1	2.6
53	13	7	47.5	14.7	62	17	9	48.4	18.6
54	26	11	107.8	10.2	65	17	6	70.4	8.5
73	7	3	26.2	11.5	70	9	3	43.9	6.8
74	13	6	47.2	12.7	71	17	1	79.1	1.3
75	10	6	32.6	18.4	72	8	0	44.1	0.0

PM: person-months

Table 7: Cluster-level rates of ART initiation among HIV-positive participants

Intervention arm					Control arm				
Cluster	Number enrolled	Number initiating ART	PM	Rate/100 PM	Cluster	Number enrolled	Number initiating ART	PM	Rate/100 PM
3	6	1	27.2	3.7	8	15	4	68.1	5.9
13	7	1	35.1	2.9	9	12	5	42.5	11.8
17	17	6	71.7	8.4	19	4	2	9.0	22.3
20	12	3	56.5	5.3	22	6	1	31.9	3.1
29	8	3	32.0	9.4	25	10	4	36.3	11.0
33	8	5	22.9	21.8	37	11	3	50.5	5.9
35	9	2	36.1	5.5	43	6	0	32.1	0.0
38	6	3	17.9	16.7	46	6	2	23.2	8.6
52	7	3	30.5	9.9	50	15	1	79.9	1.3
53	13	6	53.2	11.3	62	17	8	50.0	16.0
54	26	6	127.0	4.7	65	17	5	76.0	6.6
73	7	2	32.6	6.1	70	9	4	38.9	10.3
74	13	6	45.0	13.3	71	17	1	79.1	1.3
75	10	3	42.0	7.1	72	8	0	44.1	0.0

PM: person-months

Table 8: Proportions of HIV-positive participants adhering to CTXp in each cluster

Intervention arm			Control arm		
Cluster	Number enrolled	Number adhering to CTXp (%)	Cluster	Number enrolled	Number adhering to CTXp (%)
3	6	1 (16.7)	8	15	3 (20.0)
13	7	1 (14.3)	9	12	6 (50.0)
17	17	10 (58.8)	19	4	1 (25.0)
20	12	4 (33.3)	22	6	0 (0.0)
29	8	3 (37.5)	25	10	5 (50.0)
33	8	5 (62.5)	37	11	4 (36.4)
35	9	1 (11.1)	43	6	0 (0.0)
38	6	4 (66.7))	46	6	1 (16.7)
52	7	3 (42.9)	50	15	2 (13.3)
53	13	7 (53.8)	62	17	8 (47.1)
54	26	10 (38.5)	65	17	7 (41.2)
73	7	3 (42.9)	70	9	4 (44.4)
74	13	8 (61.5)	71	17	2 (11.8)
75	10	6 (60.0)	72	8	0 (0.0)

Table 9: Proportions of HIV-negative participants undergoing repeat HIV testing at 6 months in each cluster

Intervention arm			Control arm		
Cluster	Number enrolled	Number undergoing repeat testing (%)	Cluster	Number enrolled	Number undergoing repeat testing (%)
3	2	2 (100.0)	8	7	6 (85.7)
13	3	1 (33.3)	9	8	6 (75.0)
17	8	7 (87.5)	19	1	1 (100.0)
20	4	4 (100.0)	22	2	1 (50.0)
29	2	1 (50.0)	25	4	4 (100.0)
33	2	1 (50.0)	37	3	2 (66.7)
35	3	3 (100.0)	43	2	2 (100.0)
38	2	2 (100.0)	46	3	3 (100.0)
52	2	2 (100.0)	50	5	4 (80.0)
53	4	3 (75.0)	62	6	4 (66.7)
54	10	8 (80.0)	65	7	5 (71.4)
73	3	2 (66.7)	70	3	2 (66.7)
74	4	3 (75.0)	71	5	4 (80.0)
75	3	3 (100.0)	72	2	2 (100.0)

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Chapter 6 (manuscript 4): Factors associated with uptake of home-based HIV counselling and testing and access to HIV care services among identified HIV-positive persons in Masaka, Uganda

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SECTION A – Student Details

Student	Eugene Ruzagira
Principal Supervisor	Heiner Grosskurth
Thesis Title	Effect of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing on linkage to HIV care in south-western Uganda

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	AIDS Care
Please list the paper's authors in the intended authorship order:	Eugene Ruzagira, Kathy Baisley, Anatoli Kamali, Heiner Grosskurth
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study with input from Kathy Baisley (KB), Anatoli Kamali (AK), and Heiner Grosskurth (HG). I was the principal investigator and supervised all study aspects. I performed the analysis under KB's and HG's supervision. I prepared the manuscript, revised it after receiving comments from KB,

	AK, and HG, and submitted the final draft for publication.

Student Signature: _____ Date: 02/03/2017

Supervisor Signature: _____ Date: 3/3/2017

Factors associated with uptake of home-based HIV counselling and testing and access to HIV care services among identified HIV-positive persons in Masaka, Uganda

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Abstract

We aimed to investigate factors associated with uptake of home-based HIV testing and counselling (HBHCT) and access to care among those testing HIV-positive. We used data from a cluster-randomised trial which had demonstrated the effectiveness of a post-HBHCT counselling intervention. The trial results have been reported previously. HBHCT was offered to adults (≥18 years) from 28 rural communities from Masaka, Uganda; HIV-positive individuals not yet in care were enrolled. The primary outcome was linkage (registering with an HIV clinic) status six months post-HBHCT. Random effects logistic regression was performed to investigate predictors of HBHCT uptake, linkage, obtaining CD4 counts, adherence to cotrimoxazole prophylaxis (CTXp) (≥80% intake), and antiretroviral therapy (ART) initiation. Risk factor analysis for uptake of post-HBHCT services was adjusted for trial arm. 12,100 (89.9%) of 13,455 persons accepted HBHCT. HBHCT uptake was higher among men [adjusted odds ratio (aOR) 1.20, 95% confidence interval (CI) 1.07-1.36] than women, and decreased with increasing age. 551 (4.6%) persons tested HIV-positive, of whom 205 (37.2%) were in care (ineligible). 302 individuals (87.3% of those eligible) were enrolled; of these, 42.1% linked, 35.4% obtained CD4 counts, 29.8% initiated ART, and 36.1% reported adherence

to CTXp. None of the assessed factors predicted linkage. CD4 count receipt was lower in participants who required ≥30 minutes to reach the nearest HIV clinic (aOR 0.60, 95% CI 0.34-1.06) versus those who required less time. ART initiation was higher in older participants (≥45 versus <25, aOR 2.14, 95% CI 0.98-4.65), and lower in single (aOR 0.60, 95% CI 0.28-1.31) or divorced/separated/widowed (aOR 0.47, 95% CI 0.23-0.93) individuals versus the married/cohabiting. These differences were non-significant. In summary, HBHCT acceptability was high but care uptake among identified HIV-positive persons was low. Interventions to increase enrolment in care are needed and should focus on increasing the desire to receive care.

Key words: HIV/AIDS, HIV counselling and testing, linkage to care, Uganda, Africa

Introduction

HIV counselling and testing (HCT) is essential for expanding HIV prevention and treatment services (Matovu & Makumbi, 2007). Although access to HCT in sub-Saharan Africa (SSA) has increased significantly over the past few years, its uptake remains low (WHO, 2015). For instance, only 60% of adults living with HIV know their HIV status (UNAIDS, 2016). Consequently, many HIV-positive people present late for care (Siedner et al., 2015) and AIDS-related morbidity and mortality remain high (UNAIDS, 2014). In order to expand HCT coverage in generalised epidemic settings and to achieve the UNAIDS target of diagnosing 90% of all people with HIV by 2020, WHO recommends the use of a combination of facility-based and community-based HCT models (WHO, 2015).

Home-based HIV testing and counselling (HBHCT) has the potential to substantially increase knowledge of HIV status in SSA (Sabapathy, Van den Bergh, Fidler, Hayes, & Ford, 2012). HBHCT is highly acceptable (Sabapathy et al., 2012), cost-effective at

reaching previously untested persons compared with other HCT models (Menzies et al., 2009), and may promote uptake of HCT by couples (Mantell et al., 2014) and of services to prevent mother-to-child HIV transmission (Wachira, Kimaiyo, Ndege, Mamlin, & Braitstein, 2012). Additionally, HBHCT facilitates early HIV diagnosis and could potentially promote early linkage to care (Wachira et al., 2012). However, there are limited data on linkage to care after HBHCT (Medley et al., 2013). These data suggest that in the absence of interventions to facilitate linkage, up to 70% of HIV-positive persons identified through HBHCT in SSA do not link to care, and that among those eligible for antiretroviral therapy (ART), over 80% do not initiate it (Sharma, Ying, Tarr, & Barnabas, 2015). In order to design effective HBHCT programs, there is a need to understand the determinants of linkage to and uptake of HIV care services after HBHCT.

Methods

Setting and study population

Data used for this analysis were generated during an open-label cluster randomised trial that evaluated the effectiveness of a counselling intervention on linkage to care after HBHCT between March 2015 and March 2016 in Masaka district, Uganda (ClinicalTrials.gov, 2015). Twenty-eight rural communities (clusters) were randomly allocated to intervention (care referral and follow-up counselling) or control (care referral only) arms (n=14 clusters/arm). Randomisation was stratified on distance from the district capital (≤10 km vs >10 km) and cluster composition (larger single village vs combined small villages), and restricted to achieve balance on the following cluster-level covariates: cluster size; presence of a trading centre; location along a major road; lakeshore location; and presence of an HIV clinic within 5 km. The study population comprised resident adults (≥18 years) who tested HIV-positive, had never received HIV

care and were willing to be followed-up at home for up to 6 months after HIV diagnosis.

Study procedures

These have been described previously (Ruzagira, Baisley, Kamali, & Grosskurth, 2017). Briefly, residents in the randomised communities were informed about planned HBHCT activities through community meetings and/or door-to-door mobilisation by study staff and village health team members. Three to seven days following community mobilisation, study counsellors visited all the households in a community, enumerated resident adults and collected data on age and sex. HBHCT was offered to all consenting adults. Individuals who tested HIV-positive and were not in care were given referral letters to take to their preferred HIV clinics. Additionally, they were given information about the linkage-to-care trial and invited to participate. Consenting individuals were assessed for eligibility, enrolled if eligible, and completed a staff-administered questionnaire. Participants were not informed of their community's allocation until after enrolment. In intervention clusters, counsellors visited participants' homes at one and two months after enrolment to provide counselling aiming to encourage linkage to care. All participants were revisited six months post-enrolment to collect data on linkage to and uptake of HIV care services. Self-reported linkage was confirmed by tracking referrals and reviewing clinic records.

Outcomes

The primary outcome for the HBHCT phase was uptake of HBHCT. Primary outcomes of the trial were linkage status six months after enrolment, and time to linkage. This paper investigates factors associated with uptake of HBHCT (i.e. the proportion of all individuals offered HBHCT who accepted and had an HIV test performed at home);

linkage to care (i.e. the proportion of all individuals referred for care who registered with an HIV clinic); CD4 count receipt (i.e. the proportion of all individuals referred for care who received a CD4 count); adherence to cotrimoxazole prophylaxis (CTXp) (i.e. the proportion of all individuals referred for care who initiated CTXp and reported taking ≥80% of their doses); and ART initiation (i.e. the proportion of all individuals referred for care who initiated ART).

Ethical considerations

The trial was approved by the Uganda Virus Research Institute Research Ethics Committee (GC/127/14/12/491), the Uganda National Council for Science and Technology (HS 1732), and the London School of Hygiene and Tropical Medicine Ethics Committee (8833). Written informed consent was obtained from each participant before study procedures were conducted. All participants who did not link to care or who did not have a CD4 count test done by their care provider were offered CD4 count testing at the month six visit.

Analysis

Data were double entered in MS Access and analysed in Stata 12 (StataCorp, College Station, Texas, USA). Descriptive statistics were used to summarise participant characteristics. Pearson chi-squared statistics with the second-order correction of Rao and Scott to account for the clustered design were used to examine differences between variables of interest. Random effects logistic regression models were used to investigate factors associated with each outcome, accounting for the clustered design. Participants who were lost to follow-up were assumed not to have linked to care or attained other study outcomes. Age and sex were included a priori in the multivariable model investigating factors associated with uptake of HBHCT. Cluster-level variables were

then added one at a time and retained if associated with uptake of HBHCT at p<0.10. Trial arm and stratum were included a priori in the analysis of factors associated with linkage to care, CD4 count receipt, ART initiation and adherence to CTXp. Age and sex were then added to the models to evaluate evidence of an association with these variables after accounting for trial arm and stratum; both variables were retained in subsequent models to account for their confounding effects. Cluster-level variables were then added one by one to the trial arm, stratum, age and sex adjusted-analysis and retained if they remained associated with outcome at p<0.10. Individual-level variables were then added one by one and retained if they remained associated with outcome at p<0.10.

Results

Uptake of HBHCT

A total of 15,096 adults were enumerated in the 28 clusters; over half were women (7946, 52.6%) and under <35 years (7909, 52.4%). 13,455 (89.1%) of those enumerated were found at home and offered HBHCT. Absence from home was more common among men than women [1313 men (18.4%) vs. 328 women (4.1%); p<0.001] and among those aged ≥25 years than those under 25 years [1235 aged ≥ 25 years (11.4%) vs. 189 <25 years (4.8%); p< 0.001; age missing for 320 individuals]. 12,100 (89.9%) of those found at home accepted HBHCT. HBHCT uptake was higher among men [adjusted odds ratio (aOR) 1.20, 95% confidence interval (CI) 1.07-1.36] than women, and decreased with increasing age (Table 1). None of the cluster-level characteristics was associated with HBHCT uptake.

Prior knowledge of HIV-positive status and receipt of care was the most common reason (437, 32.3%) for failing to accept HBHCT; this was more common among

women than men [287 (3.8% of women who were offered HBHCT) vs. 150 (2.6% of men who were offered HBHCT); p=0.002] and among those aged ≥25 years than those under 25 years [401 (4.2%) vs. 21 (0.6%); p< 0.001]. Other reasons were a lack of interest in HCT (400, 29.5%); having recently tested for HIV and not wanting a repeat test (214, 15.8%); low HIV risk perception (92, 6.8%); and inability to consent (8, 0.6%). Reasons were not documented for 204 (15.1%) individuals.

Linkage to care

551 individuals (4.6% of those accepting HBHCT) tested HIV-positive, of whom 205 (37.2%) were already in care and thus ineligible. 302 individuals (87.3% of those eligible) were enrolled. Reasons for not enrolling were: a lack of interest in the study (26, 59.1%); unavailability for follow-up (5, 11.4%); inability to consent (1, 2.3%); denial of HIV status (1, 2.3%); and ongoing participation in another HIV-related study (1, 2.3%). Reasons were not documented for 10 (22.7%) individuals. Of those enrolled, most were female (54.6%), under 35 years (63.6%), married/cohabiting (60.3%), had incomplete primary school or no formal education (60.3%), and had tested for HIV previously (80.5%) (Table 2). Only 12.3% were aware of their HIV-positive status prior to this study. Twenty-five (8.3%) participants were lost during the 6 months of follow-up.

Overall, 127 (42.1%) of the enrolled participants linked to care. As reported elsewhere (Ruzagira, Grosskurth, Anatoli, & Kathy, 2017), linkage to care was significantly about 2-fold higher among participants who had received additional counselling. Linkage to care was lower among participants who required ≥30 minutes to travel to the nearest HIV clinic than those who required less time, but there was no evidence of a significant difference (aOR 0.64, 95% CI 0.36-1.11) (Table 2). Other characteristics (individual-level or cluster-level) were not associated with linkage to care. In particular, there was

no evidence that age, sex, socio-economic status, or level of education were associated with linkage.

Receipt of CD4 counts

Overall, 111 (36.8%) participants provided a blood sample for CD4 count testing; results were available for 107 of these (35.4% of all participants and 96.4% of those who provided a blood sample). There was some evidence that participants who required ≥30 minutes of travel time to the nearest HIV clinic were less likely (aOR 0.60, 95% CI 0.34-1.06) to obtain CD4 counts than those who required less time (Table 3). No other characteristics were associated with CD4 count receipt.

Initiation of ART

Of those enrolled, 90 (29.8% of all participants and 70.9% of those who linked) individuals initiated ART within six months of referral. This included 61 (95.3%) of 64 individuals who had a CD4 count of ≤500 cells/mm^3, the ART eligibility threshold at the time of the study (Uganda Ministry of Health, 2014). There was weak evidence that ART initiation was associated with age, with participants aged 45 years or older most likely to initiate ART (aOR 2.14, 95% CI 0.98-4.65, compared with those <25 years) (Table 3). Older participants (≥ 45 years) were more likely to have a CD4 count of ≤500 cells/mm^3 than those who were younger [20 (83.3%) vs. 44 (53.0%), p<0.001] at the time of linkage. There was also weak evidence of an association with marital status, with single (aOR 0.60, 95% CI 0.28-1.31) and divorced/separated/widowed (aOR 0.47, 95% CI 0.23-0.93) participants less likely to initiate ART than married/cohabiting participants. No other characteristics were associated with ART initiation.

Adherence to CTXp

A total of 119 (39.4%) participants initiated CTXp; 109 (36.1% of all participants and 85.8% of those who linked) reported good adherence to CTXp. Adherence to CTXp was lower in men than women (aOR 0.69, 95% CI 0.42-1.14), but there was no evidence of a significant difference (Table 3). There was some evidence of an association with religion, with adherence highest among Anglicans and lowest among Muslims. None of the other characteristics were associated with adherence to CTXp.

Discussion

We observed high (>80%) levels of HBHCT uptake in this rural population. These findings are consistent with those from other settings (Sharma et al., 2015), and reaffirm the potential of HBHCT to achieve universal HIV testing in SSA (Plazy et al., 2016). Although more women than men were found at home in this study, men were more likely than women to accept HBHCT. In contrast to facility-based HCT, men are equally or more (Mutale, Michelo, Jurgensen, & Fylkesnes, 2010; Sabapathy et al., 2012; Sekandi et al., 2011) likely to accept HBHCT. Reasons for this include the convenience, privacy and ease of access associated with HBHCT (Osoti et al., 2015). Similar to other studies (Dalal et al., 2013; Helleringer, Kohler, Frimpong, & Mkandawire, 2009; Sekandi et al., 2011), HBHCT uptake was highest in the youngest age group. Possible reasons for this include a lower HIV risk perception in older compared to younger persons (Sekandi et al., 2011) and the perception of HBHCT as a 'youth friendly' service (Jurgensen et al., 2013). The HBHCT model removes the need to go to a health facility, a major barrier for young people (Mulogo, Abdulaziz, Guerra, & Baine, 2011) and is well-suited to their HIV testing delivery preferences. These include the need for compassionate, friendly, and competent staff; counselling services provided alongside the testing; and testing which is both rapid and free (WHO, 2013).

In the context of our study, an additional explanation may be that compared to younger persons, older persons are more likely to be already aware of their HIV status. We did not collect data on previous HIV-testing at the time of HBHCT and therefore could not examine this possible association. However, our finding that older persons who declined HBHCT were likely to report that they had previously tested HIV-positive suggests this may be the case.

Despite a high uptake of HBHCT, overall linkage to and uptake of HIV care among HIV-positive persons who had never been in care was low. Several HBHCT studies have reported similarly low or even lower (Genberg et al., 2015; Labhardt et al., 2014; Medley et al., 2013; Parker et al., 2015; Plazy et al., 2016; Velen et al., 2016; Wringe et al., 2012) levels of linkage to care than observed in our study. In contrast, other studies have reported high (>60%) levels of linkage to care (Barnabas et al., 2016 ; Barnabas et al., 2014; Naik et al., 2015; Nakigozi et al., 2011; Tumwebaze et al., 2012; van Rooyen et al., 2013). As stated by others (Naik et al., 2015; Plazy et al., 2016), it is difficult to compare these studies as each used a different definition of linkage to care. Additionally, across these studies, populations varied in terms of age composition, setting, access to HIV care services, prior knowledge of HIV-positive status, and previous engagement in HIV care. It is also worth noting that whereas in some studies (Genberg et al., 2015; Medley et al., 2013; Parker et al., 2015; Velen et al., 2016; Wringe et al., 2012) HIV-positive persons were offered routine referral only, others (Barnabas et al., 2016 ; Barnabas et al., 2014; Naik et al., 2015; Nakigozi et al., 2011; Tumwebaze et al., 2012; van Rooyen et al., 2013) included interventions to facilitate referral. In general, linkage to care was lower in the former compared to the latter studies.

As reported previously (Ruzagira, Grosskurth, et al., 2017), participants from our study population who received an intervention comprising two follow-up counselling sessions in addition to referral were more likely to link to HIV care services than those who were referred only. Follow-up counselling may improve care seeking behaviour by providing specific information on how to access services (Ware et al., 2016), enhancing personal motivation (Knight, Van Rooyen, Humphries, Barnabas, & Celum, 2015), and by reducing psychosocial barriers that inhibit linkage to care (Hatcher et al., 2012; Knight et al., 2015; Muhamadi et al., 2011).

Surprisingly, some of the factors found in other studies to facilitate or hinder linkage were not associated with uptake of care in our study. In particular age, sex, socio-economic status, time to reach the HIV clinic or level of education, seem not to have influenced the care seeking behaviour of our study participants.

Although ART initiation was higher among older adults than their younger counterparts, the association was not statistically significant, possibly owing to the small number of persons who initiated ART. Compared to younger persons, older persons may find it easier to accept their HIV status and may be more likely to have the social support and financial resources that facilitate access to care (Naik et al., 2015). In the case of our study, it is also possible that many younger persons did not initiate ART because they were ineligible under the guidelines that were in effect at the time. Indeed, at the time of linkage, only 53.0% of persons aged 18-44 years had a CD4 count of $\leq$500 cells/mm^3, the ART eligibility threshold (Uganda Ministry of Health, 2014), compared to 84.0% among aged $\geq$45 years.

It is worth noting that while the overall proportions of enrolled participants who obtained CD4 counts, initiated ART, and adhered to CTXp were low, uptake of these services among those who linked to care was high. For instance 95.3% of those who linked and had eligible CD4 counts initiated ART. This suggests that the linkage step may be the main bottleneck to uptake of HIV care services in this population.

A limitation of our study is the lack of data on baseline CD4 counts and clinical stage of the infection, and other potential confounders. Our assumption that individuals who did not complete the month six visit did not link to care may have resulted in an underestimation of the proportion who linked to care. This is unlikely however, as such individuals are likely to have stigma or be exposed to circumstances that are associated with reduced linkage to care (Naik et al., 2015). Finally, the relatively small sample size may have limited the power to detect associations between potential risk factors and outcomes. A strength of our study is that self-reported linkage, ART initiation, and receipt of CD4 counts could be verified through clinical records for all participants. Hence it is unlikely that uptake of these services was overestimated.

In conclusion, we found a high uptake of HBHCT but low linkage to and uptake of HIV care services among HIV-positive adults. Surprisingly, in our study access to HIV care was not associated with commonly reported predictors of care uptake. Interventions to increase enrolment in care are needed and should focus on increasing the desire to receive care.

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Table 1. Factors associated with uptake of HBHCT in Masaka, Uganda (N=13455)

			Crude analysis		Adjusted analysis	
	N	Accepted HBHCT (%)	OR (95% CI)	P-value	aOR (95% CI)§	P-value
Age and sex						
Age group (years)						
18-24	3732	3595 (96.3)	1	<0.001	1	<0.001
25-34	3550	3258 (91.8)	0.42 (0.34-0.52)		0.42 (0.34-0.52)	
35-44	2419	2152 (89.0)	0.31 (0.25-0.38)		0.31 (0.25-0.38)	
45+	3651	3094 (84.7)	0.21 (0.17-0.26)		0.21 (0.17-0.26)	
Missing age	103	1 (<1.0)	-		-	-
Sex						
Female	7618	6827 (89.6)	1	0.13	1	0.003
Male	5837	5273 (90.3)	1.09 (0.97-1.23)		1.20 (1.07-1.36)	
Cluster-level variables					**aOR (95% CI)***	
Distance from district capital (stratum)						
≥10Km	7956	7106 (89.3)	1	0.23	1	0.41
<10Km	5499	4994 (90.8)	1.17 (0.91-1.52)		1.10 (0.87-1.39)	
Presence of a trading centre						
No	6825	6095 (89.3)	1	0.43	1	0.39
Yes	6630	6005 (90.6)	1.11 (0.86-1.44)		1.11 (0.88-1.39)	
Located on lakeshore						
No	11079	9988 (90.2)	1	0.44	1	0.39
Yes	2376	2112 (88.9)	0.87 (0.60-1.24)		0.87 (0.63-1.20)	
HIV clinic within 5 km						
No	2995	2665 (90.0)	1	0.40	1	0.48
Yes	10460	9435 (90.2)	1.14 (0.84-1.56)		1.11 (0.84-1.46)	
Located along a major road						
No	9823	8870 (90.3)	1	0.43	1	0.20
Yes	3632	3,230 (88.9)	0.89 (0.66-1.19)		0.84 (0.65-1.09)	

§Age and sex included a priori;*Adjusted for age and sex

Table 2. Factors associated with linkage to care after HBHCT in Masaka, Uganda

			Crude analysis		Adjusted analysis	
	N (Column %)	Linked (Row %)	OR (95% CI)	P-value	aOR (95% CI)§	P-value
Age and sex						
Age group (years)						
18-24	71 (23.5)	25 (35.2)	1	0.37	1	0.28
25-34	121 (40.1)	51 (42.2)	1.30 (0.69-2.45)		1.28 (0.68-2.40)	
35-44	59 (19.5)	24 (40.7)	1.16 (0.55-2.45)		1.23 (0.59-2.60)	
≥45	51 (16.9)	27 (52.9)	1.96 (0.91-4.22)		2.12 (0.99-4.55)	
Sex						
Female	165 (54.6)	72 (43.6)	1	0.51	1	0.44
Male	137 (45.4)	55 (40.2)	0.85 (0.53-1.38)		0.83 (0.51-1.34)	
Cluster-level variables					**aOR (95% CI)***	
Presence of a trading centre						0.92
No	177 (58.6)	72 (40.7)	1	0.73	0.97 (0.54-1.73)	
Yes	125 (41.4)	55 (44.0)	1.12 (0.60-2.09)			
Located on lakeshore						
No	237 (78.5)	100 (42.2)	1	0.95	1	0.90
Yes	65 (21.5)	27 (41.5)	1.03 (0.45-2.33)		0.95 (0.46-1.96)	
HIV clinic within 5 km						
No	80 (26.5)	31 (38.8)	1	0.69	1	0.75
Yes	222 (73.5)	96 (43.2)	1.16 (0.56-2.41)		0.90 (0.45-1.78)	
Located along a major road						
No	216 (71.5)	87 (40.3)	1	0.46	1	0.47
Yes	86 (28.5)	40 (46.5)	1.30 (0.65-2.59)		1.26 (0.67-2.36)	
Other individual-level variables					**aOR (95% CI)†**	
Marital status						
Married/cohabiting	182 (60.3)	75 (41.2)	1	0.41	1	0.86
Single	48 (15.9)	17 (35.4)	0.79 (0.39-1.58)		0.84 (0.42-1.70)	
Divorced/separated/widowed	72 (23.8)	35 (48.6)	1.33 (0.74-2.37)		1.05 (0.57-1.93)	
Education						
None/incomplete primary	182 (60.3)	78 (42.9)	1	0.94	1	0.86
Primary	66 (21.9)	26 (39.4)	0.90 (0.49-1.66)		0.84 (0.46-1.56)	
Above primary	54 (17.9)	23 (42.6)	0.93 (0.49-1.78)		0.92 (0.48-1.77)	
Socio-economic status						
Low	117 (38.7)	50 (42.7)	1	0.91	1	0.93
Middle	108 (35.8)	46 (42.6)	1.01 (0.58-1.77)		1.04 (0.60--1.81)	
High	77 (25.5)	31 (40.3)	0.89 (0.48-1.66)		0.92 (0.49-1.72)	
Religion						
Catholic	213 (70.5)	88 (41.3)	1	0.17	1	0.20
Anglican	42 (13.9)	22 (52.4)	1.55 (0.76-3.15)		1.45 (0.71-2.96)	
Muslim	34 (11.3)	10 (29.4)	0.54 (0.23-1.26)		0.53 (0.23-1.22)	
Other	13 (4.3)	7 (53.9)	1.70 (0.52-5.50		1.48 (0.45-4.83)	
Time to nearest HIV clinic						
<30 minutes	86 (28.5)	44 (51.2)	1	0.05	1	0.11
≥30 minutes	216 (71.5)	83 (38.4)	0.58 (0.33-0.99)		0.64 (0.36-1.11)	
Ever tested for HIV						
No	59 (19.5)	24 (40.7)	1	0.75	1	0.87
Yes	243 (80.5)	103 (42.4)	1.10 (0.60-2.02)		1.05 (0.57-1.95)	

			Crude analysis		Adjusted analysis	
	N (Column %)	**Linked (Row %)**	**OR (95% CI)**	**P-value**	**aOR (95% CI)§**	**P-value**
Aware of HIV-positive status						
No	265 (87.7)	112 (42.3)	1	0.91	1	0.87
Yes	37 (12.3)	15 (40.5)	0.96 (0.46-2.00)		0.94 (0.45-1.96)	

§Adjusted for trial arm and stratum; *Adjusted for trial arm, stratum, age and sex; †Adjusted for trial arm, stratum, age and sex

Table 3. Factors associated with obtaining CD4 counts, initiation of ART and adherence to CTXp after HBHCT in Masaka, Uganda

	Obtaining CD4 counts			Initiating ART			Adhering to CTXp		
		Crude analysis	Adjusted analysis		Crude analysis	Adjusted analysis		Crude analysis	Adjusted analysis
	N (%)	OR (95% CI)	aOR (95% CI)§	N (%)	OR (95% CI)	aOR (95% CI)§	N (%)	OR (95% CI)	aOR (95% CI)§
Age and sex									
Age group (years)		P=0.30	P=0.21		P=0.10	P=0.10		P=0.65	P=0.56
18-24	21 (29.6)	1	1	19 (27.8)	1	1	21 (29.6)	1	1
25-34	42 (34.7)	1.22 (0.63-2.37)	1.21 (0.63-2.32)	36 (29.8)	1.14 (0.59-2.23)	1.11 (0.57-2.17)	44 (36.4)	1.31 (0.68-2.55)	1.29 (0.67-2.50)
35-44	20 (33.9)	1.11 (0.51-2.42)	1.23 (0.57-2.69)	13 (22.0)	0.75 (0.33-1.71)	0.78 (0.34-1.79)	22 (37.3)	1.30 (0.60-2.81)	1.36 (0.63-2.94)
≥45	24 (47.1)	2.04 (0.94-4.47)	2.24 (1.03-4.88)	22 (43.1)	2.09 (0.96-4.55)	2.14 (0.98-4.65)	22 (43.1)	1.67 (0.76-3.70)	1.78 (0.81-3.93)
Sex		P=0.74	P=0.66		P=0.36	P=0.39		P=0.19	P=0.15
Female	60 (36.4)	1	1	53 (32.1)	1	1	65 (39.4)	1	1
Male	47 (34.3)	0.92 (0.56-1.51)	0.89 (0.54-1.47)	37 (27.0)	0.79 (0.48-1.31)	0.80 (0.48-1.33)	44 (32.1)	0.72 (0.43-1.18)	0.69 (0.42-1.14)
Cluster-level variables			**aOR (95% CI)***			**aOR (95% CI)***			**aOR (95% CI)***
Presence of a trading centre		P=0.93	P=0.70		P=0.55	P=0.43		P=0.98	P=0.62
No	62 (35.0)	1	1	50 (28.3)	1	1	63 (35.6)	1	1
Yes	45 (36.0)	1.03 (0.54-1.95)	0.90 (0.51-1.58)	40 (32.0)	1.18 (0.68-2.06)	1.26 (0.72-2.19)	46 (36.8)	1.01 (0.51-2.00)	0.85 (0.45-1.63)
Located on lakeshore		P=0.83	P=0.76		P=0.58	P=0.66		P=0.92	P=0.99
No	85 (35.9)	1	1	73 (30.8)	1	1	86 (36.3)	1	1
Yes	22 (33.9)	0.91 (0.40-2.10)	0.90 (0.45-1.79)	17 (26.2)	0.82 (0.41-1.65)	0.85 (0.41-1.76)	23 (35.4)	1.05 (0.43-2.57)	0.99 (0.44-2.24)
HIV clinic within 5 km		P=0.43	P=0.88		P=0.74	P=0.74		P=0.99	P=0.39
No	25 (31.3)	1	1	22 (27.5)	1	1	28 (35.0)	1	1
Yes	82 (36.9)	1.36 (0.64-2.89)	0.95 (0.50-1.81)	68 (30.6)	1.12 (0.59-2.14)	0.89 (0.43-1.81)	81 (36.5)	1.00 (0.45-2.22)	0.72 (0.33-1.56)
Located along a major road		P=0.34	P=0.56		P=0.18	P=0.34		P=0.31	P=0.29
No	72 (33.3)	1	1	59 (27.3)	1	1	73 (33.8)	1	1
Yes	35 (40.7)	1.40 (0.70-2.82)	1.25 (0.68-2.31)	31 (36.1)	1.49 (0.84-2.64)	1.36 (0.73-2.54)	36 (41.9)	1.47 (0.70-3.10)	1.45 (0.73-2.87)
Other individual-level variables			**aOR (95% CI)†**			**aOR (95% CI)†**			**aOR (95% CI)†**

	Obtaining CD4 counts			Initiating ART			Adhering to CTXp		
		Crude analysis	Adjusted analysis		Crude analysis	Adjusted analysis		Crude analysis	Adjusted analysis
	N (%)	OR (95% CI)	aOR (95% CI)§	N (%)	OR (95% CI)	aOR (95% CI)§	N (%)	OR (95% CI)	aOR (95% CI)§
Marital status		P=0.59	P=0.87		P=0.19	P=0.06		P=0.30	P=0.81
Married/cohabiting	60 (33.0)	1	1	61 (33.5)	1	1	62 (34.1)	1	1
Single	17 (35.4)	1.12 (0.55-2.25)	1.20 (0.59-2.43)	11 (22.9)	0.57 (0.27-1.23)	0.60 (0.28-1.31)	15 (31.3)	0.92 (0.45-1.90)	0.97 (0.47-2.03)
Divorced/separated/ widowed	30 (41.7)	1.37 (0.75-2.47)	1.08 (.58-2.01)	18 (25.0)	0.64 (0.34-1.21)	0.47 (0.23-0.93)	32 (44.4)	1.55 (0.85-2.81)	1.22 (0.65-2.29)
Education		P=0.98	P=0.90		P=0.87	P=0.74		P=0.81	P=0.72
None/incomplete primary	65 (35.7)	1	1	56 (30.8)	1	1	67 (36.8)	1	1
Primary	22 (33.3)	0.95 (0.50-1.78)	0.86 (0.46-1.62)	18 (27.3)	0.85 (0.45-1.61)	0.78 (0.40-1.49)	21 (31.8)	0.82 (0.43-1.55)	0.77 (0.41-1.47)
Above primary	20 (37.0)	1.00 (0.52-1.94)	0.99 (0.51-1.93)	16 (29.6)	0.92 (0.47-1.82)	0.89 (0.45-1.78)	21 (38.9)	1.01 (0.52-1.96)	1.00 (0.51-1.95)
Socio-economic status		P=0.98	P=0.97		P=0.70	P=0.80		P=0.99	P=0.96
Low	41 (35.0)	1	1	38 (32.5)	1	1	42 (35.9)	1	1
Middle	38 (35.2)	1.04 (0.58-1.85)	1.06 (0.60-1.87)	30 (27.8)	0.80 (0.44-1.43)	0.83 (0.46-1.50)	39 (36.1)	1.03 (0.58-1.84)	1.09 (0.61-1.94)
High	28 (36.4)	1.07 (0.57-2.02)	1.07 (0.57-2.03)	42 (28.6)	0.81 (0.42-1.54)	0.84 (0.44-1.63)	28 (36.4)	1.02 (0.54-1.94)	1.07 (0.56-2.05)
Religion		P=0.33	P=0.39		P=0.06	P=0.11		P=0.08	P=0.06
Catholic	74 (34.7)	1	1	57 (26.8)	1	1	79 (37.1)	1	1
Anglican	19 (45.2)	1.59 (0.78-3.27)	1.40 (0.68-2.89)	19 (45.2)	2.26 (1.12-4.54)	2.03 (0.99-4.16)	20 (47.6)	1.48 (0.72-3.04)	1.39 (0.68-2.86)
Muslim	9 (26.5)	0.62 (0.26-1.48)	0.57 (0.24-1.37)	6 (23.5)	0.82 (0.35-1.96)	0.73 (0.30-1.78)	7 (20.6)	0.40 (0.15-1.02)	0.38 (0.15-0.98)
Other	5 (38.5)	1.23 (0.36-4.15)	0.95 (0.28-3.26)	8 (46.2)	2.42 (0.76-7.71)	2.17 (0.66-7.11)	3 (23.1)	0.50 (0.13-2.00)	0.41 (0.10-1.67)
Time to nearest HIV clinic		P=0.03	P=0.08		P=0.58	P=0.81		P=0.25	P=0.38
<30 minutes	39 (45.4)	1	1	28 (32.6)	1	1	36 (41.9)	1	1
≥30 minutes	68 (31.5)	0.53 (0.30-0.92)	0.60 (0.34-1.06)	62 (28.7)	0.85 (0.49-1.49)	0.93 (0.53-1.65)	73 (33.8)	0.72 (0.41-1.26)	0.78 (0.44-1.37)
Ever tested for HIV		P=0.80	P=0.70		P=0.89	P=0.68		P=0.46	P=0.61
No	22 (37.3)	1	1	18 (30.5)	1	1	19 (32.2)	1	1
Yes	85 (35.0)	0.92 (0.50-1.71)	0.88 (0.47-1.66)	72 (29.6)	0.96 (0.51-1.79)	0.87 (0.45-1.68)	90 (37.0)	1.27 (0.67-2.39)	1.19 (0.62-2.27)
Aware of HIV-positive		P=0.96	P>0.99		P=0.22	P=0.21		P=0.70	P=0.71

	Obtaining CD4 counts			Initiating ART			Adhering to CTXp		
		Crude analysis	Adjusted analysis		Crude analysis	Adjusted analysis		Crude analysis	Adjusted analysis
	N (%)	OR (95% CI)	aOR (95% CI)§	N (%)	OR (95% CI)	aOR (95% CI)§	N (%)	OR (95% CI)	aOR (95% CI)§
status									
No	94 (35.5)	1	1	76 (28.7)	1	1	95 (35.9)	1	1
Yes	13 (35.1)	1.02 (0.48-2.17)	1.00 (0.47-2.13)	14 (37.8)	1.60 (0.76-3.36)	1.64 (0.76-3.51)	14 (37.8)	1.16 (0.54-2.47)	1.15 (0.54-2.46)

§Adjusted for trial arm and stratum; *Adjusted for trial arm, stratum, age and sex; †Adjusted for trial arm, stratum, age and sex

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Chapter 7: General discussion

7.1 Introduction

The main aims of my PhD research were: to document the currently available evidence on linkage to HIV care among individuals newly diagnosed as HIV-positive through HBHCT in SSA; and ii) to evaluate the impact of a counselling intervention delivered after HIV diagnosis through HBHCT on linkage to HIV care. The research comprised a systematic review of the literature on linkage to HIV care after HBHCT in SSA, and an open-label cluster randomised trial to evaluate the effectiveness of counselling after HIV diagnosis and referral to care, compared to referral to care only, on linkage to care among HIV-positive adults (≥18 years) identified through HBHCT in Masaka district, Uganda. The trial was conducted between March 2015 and March 2016. During this period, the Uganda national treatment guidelines recommended ART initiation for all HIV-positive adults with a CD4 count of ≤500 cells/mm^3 [1]. In addition, ART was recommended for all HIV-positive individuals who were co-infected with tuberculosis or hepatitis B, pregnant, breastfeeding, categorised as most-at-risk persons (Commercial Sex Workers, Fisher folk and Truck drivers), and partners in HIV sero-discordant couples irrespective of WHO clinical stage or CD4 count. The study setting and population have been described in chapter 2 of this thesis.

Overall, the results of my research contribute to the quantity and quality of evidence available to inform efforts intended for improving access to HIV prevention and care for adults in SSA. The systematic review is among the first to summarise available evidence on linkage to care among HIV-positive adults newly identified through HBHCT in SSA. I summarised data on the numbers and proportions of those who linked to care, and among these, the numbers and

proportions who were eligible for and initiated CTXp and ART. I described the definitions of linkage and linkage strategies used across the studies included in the review. I also assessed the included studies for risk of bias.

The cluster randomised trial is among the first randomised studies designed to evaluate the effect of an intervention on linkage to care following HIV diagnosis through HBHCT in SSA. I used data from the screening phase of the trial to quantify and identify factors associated with HBHCT uptake in the study communities. I investigated whether counselling provided subsequent to HIV testing and referral for care increased linkage to care among HIV-positive persons identified through HBHCT. Specifically, I investigated the effect of counselling on the proportion of persons linking to care as well as the time to linkage. I also investigated the effect of counselling on the time to receipt of a CD4 count and ART initiation, and on the proportion of persons initiating and adhering to CTXp. Finally, I used data from the trial to quantify and identify factors associated with linkage to care, receipt of CD4 counts, adherence to CTXp, and ART initiation.

This chapter summarises the main findings from this research and the contribution of the research to the literature. This is followed by a description of the methodological strengths and challenges. A discussion of ongoing and planned studies that are related to this PhD research is provided, and overall conclusions given.

7.2 Summary of the main findings

7.2.1 Systematic review

Medline, Embase, Global Health, Web of Science, and Africa-Wide information databases were searched, covering the period from 1st January 2000 [time at which roll-out of ART

programmes began in SSA [2]] to 19th August 2016 for published studies that investigated linkage to care after HBHCT in SSA. 14 studies from 6 countries were included in the review [3-16]; only one investigated linkage to care by means of a randomised trial [3]. These studies varied widely with regard to design, setting, definition of linkage to care, the time points of and the methods applied for ascertaining linkage, and with regard to the strategies used to facilitate linkage, hence a pooled analysis was not done. Nine studies used specific strategies in addition to routine referral to facilitate linkage to care [3-8, 10, 14, 15]. Linkage to care was typically low (<33%) after routine referral but higher (>50%) if additional linkage interventions were used. In general, linkage to care was highest (>80%) in the studies that used both POC CD4 count testing and follow-up counselling [3, 5-7]. Most of the studies were susceptible to outcome ascertainment bias. In conclusion, the systematic review showed that there is limited literature on linkage to HIV care among adults newly diagnosed with HIV through HBHCT in SSA, that HBHCT without interventions to facilitate referral uptake achieved inadequate linkage to care, and highlighted the need for randomised controlled trials to confirm the impact of promising linkage strategies before they can be recommended for large scale adoption.

7.2.2 Experimental work

7.2.2.1 Uptake of HBHCT

The study found a high (89.9%) level of HBHCT uptake. Men were more likely (aOR 1.20, 95% CI 1.07-1.36) than women to accept HBHCT. This finding is similar to those of previous studies in which men were equally or more likely to accept HBHCT compared to women [2, 17, 18]. Some of the reasons for men's preference of HBHCT may be its convenience, privacy and ease of access [19]. Similar to the results from other studies [12, 17, 20], HBHCT uptake was highest in the youngest age group (18-24 years) and decreased with increasing

age. Possible reasons for this include a lower HIV risk perception in older compared to younger persons [17], the convenience and ease of access to confidential and professional HCT afforded by the HBHCT model [21, 22], and the possibility that older persons are more likely to have previously tested HIV-positive and consequently less likely to accept HBHCT compared to their younger counterparts.

7.2.2.2 *Effect of counselling after HIV diagnosis through HBHCT on linkage to care*

Counselling provided at one and two months after HBHCT was associated with a 2.18-fold (95% CI=1.26-3.78) increase in the odds of linking to care among HIV-positive participants aged 18 years and older (linkage was 51% in the intervention arm versus 33.3% in the control arm). The intervention significantly increased the overall rates of linkage and obtaining CD4 counts but had no effect on the overall rate of ART initiation. There was however evidence of interaction between trial arm and follow-up time for these outcomes. The rate of linkage, obtaining CD4 counts, and ART initiation did not differ between arms in the first two months of follow-up but was subsequently higher in the intervention arm versus the control arm [linkage, HR=4.87 (95% CI=1.79-13.27); obtaining CD4 counts, HR=3.35 (95% CI=1.59-7.04); ART initiation, 3.90 (95% CI=1.67-9.11)]. Follow-up counselling also significantly increased reported adherence to CTXp (OR=2.15, 95% CI=1.16-3.98).

Observational studies had previously suggested that follow-up counselling provided after referral may substantially increase linkage to care among HIV-positive persons identified through HBHCT [5-7]. One randomised trial conducted in South Africa and Uganda previously evaluated the effect of follow-up counselling after community-based HCT (HBHCT or mobile HCT) on linkage [3]. HIV-positive ART naïve individuals aged ≥16 years were randomly assigned in a factorial design to receive lay counsellor clinic linkage

facilitation, lay counsellor follow-up home visits, or standard-of-care referral, and subsequently either to POC CD4 count testing or referral for clinic CD4 count testing. Follow-up counselling in this trial showed modest effects, increasing the proportions of individuals linking to care and initiating ART by 4% and 23% respectively. The smaller effect estimates observed in this trial compared to those observed in my study were probably due to the already high (89%) level of linkage in the standard-of-care (referral only) arm of that trial and the high proportion of ART-eligible participants who did not start ART due to the requirement for repeat CD4 count testing at the clinic and other clinic-level barriers to ART initiation. In contrast, linkage in the standard-of-care arm of my study was low (33.3%) and consistent with that seen in observational studies in SSA [9, 13, 16, 23, 24]. Additionally, HIV care providers in the study area were aware of my study and facilitated the verification of study outcomes for participants who sought care at their facilities. It is possible that this collaboration may have reduced clinic-level barriers to the uptake of care services specifically for participants in my study, leading to a possibly exaggerated intervention effect measured in the study. However, any reduction in clinic-level barriers to uptake of care would have been similar for participants in both treatment arms since the healthcare workers at HIV clinics were not aware of participants' group assignment.

7.2.2.3 Factors associated with uptake of HIV care services following HBHCT

Although linkage to care was significantly higher in the intervention arm, it was still only 51% of those diagnosed – and only 42% across both arms – well below the UNAIDS target of 90% [25]. These results are consistent with those of some studies [9, 13, 16, 23, 24] but not others where linkage was either lower [11, 15] or higher [4-7]. In general it is difficult to compare these studies as they used different definitions of linkage to care, had varied study

populations, and whereas some [4-7], like my study, included interventions to facilitate linkage, others did not [9, 11, 13, 16, 23, 24].

Although the overall proportions of enrolled participants who obtained CD4 counts (35.4%), initiated ART (29.8%), and adhered to CTXp (36.1%) were low, uptake of these services among those who linked to care was high [84.3% obtained CD4 counts, 70.9% initiated ART (including 95.3% of those who had eligible CD4 counts), and 85.8% reported adhering to CTXp]. This finding suggests that in settings where HIV care services are available, linkage to care may be the main bottleneck to uptake of these services.

Surprisingly and contrary to findings in other studies, factors commonly associated with reducing or increasing entry into HIV care such as age [26], sex [26], distance or travel time to a health facility [24, 27-29], socio-economic status [24], and educational attainment [30, 31] were not associated with linkage to HIV care, receipt of CD4 counts, or ART initiation in this study. This finding suggests that the counselling intervention evaluated in this study may be helpful in increasing linkage for individuals across different socio-demographic groups and that interventions to increase enrolment into care should focus on increasing the desire to enrol in care.

Although not statistically significant, older age (≥45 years) was predictive of increased (aOR 2.14, 95% CI 0.98-4.65) ART initiation. Compared to younger persons, older persons may find it easier to accept their HIV status and may be more likely to have the social support and financial resources that facilitate access to care [8]. However, it is also possible that many young people in my study did not initiate ART because they were not yet eligible under the treatment guidelines in use at the time. Indeed, at the time of linkage, only 53.0% of persons

aged 18-44 years had a CD4 count of ≤500 cells/mm^3, the ART eligibility threshold [1], compared to 83.3% among those 45 years and older.

7.3 Contribution of the research to the literature

The systematic review contributes to our understanding of the extent to which HIV-positive adults who are newly identified through HBHCT in SSA are linked to care. The review also highlights the need for high quality evidence on the effectiveness of strategies used to promote linkage to care following HBHCT in SSA in order to inform HIV policy and programmes. One previous review has reported on linkage to HIV care after HBHCT in SSA [32]. However, this review did not distinguish linkage outcomes between HIV-positive persons identified through HBHCT and those identified through HCT that is provided within multi-disease campaigns in mobile clinics, between newly and previously diagnosed HIV-positive individuals, or between children/adolescents and adults.

Findings from the experimental component of this research contribute to the evidence on the potential of HBHCT as a platform for achieving the UNAIDS target of getting 90% of all HIV-positive persons to learn their HIV status. The cluster randomised trial contributes new and robust evidence on the effectiveness of counselling on linkage to HIV care after HIV diagnosis through HBHCT. Additionally, the trial provides evidence of the effect of counselling on ART initiation. This is important because as HIV care programmes adopt the new WHO guidelines to initiate ART for all HIV-positive persons irrespective of CD4 count, these programmes will need to implement interventions that promote immediate linkage to ART care [33]. Finally, this research contributes to the small evidence base on factors associated with uptake of HIV care services following HIV diagnosis through HBHCT in SSA.

7.4 Methodological strengths and challenges

7.4.1 Strengths

The experimental work in my PhD was a randomised controlled trial. Therefore, the observed effect estimates are not prone to the effects of confounding factors. The randomised design as well as the high participation and retention rates that were similar across treatment arms ensured that risk of selection bias was low. The inclusion of buffer zones between clusters minimised the risk of contamination between treatment arms, and consequently that of diluting the intervention effects.

Referrals were tracked and medical records examined to verify self-reported linkage, receipt of CD4 counts, and ART initiation for all participants (including those who linked to clinics outside of the study area) thereby minimising the risk of reporting bias for these outcomes. Individuals whose information on self-reported linkage could not be verified by clinic records were re-interviewed; all revealed that they had not linked to care. Use of clinic-verified data to ascertain linkage outcomes has been infrequent and inconsistent in previous studies. For instance, none of the studies included in the systematic review component of this work used clinic-verified data to ascertain linkage for all participants. Linkage was either ascertained by use of self-reports alone [5, 9, 12, 14], a mixture of self-reported and clinic-verified data [4, 8], review of documentation issued to patients by HIV clinics (e.g. clinic cards) [3, 6, 7], or clinic-verified data but only for participants who linked to HIV clinics within the areas where the studies were conducted [10, 11, 13, 15, 16].

Finally, the trial was conducted under real-world conditions in a relatively large geographical area. Participants were free to and did attend their preferred HIV clinics including those located outside of Masaka district. Also, participants did not receive monetary or other

incentives to participate. Hence, the trial results are likely to be generalizable to other settings in Uganda and SSA. The results are likely to be relevant even for settings where ART is initiated in all HIV-positive persons irrespective of CD4 count. This is because the availability of immediate ART may not translate into increased linkage to care. In a recently completed trial in rural KwaZulu-Natal, South Africa, that investigated the impact of immediate ART versus ART initiation according to standard-of-care (CD4 $\leq$350 cells/mm^3 at the time of the study) on HIV incidence, uptake of immediate ART was high (87.3%) among those who linked to care but linkage to care within 6 months of HIV diagnosis was only 47.5%, and did not differ between arms [10]. Indeed the investigators of this study acknowledge the need for interventions to increase linkage to HIV care if the UNAIDS target of initiating ART for 90% of all persons with diagnosed HIV infection is to be achieved [24].

7.4.2 Limitations

The trial used an open-label design hence it was prone to selection and outcome reporting bias. As mentioned above, selection bias does not seem to have been a major issue since baseline participant characteristics were generally balanced between trial arms and participation and retention rates were high and did not differ by treatment arm. Data on adherence to CTXp was based on self-report so outcome reporting bias cannot be ruled out for this outcome. It is possible that participants in the intervention arm reported good adherence to CTXp more frequently than those in the control arm. In general, reporting bias is unlikely to have been a major issue since all the primary outcomes and other secondary outcomes were based on clinic-verified data.

The assumption that individuals who did not complete the month six visit did not link to care may have resulted in an underestimation of the proportion who linked to care if such

individuals had in fact linked. The proportion who linked to care might also have been underestimated if some of the participants who reported not linking to care had actually linked. It is however unlikely that individuals would link to care but choose to report otherwise. A related issue is that participants who permanently left the study area were assumed to have been in follow-up for at least 3 months i.e. they were censored mid-way between the enrolment and the month 6 visit. This assumption may have resulted in biased estimates of time to linkage, and time to other outcomes. However, this is unlikely to have had a large impact on the estimates since few (<5%) participants were reported to have permanently left the study area.

I defined linkage to HIV care as registering with an HIV clinic following HIV diagnosis because this is the first step towards receiving ART [33, 34]. Another reason was to enable comparison of my research findings with those of several previous studies that have defined linkage to HIV care in a similar way [3-7, 9-12, 14-16, 35]. Other definitions of linkage to HIV care include attending clinic for a CD4 count measurement [36], obtaining a CD4 count [8], screening for ART eligibility [13], and starting ART [36] with time points for ascertaining linkage ranging from ≤1 month [12, 14, 15] to 12 months [6, 13]. I chose 6 months as the time point for assessing linkage status in my study to allow time for the delivery of the intervention, enable an assessment of the intervention effect on post-linkage outcomes such ART initiation and adherence to CTXp, and facilitate comparisons with other studies that assessed linkage at a similar time point. Whereas registering with an HIV care provider is a critical step in the HIV care cascade, it may not result into improved long-term care outcomes such as viral suppression [37]. Moreover, as the new WHO guidelines recommending ART initiation in all HIV-positive persons regardless of CD4 count become

widely adopted, future efforts to increase linkage to care are likely to shift focus from just registering in care to ART initiation as the next step after HIV diagnosis [10].

A limitation of the short follow-up period is that it was not possible to assess the effect of follow-up counselling on longer term outcomes such as retention in care, adherence to ART, and viral suppression.

I did not evaluate the cost-effectiveness of the counselling intervention. Although the intervention is simple and may easily be incorporated into routine HBHCT programmes, cost-effectiveness data may be required to support efforts for its scale up.

A limitation of the analysis of factors associated with linkage to care and uptake of HIV care services is that baseline data were not available for a number of factors that have been shown to predict these outcomes. It was therefore not possible to control for their confounding effects. These factors include: CD4 count at the time of HIV diagnosis [35], knowledge of ART [8, 38], anticipated stigma [38], psychological [8] or physical [23, 38] health status, living with an HIV-positive person who is receiving HIV care [23] or knowing an HIV-positive family member [24], wanting to seek care after HIV diagnosis [23, 24], and alcohol use [8, 38]. A further limitation of this analysis is that the relatively small sample size may have limited the power to investigate associations between potential risk factors and linkage to care or other outcomes.

7.4.3 Sample size estimation

The target population for my study was HIV-positive adults who had not been engaged in care before. Data from the 2011 national HIV sero-prevalence survey in which the study area

in Masaka district was included had shown that 60% of HIV-positive adults were unaware of their HIV status and therefore not in care [41]. However, national-level data showed a significant increase in the awareness of HIV status and availability of treatment services in the period between the survey and end of 2014 (just before my study was initiated). For instance, the number of persons aged ≥15 years who had received HCT in the last 12 months and knew their results had increased from 0.9 million in 2011 to 8.6 million while the number of health facilities that offered ART had increased from 400 to 1062 in the same period [42]. Therefore, for the sample size calculations, I adjusted the estimate of the proportion of HIV-positive adults who were not in care to 40%. In spite of this adjustment however, self-reported engagement in care was a common reason for refusal of HBHCT and study ineligibility from the start of the trial. In the end, self-reported engagement in care was the commonest reason for refusal of HBHCT (437, 32.3%), and study ineligibility among those who tested HIV-positive and were not enrolled into the study (205, 82.3%). Consequently, the number of eligible HIV-positive persons per cluster was smaller than originally expected.

In order to maintain the original study power of ≥90% to detect the hypothesised intervention effect, at least 12 additional clusters (6 per arm) were needed. However, due to logistic and budget constraints, only 6 (3 per arm) additional clusters could be recruited; thus the sample size was increased from 22 (11 per arm) to 28 clusters (14 per arm). This sample size allowed for detection of the same effect but with a reduced power of ≥80%. As a result, the study may have had limited power to detect a smaller effect size, or associations with linkage to care or other outcomes.

As evidenced by my trial results, the finding that self-reported engagement in care was common does not mean that prompt linkage to care after HIV diagnosis is high in this

population, and therefore that interventions to enhance it are not needed. The high level of self-reported engagement in care may instead be a result of the increased number of HIV-positive persons enrolled into care following protracted efforts to expand HIV prevention and treatment services [42]. It is also possible that some individuals reported being engaged in care whereas they were not. As observed in the trial, about 5% of HIV-positive participants who reported that they had linked to care after HBHCT had actually not done so.

An additional remark is that the observed *k* was higher than that used for estimating the required sample size for the trial (0.33 versus 0.25). Hence, the trial could potentially have been slightly underpowered.

7.4.4 Analysis

I prepared the trial analysis plan (Appendix 1) before any analyses were performed. However, certain unanticipated difficulties arose once I initiated the analyses. After obtaining additional advice from Kathy Baisley and Richard Hayes, I updated the plan to address the issues as described below.

Clusters with zero outcomes

A major difficulty related to the analysis of clusters with zero outcomes. I had originally planned to log-transform cluster-level summaries e.g. the proportion linking to care, in order to obtain more symmetric distributions before conducting cluster-level analysis. However log-transformation of cluster-level summaries was not possible since some clusters had zero outcomes e.g. no one linked to care in two clusters (the logarithm of zero does not have a finite value). A possible solution to this problem is to add a small constant (e.g. 0.5) to the number of events in each cluster, obtaining the observed cluster-level rates or proportions

and finally applying the log-transformation to these cluster-level summaries [39]. I did not use this procedure since it has been shown in simulations not to be very robust, and could affect the conclusions of hypothesis testing [40]. I instead used the non-transformed rates/risks to estimate rate/risk ratio and the corresponding 95% CI. Since the non-transformed rates/risks were reasonably normally distributed, I used the t-test to obtain a p-value for the test of the null hypothesis of no intervention effect.

The cluster-level analyses were done to check the robustness of the results from the individual-level analyses, so this change to the analysis plan did not affect the primary analyses.

Secondary outcome analysis

Another other issue is that I had considered two approaches for the secondary outcome analysis among HIV-positive participants: i) to restrict the analysis to certain subgroups i.e. time to obtaining a CD4 count among participants that linked to care and provided a blood sample for CD4 count testing, time to ART initiation among participants who linked to care and learnt that they were eligible for ART, and adherence to CTXp among persons that linked to care; ii) to do the analysis in all participants who were randomised. After taking advice, I dropped the former approach in order to demonstrate overall intervention effects for all outcomes and avoid selection bias associated with non-randomised comparisons.

7.5 Ongoing and planned studies related to this PhD research

I am aware of four other randomised studies in SSA designed to investigate the impact of an intervention on linkage to care following HIV diagnosis through HBHCT.

The first is a completed but not yet published cluster randomised trial that assessed the accuracy, feasibility and acceptability of POC CD4 count testing for HIV-positive persons identified through HBHCT, and the (cost-) effectiveness of this intervention in improving linkage to care and time to ART initiation in rural western Kenya [41]. Linkage to care, defined as visiting an HIV clinic within six months of enrolment, was ascertained by participant interview and review of HIV clinic records. This is the first randomised controlled trial to evaluate the impact of POC CD4 testing on linkage to care among HIV-positive persons identified through HBHCT [42]. Preliminary results from the trial show that POC CD4 testing strongly increases linkage to care (risk ratio (RR)=1.73, $p<0.001$) and ART initiation (RR=1.65, $p<0.01$) [43]. These results are comparable to those observed in my study and suggest that POC CD4 count testing and follow-up counselling may be equally effective in linking HIV-positive persons identified through HBHCT to care. However, the new WHO recommendation to initiate ART in all HIV-positive persons regardless of CD4 count [25] means that POC CD4 count testing will have a diminished role in promoting linkage in the future. This is because the rationale for providing POC CD4 testing i.e. to eliminate delays between testing HIV-positive and ART initiation among eligible patients resulting from centralised laboratory CD4 testing [42, 44], will become less relevant as the new treatment guidelines are adopted.

The second study is an ongoing cluster randomised trial that will evaluate the effectiveness of a linkage to care counselling intervention at achieving HIV viral suppression and intermediate outcomes of linkage/time to care, time to/receipt of opportunistic infection prophylaxis, and ART among HIV-positive adults (18-59 years) identified through HBHCT in rural Uganda [45]. Counselling sessions will be delivered by an HIV counsellor at the participant's home, clinic, and over the phone. Participants will be followed for 12 months.

The trial will provide more evidence on the impact of follow-up counselling on linkage to care, receipt of CTXp, and ART initiation as well as on additional outcomes i.e. retention in care and viral suppression. The trial will also provide data on the cost-effectiveness of counselling as compared to standard of care. The trial is expected to end in 2020.

The third study is an ongoing cluster randomised trial to evaluate the impact of same day home-based ART initiation on linkage to and retention in care, ART initiation, and viral suppression among HIV-positive adults (≥18 years) identified through community-based HIV testing in rural district of Butha-Buthe, in northern Lesotho [46]. This is among the first trials to assess immediate ART initiation within the context of HBHCT [47]. The trial has a longer duration of follow-up (12 months) than my study and will provide data on extra endpoints including retention in care and viral suppression. The trial is expected to end in 2017.

The fourth trial is part of a larger study that will compare home and other community recruitment strategies and HIV testing strategies (self-testing, HCT in a home/mobile setting, and facility-based HCT) among young at-risk women, 15-24 years old, in western Kenya [48]. Newly identified HIV-positive participants will be initially randomized to receive either standard referral or standard referral plus short messaging service (SMS) message reminders to link to care. Participants who do not link to care after the first randomization will be re-randomized to receive either an SMS message reminder or financial incentive to link to care. Participants who link to care will receive SMS reminders combined with health status surveys at 3, 6, 9, and 12 months. The trial will contribute evidence on linkage to care and on effectiveness of interventions to increase linkage to care among adolescent girls and young

women, a population with a high burden of HIV in SSA [49]. Unlike my study, this trial will provide data on retention in care and cost-effectiveness of the linkage interventions.

In summary, results from the above studies will contribute new evidence on the feasibility, cost-effectiveness, and impact of different interventions on linkage to care and on long term outcomes (retention in care and viral suppression) following HIV diagnosis through HBHCT. For interventions that are shown to be effective, research will be required to identify how best they can be introduced into existing HIV care programmes. Also, as the new WHO recommendations to initiate ART regardless of CD4 count become adopted, the main goal of linkage to care interventions is likely to be ART initiation among newly identified HIV-positive individuals [50]. It will therefore be important to demonstrate the effectiveness of these interventions under the new treatment guidelines.

7.6 Conclusion

The number and proportion of people who link to HIV care after HBHCT in SSA is inadequate. Some studies showed improved linkage when HBHCT was combined with additional strategies to facilitate referral. However, these have been observational studies, not trials. The present trial, one of the few to evaluate the effect of an intervention on linkage to care following HIV diagnosis through HBHCT in SSA, has shown that brief follow-up counselling, provided by non-medical personnel to HIV-positive adults identified through HBHCT, can substantially increase linkage to care and uptake of HIV care services including ART. HBHCT plus follow-up counselling may be a useful strategy in achieving the UNAIDS target of ensuring that 90% of HIV-positive persons who know their HIV status access treatment [25] and should be considered for scaling up.

7.7 References

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Chapter 8: Appendices

8.1 Appendix 1: Analysis plan

Study summary

Background: Data on linkage to HIV care after HIV diagnosis through HBHTC in SSA are scarce. Few studies have rigorously evaluated interventions aimed at improving linkage to HIV care following HBHTC in SSA.

Aim: To evaluate the effect of follow-up counselling after HIV diagnosis through HBHTC on linkage to HIV care in Masaka, south-western Uganda.

Methods: A cluster randomised trial of the effectiveness of referral to HIV care and follow-up counselling (intervention) compared to referral to HIV care only (control), for individuals diagnosed with HIV through HBHTC. The intervention is administered at months 1 and 2, and linkage to care assessed at month-6 post-HBHTC. Data is collected on socio-demographic characteristics, HIV testing history, linkage to care, CD4 count testing and results, initiation of and adherence to CTXp, and ART initiation. Approximately 196 HIV-positive participants from 28 clusters (14/study arm) are expected to enrol and complete the study. This sample size will allow for >80% power to detect an increase in linkage to HIV care from 35% to 60%, at a significance level of 5%. To conceal participants' HIV status, approximately 84 HIV-negative persons will also be recruited into the study. Primary outcomes are: the proportion of HIV-positive participants that register with an ART provider within six months of HIV diagnosis, and the time between HIV diagnosis and linkage to HIV care. Secondary outcomes are: time

between HIV diagnosis and obtaining CD4 counts, time between HIV diagnosis and ART initiation, and the proportion of participants who report adherence to daily CTXp six months after HIV diagnosis. A further secondary outcome is the proportion of HIV-negative participants who agree to repeat HIV testing six months after HBHCT. The effect of the intervention and 95% confidence intervals (CI) will be estimated using individual-level random effects regression models. Likelihood ratio tests will be performed for hypothesis testing. Because of the relatively small number of clusters per arm, analyses based on cluster-level approaches will also be performed to check the robustness of the results from the individual-level analyses.

Study objectives

Primary objectives

- To determine the effect of follow-up counselling on the proportion of individuals linking to HIV care within six months of HIV diagnosis through HBHTC.
- To determine the effect of follow-up counselling on the time to linkage to HIV care after HIV diagnosis through HBHTC.

Secondary objectives

- To investigate the effect of follow-up counselling on time to obtaining CD4 counts after HIV diagnosis through HBHTC.
- To investigate the effect of follow-up counselling on time to ART initiation after HIV diagnosis through HBHTC.
- To determine the effect of follow-up counselling on adherence to CTXp six months after HIV diagnosis through HBHTC.

Other objectives

- To determine the effect of follow-up counselling on the uptake of repeat HIV testing among HIV negative individuals six months after HBHTC.

Study setting

The study is being conducted in three rural sub-counties in Masaka district, Uganda. Adult HIV prevalence in the district has been reported at 10%. HIV care services are provided at no cost through government and non-governmental organisation health facilities.

Study design

The study is an open-label cluster randomised controlled trial of referral to HIV care and follow-up counselling (14 clusters) compared to referral to HIV care only (14 clusters), for participants diagnosed as HIV-positive through HBHTC.

Study population

The study population consists of HIV-positive adults identified through HBHTC that fulfil study eligibility criteria (see below). HIV-negative individuals are recruited from each randomised community to reduce the possibility of revealing the sero-status of HIV-positive (main) participants.

Eligibility criteria

HIV-positive participants

Inclusion criteria

- HIV-positive adult (≥18 years)
- Willing to provide informed consent

- Willing to receive follow-up counselling at home

Exclusion criteria

- Previous or current receipt of HIV care
- On-going participation in other health-related research
- Intention to change residence in the next six months
- Inability to provide informed consent

HIV-negative participants

Inclusion criteria

- HIV negative adult (≥18 years)
- Willing to provide informed consent
- Willing to receive follow-up counselling at home

Exclusion criteria

- Intention to change residence in the next six months
- Inability to provide informed consent

Definition of clusters

Clusters comprise one or more villages i.e. the smallest administrative areas. To ensure a reasonable number of eligible participants in each cluster, small (<400 adults) villages are combined with adjacent villages into larger clusters of at least 400 adults. Therefore, a cluster is defined as a village or a set of villages with at least 400 adults. Clusters are separated by a buffer zone of at least one non-participating village to minimise the risk of contamination.

Sample size

Sample size was calculated to ensure adequate power to address the hypothesis that follow-up counselling would increase the proportion of individuals that link to care. Based on previous studies, we assumed an adult HIV prevalence of 10%. The 2011 Uganda national HIV sero-prevalence survey (Masaka district was included in the survey) found that 60% of HIV-positive adults are unaware of their HIV status and are therefore not in care. However, this figure is likely to be lower due to increased HTC coverage since the survey. Based on these figures and the population estimates from the mapping data, the estimated harmonic mean number of potential HIV positive study participants in a cluster was 11. Assuming that 25% of the potential participants would refuse to participate/be away from home, and that a further 10% would be lost to follow-up, the harmonic mean number of HIV positive individuals that was expected to enrol and complete the study from each cluster was 7.

We assumed a coefficient of variation, *k*, of 0.25. This was based on past studies of linkage to HIV care that were conducted in settings similar to Masaka in which *k* ranged from 0.12 to 0.33. We assumed linkage of 35% in the control arm based on findings from HBHTC studies in which participants received only referrals following HIV diagnosis. The estimated intervention effect was based on findings from HBHTC studies that have used follow-up counselling to facilitate linkage to care. With a sample of 28 clusters (14 per arm) and a harmonic mean of 7 participants completing the study in each cluster, the study would have 83% power to detect an increase in linkage to care from 35% in the control arm to 60% in the intervention arm at a significance level of 0.05. This sample size would also give us 85% power to detect a hazard ratio of 1.7 for the effect of the intervention on time to linkage.

Randomisation of clusters

Randomisation of clusters was stratified on distance (≤10 km or >10 km) from Masaka town, because of availability of HIV care facilities, and whether the cluster was composed of a single large village or several small villages. Restricted randomisation was applied to achieve balance on the following covariates: cluster size (number of adults in a cluster); presence of a trading centre; location along a major road; lakeshore location; and presence of an HIV clinic within 5 km. The tolerance thresholds for balance were defined through an iterative process in which different thresholds were tried and the number and the validity of the acceptable allocations examined. A list of 1000 acceptable allocations was randomly generated from which one allocation was selected at public randomisation ceremony.

Data management

Data are collected using paper-based questionnaires. Questionnaires are checked for completeness, logic flow and correct entry before data entry. Data are double-entered and validated in Microsoft Access. Queries are run on the entered data every fortnight and reports sent to the study team for resolution. Data arising from the resolved queries are resubmitted for entry and the process is repeated until no more queries are generated.

Outcomes

Outcome data are collected six months post-enrolment using two methods:

- Completion of a staff-administered questionnaire to collect self-reported data on linkage and other outcomes.
- Review of HIV clinic records to verify and document self-reported outcomes

Self-reported data includes: whether and when the participant registered with an HIV clinic following referral (response categories are <1 month, 1-3 months, and >3 months ago, since it is anticipated that participants may have difficulty recalling actual dates); clinic name and address; clinic registration number assigned to participant (may be obtained from clinic documents e.g. appointment card, drug prescription forms etc.); and whether the participant was already engaged in care by the time he/she joined the study (Yes, No, Refused to answer). Although individuals who are already in care are not eligible for enrolment, we anticipate that some individuals who are in care may not reveal this information at the time of enrolment in order not to miss out on perceived research-related health care benefits, but that they may be willing to do so at the exit visit. Other reported data include: whether the participant; provided a blood sample for CD4 count testing and obtained the results, initiated ART, and CTXp following linkage to care. Additional data collected for those who report having initiated CTXp include: whether they have missed any doses in the past month and number of doses missed (0-5 tablets, ≥6 tablets, don't know) in that period; whether they have missed taking their tablets for 3 or more days in a row; and how often this has happened in the past month (once, twice, more than twice, don't know).

Clinic-verified data: for participants who report having registered with an HIV clinic, the study counsellor visits the clinic and with the help of clinic staff confirms that the registration number is authentic and that it is assigned under the participant's names. The counsellor then reviews clinic records (participant's referral letter, pre-ART and/or ART register, and medical forms) and records the registration number assigned to participant, date of registration, and whether the participant was registered at this or other HIV clinic before his/her enrolment in the study. The counsellor also collects data on whether and when the participant: had CD4 count testing and obtained the results, started CTXp and

initiated ART. Participants whose records are not found at the HIV clinic are re-contacted, informed of the verification outcome, and asked to clarify if they actually registered for care or not.

All HIV-negative participants are offered repeat HIV testing at the month-6 visit. Data on willingness to have repeat HIV testing (Yes, No) and the repeat HIV test result (positive, negative or indeterminate) is recorded.

Information on whether participants who are not seen at the month-6 visit have permanently left the study area or not is obtained from household members, neighbours and/or other village residents.

Primary outcomes

1) The proportion of HIV-positive participants that link to HIV care within six months of HIV diagnosis and referral.
2) The time between HIV diagnosis and linkage to HIV care.

- Linkage to HIV care is defined as confirmed registration (i.e. clinic-verified) with an HIV clinic following HBHTC and referral.
- The analysis population will comprise all randomised participants. Participants whose clinic-verified registration date precedes the date of enrolment into the study will be considered to have been ineligible for the study, and will be excluded from the analysis.
- Participants who report not to have registered with an HIV clinic, those who report to have registered but whose registration cannot be verified, and those lost to follow-up will be considered not to have linked to care.

- Time to linkage will be calculated from the date of enrolment in the study to the date that the participant was registered at the HIV clinic as per the clinic records. Participants who have not linked to care will be censored at the month-6 visit date. Participants who have permanently left the study area will be censored mid-way between the enrolment and 6 months. Those who are still in the study area but do not complete the month-6 visit will be censored at 6 months.

Secondary outcomes

1) Time between HIV diagnosis and obtaining CD4 count results.
    - The analysis population will comprise all randomised participants as described for the primary outcome.
    - Participants who report not to have obtained a CD4 count, those who report to have obtained a CD4 count but whose clinic records cannot be verified, and those lost to follow-up will be considered not to have a obtained CD4 count.
    - Time to obtaining first CD4 count will be calculated from the date of enrolment in the study to the date that the participant obtains his/her first CD4 count results. Participants who have not obtained a CD4 count will be censored at the month-6 visit date. Participants who have permanently left the study area will be censored mid-way between the enrolment and 6 months. Those who are still in the study area but do not complete the month-6 visit will be censored at 6 months.

2) The time between HIV diagnosis and ART initiation.
    - The analysis population will comprise all randomised participants as described for the primary outcome.

- Participants who report not to have initiated ART, those who report to have initiated ART but whose clinic records cannot be verified, and those lost to follow-up will be considered not to have initiated ART.
- Time to ART initiation will be calculated from the date of enrolment in the study to the date that ARV drugs were first prescribed as per clinic records.
- Participants who have not initiated ART will be censored at the month-6 visit date. Participants who have permanently left the study area will be censored mid-way between the enrolment and 6 months. Those who are still in the study area but do not complete the month-6 visit will be censored at 6 months.

3) The proportion of participants who report adherence to daily CTXp at six months after HIV diagnosis through HBHTC.
    - The analysis population will comprise all randomised participants as described for the primary outcome.
    - Participants who report not to have initiated CTXp, those who report to have initiated CTXp but whose clinic records cannot be verified, and those lost to follow-up will be considered not to have initiated CTXp.
    - Adherence to CTXp will be defined as a reported intake of >80% (missing 0-5 tablets only) of tablets in the month preceding the month-6 visit. Participants who report not taking their tablets for ≥3 consecutive days on two or more occasions will be classified as poor adherers i.e. ≤80% intake.

The analysis population for secondary outcomes will comprise all randomised participants rather than those who linked in order to avoid potential selection bias associated with sub group analyses, and to allow for the evaluation of the overall intervention effect on all outcomes.

4) The proportion of individuals who undergo repeat HIV testing within six months of testing HIV negative through HBHTC.
    - The analysis population will comprise all randomised HIV-negative participants.
    - Participants lost to follow-up will be assumed not to have accepted repeat HIV testing.

Baseline cluster and individual level characteristics

Baseline cluster- and individual-level variables will be summarised by trial arm to describe the study participants and assess their distribution between trial arms (balance):

Cluster-level variables included in the restricted randomisation

The following cluster-level variables were included in the restricted randomisation:

- Location along a major road (Yes, No)
- Lakeshore location (Yes, No)
- Presence of a trading centre (Yes, No)
- HIV clinic within 5 km (Yes, No)
- Cluster size (number of adults in a cluster)

Restricted randomised was used to ensure these variables were balanced between intervention and control arms within the following tolerance limits:

- Similar number of communities located along a major road in each arm (maximum difference of 1)
- Equal number of lakeshore communities in each arm

- Similar number of communities with a trading centre in each arm (maximum difference of 2)
- Similar number of communities with an ART clinic <5km of some households in each arm (maximum difference of 2)
- Maximum difference in mean cluster size between intervention & control communities of 95 adults

Other cluster-level variables

- Number of individuals enumerated
- Number of individuals contacted (% of all enumerated)
- Number of individuals that accept HBHCT (% of all contacted)
- Number of individuals that test HIV positive (% of all tested)
- Number of individuals that test HIV positive and are not in care (% of all positive)

Individual-level variables

Overall summaries of individual-level variables at baseline will be obtained by trial arm for all participants. These include:

- Age in years
- Sex (Male, Female)
- Marital status (Single, Married, Cohabiting, Widowed, Divorced/separated).
- Education level [No formal education, Incomplete primary, Complete primary, Secondary (O level), Secondary (A level), University/College]
- Household ownership of the following items: bicycle, motorcycle, motor vehicle, sewing machine, radio, television, refrigerator, electric/gas cooker, telephone

(landline), mobile phone, goats, cows, property rented for income; and having electricity in the household.

- Religion (Roman Catholic, Anglican, other Christian, Muslim, Traditional, Other, None)
- Travel time nearest HIV clinic (<30 minutes, 30 to 60 minutes, and >60 minutes).
- Ever tested for HIV (No, Yes)
- Results of last HIV test (Positive, negative, don't know)
- Previous awareness of HIV-positive status (HIV-positive participants only) (No, Yes)

Data for this variable will be derived from responses to the above HIV testing history questions. The 'No' response will be assigned to persons who report that they have never tested for HIV, those whose last HIV test result was negative and those who do not know the results of their last HIV test. The 'Yes' response will be assigned to persons who report that their last HIV test result was positive.

Data reduction

- Age will be categorised into: 18-24, 25-34, 35-44, and 45+
- Socio-economic status categories (Low, Middle, and High) will be created based on household ownership of selected items using principal component analysis.
- For some variables, categories observed to have few participants after collection of baseline data will be combined with others to form larger groups. The affected variables are:
    - Marital status

      New categories: Single, Married/Cohabiting, and, Widowed/Divorced/Separated.

- Education level

  New categories: None/incomplete primary, Primary, and Above primary

- Religion

  New categories: Roman Catholic, Anglican, Muslim, and Other.

- Travel time to nearest HIV clinic

  New categories: <30 minutes, and ≥30 minutes

Trial flow

A consort diagram will be used to show the flow of clusters and participants through the trial i.e. from group assignment to analysis.

Analysis

Analyses will be intention to treat and based on individual-level data. Random effects logistic and Cox regression models (i.e. with shared frailty) will be used to estimate the effects of the intervention on the proportion of participants linking to care and time to linkage, respectively. Likelihood ratio tests will be performed for hypothesis testing. Similar methods will be used to estimate the effect of the intervention on the proportions of participants that adhere to CTXp and undergo repeat HIV testing, and on time to obtaining CD4 count results, and to ART initiation. The primary analysis of the intervention effect for all outcomes will be adjusted for randomisation stratum as a fixed effect. Exploratory analyses adjusting for age and sex a priori, and other characteristics that show substantial baseline imbalance, will also be carried out. It is expected that the effect of the intervention might change over time due to the nature of the intervention i.e. repeated counselling sessions. Therefore, the proportional hazards assumption will be

examined by splitting follow-up time into two intervals (0-2 months and >2 months) at a point corresponding with the time of the second counselling session, and testing for an interaction between trial arm and follow-up time. Although the primary analyses will be based on individual-level approaches, sensitivity analyses based on cluster-level methods [1] will also be performed to check the robustness of the results. All analyses will be conducted in Stata 12.

Individual-level analysis

Individual-level analysis for binomial outcomes

Unadjusted analysis

The effect of follow-up counselling on the proportions of participants that link to care, report adherence to daily CTXp, and undergo repeat HIV testing will be estimated using random effects logistic regression to account for the clustered design. Randomisation strata will be included in the models as a fixed effect. A likelihood ratio test of the null hypothesis of no treatment effect will be performed by comparing the model with the exposure (trial arm) and strata to a model with only a term for strata.

Adjusted analysis

Age and sex will be included a priori in the adjusted models. In addition, models will be adjusted for variables for which there is substantial baseline imbalance between study arms for the respective analysis populations. A likelihood ratio test of the null hypothesis of no treatment effect will be performed by comparing the model with the exposure (trial arm), randomisation strata, age, sex and any other variables that show substantial baseline imbalance to a model with only the strata, sex, age and the variables that show baseline imbalance (i.e. without the term for trial arm).

Individual-level analysis for time-to-event outcomes

Unadjusted analysis

The effect of the intervention on time to: linkage, obtaining CD4 counts, and ART initiation will be estimated using a shared frailty Cox regression model to account for the clustered design. Randomisation strata will be included in the model as a fixed effect. A likelihood ratio test of the null hypothesis of no treatment effect will be performed by comparing the model with the exposure (trial arm), and strata to a model with only a term for strata.

Adjusted analysis

Age and sex will be included a priori in the adjusted models. In addition, an adjusted analysis to take into account any substantial imbalance that may occur between study arms in baseline variables for the respective study populations will be performed. A likelihood ratio test of the null hypothesis of no treatment effect will be performed by comparing the model with the exposure (trial arm), strata, age, sex and any other variables that show substantial baseline imbalance to a model with only strata, sex, age and the variables that show substantial baseline imbalance.

Proportional hazards assumption

The proportional hazards assumption will be examined as described above, for the unadjusted and adjusted analyses of all time-to-event outcomes.

Cluster-level analysis

Some clusters have zero outcomes e.g. no one linked to care. Therefore cluster-level summaries will not be log-transformed before conducting analyses. Instead raw

(untransformed) rates/risks will be used to obtain intervention effects and their 95% confidence intervals.

Cluster-level analysis for binomial outcomes

Unadjusted analysis

Linkage to care will be measured using prevalence ratios (PR). For each study arm, the cluster-specific proportions of individuals linking to HIV care will be obtained and their mean calculated. The PR will be calculated as the ratio of the arithmetic means of the cluster-specific proportions of individuals linking to care in each arm. The 95% CI for the PR will be obtained by dividing and multiplying the estimated PR by the error factor (EF). The EF is given by the following formula:

$$EF = exp\left(t_{v,0.025} \times \sqrt{V}\right)$$

Where,

$t_{v,0.025}$ $= the\ upper\ 2.5\%\ point\ of\ the\ t\ ditsribution\ with\ v\ degrees\ of\ freedom$

$v = \Sigma c_{si} - 2S$

$c_{si} =$ $number\ of\ clusters\ in\ the\ sth\ stratum\ in\ the\ ith\ treatment\ arm$

$S = number\ of\ strata$

$V = variance\ of\ the\ prevalence\ ratio$

$Since\ equal\ numbers\ of\ clusters\ are\ allocated\ to\ the\ two\ treatment\ arms\ within\ each\ stratum$

$$V = \frac{s^2}{c_1 \times \bar{\pi}_1^2} + \frac{s^2}{c_0 \times \bar{\pi}_0^2}$$

$s^2 =$ $pooled\ estimate\ of\ the\ within\text{-}stratum\ between\text{-}cluster\ variance\ of\ the\ observed$

$cluster\text{-}specific\ proportions\ linking\ to\ care\ within\ treatment\ arms, calculated\ as\ described\ below$

$c_1 =$ $number\ of\ clusters\ in\ the\ intervention\ arm$

$\bar{\pi}_1 =$ $mean\ of\ cluster\text{-}specific\ proportions\ linking\ to\ care\ in\ the\ intervention\ arm$

$c_0 =$ $number\ of\ clusters\ in\ the\ control\ arm$

$\bar{\pi}_0 =$ $mean\ of\ the\ cluster\text{-}specific\ proportions\ linking\ to\ care\ in\ the\ control\ arm$

An estimate of the pooled within-stratum between-cluster variance, s^2, will be obtained as the residual mean square from a two-way analysis of variance of the proportions linking to care per cluster including the interaction between stratum and trial arm.

A stratified t-test of the null hypothesis of no intervention effect will be conducted using the following formula: $t_s = (\log(PR))/\sqrt{V}$

Adjusted analysis

The same variables as identified in the individual level analysis will be adjusted for in the cluster-level analysis. The analysis will be conducted as follows:

- An individual-level logistic regression analysis of linkage to care (outcome) against stratum, age group, sex, and variables for which there is imbalance between study arms will be performed. This will be a standard logistic regression analysis; the model will not include trial arm, and will not account for clustering.
- The expected numbers who linked to care will be predicted from the regression model.
- The sum of the observed and expected numbers who linked to care in each cluster will be obtained.
- Ratio residuals will be obtained by dividing the total observed number who linked to care by the total expected number in each cluster
- The ratio residuals will then be used to obtain an adjusted PR (and its 95% CI) and perform the stratified t-test using the formulae given above.

The same methods will be used to estimate the effect of the intervention on the proportions of participants who: report adherence to daily CTXp and undergo repeat HIV testing.

Cluster-level analysis for time-to-event outcomes

Unadjusted analysis

The effect of follow-up counselling on time to linkage will be measured using rate ratios (RR). For each study arm, the cluster-specific linkage rates will be obtained as the number of events divided by person-time in each cluster, and their mean calculated. The RR will be calculated as the ratio of the arithmetic means of the cluster-specific rates of linkage in each arm. The 95% CI for the RR will be obtained by dividing and multiplying the estimated RR by the error factor (EF). The same formulae as described for PRs will be used but replacing cluster specific prevalences with cluster-specific rates.

Adjusted analyses

The same methods as described for binary outcomes will be used for the adjusted analyses, with the exception that a standard Poisson regression model will be used to calculate the predicted (expected) number of events

The same methods will be used to estimate the unadjusted and adjusted effects of the intervention on time to: obtaining CD4 counts and ART initiation.

Estimation of the coefficient of variation

Data from the control arm will be used to estimate the actual coefficient of variation in the proportion of persons linking to care. The following formula will be used:

$\hat{k}_m = \sum k_{ms}/S$.

Where,

$\hat{k}_m = \ within\text{-}stratum\ coefficient\ of\ variation\ between\ clusters$

$k_{ms} = coefficient\ of\ variation\ k_m\ in\ the\ s^{th} stratum$

$S = number\ of\ strata$

$k_{ms} = \ \hat{\sigma}_{Bs/p_s}$

$\hat{\sigma}_{Bs} = the\ estimate\ of\ the\ between\text{-}cluster\ standard\ deviation\ in\ the\ s^{th} stratum$

$p_s = Overall\ observed\ proportions\ linking\ to\ care\ in\ the\ s^{th} stratum$

$$\hat{\sigma}_{Bs} = \sqrt{s_s^2 - \frac{p_s(1-p_s)}{\bar{m}_{Hs}}}$$

$s_s^2 = Variance\ of\ the\ observed\ proportions\ linking\ to\ care\ in\ the\ s^{th} stratum$

$\bar{m}_{Hs} = harmonic\ mean\ of\ the\ cluster\ size\ in\ the\ s^{th} stratum$

$s_s^2 = \sum(\pi_s - \ \bar{\pi}_s)^2/(c_s - 1)$

$\pi_s = observed\ proportion\ linking\ to\ care\ in\ the\ j^{th}\ cluster\ in\ the\ s^{th} stratum$

$\bar{\pi}_s = mean\ of\ the\ cluster\text{-}specific\ proportions\ linking\ to\ care\ in\ the\ s^{th} stratum$

$c_s = number\ of\ clusters\ in\ the\ s^{th} stratum$

$$\bar{m}_{Hs} = \frac{1}{\sum(1/m)/c_s}$$

$m = cluster\ size$

References

1. Hayes JR, Moulton HL. Cluster randomised trials. Boca Raton: Taylor & Francis; 2009. 201 p.

8.2 Appendix 2: Household data form

Linkage to pre-ART care study- Household Data Form

Cluster number: |__|__|CLUSN Village name: _____VILL

Household number	Names of household members aged ≥18 years	VCT number	Age	Sex	Visit 1		Visit 2		Visit 3		Comments (provide telephone number if enrolled)
					Date	Laboratory number	Date	Laboratory number	Date	Laboratory number	

Interviewer's initials: ¦___¦___¦___¦

8.3 Appendix 3: HIV counselling and testing worksheet

Linkage to HIV care study - Field HIV counselling & testing worksheet

Cluster number: |__|__| Village Number:

Date	VCT number	Visit code (1, 2, …)	Sex (1=M, 2=F)	Age	Test (0=Negative,1=Positive)	Laboratory number	Staff initials

8.4 Appendix 4: Informed consent document - English v1.1 26Jan15

INFORMED CONSENT DOCUMENT: LINKAGE TO HIV CARE STUDY

PARTICIPANT INFORMATION

Study Title: The effectiveness of a counseling intervention on the uptake of HIV care services among HIV infected patients in Uganda.

Study purpose: The purpose of this study is to find out whether follow-up counseling for persons who are counseled and tested for HIV from their homes makes it easier for them to; 1) take up HIV care services; 2) test again for HIV. Results from this study will contribute to HIV prevention and care efforts in Uganda.

Study participants: The study will be conducted in twenty-two randomly selected communities in Mukungwe and Buwunga sub-counties, Masaka district. Counselors will visit all households in the 22 communities and offer counseling and testing for HIV to all adults in each home. Participants for the study will be identified from those individuals that undergo counseling and testing for HIV in their homes. Up to 500 individuals with and without HIV infection will participate in the study.

Study duration: You will be in the study for a total of 6 months. You may have up to 3 follow up visits at one, two, and six months after you join the study. All study visits will be conducted in your home.

Study visits

Screening/Enrolment visit: After you receive your HIV test results, you will be given information about the study and invited to participate. If you agree to participate, you

will be asked questions about your personal details including HIV testing experiences. If you are found to have HIV infection, the counselor will give you information about the available HIV care services in your area, and refer you to an HIV care provider of your choice for care and support.

Month 1 and 2 follow-up visits: At one and at two months after joining the study, counselors will visit participants in 11 randomly selected communities to provide follow-up counseling. Participants in the remaining 11 communities will not have month 1 and 2 follow-up visits and will not have follow-up counseling. You will be informed by a study counselor if and when you will be receiving follow-up counseling or not.

Month 6 follow-up visit: Six months after joining the study, study counselors will visit participants in all the 22 communities. If you have HIV infection, you will be asked if you registered for and are receiving HIV care. You will also be asked about the laboratory tests that you have had and details of the drugs you are taking. If you have not had a CD4 cell count test done, the counselor will ask you to provide a blood sample for CD4 cell count testing. If you do not have HIV infection, the counselor will offer you another HIV test. Written CD4 cell count or HIV test results will be delivered to you within 1 week.

- **Review of medical records:** If you have HIV and are receiving care; we will visit your HIV care provider to collect details about the care that you are receiving.

Interviews on uptake of HIV care and repeat HIV testing: You may be selected to participate in interviews to get your thoughts about uptake of HIV care services and getting another HIV test. If you are selected, a study staff will visit your home 2-3 months after the month 6 follow-up visit to conduct the interview. The interview will take approximately 45 minutes.

Risks and discomforts: This study involves visits by study staff to your home. This may inconvenience you or cause you some discomfort. You may feel pain and get bruising where the needle goes into your arm while drawing blood. You may also feel dizzy or faint at the time of drawing blood but this is not common. You may become worried, or anxious when discussing sex and HIV, while undergoing HIV testing, and when you receive HIV positive results. The counsellor will help you with any feelings or questions you may have. If you are HIV-infected and other people learn about it, they may treat you unfairly. This study will enroll HIV-infected and uninfected persons. This may decrease the chance of other people knowing your HIV status.

Benefits: You will learn your HIV status and receive information about HIV prevention and care services. If you have HIV, you will be referred to an HIV care facility where you will receive treatment and support. If you do not have HIV, you will be given information on ways to reduce the risk of getting HIV. If you are male and would like to get circumcised in order to reduce your risk of getting HIV, you will be provided a written referral to a facility where you can undergo safe male circumcision.

Your participation is voluntary: You will sign or make a thumb print on 2 copies of this form to indicate that you voluntarily agree to take participate in the study; one copy will be given to you and the other will be kept at the MRC/UVRI Masaka office. You

may withdraw from the study at any time. If you decide not to participate in or withdraw from the study, you will not lose any rights or benefits.

Supervision of the study: Approvals for this study have been obtained from the UVRI Research Ethics Committee, the London School of Hygiene & Tropical Medicine Ethics committee, and the Uganda National Council for Science and Technology. The study will be monitored by someone who is not involved in its conduct.

Confidentiality: Your participation in the study, all information collected about you and laboratory test results are confidential. You will have your own unique study number that will only be known to you and the study staff. Your blood specimens will only be identified by this number. Any documents containing your name will be locked away in a secure place at the MRC/UVRI- Masaka office.

Contact numbers: If you have any questions about the study, please call Dr. Eugene Ruzagira on Tel: 0481421211 or 0701030782 at the MRC/UVRI Masaka clinic. If you have a question about your rights as a study volunteer please contact Mr. Tom Lutalo, the Chairman of the UVRI Research Ethics Committee on Tel: 0414321962.

CONSENT FORM

I, (name of participant)……

of (address)……..

agree to take part in the study entitled**: "The effectiveness of a counseling intervention on the uptake of HIV care services among HIV infected patients in Uganda".** I have read/been read to this study's information sheet and I understand what will be required of me if I take part in this study. My questions regarding this study have been answered. I understand that at any time, I may withdraw from this study without giving a reason and without affecting my normal medical care and management.

Participant signature/Thumb print Date

Study staff obtaining consent: I have explained the nature, purpose, demands and foreseeable risks of the above study to the participant. I have answered all the participant's questions to the best of my ability.

Study staff signature Date

Impartial witness *(only necessary if participant was not able to read and understand this Informed Consent Document):* I affirm that the Informed Consent Document has been read to the participant and he/she understands the study, had his/her questions answered, and I have witnessed the participant's consent to study participation.

Impartial witness signature Date

8.5 Appendix 5: Informed consent document - Luganda v1.1 26Jan15

EKIWANDIIKO E'KYOKUNNYONNYOLA ANETABA MUKUNOONYEREZA ANEETABAMU BYALINA OKUMANYA

Omutwe gw'okunoonyereza: Okunoonyereza okugenderera okuzuula oba nga okulungamya abantu abalina akawuka ka silimu mu Uganda kibayambako okweyunira okufuna obujjanjabi bwakawuka kano.

Ekigendererwa ky'okunoonyereza: Ekigendererwa ky'okunoonyereza kuno kwe kuzuula oba okulondoola n'okulungamya abantu ababa bakeberebbwa akawuka ka silimu mu maka gabwe kiyinza okubayamba: 1) okweyunira okufuna obujjanjabi bwa kawuka kano; 2) okuddamu okwekebeza akawuka ka silimu. Ebinaava mu kunoonyereza kuno bijja kuyamba mu kawefube w'okuziyiza n'okujjanjaba akawuka ka silimu mu Uganda.

Abaneetaba mu kunoonyereza: Okunoonyereza kuno kujja kukolebwa mu bitundu 22 mu magombolola g'e Buwunga ne Mukungwe Mu Masaka disitulikiti. Abalungamya bajja kukyalira amaka gona mu bitundu bino 22 bawe okulangamya n'okukebera akawuka ka silimu eri abantu abakulu bonna mu buli maka. Abanetaba mukunoonyereza kunno bajja kuva mwabo abanaba balungamiziddwa era nebakeberebwa akawuka ka silimu ngabasangibwa mu maka gabwe. Abantu nga 500 abalina nabatalina kawuka ka siliimu be baneetaba mu kunoonyereza kuno.

Ebbanga okunoonyereza lye kunaamala: Ojja kubeera mu kunoonyereza okumala emyezi nga 6. Oyinza okukyalilwa emirundi essatu: oluvanyuma lwomwezi 1, emyezi

2, ne 6 nga oyingidde mu kunoonyereza. Enkyala z'okunoonyereza zonna zijja kukolebwa mu maka go.

Enkyala z'okunoonyereza

Olukyala olwokuyingizibwa mu kunoonyereza: Nga omaze okufuna ebivudde mu kukeberebwa akawuka ka silimu, ojja kunnyonnyolwa ebikwata kunoonyereza kuno era osabibwe okukwetabamu. Bw'okkiriza okwetabamu, ojja kubuuzibwa ebibuuzo ku bikwatako ng'omuntu nebikwata ku kwekebeza akawuka ka siliimu. Bw'nosangibbwa ng'olina akawuka ka siliimu, omulungamya ajja kukuwa ebikwata ku w'oyinza okufuna obujjanjabi bw'embeera eno ate akuwe n'ebbaluwa ekwanjula eyo gye wandyagadde okufuna obujjanjabi buno n'obuyambi obulala.

Olukyala kumwezi 1 ne 2: Ku mwezi ogusooka, nemyezi ebiri oluvanyuma lwokuyingira mukonoonyereza, mu bitundu 11 ebinalondebwa mu ngeri yakalulu, abalungamya bajja kukyalira abantu abanaba betabye mukonoonyereza bongere okubalungamya kubikwatagana n'akawuka ka silimu. Abantu abanaba betabye mukunoonyereza mubitundu 11 ebinaba bisagadde tebagya kukyalilwa era tebagya kufuna kulungamizibwa mu biseera bino. Omulungamya mu kunoonyereza kuno ajja kukutegeza oba oli mwabo abanayongera okulungamizibwa era nebisera mwonalungamizibwa abikubulire.

Olukyala ku myezi 6: Nga emyezi 6 gyiweze oluvanyuma lwokuyingira mukonoonyereza, abalungamya mu kunoonyereza bajja kukyalira abantu bona abanaba bakutabyemu mu bitundu ebyo 22. Bwoba olina akawuka ka silimu, ojja kubuzibwa oba watandika okufuna obujjanjabi, ebyakukeberwako, n'eddagala lyokozesa. Bw'oba nga tokeberebwanga bungi bwa butofaali obwa CD4; omulungamya ajja kukusaba oweyo

omusaayi gukeberebwe obutofaali. Bw'oba tolina kawuka ka siliimu, omulungamya ajja kukuwa omukisa ogwokudamu okwekebeza akawuka ka siliimu. Ebinava mukukeberebwa kw'obutofaali oba akawuka ka silimu bijja kukudizibwa mu buwandiike mu bbanga eritassukka wiiki 1.

- **Okufuna n'okuyita mu biwandiiko ebikwata ku bujjaanjabi:** Bw'oba nga olina akawuka ka siliimu ate ng'olina gyofuna obujjanjabi; tujja kutuukirira eyo gy'ofunira obujjanjabi okuyita mu biwandiiko byo n'okufuna ebikwata ku bujjaanjabi bw'ofuna.

Ebibuuzo ebikwata ku kufuna obujjanjabi bw'akawuka ka siliimu n'okuddamu okwekebeza akawuka kano: Okyayinza okulondebwa okwetaba mukubuzibwa ebibuzo okumanya endowoza yo kukyokweyunira okufuna obujanjabi bwa kawuka ka silimu n'ekyokudangamu okwekebeza akawuka kano. Bw'onolondebwa, omukozi mu kunoonyereza kuno ajja kukukyalira ewaka wo wakati we myezi 2-3 oluvanyuma lw'olukyala olw'emyezi 6 okukubuuza ebibuuzo bino. Okubuzibwa kuno kujja kutwala eddakika nga 45.

Obuzibu n'obutayisibwa bulungi: Okunoonyereza kuno kulimu abakozi ku mulimu guno okukukyalira ewaka. Kino kiyinza okukutataganya oba obutakuyisa bulungi. Oyinza okufuna obulumi n'okunubuka awo empiso weyingirira mu mukono gwo nga ojjibwako omusayi. Okyayinza okuwulira kamunguluze oba okuggwamu amanyi mu kaseera akokujibwako omusayi naye kino tekitera kubaawo. Oyinza okweraliikirira oba okwewanika omutima nga mukubaganya ebirowoozo ku by'okutaabagana mu bikolwa eby'ekyaama n'akawuka ka siliimu, ng'okeberebwa akawuka ka siliimu oba ebivuddemu bwe biraga nti olina akawuka kano. Omulungamya ajja kukuyamba ku mbeera eno n'okuddamu ebibuuzo by'oyinza okuba nabyo. Bw'oba olina akawuka ka

siliimu ate abantu abalala ne bakimanyako, bakyayinza obutakuyisa bulungi. Okunoonyereza kuno kujja kubaamu abantu abalina n'abatalina kawuka kano. Kino kikyayinza okukendeeza obuzibu bw'abantu abalala okumanya embeera y'obulamu bwo ku kawuka ka siliimu.

Ebyokuganyulwa: Ojja kumanya oba olina akawuka ka silimu oba tokalina era otegezebwe ku ntekateka z'okwetangira n'okujjanjaba akawuka kano. Bw'oba ng'olina akawuka ka siliimu ojja kuweerezebwa gy'osobola okufuna obujjaanjabi n'okuyambibwa. Bw'oba tolina kawuka ka siliimu ojja kutegezebwa engeri gyoyinza okwetangiramu akawuka kano. Bw'oba nga olimusajja era ng'awandyagade okomolebwe okusobola okunkendeza ku katyabaga kokwatibwa akawuka ka silimu, ojjakuwebwa ebbaluwa ekusindika kudwaliro woyinza okukumolebwa.

Okwetabamu kwa kyayagalire: Oja kusa omukono oba ekinkumu ku kopi bbiri ez'ekiwandiko kino okulaga nti okwetabamu ko kwa kyeyagalire; kopi emu ejja kukuwebwa ate endala eterekebwe ku kitebe kya MRC/UVRI e Masaka. Okyayinza okuva mu kunoonyereza kuno obudde bwonna. Bw'osalawo obutetabaamu oba okuvaamu, tolina ddembe ly'abuntu oba by'obadde olina okufuna by'ofiirwa.

Okulondola engeri okunoonyereza gye kunaakolebwamu: Olukusa lw'okukola okunoonyereza kuno lwaweereddwa okuva mu bukiiko obukwasisa empisa n'amateeta mubyokunoonyereza obwebitongole bino: Uganda Virus Research Institute, London School of Hygiene and Tropical Medicine, ne Uganda National Council for Science and Technology. Okunoonyereza kujja kulondolwa omuntu eyeetengeredde atali omu kwabo abakola okunoonyereza.

Okukuuma ebyaama: Okwetaba kwo mu kunoonyereza, byonna by'etukunganyako n'ebyo ebiva mu kukeberebwako bya kyaama. Ojja kuba ne nnamba eyiyo ku bubwo ekwawula ku muntu omulala yenna era nga emanyiddwa gwe wekka n'abo abakola okunoonyereza. Omusaayi ogukugyibwako okukeberebwa gujja kulambibwa ne nnamba yo yokka. Ekiwandiiko kyonna ekiriko amannya go kijja kukuumirwa awantu awekusifu ku kitebe kya MRC/UVRI Masaka.

Nnamba z'essimu: Bw'oba n'ekibuuzo kyonna ku kunoonyereza, mwattu kubira Dr. Eugene Ruzagira ku 0481421211 oba 0701030782 ku ddwaliro lya MRC/UVRI Masaka. Bw'oba n'ekibuuzo ku dembe lyo nga nakyewa eyetabye mu kunoonyereza, mwattu tuukirira Mwami Tom Lutalo, ssentebe w'akakiiko ka sayaansi, amateeka n'empisa aka UVRI ku ssimu 0414321962.

FOOMU Y'OKUKIRIZA OKWETABA MU KUNOONYEREZA

Nze, (erinya ly'etabyemu)……

owe (gyabera)……nzirikiriza okwetaba mu kunoonyereza okugenderera okuzuula oba nga okulungamya abantu abalina akawuka ka silimu mu Uganda kibayambako okweyunira okufuna obujjanjabi bwakawuka kano. Nsomye/nsomeddwa ekiwandiiko ekinnyonnyola ebikwata ku kunoonyereza kuno era ntegede ekineetagisa bwenkwetabamu. Ebibuuzo byange ku kunoonyereza kuno bididdwamu. Nkitegeera nti obudde bwonna nsobola okuva mukunoonyereza kuno nga siwadde nsonga era kino tekikosa bujjanjabi bwenina kufuna.

Omukono (ekinkumu) gw'eyatabyemu	**Ennaku z'omwezi**

<u>Oyo annyonnyode ebikwata ku kunoonyereza:</u> Omuntu ono munnyonnyodde ekigendererwa ky'okunoonyereza kuno, ebyetaagisa, n'obuzibu obuyinza okubamu. Ebibuuzo bye byonna mbizeemu nga bwensobola

Omukono gw'oyo annyonnyode ebikwata ku kunoonyereza	**Ennaku z'omwezi**

<u>Omujjulizi atalina kyekubiira:</u> ***(****Kino kyetaagisa singa omuntu akirizza okwetaba mukunonyereza tasobola kwesomera biri mu kiwandiiko ekinnyonnyola ku kunoonyereza kuno):* Nkakasa nti ekiwandiiko ekinnyonnyola ebikwata ku kunonyereza kuno omuntu ono kimusomeddwa era okunoonyereza akutegedde bulungi, ebibuuzo bye bididdwamu era mbaddewo ng'omujjulizi nga akkiriza okwetaba mu kunoonyereza kuno

Omukono gw'omujjulizi atalina kyekuubiira	**Ennaku z'omwezi**

8.6 Appendix 6: Informed consent document - English v2.0 15May15

INFORMED CONSENT DOCUMENT: LINKAGE TO HIV CARE STUDY

PARTICIPANT INFORMATION

Study Title: The effectiveness of a counseling intervention on the uptake of HIV care services among HIV infected patients in Uganda.

Study purpose: The purpose of this study is to find out whether follow-up counseling for persons who are counseled and tested for HIV from their homes makes it easier for them to; 1) take up HIV care services; 2) test again for HIV. Results from this study will contribute to HIV prevention and care efforts in Uganda.

Study participants: The study will be conducted in twenty-eight randomly selected communities in Mukungwe, Buwunga, and Kyanamukaaka sub-counties, Masaka district. Counselors will visit all households in the 28 communities and offer counseling and testing for HIV to all adults in each home. Participants for the study will be identified from those individuals that undergo counseling and testing for HIV in their homes. Up to 308 individuals with and without HIV infection will participate in the study.

Study duration: You will be in the study for a total of 6 months. You may have up to 3 follow up visits at one, two, and six months after you join the study. All study visits will be conducted in your home.

Study visits

Screening/Enrolment visit: After you receive your HIV test results, you will be given information about the study and invited to participate. If you agree to participate, you will be asked questions about your personal details including HIV testing experiences. If you are found to have HIV infection, the counselor will give you information about the available HIV care services in your area, and refer you to an HIV care provider of your choice for care and support.

Month 1 and 2 follow-up visits: At one and at two months after joining the study, counsellors will visit participants in 14 randomly selected communities to provide follow-up counselling. Participants in the remaining 14 communities will not have month 1 and 2 follow-up visits and will not have follow-up counseling. You will be informed by a study counselor if and when you will be receiving follow-up counseling or not.

Month 6 follow-up visit: Six months after joining the study, study counselors will visit participants in all the 28 communities. If you have HIV infection, you will be asked if you registered for and are receiving HIV care. You will also be asked about the laboratory tests that you have had and details of the drugs you are taking. If you have not had a CD4 cell count test done, the counselor will ask you to provide a blood sample for CD4 cell count testing. If you do not have HIV infection, the counselor will offer you another HIV test. Written CD4 cell count or HIV test results will be delivered to you within 1 week.

- **Review of medical records:** If you have HIV and are receiving care; we will visit your HIV care provider to collect details about the care that you are receiving.

Interviews on uptake of HIV care and repeat HIV testing: You may be selected to participate in interviews to get your thoughts about uptake of HIV care services and getting another HIV test. If you are selected, a study staff will visit your home 2-3 months after the month 6 follow-up visit to conduct the interview. The interview will take approximately 45 minutes.

Risks and discomforts: This study involves visits by study staff to your home. This may inconvenience you or cause you some discomfort. You may feel pain and get bruising where the needle goes into your arm while drawing blood. You may also feel dizzy or faint at the time of drawing blood but this is not common. You may become worried, or anxious when discussing sex and HIV, while undergoing HIV testing, and when you receive HIV positive results. The counselor will help you with any feelings or questions you may have. If you are HIV-infected and other people learn about it, they may treat you unfairly. This study will enroll HIV-infected and uninfected persons. This may decrease the chance of other people knowing your HIV status.

Benefits: You will learn your HIV status and receive information about HIV prevention and care services. If you have HIV, you will be referred to an HIV care facility where you will receive treatment and support. If you do not have HIV, you will be given information on ways to reduce the risk of getting HIV. If you are male and would like to get circumcised in order to reduce your risk of getting HIV, you will be provided a written referral to a facility where you can undergo safe male circumcision.

Your participation is voluntary: You will sign or make a thumb print on 2 copies of this form to indicate that you voluntarily agree to take participate in the study; one copy will be given to you and the other will be kept at the MRC/UVRI Masaka office. You may withdraw from the study at any time. If you decide not to participate in or withdraw from the study, you will not lose any rights or benefits.

Supervision of the study: Approvals for this study have been obtained from the UVRI Research Ethics Committee, the London School of Hygiene & Tropical Medicine Ethics committee, and the Uganda National Council for Science and Technology. The study will be monitored by someone who is not involved in its conduct.

Confidentiality: Your participation in the study, all information collected about you and laboratory test results are confidential. You will have your own unique study number that will only be known to you and the study staff. Your blood specimens will only be identified by this number. Any documents containing your name will be locked away in a secure place at the MRC/UVRI- Masaka office.

Contact numbers: If you have any questions about the study, please call Dr. Eugene Ruzagira on Tel: 0481421211 or 0701030782 at the MRC/UVRI Masaka clinic. If you have a question about your rights as a study volunteer please contact Mr. Tom Lutalo, the Chairman of the UVRI Research Ethics Committee on Tel: 0414321962.

CONSENT FORM

I, (name of participant)……

of (address)……

agree to take part in the study entitled**: "The effectiveness of a counseling intervention on the uptake of HIV care services among HIV infected patients in Uganda".** I have read/been read to this study's information sheet and I understand what will be required of me if I take part in this study. My questions regarding this study have been answered. I understand that at any time, I may withdraw from this study without giving a reason and without affecting my normal medical care and management.

Participant signature/Thumb print Date

Study staff obtaining consent

I have explained the nature, purpose, demands and foreseeable risks of the above study to the participant. I have answered all the participant's questions to the best of my ability.

Study staff signature Date

Impartial witness *(only necessary if participant was not able to read and understand this Informed Consent Document):* I affirm that the Informed Consent Document has been read to the participant and he/she understands the study, had his/her questions answered, and I have witnessed the participant's consent to study participation.

Impartial witness signature Date

8.7 Appendix 7: Informed consent document - Luganda v2.0 15May15

EKIWANDIIKO E'KYOKUNNYONNYOLA ANETABA MUKUNOONYEREZA ANEETABAMU BYALINA OKUMANYA

Omutwe gw'okunoonyereza: Okunoonyereza okugenderera okuzuula oba nga okulungamya abantu abalina akawuka ka silimu mu Uganda kibayambako okweyunira okufuna obujjanjabi bwakawuka kano.

Ekigendererwa ky'okunoonyereza: Ekigendererwa ky'okunoonyereza kuno kwe kuzuula oba okulondoola n'okulungamya abantu ababa bakeberebbwa akawuka ka silimu mu maka gabwe kiyinza okubayamba: 1) okweyunira okufuna obujjanjabi bwa kawuka kano; 2) okuddamu okwekebeza akawuka ka silimu. Ebinaava mu kunoonyereza kuno bijja kuyamba mu kawefube w'okuziyiza n'okujjanjaba akawuka ka silimu mu Uganda.

Abaneetaba mu kunoonyereza: Okunoonyereza kuno kujja kukolebwa mu bitundu 28 mu magombolola g'e Buwunga, Mukungwe, ne Kyanamukaaka Mu Masaka disitulikiti. Abalungamya bajja kukyalira amaka gona mu bitundu bino 28 bawe okulangamya n'okukebera akawuka ka silimu eri abantu abakulu bonna mu buli maka. Abanetaba mukunoonyereza kunno bajja kuva mwabo abanaba balungamiziddwa era nebakeberebwa akawuka ka silimu ngabasangibwa mu maka gabwe. Abantu nga 308 abalina nabatalina kawuka ka siliimu be baneetaba mu kunoonyereza kuno.

Ebbanga okunoonyereza lye kunaamala: Ojja kubeera mu kunoonyereza okumala emyezi nga 6. Oyinza okukyalilwa emirundi essatu: oluvanyuma lwomwezi 1, emyezi

2, ne 6 nga oyingidde mu kunoonyereza. Enkyala z'okunoonyereza zonna zijja kukolebwa mu maka go.

Enkyala z'okunoonyereza

Olukyala olwokuyingizibwa mu kunoonyereza: Nga omaze okufuna ebivudde mu kukeberebwa akawuka ka silimu, ojja kunnyonnyolwa ebikwata kunoonyereza kuno era osabibwe okukwetabamu. Bw'okkiriza okwetabamu, ojja kubuuzibwa ebibuuzo ku bikwatako ng'omuntu nebikwata ku kwekebeza akawuka ka siliimu. Bw'nosangibbwa ng'olina akawuka ka siliimu, omulungamya ajja kukuwa ebikwata ku w'oyinza okufuna obujjanjabi bw'embeera eno ate akuwe n'ebbaluwa ekwanjula eyo gye wandyagadde okufuna obujjanjabi buno n'obuyambi obulala.

Olukyala kumwezi 1 ne 2: Ku mwezi ogusooka, nemyezi ebiri oluvanyuma lwokuyingira mukonoonyereza, mu bitundu 14 ebinalondebwa mu ngeri yakalulu, abalungamya bajja kukyalira abantu abanaba betabye mukonoonyereza bongere okubalungamya kubikwatagana n'akawuka ka silimu. Abantu abanaba betabye mukunoonyereza mubitundu 14 ebinaba bisagadde tebagya kukyalilwa era tebagya kufuna kulungamizibwa mu biseera bino. Omulungamya mu kunoonyereza kuno ajja kukutegeza oba oli mwabo abanayongera okulungamizibwa era nebisera mwonalungamizibwa abikubulire.

Olukyala ku myezi 6: Nga emyezi 6 gyiweze oluvanyuma lwokuyingira mukonoonyereza, abalungamya mu kunoonyereza bajja kukyalira abantu bona abanaba bakutabyemu mu bitundu ebyo 28. Bwoba olina akawuka ka silimu, ojja kubuzibwa oba watandika okufuna obujjanjabi, ebyakukeberwako, n'eddagala lyokozesa. Bw'oba nga tokeberebwanga bungi bwa butofaali obwa CD4; omulungamya ajja kukusaba oweyo

omusaayi gukeberebwe obutofaali. Bw'oba tolina kawuka ka siliimu, omulungamya ajja kukuwa omukisa ogwokudamu okwekebeza akawuka ka siliimu. Ebinava mukukeberebwa kw'obutofaali oba akawuka ka silimu bijja kukudizibwa mu buwandiike mu bbanga eritassukka wiiki 1.

- **Okufuna n'okuyita mu biwandiiko ebikwata ku bujjaanjabi:** Bw'oba nga olina akawuka ka siliimu ate ng'olina gyofuna obujjanjabi; tujja kutuukirira eyo gy'ofunira obujjanjabi okuyita mu biwandiiko byo n'okufuna ebikwata ku bujjaanjabi bw'ofuna.

Ebibuuzo ebikwata ku kufuna obujjanjabi bw'akawuka ka siliimu n'okuddamu okwekebeza akawuka kano: Okyayinza okulondebwa okwetaba mukubuzibwa ebibuzo okumanya endowoza yo kukyokweyunira okufuna obujanjabi bwa kawuka ka silimu n'ekyokudangamu okwekebeza akawuka kano.Bw'onolondebwa, omukozi mu kunoonyereza kuno ajja kukukyalira ewaka wo wakati we myezi 2-3 oluvanyuma lw'olukyala olw'emyezi 6 okukubuuza ebibuuzo bino. Okubuzibwa kuno kujja kutwala eddakika nga 45.

Obuzibu n'obutayisibwa bulungi: Okunoonyereza kuno kulimu abakozi ku mulimu guno okukukyalira ewaka. Kino kiyinza okukutataganya oba obutakuyisa bulungi. Oyinza okufuna obulumi n'okunubuka awo empiso weyingirira mu mukono gwo nga ojjibwako omusayi. Okyayinza okuwulira kamunguluze oba okuggwamu amanyi mu kaseera akokujibwako omusayi naye kino tekitera kubaawo. Oyinza okweraliikirira oba okwewanika omutima nga mukubaganya ebirowoozo ku by'okutaabagana mu bikolwa eby'ekyaama n'akawuka ka siliimu, ng'okeberebwa akawuka ka siliimu oba ebivuddemu bwe biraga nti olina akawuka kano. Omulungamya ajja kukuyamba ku mbeera eno n'okuddamu ebibuuzo by'oyinza okuba nabyo. Bw'oba olina akawuka ka

siliimu ate abantu abalala ne bakimanyako, bakyayinza obutakuyisa bulungi. Okunoonyereza kuno kujja kubaamu abantu abalina n'abatalina kawuka kano. Kino kikyayinza okukendeeza obuzibu bw'abantu abalala okumanya embeera y'obulamu bwo ku kawuka ka siliimu.

Ebyokuganyulwa: Ojja kumanya oba olina akawuka ka silimu oba tokalina era otegezebwe ku ntekateka z'okwetangira n'okujjanjaba akawuka kano. Bw'oba ng'olina akawuka ka siliimu ojja kuweerezebwa gy'osobola okufuna obujjaanjabi n'okuyambibwa. Bw'oba tolina kawuka ka siliimu ojja kutegezebwa engeri gyoyinza okwetangiramu akawuka kano. Bw'oba nga olimusajja era ng'awandyagade okomolebwe okusobola okunkendeza ku katyabaga kokwatibwa akawuka ka silimu, ojjakuwebwa ebbaluwa ekusindika kudwaliro woyinza okukumolebwa.

Okwetabamu kwa kyayagalire: Oja kusa omukono oba ekinkumu ku kopi bbiri ez'ekiwandiko kino okulaga nti okwetabamu ko kwa kyeyagalire; kopi emu ejja kukuwebwa ate endala eterekebwe ku kitebe kya MRC/UVRI e Masaka. Okyayinza okuva mu kunoonyereza kuno obudde bwonna. Bw'osalawo obutetabaamu oba okuvaamu, tolina ddembe ly'abuntu oba by'obadde olina okufuna by'ofiirwa.

Okulondola engeri okunoonyereza gye kunaakolebwamu: Olukusa lw'okukola okunoonyereza kuno lwaweereddwa okuva mu bukiiko obukwasisa empisa n'amateeta mubyokunoonyereza obwebitongole bino: Uganda Virus Research Institute, London School of Hygiene and Tropical Medicine, ne Uganda National Council for Science and Technology. Okunoonyereza kujja kulondolwa omuntu eyeetengeredde atali omu kwabo abakola okunoonyereza.

Okukuuma ebyaama: Okwetaba kwo mu kunoonyereza, byonna by'etukunganyako n'ebyo ebiva mu kukeberebwako bya kyaama. Ojja kuba ne nnamba eyiyo ku bubwo ekwawula ku muntu omulala yenna era nga emanyiddwa gwe wekka n'abo abakola okunoonyereza. Omusaayi ogukugyibwako okukeberebwa gujja kulambibwa ne nnamba yo yokka. Ekiwandiiko kyonna ekiriko amannya go kijja kukuumirwa awantu awekusifu ku kitebe kya MRC/UVRI Masaka.

Nnamba z'essimu: Bw'oba n'ekibuuzo kyonna ku kunoonyereza, mwattu kubira Dr. Eugene Ruzagira ku 0481421211 oba 0701030782 ku ddwaliro lya MRC/UVRI Masaka. Bw'oba n'ekibuuzo ku dembe lyo nga nakyewa eyetabye mu kunoonyereza, mwattu tuukirira Mwami Tom Lutalo, ssentebe w'akakiiko ka sayaansi, amateeka n'empisa aka UVRI ku ssimu 0414321962.

FOOMU Y'OKUKIRIZA OKWETABA MU KUNOONYEREZA

Nze, (erinya ly'etabyemu)……

owe (gyabera)…….

nzirikiriza okwetaba mu kunoonyereza okugenderera okuzuula oba nga okulungamya abantu abalina akawuka ka silimu mu Uganda kibayambako okweyunira okufuna obujjanjabi bwakawuka kano. Nsomye/nsomeddwa ekiwandiiko ekinnyonnyola ebikwata ku kunoonyereza kuno era ntegede ekineetagisa bwenkwetabamu. Ebibuuzo byange ku kunoonyereza kuno bididdwamu. Nkitegeera nti obudde bwonna nsobola okuva mukunoonyereza kuno nga siwadde nsonga era kino tekikosa bujjanjabi bwenina kufuna.

Omukono (ekinkumu) gw'eyatabyemu	**Ennaku z'omwezi**

<u>Oyo annyonnyode ebikwata ku kunoonyereza:</u> Omuntu ono munnyonnyodde ekigendererwa ky'okunoonyereza kuno, ebyetaagisa, n'obuzibu obuyinza okubamu. Ebibuuzo bye byonna mbizeemu nga bwensobola

Omukono gw'oyo annyonnyode ebikwata ku kunoonyereza	**Ennaku z'omwezi**

<u>Omujjulizi atalina kyekubiira:</u> *(Kino kyetaagisa singa omuntu akirizza okwetaba mukunonyereza tasobola kwesomera biri mu kiwandiiko ekinnyonnyola ku kunoonyereza kuno):* Nkakasa nti ekiwandiiko ekinnyonnyola ebikwata ku kunonyereza kuno omuntu ono kimusomeddwa era okunoonyereza akutegedde bulungi, ebibuuzo bye bididdwamu era mbaddewo ng'omujjulizi nga akkiriza okwetaba mu kunoonyereza kuno

Omukono gw'omujjulizi atalina kyekuubiira	**Ennaku z'omwezi**

8.8 Appendix 8: Eligibility assessment form

Linkage to pre-ART care study- eligibility assessment form

HCT Lab number: MC|__|__|__|__|__|__|__|LABN Cluster number: |__|__|CLUSN

Village name: _____VILL Household ID: |__|__|__|HHN

HIV positive		
Inclusion criteria		
Aged ≥18 years	Yes ¦___¦	No ¦___¦
Willing to provide informed consent	Yes ¦___¦	No ¦___¦
Willing to receive follow-up counselling at home	Yes ¦___¦	No ¦___¦
Exclusion criteria		
Previous or current receipt of HIV care from an ART provider	Yes ¦___¦	No ¦___¦
On-going participation in other health-related research	Yes ¦___¦	No ¦___¦
Intending to change residence in the next 6 months	Yes ¦___¦	No ¦___¦
Conditions that may make it difficult to provide informed consent	Yes ¦___¦	No ¦___¦
HIV negative		
Inclusion criteria		
Age: ≥18 years	Yes ¦___¦	No ¦___¦
Willing to provide informed consent	Yes ¦___¦	No ¦___¦
Willing to receive follow-up counselling at home	Yes ¦___¦	No ¦___¦
Exclusion criteria		
Intending to change residence in the next 6 months	Yes ¦___¦	No ¦___¦
Conditions that make it difficult to provide informed consent	Yes ¦___¦	No ¦___¦
Individual eligible for enrolment	Yes ¦___¦	No ¦___¦
If eligible, assign study number:	HCT-¦___¦___¦___¦___¦___¦ (e.g. HCT-888Z, HCT-999X,….)	
Interview date	**|__|__||__|__|__||__|__|__|__| dd MMM yyyy**	
Interviewer's initials	**¦___¦___¦___¦**	

8.9 Appendix 9: Sociodemographic questionnaire

Linkage to pre-ART care study- Socio-demographic questionnaire

HCT Lab number: MC|__|__|__|__|__|__|__|__|LABN **Cluster number: |__|__|CLUSN**

Village name: _____VILL **Household ID: |__|__|__|HHN**

Study number: HCT-|__|__|__|__|SN

No.	Code	Questions and filters	Coding categories	Skip
1.	SC	Sub-county	Mukungwe 1 Buwunga 2 Kyanamukaaka 3	
2.	SEX	Sex	Male 1 Female 2	
3.	AGE	Age	|__|__|Years	
4.	MSTAT	Marital status	Single 1 Married 2 Cohabiting 3 Widowed 4 Divorced/separated 5	
5.	EDUC	Highest level of education attained	No formal education 1 Incomplete primary 2 Complete primary 3 Secondary (O level) 4 Secondary (A level) 5 University/College 6	
6.		What is your occupation? **(Multiple responses allowed)**	Yes No	
	OCC1	Subsistence farmer	1 2	
	OCC2	Fishing/fish-related work	1 2	
	OCC3	Own small business	1 2	
	OCC4	Shopkeeper/market salesperson	1 2	
	OCC5	Craftsman	1 2	
	OCC6	Housewife	1 2	
	OCC7	Professional worker	1 2	
	OCC8	Casual labourer	1 2	
	OCC9	Student	1 2	
	OCC10	Unemployed	1 2	
	OTHOCC	Other	1 2	
	SOTHOCC		Specify other:_____	
7.	REL	Religion	Roman Catholic 1 Anglican 2 Other Christian 3 Muslim 4 Traditional 5 Other (specify)..... 6 None 7	

8.9 Appendix 9: Sociodemographic questionnaire

Linkage to pre-ART care study- Socio-demographic questionnaire

HCT Lab number: MC|__|__|__|__|__|__|__|LABN Cluster number: |__|__|CLUSN

Village name: _____VILL Household ID: |__|__|__|HHN

Study number: HCT-|__|__|__|__|SN

No.	Code	Questions and filters	Coding categories	Skip
8.		Ku bantu ababeera mu nyumba eno nga naawe mw'oli, waliwo alina ebintu bino wammanga? ***(Does any member of your household (including yourself) own any of the following?)*** (**Prompt all responses**)	Yes No	
	BICY	Eggaali (Bicycle)	1 2	
	MOTCY	Pikipiki (Motorcycle)	1 2	
	CAR	Emmotoka (Car/van/truck)	1 2	
	SEWM	Ekyalaani (Sewing machine)	1 2	
	RADIO	Ladiyo (Radio/cd player)	1 2	
	TELE	TV (Television)	1 2	
	FRIDG	Firiigi (Refrigerator)	1 2	
	STOVE	Amasiga g'amasanyalaze oba gaasi (Electricity/gas cooking stove)	1 2	
	TEL	Essimu eyomunyumba [Telephone (landline)]	1 2	
	MOB	Essimu ey'omungalo (Mobile phone)	1 2	
	GOAT	Embuzi(Goat)	1 2	
	COW	Ente (Cow)	1 2	
	PROP	Enyumba epangisibwa (Property rented for income)	1 2	
9.	HHS	Bantu bameka abaweza emyaka 18 egy'obukulu ababeera mu nyumba eno? ***(How many people aged 18 years and above, including you live in this household?)***	|__|__|	
10.	ROOM	Enyumba yo erina ebisenge bimeka ebisulwamu? ***How many rooms in your household are used for sleeping?***	|__|__|	
11.	ELEC	Olina amasanyalaze mu nyumba yo? ***(Do you have electricity in your household?)***	No 1 Yes 2	**If No, skip to Q13**
12.	WELEC	Mu bbanga ery'emyezi essatu egiyise, nnaku meka z'otaalina masanyalaze mu nyumba yo? ***(How many days was your household without working electricity In the past 3 months?)***	|__|__|	
13.	DHC	Kitwala banga ki okutuuka ku ddwaliro erijjanjaba abalwadde ba siliimu erisinga okuba okumpi n'ewakawo? ***(How long does it take to travel to the ART provider nearest to your home?)***	Less than 30 minutes 1 30 to 60 minutes 2 More than 60 minutes 3	

No.	Code	Questions and filters	Coding categories	Skip
14.	ETEST	Wali wekebezaako akawuka siliimu? ***(Have you tested for HIV before?)***	Yes 1 No 2	**If No, skip to Q18**

8.9 Appendix 9: Sociodemographic questionnaire

Linkage to pre-ART care study- Socio-demographic questionnaire

HCT Lab number: MC|__|__|__|__|__|__|__|LABN Cluster number: |__|__|CLUSN

Village name: _____VILL Household ID: |__|__|__|HHN

Study number: HCT-|__|__|__|__|SN

15.	LTEST	Wasemba ddi okwekebeza akawuka ka silimu? ***(When did you last test for HIV?)***	Past 3 months 1 Past 6 months 2 Past 12 months 3 Over 12 months ago 4	
16.	LTESTR	Ebyaava mu kukwebeza akawuka ka siliimu ku mukundi ogwasemba byalaga ki? ***(What were the results of your last HIV test?)***	Positive 1 Negative 2 Don't know 3	**If Negative/Don't know, skip to Q18**
17.	INCARE	Bw'oba olina akawuka ka siliimu, ofuna obujjanjabi bw'obulwadde buno? **(If HIV positive, do you receive regular medication for your HIV infection?)** **(Probe for receipt of daily septrin prophylaxis and/or ARVs)**	Yes 1 No 2 Refused to answer 3	
18.	SPTEST	Omanyi omwagalwawo bwayimiridde ku kawuka ka siliimu? ***(Do you know your spouse/partner's HIV status?)***	Yes 1 No 2 No spouse/partner 3	**If No/ No spouse, stop here**
19.	SPSTAT	Omwagalwawo ayimiridde atya ku by'akawuka ka siliimu? ***(What is your spouse/partner's HIV status?)***	Positive 1 Negative 2 Don't know 3 Refused to answer 4	**If Negative, /Don't know/refused to answer, stop here**
20.	SPCARE	Omwagalwawo bw'aba nga alina akawuka ka siliimu, afuna obujjanjabi bw'obulwadde buno? ***(If your spouse/partner is HIV positive, is he/she receiving regular medication for his/her HIV infection?)*** **(Probe for receipt of daily septrin prophylaxis and/or ARVs)**	Yes 1 No 2 Don't know 3 Refused to answer 4	
	INTD	**Interview date**	**|__|__||__|__|__||__|__|__|__|** **dd MMM yyyy**	
	INT	**Interviewer's initials**	**|__|__|__|**	

8.10: Appendix 10: Locator form

Linkage to pre-ART care study- Locator form

Cluster number: |__|__|CLUSN Study number: HCT-|__|__|__|__|SN

Enrolment date: ¦__¦__¦¦__¦__¦__¦¦__¦__¦__¦__¦ENDAT
ddMMMyyyy

1. Participant's name:_____PNAM
2. Partner's names: _____SPOUSE
3. Village name :_____VILG
4. Household number |__|__|__|HHN
5. Name of household head:_____HHNAM
6. Phone number: ¦__¦__¦__¦__¦__¦__¦__¦__¦__¦__¦PHON
7. Additional locator information_____

_____

_____

_____

_____

_____

Interviewer's name: _____

8.11 Appendix 11: HIV test certificate and referral form

MEDICAL RESEARCH COUNCIL/UVRI RESEARCH UNIT ON AIDS

HIV TEST CERTIFICATE

Name: ……Signature: ……

Age: ……Sub-county/District: ...……

Village: ……Sex:.……

The above named person tested Positive HIV antibodies on (Date): ……

This test was carried out at the National HIV Reference Centre, Uganda Virus Research Institute Entebbe.

Referred to…….Date of reporting……

Signed:…….....Name:……

Position:……...Date: ……

Note: This slip should be filed by the receiving Institution.

MEDICAL RESEARCH COUNCIL/UVRI RESEARCH UNIT ON AIDS

HIV TEST CERTIFICATE

Name: ……Signature: ……

Age: ……Sub-county/District: ...……

Village: ……Sex:.……

The above named person tested Positive HIV antibodies on (Date): ……

This test was carried out at the National HIV Reference Centre, Uganda Virus Research Institute Entebbe.

Referred to…….Date of reporting……

Signed:…….....Name:……

Position:……...Date: ……

Note: This slip should be filed by the Counselor.

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

Complete at the month-6 visit for all HIV-infected study participants

No.	Code	Questions and filters	Coding categories	Skip
1.	DISCL	Wali obuuliddeko omuntu yenna nga bw'olina akawuka ka siliimu? *(Have you disclosed your HIV status to anyone?)*	Yes 1 No 2	**If No, skip to Qn3**
2.		Ani gwewabuulilako *(Who have you disclosed your HIV status to?)*		**Skip to Qn4**
		(Prompt all responses)	Yes No	
	DISCSPO	Omwagalwawo *(Spouse/partner)*	1 2	
	DISCFAM	Ow'oluganda *(Other family member)*	1 2	
	DISCFR	Mukwano gwo *(Friend)*	1 2	
	DISCSPIR	Omukulu w'eddini *(Spiritual leader)*	1 2	
	DISCHW	Omusawo *(Health care worker)*	1 2	
	DISCOTH	Omuntu omulala *(Other person)*	1 2	
	DISCOTHS	Specify other person:		
3.		Oba nedda, lwaki tewali muntu gwe wali obuuliddeko nga bw'oyimiredde ku ky'akawuka ka siliimu? *(If no, why haven't you disclosed your HIV status to anyone?)*		
		(Prompt all responses)	Yes No	
	NDJUDG	okutya abantu okunjogerera *(Fear of being judged by others)*	1 2	
	NDABU	Okutya omwagalwa wange okunkijjanya/okumpisa obubi *(Fear of abuse/violence by partner)*	1 2	
	NDRELB	Okutya okwawukana n'omwagalwa wange *(Fear of relationship break-up)*	1 2	
	NDDISCR	Okutya okusosolebwa *(Fear of discrimination)*	1 2	
	NDTRST	Tewali muntu gwenesiga *(Do not trust anyone)*	1 2	
	NDDOUT	Ssikakasa nti nina akawuka ka siliimu *(Doubt HIV status)*	1 2	
	NDINCO	Okutya okufiirwa omulimu/eby'enfuna *(Fear of job/income loss)*	1 2	
	NDOTH	Ensonga endala *(Other reason)*	1 2	
	NDOTHS	Specify other reason:		
4.	RG	Okuva lwewawerezebwa okufuna obujjanjabi bw'obulwadde bwa siliimu, wali wewandiisizza ku ddwaliro erijjanjaba obulwadde buno era nga ligaba n'eddagala eribuweweeza (ARV)? (*Have you registered with an HIV clinic that also provides ARV drugs since you were referred for HIV care?*)	Yes 1 No 2	**If Yes, skip to Qn6**

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories	Skip
5.		Lwaki toneewandiisa ku ddwaliro lijjanjaba bulwadde bwa siliimu? *(Why haven't you registered with an HIV clinic?)*		**Skip to Qn36**
		(Multiple responses allowed)	Yes No	
	NRGM	Kubulwa sente zantambula *(Lack money for transport)*	1 2	
	NRGD	Eddwaliro liri wala *(Health centre is far away)*	1 2	
	NRGT	Kubulwa budde *(lack of time)*	1 2	
	NRGW	Sewuliramu bulwadde *(I do not feel sick)*	1 2	
	NRGSE	Okutya okuyisibwa obubi eddagala *(Fear ARV side effects)*	1 2	
	NRGTR	Nkozesa ddagala lya kinnaansi *(Using herbal/other medicines)*	1 2	
	NRGSTG	Okutya okulabibwa ku ddwaliro ewajjanjabirwa obulwadde bwa siliimu *(Fear being seen at the HIV clinic)*	1 2	
	NRGDUT	Ssikakasa nti nina akawuka ka siliimu *(Doubt HIV status)*	1 2	
	NROTH	Ensonga endala *(Other reason)*	1 2	
	NROTHS	Specify other:		
6.	CLNAM	Eddwaliro gyewewandiisiza baliyita batya? *(What is the name of the HIV clinic where you registered?)*		
7.	CLADD	Eddwaliro lino lisaangibwa wa? *(Where is the HIV clinic located?)*		
8.	RGNO	Ennamba eyakuwebwa kulw'okwewandiisa eri ki? *(What is your HIV clinic registration number?)* **(Obtain clinic registration number from clinic documents e.g. appointment card, drug prescription forms etc.)**	|__|__|__|__|__|__|__|__|	
9.	RGDAT	Wayiseewo bbanga ki okuva lw'ewewandiisa? *(How long ago did you register with the HIV clinic?)*	Less than 1 month 1 1-3 months 2 More than 3 months 3	

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories	Skip
10.		Lwaki wewandiisa ku ddwaliro erijjanjaba siliimu? *(Why did you register with an HIV clinic?)*		
		(Multiple responses allowed)	Yes No	
	RGSIC	Nali sewulira bulungi *(Was feeling sick)*	1 2	
	RGCON	Okukasa bwenyimiridde ku ky'akawuka ka siliimu *(To confirm my HIV status)*	1 2	
	RGCD4	Okumanya obutofaali bw'omusayi gwange bwebwenkana *(To know my CD4 count)*	1 2	
	RGELI	Okumanya oba nga nsaanidde okutandika *(To know eligibility for ARV drugs)*	1 2	
	RGART	okufuna eddagala eriweweeza ku kawuka ka siliimu *(To start taking ARV drugs)*	1 2	
	RGMON	Okukeberebwanga okumanya obulamu bwange bwe buyimiridde *(To receive regular health monitoring)*	1 2	
	RGOTH	Ensonga endala *(Other)*	1 2	
	RGOTHS	Specify other:		
11.	FUV	Wali ozeeyoko ku ddwaliro erijjanjaba siliimu okuva lwewewandiisa? *(Have you attended the HIV clinic again since you registered?)*	Yes 1 No 2	**If No, skip to Qn13**
12.	TOTV	Emirundi emeka gy'ozeeyo ku ddwaliro lino okuva lwewewandiisa? *(How many total visits have you made to the HIV clinic since you registered?)*	|__|__|	**Skip to Qn15**
13.		Lwaki toddangayo ku ddwaliro lino? *(Why haven't you visited the HIV clinic again?)*		
		(Multiple responses allowed)	Yes No	
	FUVMON	Kubulwa sente zantambula *(Lack of money for transport)*	1 2	
	FUVDIST	Eddwaliro liri wala *(Health centre is far away)*	1 2	
	FUVTIM	Kubulwa budde *(lack of time)*	1 2	
	FUVHTHY	Ssewulira bubi *(Feeling well)*	1 2	
	FUVSE	Ntya okuyisibwa obubi eddagala lya kawuka ka siliimu *(Fear of ARV drug side effects)*	1 2	
	FUVTR	Nkozesa ddagala lya kinnaansi *(Using traditional/alternative medicines)*	1 2	
	FUVSTIG	Ntya okulabibwa ku ddwaliro awajjanjabirwa obulwadde obwa siliimu *(Fear being seen at the HIV clinic)*	1 2	
	FUVDUT	Sikakasa nti nina akawuka ka siliimu *(Doubtful of HIV status)*	1 2	
	FUVAPP	Nindiridde olunaku olwampebwa okuddayo	1 2	

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories	Skip
		(Awaiting appointment date)		
	FUVOTH	Ensonga endala ***(Other reason)***	1 2	
	FUVOTHS	Specify other reason:		
14.	FUTVIS	Olina ekirowoozo ky'okuddayo ku ddwaliro lino gye bujja? (***Do you plan to visit the HIV clinic again in future?)***	Yes 1 No 2 Not sure 3	
15.	CD4SAMP	Wawaayo omusaayi okukeberebwa obutofaali bw'omusaayi ku ddwaliro? ***(Did you provide a blood sample for CD4 cell count testing at the HIV clinic?)***	Yes 1 No 2 Not sure 3	**If No/Not sure, skip to Qn24**
16.	CDSAMDT	Wayitawo bbanga ki ng'omaze okwewandiisa olyoke oweeyo omusaayi okukeberebwa obutofaali bw'omusaayi? ***(How soon after registering with the clinic did you provide a sample for CD4 cell count testing?)***	Less than 1 month 1 1-3 months 2 Over 3 months 3 Don't know 4	
17.	CDSDAY	Ebyaava mukukebera obutofaali bw'omusaayi omulundi ogwasooka wabifunirawo ku lunaku olwo lwewawaayo omusaayi? ***(Did you receive your CD4 cell count test result on the same day that you provided a sample?)***	Yes 1 No 2 Not sure 3	**If Yes, skip to Qn22**
18.	ASKRTCD	Wasabibwa okuddayo ku ddwaliro okufuna ebyaava mu kukebera obutofaali bw'omusaayi gwo ku lunaku olulala? ***(Were you asked to return to the clinic to collect your CD4 count test results on another day?)***	Yes 1 No 2 Not sure 3	
19.	RTCD	Waddayo ku ddwaliro okufuna ebyaava mu kukebera obutofaali bw'omusaayi gwo? ***(Did you return to the clinic to collect your CD4 count test results?)***	Yes 1 No 2	**If No, skip to Qn23**
20.		Emirundi emeka gyewadda ku ddwaliro okufuna ebyaava mu kukebera obutofaali bw'omusaayi gwo? ***(How many times did you return to the clinic to collect your CD4 cell count test results?)***	|__|__|	
21.	RESREC	Wafuna ebyaava mukukeberebwa obutofaali bw'omusaayi gwo? ***(Did you receive your CD4 cell count test result?)***	Yes 1 No 2 Don't know 3	**If No/don't know, skip to Qn24**
22.	CLCCD4	Obutofaali bw'omusaayi gwo bwali bwenkana ki? ***(What was your CD4 cell count?***	|__|__|__|__| **9999 if do not remember/not available**	

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories		Skip
23.		Lwaki toddanga ku ddwaliro kufuna byaava mu kukebera butofaali (CD4) bwo? ***(Why didn't you return to the clinic to collect your CD4 count test results?)***			
		(Multiple responses allowed)	Yes	No	
	RTTRANS	Kubulwa sente zantambula ***(Lack of money for transport)***	1	2	
	RTDIST	Eddwaliro liri wala ***(HIV clinic is far away)***	1	2	
	RTTIME	Kubulwa budde ***(lack of time)***	1	2	
	RTWELL	Ssewulira bubi ***(Feeling well)***	1	2	
	RTARVE	Ntya okuyisibwa obubi eddagala lya kawuka ka siliimu ***(Fear of ARV side effects)***	1	2	
	RTHERB	Nkozesa ddagala lyakinnansi ***(using herbal/other medicines)***	1	2	
	RTSTIG	Ntya okulabibwa ku ddwaliro awajjanjabirwa obulwadde bwa siliimu ***(Fear being seen at the HIV clinic)***	1	2	
	RTFORG	Neerabira ***(Forgot)***	1	2	
	RTOTH	Ensonga endala ***(Other reason)***	1	2	
	RTOTHS	Specify other reason			
24.	CTXP	Watandisibwa ku kumira septrin owa buli lunaku? ***(Were you started on daily Septrin prophylaxis at the HIV clinic?)***	Yes No Don't know	1 2 3	**If No/Don't know, skip to Qn31**
25.	CTXSTAT	Ku mulundi gwa kumeka kw'egyo gy'ogenze ku ddwaliro kwewatandisibwako septrin owabulilunaku? ***(At which clinic visit were you started on Septrin prophylaxis)***	First visit Second visit Third or later visit	1 2 3	
26.	CTXADH	Mu wiiki 4 eziyise, waliwo lw'otamizze septrin? ***(Have you missed any of your Septrin doses in the past 4 weeks?)***	Yes No	1 2	**If No, skip to Qn31**
27.	MISDOS	Ddoozi eza septrin meka z'otamizze mu wiiki 4 eziyise? ***(How many Septrin doses have you missed in the last 4 weeks?)***	0-5 tablets 6 or more tablets Don't know	1 2 3	
28.	MISDAY	Wali oyosezaako ennaku 3 eziddiringana oba okusingawo nga tomize mpeke za septrin ***(Have you ever missed taking your Septrin tablets for 3 or more days in a row?)***	Yes No Don't remember	1 2 3	
29.	MISDAYF	Mu bbanga lya wiiki 4 eziyise, mirundi emeka	Once	1	

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories		Skip
		gy'otasobode kumira septrin okumala ennaku 3 eziddiringana oba ezisingawo? ***(In the last 4 weeks, how often have you missed taking your Septrin tablets for 3 or more days in a row?)***	Twice More than twice Don't know	2 3 4	
30.		Nsonga ki ezaakuleetera obutamira septrin? ***(Reasons for missing Septrin doses)***			
		(Multiple responses allowed)	Yes	No	
	MISFGT	Nerabira ***(Forgot)***	1	2	
	MISAWE	Ssaali waka ***(Was away from home)***	1	2	
	MISRO	Amakerenda ganzigwako ***(Ran out of pills)***	1	2	
	MISOS	Septin teyaliyo ku ddwaliro ***(Septrin was out of stock at the clinic)***	1	2	
	MISWEL	Nali seewulira bubi ***(Do not feel sick)***	1	2	
	MISSIC	Septrin andwaza ***(Septrin makes me feel sick)***	1	2	
	MISSTIG	Nali ssaagala bantu kundaba/kumanya ***(Did not want others to notice)***	1	2	
	MISFAT	Nali nkooye okumira amakerenda ***(Tired of taking pills)***	1	2	
	MISSEFF	Okutya okukosebwa eddagala ***(Fear of side effects)***	1	2	
	MISOTH	Ensonga endala ***(Other)***	1	2	
	MISOTHS	Specify other			
31.	ARVELINF	Abasawo ku ddwaliro balina kye bakubuuliddeko ku ddi lw'olina okutandisibwa eddagala eriweweeza ku kawuka ka siliimu (ARVs)? ***(Have you received any information from the HIV clinic staff regarding your eligibility for antiretroviral drugs?)***	Yes No Don't remember	1 2 3	**If No/don't remember, skip to Qn36**
32.	ARTELI	Kiki ekyagugambibwa ku ky'okutuusa ekiseera eky'okufuna eddagala eriweweza ku kawuka ka siliimu (ARVs)? ***(What have you been told regarding your eligibility for antiretroviral drugs?)***	Eligible Not eligible Don't remember	1 2 3	**if Not eligible/ don't remember, skip to Qn36**
33.	ELIDT	Wayise bbanga ki ng'okitegedde nti olina okufuna eddagala eriweweeza akawuka ka siliimu? ***(For how long have you known that you are eligible for antiretroviral drugs?)***	Less than 1 month 1-3 months Over 3 months Don't remember	1 2 3 4	
34.	ARTIN	Watandika okumira eddagala eriweweeza ku bulwadde bwa siliimu? (***Have you started taking antiretroviral drugs?***)	Yes No Not sure	1 2 3	
35.	ARTDT	Omaze bbanga ki ng'okozesa eddagala	Less than 1 month	1	

8.12 Appendix 12: Linkage status questionnaire

Linkage to pre-ART care study- Linkage status questionnaire

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories	Skip
		eriweweeza ku bulwadde bwa siliimu? ***(For how long have you been taking antiretroviral drugs now?)***	1-3 months 2 Over 3 months 3 Don't remember 4	
36.	KNOSTAT	Wali okimanyi nti olina akawuka ka siliimu nga tonayingizibwa mu mukunoonyereza kuno? ***(Did you know that you were HIV positive before joining this study?)***	Yes 1 No 2 Refused to answer 3	**If No/refused to answer, skip to Qn38**
37.	INCARE	Nga tonayingizibwa mu mukunoonyereza kuno, wali ofuna obujjanjabi bwa kawuka ka siliimu? ***(Were you already attending an HIV care clinic by the time you joined this study?)***	Yes 1 No 2 Refused to answer 3	
38.	KNOWSP	Waliwo abantu abalala b'omanyi mu byalo eby'omuliraano abetabye mu kunoonyereza kuno? ***(Do you know of other persons in neighbouring villages who are participating in this study?)***	Yes 1 No 2	**If No, stop here**
39.	DISCSP	Wali okubaganyizaako ebirowoozo ku kunoonyereza kuno n'abantu abalala abakwetabyemu abali mu byalo ebirala? ***(Have you discussed this study with these other study participants in other villages?)***	Yes 1 No 2	**If No, stop here**
40.	 VOTHP1 VOTHP2	Oba yee, abantu bano bali mu byalo ki? ***(If yes, in which villages do these persons live?)*** Village 1:_____ Village 2:_____		
	INTD	**Interview date**	|__|__||__|__|__||__|__|__|__|	
	INT	**Interviewer's initials**	|__|__|__|	

8.13 Appendix 13: CD4 count & repeat HIV test form

Linkage to pre-ART care study **CD4 count & repeat HIV test form**

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

Lab number: MC|__|__|__|__|__|__|__|LABN (if CD4 or repeat HIV test done)

No.	Code	Questions and filters	Coding categories		Skip
1.	BSTAT	Participant's baseline HIV status	Positive Negative	1 2	**If positive, skip to Qn5**
2.	WRHIV	Is participant willing to have repeat HIV testing?	Yes No	1 2	**If no, skip to Qn9**
3.	RHIVDAT	Repeat HIV test sample collection date	|__|__||__|__|__||__|__|__|__| ddd MMM yyyy		
4.	RHIVRES	Repeat HIV test result	Positive Negative Indeterminate	1 2 3	**Skip to Qn9**
5.	KNOCD4	Does participant know his/her CD4 cell count? **(Offer CD4 cell count testing to only participants who have not had the test and those who have had the test but have not received the results)**	Yes No	1 2	**If yes, skip to Qn9**
6.	WSCD4	Is participant willing to have CD4 count testing?	Yes No	1 2	**If no, skip to Qn9**
7.	SCD4DAT	Study CD4 sample collection date	|__|__||__|__|__||__|__|__|__| ddd MMM yyyy		
8.	SCD4COU	Study CD4 cell count	|__|__|__|__| (10^3cells/uL or 10^9cells/L)		
9.	DATCOM	Date form completed	|__|__||__|__|__||__|__|__|__| ddd MMM yyyy		
10.	STAF	Staff initials	|__|__|__|		

8.14 Appendix 14: Follow-up visit form

Linkage to pre-ART care study- Follow-up visit form

Cluster number: |__|__|CLUSN Village name: _____VILL

Study number: HCT-|__|__|__|__|SN

Complete this form at months 1 & 2 (participants in the intervention arm) & month 6 (all participants) follow-up visits

No.	Code	Questions and filters	Coding categories
1.	FUV	Specify follow-up visit	Month 1 follow-up visit 1 Month 2 follow-up visit 2 Month 6 follow-up visit 3
2.	FUD	Date of follow-up visit	|__|__||__|__|__||__|__|__|__| dd MMM yyyy
3.	PSTAT	Participant status	Completed visit 1 Refused follow-up 2 Withdrawn 3 Died 4 Not contacted 5 Missed visit 6 Late visit **(>7 days after expected date of follow-up)** 7
4.	COM	Comments ***(e.g. in care at time of enrolment)***	
5.	FCD	Form completion date	|__|__||__|__|__||__|__|__|__| dd MMM yyyy
6.	INT	Interviewer's initials	|__|__|__|__|

8.15 Appendix 15: Medical records form

Linkage to pre-ART care study- Medical records form

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

Complete at the month-6 visit for participants who report having registered with an HIV clinic

No.	Code	Questions and filters	Coding categories	Skip
1.	CLINIC	Name of HIV clinic where the participant registered		
2.	RCLINIC	Did the participant register for care at this clinic?	Yes 1 No 2	**If No, stop here**
3.	REGNO	Unique HIV clinic assigned patient number	|__|__|__|__|__|__|__|__|	
4.	REGDAT	Date participant was registered at HIV clinic	|__|__||__|__|__||__|__|__|__|	
5.	REGBEF	Was the participant registered at this or other HIV clinic before his/her enrolment in the current study?	Yes 1 No 2	**If Yes, stop here**
6.	CTXP	Was daily septrin prescribed?	Yes 1 No 2	**If No, skip to Qn8**
7.	CTXD	Was septrin dispensed?	Yes 1 No/Not documented 2	
8.	STAGE	Was participant's HIV disease staged?	Yes 1 No/Not documented 2	**If No/Not documented, skip to Qn10**
9.	FSTAGE	First documented WHO HIV disease stage	Stage one 1 Stage two 2 Stage three 3 Stage four 4	
10.	CD4	Was CD4 cell count testing done?	Yes 1 No/Not documented 2	**If No/Not documented, skip to Qn12**
11.	CD4COUNT	First CD4 cell count test result	|__|__|__|__|	
12.	ARVP	Have antiretroviral drugs been prescribed?	Yes 1 No 2	**If No, skip to Qn14**
13.	ARVDATE	Date antiretroviral drugs prescribed	|__|__||__|__|__||__|__|__|__|	
14.	FUVT	Has participant had any follow-up visits?	Yes 1 No 2	**If No, stop here**
15.	NFUV	Number of follow-up visits?	|__|__|	

8.15 Appendix 15: Medical records form

Linkage to pre-ART care study- Medical records form

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

No.	Code	Questions and filters	Coding categories		Skip
16.	FIRFVR	Main reason for 1st follow-up visit	Provide sample for CD4 cell count test Collect CD4 cell count test results Collect septrin Collect ARVs Medical complaint Routine visit Other (specify)……. ……	1 2 3 4 5 6 7	**Stop here if only 1 follow-up visit**
17.	SECFVR	Main reason for 2nd follow-up visit	Provide sample for CD4 cell count test Collect CD4 cell count test results Collect septrin Collect ARVs Medical complaint Routine visit Other (specify)……. ……	1 2 3 4 5 6 7	**Stop here if only 2 follow-up visits**
18.	THIRFVR	Main reason for 3rd follow-up visit	Provide sample for CD4 cell count test Collect CD4 cell count test results Collect septrin Collect ARVs Medical complaint Routine visit Other (specify)……. ……	1 2 3 4 5 6 7	**Stop here if only 3 follow-up visits**
19.	FORFVR	Main reason for 4th follow-up visit	Provide sample for CD4 cell count test Collect CD4 cell count test results Collect septrin Collect ARVs Medical complaint Routine visit Other……. ……	1 2 3 4 5 6 7	
	Date	**Date**	|__|__||__|__|__||__|__|__|__|	
	STAF	**Staff initials**	|__|__|__|	

8.15 Appendix 15: Medical records form

Linkage to pre-ART care study- Medical records form

Study number: HCT-|__|__|__|__|SN **Cluster number: |__|__|CLUSN**

Village name: _____VILL

Complete at the month-6 visit for participants who report having registered with an HIV clinic

Linkage to pre-ART care study- Addendum to Medical records form

No.	Code	Questions and filters	Coding categories
20.	CD4SMPDAT	Date participant provided sample for first CD4 cell count testing	|__|__||__|__|__||__|__|__|__|
21.	CD4RESDAT	Date participant obtained first CD4 cell count test results	|__|__||__|__|__||__|__|__|__|
22.	FIRFVRDAT	1st follow-up visit date	|__|__||__|__|__||__|__|__|__|
23.	SECFVRDAT	2nd follow-up visit date	|__|__||__|__|__||__|__|__|__|
24.	THIRFVRDAT	3rd follow-up visit date	|__|__||__|__|__||__|__|__|__|
25.	FORFVRDAT	4th follow-up visit date	|__|__||__|__|__||__|__|__|__|
	Date	**Date**	**|__|__||__|__|__||__|__|__|__|**
	STAF	**Staff initials**	**|__|__|__|**

8.16. Appendix 16: Study monitoring report

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INTERIM SITE MONITORING REPORT

Protocol: **The effectiveness of a counseling intervention on the uptake of HIV care services among HIV infected patients in Uganda (Linkage to care study)**	
Study ID N°: **NCT 02497456**	
Test Product: NA	
Institution: **Medical Research Council**	Centre N°: 19
Principal investigator: **Dr. Ruzagira Eugene**	

Monitor: Bernadette Nayiga Kalanzi	
Visit Date: 19th -21st January, 2016	Previous Visit: NA

Key study staff present and met during monitoring visit	
Name of the staff	**Function in the study**
NANSERE ANGEL	CONSELLOR
NAKALEMA J	CONSELLOR
WASWA SOLOMON	CONSELLOR

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8.16. Appendix 16: Study monitoring report

BAYIGA JOSEPHINE	COUNSELLOR
MAWOGOLE RICHARD	COUNSELLOR/ FIELD TECHNICIAN
LUYIGA LUCY	DEO
NAMIREMBE AERON	DEO
NALUBOWA CHRISTINE	DEO
ALING EMMANUEL	DATA MANAGER
ABAASA ANDREW	STASTICIAN

Status of the site at the time of the monitoring visit	
Enrolment: Finished	Subjects follow up: Ongoing

SUMMARY
This was the first interim monitoring visit for the Linkage to care study. This is a cluster randomized study comprising of 28 clusters. A total of 338 HIV positive participants were enrolled into the study, Additionally, 110 HIV negative participants were enrolled for community blinding. A total of 387 out of 448 have reached their month 6 follow up visit and have exited the study, the remaining 61 participants are expected to exit by end of February, 2016. The Clinical Research Coordinator (Internal monitor), discussed findings from the interim monitoring visit with Dr. Eugene Ruzagira, the principal investigator, Lucy Luyiga, Wasswa

8.16. Appendix 16: Study monitoring report

UGANDA VIRUS RESEARCH INSTITUTE

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SUMMARY

Solomon and Elizabeth Mbabazi.

The following is a brief summary of the interim monitoring activities;

1. **Review of the Investigator Site file**

   The investigator site file was well maintained with filing index. Some key items were missing; the contact section, listing emails and telephone contacts of site personnel, the protocol deviation log, under participant information, Site staff details, With the exception of the PI and the co-investigators, the CVs of the rest of the study team together with their GCP, HSP certificates were missing. All CVs should be signed and dated. There was no section on team meetings or note to file indicating where the minutes are filed. A separate file was used for the signed consent forms but a note to file indicating this was missing.

   The older versions of the protocol and consent forms need to be stamped super ceded. The last version of the amended protocol version 2.1 missing on file.

   Some members of the study team; Aeron Namirembe, Aling Emmanuel, and Andrew Abaasa were missing on the staff signature log.

   The Roles and responsibility log was missing, the PI should summarize the specific tasks the different study staff were performing during the study execution.

   The CV for the laboratory head plus the accreditation certificates were missing.

   The training binders for the research team and all the applicable SOPs were not on file.

   UVRI-REC Membership list not on file.

   Applications/ Submissions to the different regulatory did not bear a stamp acknowledging receipt.

2. **Review of the informed Consents**

   Informed consents for all enrolled participants were reviewed. All participants had consent forms on file.

   HCT036R,HCT037L,HCT006P,HCT005U,HCT004Z,HCT003E,HCT002L,HCTOO1R,HCT046J,HCT091X,HCT141Y Consented on unstamped consent forms.

   HCT013X, HCT028N, HCT036R, HCT037R, HCT298L, HCT307X used thumb print but were not witnessed.

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8.16. Appendix 16: Study monitoring report

SUMMARY
HCT359Y, HCT369R, HCT435Y, HCT446L Consented on the wrong versions of the consent form. HCT058Q study staff that administered the consent did not sign. The PI to write a note to file. **3. Source data/CRF Review.** The participant records were sampled out by modified monitoring plan, at least 10 records per cluster. The CRFs were well filed in batches under the different clusters. Data query identification and resolution was on going. The team was advised to cross out all un-filled boxes say on CD4 results. **4. Protocol deviations** There are no protocol deviations identified at this visit The next monitoring visit/ close out monitoring is scheduled for 14th -15th March 2016. In the interim should there be anything I can do to support you and your team, do not hesitate to contact me. Please share the contents of this report with the team and file it under monitoring section in the investigator site file.

A. GENERAL ASPECTS		Comment
1. Was the visit performed according to the monitoring plan?	YES	
2. Was there any change in the facilities?	NO	
2.1. If yes, do the facilities remain still adequate for the study?		
3. Have relevant changes in Study staff occurred since the last visit?	NO	
3.1. Curriculum Vitae files in Investigator File if appropriate?	NA	
3.2. Are the education/ training of the new staff appropriate to perform their role in the study?	NA	
3.3. Has the new staff been properly trained (GCP, protocol, SOP, and others if applicable)?	NA	
3.4. Is training of new staff documented?	NA	
3.5. Is the Study Staff and Authorized Staff for Study Document Completion Form updated?	NA	
3.6. Notification to the IEC/IRB if appropriate	NA	

8.16. Appendix 16: Study monitoring report

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A. GENERAL ASPECTS		Comment
4. Is the PI regularly present at the site to provide supervision of the study or does it hold regular routine meeting with the staff, and does the PI meet on regular basis with the monitor?	YES	
5. Did the investigators encounter any problems since your last visit?	NO	
6. Is there any change in the country regulations since last visit?	NO	
7. Has the site received any notification from the regulatory authorities or local ethics committee?	YES	
8. Has the following been discussed with Investigator and his/her staff?	NA	
8.1. Up-to-date information on the test product including changes to the risk/benefit ratio as communicated by Sponsor	NA	
8.2. Protocol and/or ICF amendment and/or modification, if any	YES	
a) All amendments were approved by Sponsor and documented before submission/notification to the IEC/IRB	YES	
b) Protocol amendment/modification if any submitted/notified to IEC/IRB	YES	
c) Protocol amendment/modification if any notified to local authorities if applicable	YES	
8.3. Recruitment at site, reviewing any recruitment issues and discussing possible strategies for improvement, if appropriate	NA	Enrolment ended
a) Is the recruitment following recruitment plan?	NA	
8.4. Participants follow up, premature discontinuation, withdrawal and loss to follow up	YES	
9. Are queries (from data management and monitor) being resolved on a regular basis and timely by the site?	YES	
10. Have pending corrective actions been implemented?	NA	
11. Did any formal training session given by the monitor take place during the visit? (if yes, please attach to this report the agenda and training material used)	NO	
12. Was the Investigator File verified during the visit?	YES	
12.1. If yes, was it globally in order?	YES	

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8.16. Appendix 16: Study monitoring report

A. GENERAL ASPECTS	Comment
COMMENTS AND ACTIONS:	

B. INFORMED CONSENT			Comment
1.	Has informed consent procedure been reviewed?	NO	Enrolment ended
	a. If yes, is the procedure used suitable to properly inform potential study subjects?	NA	
2.	Were informed consent forms for subjects screened and / or enrolled since last visit verified?	YES	
3.	Consent forms verified during the visit:		
	a. Enrolled participants consents verified: ...MARCH 2015..... to September 2015.....		
	b. Screened but not enrolled participants consents verified: March 2015..... to September 2015.....		
4.	Were there any problems in the informed consent form? (If yes, please list problems in the table)	YES	Errors identified already described in text above
5.	Summary Statistics ICF compliance: Total number of ICF reviewed during the visit for first time: 448 7# (0.016%) ICF with problem of missing date / signature / fields: 0# (0%) ICF with date or name of the subject not written by subject / witness: 0# (0%) ICF with error in date: 15# (0.03%) ICF with problems (any kind of non-compliance):		
6.	Were there from last visit pending corrections / actions to be taken regarding ICF?	NA	
	a. If yes, were the corrections or corrective action plan put in place?	NA	
COMMENTS AND ACTIONS:			

8.16. Appendix 16: Study monitoring report

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C. ENROLLMENT, SCREENED FAILURE, WITHDRAWAL, LOST TO FOLLOW UP AND DISCONTINUED		Comment
1. Were any new subjects screened since last visit?	NA	
2. Were any new participants enrolled since last visit?	NA	
1.1. If yes, did all of them meet the inclusion / exclusion criteria?	NA	
3. Were there new participants found screen failure (screened but not enrolled)?	YES	
3.1. If yes, were the files checked for assessment eligibility	YES	
3.2. Were the participants screen failure rightly excluded based on the inclusion/exclusion criteria of the approved protocol	YES	
3.3. Was the reason for exclusion properly documented in the subject file or screening log?	YES	
4. Were any participants withdrawn from study medication since last visit?	NA	
4.1. If yes, specify number and reason for withdrawal	NA	
4.2. Was the withdrawal properly documented in the source documents and CRF?	NA	
5. Were any participants prematurely discontinued from the study since last visit? (other than lost to follow up)	NO	
5.1. If yes, specify number and reason for discontinuation	NA	
5.2. Was the discontinuation properly documented in the source documents and CRF?	NA	
6. Were any new lost to follow-up since last visit?	YES	
6.1. Are all efforts applied to trace the participants lost to follow up and are those attempts documented?	YES	
COMMENTS AND ACTIONS:		

D. RANDOMIZATION, BLINDING AND UNBLINDING PROCEDURE		Comment
1. Is the study randomized ?	YES	

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D. RANDOMIZATION, BLINDING AND UNBLINDING PROCEDURE		Comment
1.1. If yes, is the procedure for randomization respected?	YES	
1.1.1. Have the subjects been randomized in chronological order of their screening or enrolment?	NO	
1.2. If yes, are list / envelopes of randomization kept at the site	NA	
1.2.1. If yes, are the list / envelopes of randomization securely stored?	NA	
2. Is the study blinded?	NO	
2.1. If yes, is the blinding maintained as per protocol?	NA	
2.2. Does the site have a randomization list or envelops for emergency un-blinding ?	NA	
2.2.1. If yes, were the randomization lists or envelopes checked?	NA	
2.2.2. If yes, are the randomization list / envelopes securely stored?	NA	
3. Has any randomization code been broken? (if yes specify below)	NA	

Participant N°	Participant Initials	Date and reason for un-blinding

3.1. Reason for broken code reported on the appropriate documents	
3.2. In case of accidental unblinding, was the procedure reviewed?	

COMMENTS AND ACTIONS: This is a cluster randomized study

E. PROTOCOL COMPLIANCE AND PROTOCOL DEVIATION		Comment
1. Have there been any deviations from the approved protocol?	NO	
2. If yes, describe below:	NA	

Participant N°/ID	Type of deviation, when and how, what actions have been/will be taken

8.16. Appendix 16: Study monitoring report

UGANDA VIRUS RESEARCH INSTITUTE

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E. PROTOCOL COMPLIANCE AND PROTOCOL DEVIATION		Comment
3. Has the protocol deviation been documented in study documents and protocol deviation log?	NA	
4. Has the investigator informed the sponsor that protocol deviation occurred?	NA	
5. Has the investigator informed the ethics committees that protocol deviation occurred?	NA	
6. Were the investigator and staff retrained to avoid recurrence in the future?	NA	
COMMENTS AND ACTIONS:		

F. SOURCE DOCUMENTS AND CRF		Comment
1. Were source documents available and did you have direct access?	YES	
2. Is the CRF used as source document?	YES	
2.1. If yes, was it defined in the protocol?	YES	
2.2. If yes, is it in agreement with the form "Source documents agreement and clarification"?	YES	
3. Is the quality of source documents good (attributable, legible, contemporaneous, original and accurate)?	YES	
4. If there are source documents printed in thermal paper, were they copied (certified copies)?	NA	
5. Were CRFs checked against source documents? If yes fill table at the end of the report	NA	
6. Was SDV done in accordance with the monitoring plan?	NO	
7. Were CRFs legible, accurate and complete?	YES	
8. Were Trial related logs legible, accurate and complete?	YES	
a. Identification of screened and enrolled participants	YES	
b. Assignment Sheet	NA	
c. Specimen log	NA	

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8.16. Appendix 16: Study monitoring report

F. SOURCE DOCUMENTS AND CRF		Comment
9. Were CRF/trial related documents corrected during the visit?	YES	
10. Are there any corrections pending? If yes, specify	YES	
a. Correction on CRF, source documents and other trial related documents	YES	
b. CRF Data Resolution Queries generated by Data Management	YES	
COMMENTS AND ACTIONS:		

CURRENT ETHICAL AND REGULATORY APPROVAL DATES FOR SITE

	Date	Duration of approval (if applicable)
Approval from NDA	NA	NA
Approval from UNCST	07th Jan 2015	One year
Approval from local Regulatory Authorities (UVRI-REC)	12 Dec 2015	One Year

SITE STATUS

8.16. Appendix 16: Study monitoring report

UGANDA VIRUS RESEARCH INSTITUTE

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Planned enrolment	Screened	Enrolled	Ongoing	Premature discontinuation	Lost to follow up	Completed
224	12,145	448	61	00	16	387

Reported by:

Bernadette Nayiga Kalanzi

(Clinical Research Coordinator)

Signature: _____

Date: 14th Feb 2016 *(dd/mm/yy)*

Reviewed by:

Prof. Pontiano Kaleebu

Director MRC/UVRI

Signature: _____

Date: 15/08/16 *(dd/mm/yy)*

Reviewed by: Dr. Eugene Ruzagira (PRINCIPAL INVESTIGATOR)

Signature: _____

Date: : 15/08/16 *(dd/mm/yy)*

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8.17 Appendix 17: UVRI Research Ethics Committee approval letter

UNHRO
Uganda National Health Research Organisation

Uganda Virus Research Institute
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Tel: +256 414 320 385 / 6
Fax: +256 414 320 483
Email: directoruvri@uvri.go.ug

REPUBLIC OF UGANDA

Our Ref: GC/127/14/12/491
Your Ref: ……

12th December 2014

Dr. Eugene Ruzagira,

RE: UVRI REC review of protocol titled **"A cluster randomised trial to evaluate the effect of follow-up counselling after HIV diagnosis through home-based HIV counselling and testing on linkage to pre-antiretroviral therapy care in Masaka SW Uganda."**

Thank you for submitting your responses to the queries addressed to you by UVRI REC.

This is to inform you that your responses dated 12th December 2014 were reviewed and met the requirements of the UVRI Research Ethics Committee.

UVRI REC annual approval has been given for you to conduct your research up to 12th December 2015. Annual progress report and request for extension should be submitted to UVRI REC prior to the expiry date, to allow timely review.

The reviewed and approved documents included;

1. UVRISEC Application form- Linkage study-26Nov14
2. Protocol- Linkage to study- version 26Nov14
3. Informed consent document-Linkage study-v1.0 26Nov14
4. Baseline socio-demographic questionnaire- Linkage study-v1.0 26Nov14
5. Linkage status questionnaire-Linkage study-v1.0 26Nov14
6. Medical records form-Linkage study-v1.0 26Nov14
7. LSHTM supervisor's letter
8. Copies of applicants' curriculum vitae

You can now continue with your study after registration with the Uganda National Council for Science and Technology (UNCST).

Note: UVRI REC requires you to submit a copy of the UNCST approval letter for the above study before commencement.

Yours sincerely,

Mr. Tom Lutalo
Chair, UVRI REC
C.C The Director-UVRI, Secretary, UVRI REC

8.18 Appendix 18: LSHTM provisional opinion

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Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Eugene Ruzagira
LSHTM

21 January 2015

Dear Dr. Ruzagira ,

Study Title: A CRT of the effectiveness of referral to pre-ART care & follow-up counselling compared to referral to pre-ART care only, for individuals diagnosed with HIV through home-based HCT in Masaka, SW Uganda

LSHTM Ethics Ref: 8833

The Interventions Committee reviewed the above application.

The documents reviewed were:

Document Type	File Name	Date	Version
Protocol / Proposal	Protocol- Linkage to pre-ART care study- version 26Nov14.doc	26/11/2014	1.0
Protocol / Proposal	Baseline SD questionnaire- Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Protocol / Proposal	Linkage status questionnaire-Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Protocol / Proposal	Medical records form-Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Information Sheet	Informed consent document-Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Investigator CV	Eugene Ruzagira CV- Nov14.doc	28/11/2014	1
Investigator CV	Kathy Baisley CV-Nov14.doc	28/11/2014	1
Investigator CV	Anatoli Kamali CV- Sep14.doc	28/11/2014	1
Investigator CV	Heiner Grosskurth CV-Nov14.doc	28/11/2014	1
Sponsor Letter	Research project sponsorship letter-Linkage study.pdf	01/12/2014	1

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

The Committee will delegate authority to confirm its final opinion on the application to the Chair.

Further information or clarification required

1. Information Sheet: please amend the participant information sheet so that it is written more clearly and use simpler language to make it easier to understand. Has the information sheet been tested for lay understanding or had any input from potential participants? If not, it is recommended that you have some input to be rewritten for the lay public to understand

2. Project title: the title of this project is difficult to read and understand. This is likely not to be acceptable to a scientific journal or in any public information. It is important that researchers consider at this stage who will be able to understand this title. Please comment

When submitting your response to the Committee, please submit a revised copy of the application form through the ethics online applications website: http://leo.lshtm.ac.uk

Please list the changes and requested clarification in a covering letter addressed to the Committee. Please send any revised documentation, where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates as well as making any necessary changes to the application form. For further instructions, in the 'Help' section on the website, please refer to the section on 'Provisional Approvals - submitting responses to queries raised by the committee'.

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

8.19. Appendix 19: LSHTM Ethics Committee approval letter

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United Kingdom
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www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr. Eugene Ruzagira
LSHTM

30 January 2015

Dear Dr Ruzagira

Study Title: The effectiveness of a counselling intervention on the uptake of HIV care services among HIV infected patients in Uganda.

LSHTM Ethics Ref: 8833

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Baseline SD questionnaire- Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Protocol / Proposal	Linkage status questionnaire-Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Protocol / Proposal	Medical records form-Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Information Sheet	Informed consent document-Linkage study-v1.0 26Nov14.doc	26/11/2014	1.0
Protocol / Proposal	Protocol- Linkage to pre-ART care study- version 26Nov14	26/11/2014	1.0
Protocol / Proposal	Protocol- Linkage to pre-ART care study- version 26Nov14.doc	26/11/2014	1.0
Investigator CV	Eugene Ruzagira CV- Nov14.doc	28/11/2014	1
Investigator CV	Kathy Baisley CV-Nov14.doc	28/11/2014	1
Investigator CV	Anatoli Kamali CV- Sep14.doc	28/11/2014	1
Investigator CV	Heiner Grosskurth CV-Nov14.doc	28/11/2014	1
Sponsor Letter	Research project sponsorship letter-Linkage study.pdf	01/12/2014	1
Protocol / Proposal	Protocol- Linkage to HIV care study- v1.1 26Jan15	26/01/2015	1.1
Information Sheet	Informed consent document-Linkage to HIV care study-v1.1 26Jan15	26/01/2015	1.1
Covering Letter	Cover letter- response to LSHTM ethics queries- 29Jan15	29/01/2015	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

8.19. Appendix 19: LSHTM Ethics Committee approval letter

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

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8.20. Appendix 20: UNCST approval letter

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS 1732

19th January 2015

Dr. Eugene Ruzagira
Medical Research Council
Uganda Virus Research Institute
Entebbe

Re: Research Approval: **A Cluster randomized trial of the effectiveness of referral to pre-antiretroviral therapy (Pre-ART) care and follow-up counselling compared to referral to Pre-ART care only, for individuals diagnosed with HIV through Home-Based HIV counselling and testing in Masaka**

I am pleased to inform you that on **07/01/2015**, the Uganda National Council for Science and Technology (UNCST) approved the above referenced research project. The Approval of the research project is for the period of **07/01/2015** to **07/01/2016**.

Your research registration number with the UNCST is **HS 1732**. Please, cite this number in all your future correspondences with UNCST in respect of the above research project.

As Principal Investigator of the research project, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the research protocol or the consent form (where applicable) must be submitted to the designated local Institutional Review Committee (IRC) or Lead Agency for re-review and approval **prior** to the activation of the changes. UNCST must be notified of the approved changes within five working days.
3. For clinical trials, all serious adverse events must be reported promptly to the designated local IRC for review with copies to the National Drug Authority.
4. Unanticipated problems involving risks to research subjects/participants or other must be reported promptly to the UNCST. New information that becomes available which could change the risk/benefit ratio must be submitted promptly for UNCST review.
5. Only approved study procedures are to be implemented. The UNCST may conduct impromptu audits of all study records.
6. A progress report must be submitted electronically to UNCST within four weeks after every 12 months. Failure to do so may result in termination of the research project.

Below is a list of documents approved with this application:

	Document Title	Language	Version	Version Date
1	Research proposal	English	1.0	26 November 2014
2	Questionnaire	English	1.0	26 November 2014
3	Participant Information	English, Luganda	1.0	26 November 2014
4	Consent forms	English, Luganda	1.0	26 November 2014
5	Medical records form	English	1.0	26 November 2014

Yours sincerely,

Leah N Omongo
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

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