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TITLE

The effect of weekly short message service communication on patient retention in care in the first year after HIV diagnosis: study protocol for a randomised controlled trial (WelTel Retain)

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ARTICLE SUMMARY

Article focus

- Improving retention in care in the first year after HIV diagnosis is critical to optimize patient health outcomes; few interventions specifically designed to retain patients in the early stages of HIV care have been tested.
- This article outlines a randomised controlled trial protocol to determine the effectiveness and cost-effectiveness of a text-messaging intervention (WelTel) to retain patients in HIV care in the first year after diagnosis.

Key messages

- The WelTel intervention has been found effective at promoting adherence among HIV patients taking antiretroviral therapy; this trial will determine whether the intervention is also effective in earlier stages along the continuum of HIV care.
- Mobile health interventions need to be evidence-based and rigorously tested before they are considered for implementation and scale-up.

Strengths and limitations of this study

- The trial has a tracing component to ascertain the true outcome of participants initially deemed 'lost-to-follow-up', leading to a more accurate assessment of retention in care.
- The primary limitation is that WelTel Retain is a single-site study in a resource-limited setting; generalizability to other settings may be limited.

ABSTRACT

Introduction: Interventions to improve retention in care after HIV diagnosis are necessary to optimize the timely initiation of antiretroviral therapy (ART) and HIV/AIDS control outcomes. Widespread mobile phone use presents new opportunities to engage patients in care. A randomized controlled trial (RCT), WelTel Kenya1, demonstrated that weekly text-messages led to improved ART adherence and viral load suppression among those initiating ART. The aim of this study is to determine whether the WelTel intervention is an effective and cost-effective method of improving retention in care in the first year of care following HIV diagnosis.

Methods and analysis: WelTel Retain is an open, parallel group RCT that will be conducted at the Kibera Community Health Centre in Nairobi, Kenya. Over one year, we aim to recruit 686 individuals newly diagnosed with HIV who will be randomly allocated to an intervention or control arm (standard care) at a 1:1 ratio. Intervention arm participants will receive the weekly WelTel SMS "check-in" to which they will be instructed to respond within 48 hours. An HIV clinician will follow-up and triage any problems that are identified. Participants will be followed for one year, with a primary endpoint of retention in care at 12 months. Secondary outcomes include retention in Stage 1 HIV care (patients return to the clinic to receive their first CD4 results) and timely ART initiation. Cost-effectiveness will be analysed through decision-analytic modelling.

Ethics and dissemination: Ethical approval has been obtained from the University of British Columbia and the African Medical and Research Foundation. This trial will test the effectiveness and cost-effectiveness of the WelTel intervention to engage patients during

the first year of HIV care. Trial results and economic evaluation will help inform policy and practice on the use of WelTel in the early stages of HIV care.

Trial registration: ClinicalTrials.gov NCT01630304

INTRODUCTION

As HIV care and treatment programs in resource-limited settings move away from emergency delivery of care to long-term management, patient retention in care is increasingly recognized as critical to the success of these programs. Along the cascade of care (figure 1), from diagnosis to clinical evaluation and readiness for antiretroviral therapy (ART), through to long-term follow-up, high rates of attrition from care occur at several intervals. Between diagnosis and initiation of ART, fewer than two-thirds of patients remain continuously in care.[1] In Kenya, a study at a large HIV care centre estimated 12-month clinic retention among ART-ineligible patients at 63%; after introducing the provision of free co-trimoxazole to pre-ART patients, 12-month retention increased to over 80%.[2] Consequences of attrition include an increased risk of morbidity, mortality and a greater strain on limited healthcare resources (resulting from patients returning to care when they are seriously ill).[3-4] Conversely, retaining patients in care before they start HIV treatment facilitates the timely initiation of ART, and the provision opportunistic infection prophylactic medication and prevention of mother-to-child transmission (PMTCT) services. A review of individual studies indicates that few interventions specifically designed to promote retention in care among individuals with HIV have been tested. Of these, financing transportation costs (N Emenyonu *et al.*, 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2010), targeted social support (V Otieno *et al.*, 17th International AIDS Conference, Mexico City, 2008), and the provision of free co-trimoxazole as prophylaxis for opportunistic infections[2] have been shown to reduce loss to care. An effective intervention has not yet been widely implemented.

The global expansion in mobile phone use, with high rates of uptake in Africa, presents new opportunities to incorporate the use of cell phones into health service delivery to help engage patients in care. In 2012, the cell phone penetration rate (number of subscribers as a proportion of the population) in Kenya was 77%, with continued growth in the use of short message service (SMS).[5] Shared phone use is common in the region and further increases the proportion of Kenyans who use a mobile phone.[6] The WelTel Kenya1 study sought to capitalize on this expansion in mobile phone access to improve health care delivery, and through a multi-site randomized controlled trial (RCT), demonstrated that the WelTel text-messaging intervention is effective in improving adherence to medication and viral load suppression in HIV-infected individuals who had initiated ART.[7] Narrative reports from participants explained that communication with their providers allowed them to feel connected with the healthcare system. It is unknown; however, whether the WelTel intervention can help prevent attrition across the cascade of care. This study will examine the effectiveness, and cost-effectiveness, of the WelTel mobile health (mHealth) intervention to improve retention in care in the early stages of HIV care in Kenya.

Research hypothesis

The WelTel patient-centered SMS service is a cost-effective strategy to improve patient retention in care in the first year following HIV diagnosis.

Study objectives

Primary objective

To determine the effect of the WelTel intervention compared to standard care on 12-month retention in care in patients newly diagnosed with HIV.

Key secondary objectives

- Determine the effect of the WelTel intervention compared to standard care on retention in Stage 1 HIV care (patient returns to the clinic to receive the first CD4 count results).
- Evaluate the cost-effectiveness of the WelTel intervention on patient retention in care over one year. Employ lifetime decision analytic modelling to describe the benefit on lifetime clinical and economic outcomes of additional patients retained in care.

Other secondary objectives

- Determine the effect of the intervention on 6-month retention in care, level of engagement in care, timely initiation of ART, social support and satisfaction with care.
- Determine whether the effect of the WelTel intervention differs among important subgroups (sex, age, phone ownership, distance from clinic, and baseline ART-eligibility status).

METHODS AND ANALYSIS

Trial design

WelTel Retain is a single site, two-arm, open, randomised, parallel-group study with a 1:1 allocation ratio.

Study setting

The trial will take place at the Kibera Community Health Centre, an African Medical and Research Foundation (AMREF) clinic in Nairobi, Kenya, which serves over 4,000 HIV-infected individuals. The health centre is a comprehensive care clinic, and there are no direct patient costs for HIV/AIDS care and treatment. The clinic is located in the heart of Kibera, one of the largest informal settlements in Africa, with an ethnically diverse population of approximately 170,000.[8] The population the clinic serves lacks or has

minimal access to services such as education, water, sanitation, or other public services. Transport infrastructure is minimal. In 2008, HIV prevalence among adults tested for the first time was estimated at 13%.[9]

Study population

The study population consists of adults aged 18 or over who test positive for HIV at the Kibera Community Health Centre and have not been previously assessed for ART eligibility. Individuals who test positive for HIV based on two rapid HIV tests will be referred to a research nurse. The research nurse will complete an eligibility checklist: individuals must fulfil all inclusion criteria and none of the exclusion criteria to participate.

Inclusion criteria:

- adult (18 years of age or older)
- have an HIV test at the Kibera Community Health Centre
- evidence of HIV infection
- own or have sufficient access to a cell phone
- able to operate a cell phone using simple text-messaging, or have a partner, relative, etc., respond on their behalf
- able and willing to provide informed consent to participate

Exclusion criteria:

- previous ART exposure
- currently taking ART
- previously assessed for ART eligibility

- pregnant

Women who are pregnant at the time of diagnosis are excluded from participation because of their differing motivational factors to remain in care compared to a non-pregnant newly diagnosed population; interventions specifically targeted to this population to enhance their retention in care; and different ART treatment guidelines. Pregnant women will be enrolled in a parallel evaluation focused on PMTCT services.

Interventions

Participants will be randomly assigned to receive the WelTel text-messaging service or to usual care. The WelTel intervention involves a weekly short message service (SMS) to check-in on how patients are doing and provide them the opportunity to identify whether assistance is required (figure 2). For example, on Monday mornings, an automated text message from a central computer platform at the clinic will be sent to intervention arm participants asking "Mambo?" (Kiswahili for "How are you?"). Participants will be instructed to indicate within 48 hours of receiving the message either that they are well (e.g. "OK" or "Sawa") or that they have a problem (e.g. "Problem" or "Shida"). A nurse experienced in HIV care will follow-up all participants who identify a problem. Those who do not respond after 48 hours will be called by the nurse to inquire as to their status. Participants will be informed that the SMS support service supplements, but does not replace, existing counseling or clinical services and that all emergencies should be handled by usual means. All cell phone communication resulting from the SMS queries will

be recorded by the technological platform, and the clinician will be able to enter any actions taken directly into this system.

Participants in the control and intervention groups will receive usual care at the discretion of their clinician (physician, nurse, counsellor). Standard care for HIV patients at the Kibera Community Health Centre includes psychosocial support and counselling, patient education, treatment, CD4 testing, tuberculosis and opportunistic infection screening, STI screening and support, nutritional counselling, PMTCT and family planning services.

Outcomes

Primary outcome

The primary outcome is 12-month retention in care: defined as the proportion of participants retained in care at 12-months from baseline, measured as whether the participant attended a follow-up appointment in the 10 to 14 month time frame.

Key secondary outcome

Retention in Stage 1 HIV care: defined as the proportion of participants who return to the clinic to complete their first ART eligibility assessment after receiving a positive HIV test.[10]

Additional secondary outcomes

- The proportion of participants who are ART-eligible at baseline who initiate ART within three months of HIV diagnosis.
- Time to ART initiation (for those who are ART-eligible at baseline)
- 6-month retention in care (attendance at a 6-month appointment within the 5-7 month timeframe)

- Mean proportion of scheduled appointments kept
- Level of engagement, defined as the proportion of participants who are non-engagers (participants who do not return after their initial visit), sporadic users (participants who attend up to 70% of their scheduled appointments), and regular users (participants who attend between 70 and 100% of their appointments).
- Level of social support (adapted Medical Outcomes Study Social Support Survey)[11]
- Satisfaction with care
- Adverse events (number and grade)
- Mortality (all-cause)

A summary of primary and secondary outcomes and related hypotheses is presented in table 1.

Rosen and Fox have proposed three stages of pre-ART HIV care, the first of which is the basis of one of our trial outcomes: retention in Stage 1 HIV care. Our definition includes their proposed start point (first positive HIV test) and outcome (first ART eligibility assessment [patient returns to the clinic to receive the results of their CD4 count]). Tracking retention in Stage 1 care is facilitated at the trial site because patients who test positive at the clinic commonly receive HIV care at the clinic (thereby eliminating a referral process in patients who receive a diagnosis at a stand-alone testing centre). Recent changes in clinical practice at the Kibera Community Health Centre aimed at improving patient enrolment have further simplified processes in this stage. Patients who test positive for HIV have a CD4 test at the same visit, eliminating the extra step of having to return to the clinic to have CD4 testing done. Given the truncated Stage 1 care procedures at the

clinic site, we have chosen to measure retention in Stage 1 at care three weeks, rather than at Fox et al.'s proposed time points of three and 12 months.[10]

For those initially deemed ART-ineligible, Stage 2 HIV care is the time from completing the first ART eligibility assessment to ART eligibility, while Stage 3 is the period from when a patient learns of their ART eligibility to ART initiation.[10] We will recruit participants at the time of their first positive HIV test, at which point the intervention is randomly allocated; therefore, we are precluded from measuring whether the intervention has an effect on retention in Stage 2 or 3 of pre-ART HIV care i.e. because participants' baseline does not coincide with the start of the time period for later stages of pre-ART HIV care. For our primary outcome, 12-month retention in care, we will use a timeframe of 10-14 months will be used in order to accommodate differing visit schedules, which vary according to whether patients are taking ART, how recently they have started treatment (ART or co-trimoxazole), and how adherent they are to medication (ART or co-trimoxazole). Since our primary endpoint involves attendance at one appointment only, to better capture patient engagement in care we have included secondary outcomes to measure the effect of the intervention on engagement throughout the 12-month period (table 2).

With retention in care as the primary trial outcome, it is important distinguish between retention in care and retention *in clinic*. This is particularly relevant given the decentralization and expansion of HIV care in the area. As patients have increasing options as to where they seek their care, a lack of retention in clinic is not necessarily equivalent to a lack of retention in care. A review by Geng *et al* suggests that retention in clinic is a poor proxy for retention in care,[12] and studies have revealed significant differences in estimates of patients retained in care when a concerted effort has been made to trace those initially

believed to be lost to care. [13] We have taken a patient perspective in our definition of retention in care, with retention defined as patients who remain in care at 12-months, even if they are accessing care outside the Kibera Community Health Centre. To determine whether participants have been retained in care, we will actively trace participants deemed "lost to follow up" in both the intervention and control groups after participants have reached the end of the follow-up period. A trained health care worker knowledgeable in the community setting will trace participants, who will have given their consent during the enrolment process. The tracing aspect of the trial will enable us to ascertain the participants' true status (death, transfer of care, or lost to care). Transferred patients active in care will be considered retained.

Sample size

Based on a 1:1 allocation ratio, an alpha of 0.05 (two-sided) and 80% power, it is estimated that we require 343 participants in each study arm. This calculation is based on finding a significant difference between the intervention and control arms in the primary outcome: the proportion of retained versus non-retained participants at 12 months. Sample size was calculated using the IcebergSim software version beta 4.0.3 (Practihc Coordinating Office, Oslo, Norway), a clinical trial simulator using a Monte Carlo model with 5,000 simulations. Our estimate assumes 12-month retention in 65% of control arm participants (K Kinagwi, personal communication, 2011) and a conservative estimate of 75% of patients retained at 12-months in the intervention group. This difference was selected as the smallest difference that would be important to detect and is assumed to be reasonable in the sense that an effect of this magnitude might be anticipated in this field of research.

Recruitment

Clinic staff will identify potential participants at the time of HIV diagnosis and inform them about the study (figure 3). If an individual expresses interest in the study, the clinic staff will introduce them to the research nurse who will explain the trial in further detail. The research nurse will use a checklist to assess eligibility; eligible individuals will be invited to participate and informed consent will be sought. The research nurse will maintain a recruitment log to document screened patients and will report the number of participants recruited on a weekly basis. We expect to enrol 686 participants over a one-year period. Participants will receive 150 Kenyan Shillings (KES) at the baseline visit (enrolment) and 150 KES for each subsequent study visit (6- and 12-months) to reimburse them for their time. They will not be reimbursed for costs associated with responding to the weekly messages. Participants will be informed through the consent process that they may withdraw from the study at any time for any reason without it affecting their medical care.

Randomization and allocation

Randomization of participants to the intervention or control arm will be at a 1:1 ratio, using a computer-generated randomization list. To achieve balance between the treatment arms during the trial, blocked randomization will be used, with random sequences of different block sizes. The block sizes will not be disclosed, to ensure concealment. Allocations have been computer generated using the ralloc procedure[14] in Stata 12.0 (Stata Corporation, College Station, Texas, USA). The individual responsible for sequence generation and allocation concealment will not be involved in the implementation of treatment

assignments. Written allocation of assignment will be sealed in individual, sequentially numbered, non-resealable, opaque envelopes that will be distributed to the clinic in sufficient quantity to allocate the target number of participants. After meeting inclusion criteria, consenting to participate, and completing baseline assessments, participants will be immediately assigned to the randomized study arm by the research nurse who will open one of the sequentially numbered envelopes to determine allocation. Before opening the envelope, the participant's details will be written on the envelope. The assignment schedule will be kept off-site in a locked filing cabinet at the University of Nairobi.

Blinding

Participating clinic staff and participants cannot be blinded because the intervention requires overt participation; however, the data analyst will be blinded.

Follow-up

Follow-up visits will occur as per routine clinical practice; each visit will be recorded. For all patients who test HIV positive, a visit is scheduled in two weeks to receive CD4 test results. For ART-ineligible patients, if they are adherent to co-trimoxazole and do not experience side effects, they are usually followed up once a month for the first six months. If patients remain adherent after six months, visits are scheduled every two months. ART-eligible patients are initially followed-up monthly; however, the interval between visits may increase to up to three months. In both the intervention and control groups, study procedures will occur at the 6 and 12-month clinical visits, during which the research nurse will administer a follow-up questionnaire. The locator form will be updated; and clinical and laboratory data retrieved. The final follow-up visit will be the

clinic visit nearest to 12 months after their baseline enrolment, allowing for some natural scheduling flexibility. This visit must occur after 10 months but before 14 months from the participants' baseline visit.

Data collection and management

WelTel's technological platform will capture the outgoing weekly SMS messages and incoming participant responses and instances of non-response. The research nurse will use the platform to record reasons why a participant responded with a problem or did not respond, and actions taken. Data captured by the platform will be backed up on a daily basis.

Questionnaire and other study-related data will be paper-based and entered into a Microsoft Access database at the clinic site by the data manager. Questionnaires were developed using validated measures where possible. They were translated into Kiswahili and then back-translated to English. The questionnaire is in both languages. After translation, the questionnaire was pilot tested during staff training and with patients. The data manager will check all forms for completeness. Data processing will include range and consistency checks. Any queries will be resolved promptly. Data quality will be verified by re-checking a random sample of 10% of data collected. Participant files will be stored in a locked office at the trial site.

Statistical methods

Descriptive statistics of participants' baseline characteristics will be presented to assess their comparability. These statistics will be reported as a mean (standard deviation [SD]) or median (first quartile, third quartile) for continuous variables, and count (percent) for

categorical variables. Baseline characteristics will include: gender, age, education, income, clinical stage, CD4 count, ART eligibility and mobile phone access.

For the primary analysis, we will compare the proportion of participants retained at 12-months in the SMS group to the control group using a Chi-square test (table 1). Our analysis will be intention-to-treat; therefore, we will include all randomized patients according to the study group to which they were originally allocated regardless of subsequent intervention received. Results will be reported as the number of participants (with percentages) for each treatment group, the relative risk (RR) with 95% confidence intervals (CI) and p-values. We will also calculate the number needed to treat (NNT) for the primary outcome. Secondary binary outcomes will be similarly analyzed. For other types of secondary outcomes, we will use t-tests for continuous variables and Kruskal-Wallis tests for non-normally distributed variables. For time-to-event outcomes, we will analyze the data with the Kaplan-Meier approach and Cox proportional hazards model.

Subgroup analyses will be performed by conducting the statistical analysis of the primary and secondary outcome within pre-determined subgroups of patients. These include: sex (male versus female), age (18-29, 30-39, 40-49, ≥50 years of age) phone ownership (owned versus shared), distance from clinic (≤1 hour versus >1 hour), and ART-eligibility status at baseline (ART eligible versus ineligible [CD4<350 cells/mm^3]). Sub-groups were selected because of potential heterogeneity in the risk of loss to care without an intervention (with males, those who are at a greater distance from clinic, and those ineligible for ART more likely to be lost to care)[12] and potential variance in the effect of the intervention resulting from underlying differences between groups of patients in adopting a cell phone intervention

(sex, age, and phone ownership). We will assess whether the intervention effect is homogeneous across these subgroups by including an interaction term between the intervention allocation and subgroup-defining variables in the model. P-values for the interaction tests, rather than the treatment effect within groups, will be reported. We will report all subgroup results, regardless of significance.

Missing data will be handled using multiple imputation methods.[15] The criterion for statistical significance will be set at alpha=0.05. The results will be reported as estimate of the effect, corresponding 95% confidence interval and associated p-values. All p-values will be reported to three decimal places with those less than 0.001 reported as p<0.001.The data will be analyzed with up-to-date versions of Stata statistical software (Stata Corporation, College Station, Texas, USA).

Data monitoring, interim analysis and stopping guidelines

A Data and Safety Monitoring Board (DSMB), independent of the study sponsor and investigators, has been established for the trial. The board comprises a clinic trials specialist who is the Chair, a biostatistician, and an expert in HIV clinical care and trials in Kenya. The DSMB will periodically review safety and efficacy data. A single interim analysis will be conducted when half of the patients have reached the scheduled time of their 12-month follow-up visit. The DSMB will use the Hayebittle-Peto rule, with a conservative p-value of <0.001, as a guideline to recommend that the trial be stopped.[16-17] This enables us to maintain an alpha error of 0.05 for the final analysis. Recommendations for termination of the trial will be considered if there are differences in favour of one group or the other.

Harms

All adverse events occurring after enrolment until study exit (12-months follow-up for retained participants and until the end of the tracing aspect of the study for those not retained in clinic) will be recorded. Adverse events include those directly attributable to the intervention, such as accidental disclosure of HIV status, and those resulting from participation in the trial. Potential harms will be outlined during the informed consent process and potential participants will be notified as to whom these events should be reported. An adverse event report form based on standard forms of the relevant institutional review boards (IRB) will be used as a reporting tool. The research nurse will document adverse events in a weekly study log and during follow-up visits with participants. Before the start of the trial, health care staff will undergo training with respect to the recognition and reporting of adverse events. The DSMB will have access to the study data to review the occurrence of such events. Descriptive statistics will be used to report adverse events.

All unanticipated problems involving risks to human participants or others will be reported to the supporting Health & Human Services (HHS) agency head (or designee), the Office for Human Research Protections (OHRP), research sponsor, and the IRBs. Unanticipated problems will be defined by OHRP criteria, as outlined in documentation on 'Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events'.[18] Adverse events and unanticipated problems will be promptly reported to the appropriate officials in accordance with OHRP recommendations and IRB regulations. Unanticipated problems will be reported to the IRBs within two weeks of the investigator becoming aware of the problem, unless the unanticipated problem is serious, in which case problems will be reported within one week. Unanticipated problems will be reported to the research sponsor, supporting agency head

(or designee) and OHRP within one month of the IRBs' receipt of the report of the problem.

Qualitative aspects

Formative and post-trial qualitative studies involving patients and healthcare workers from the study site will be conducted. The purpose of the formative phase is to gain an understanding of potential barriers and patient knowledge of retention in care generally, and to inform any necessary adaptation of the WelTel intervention. Semi-structured interviews will be conducted with five healthcare workers and 15 patients, recruited through convenience sampling. Eligibility criterion for healthcare workers is employment at the Kibera Community Health Centre (KCHC). Patients will be eligible if they are a KCHC client, ≥18 years, HIV positive, and willing to provide consent. Interviews will be conducted in English with a translator fluent in Kiswahili and English present to assist. The interviews will be recorded, translated into English (if needed), and transcribed verbatim. Data will be analyzed using an inductive thematic approach. Two researchers will read interview transcripts numerous times to identify important concepts, events and experiences.[19] Once a consistent coding framework is established, transcripts will be coded using NVivo 9 (QSR International Pty Ltd, Doncaster, Australia) software. To increase reliability, 20% of transcripts will be double coded.

The follow-up qualitative study will be conducted after the trial is complete, the purposes of which are to gain an understanding of participants' experiences during the first year of HIV care, specifically as they relate to retention, and with the WelTel intervention. Theoretical sampling will be used to identify potential participant groups for recruitment.[19] For example, we may recruit individuals who were initially deemed lost to follow-up but

traced, stopped responding to the intervention, shared a phone, were treated with ART, etc., in order to gain a range of perspectives. We will recruit patients who participated in the trial and healthcare providers involved in the trial until data saturation is achieved.

Cost-effectiveness evaluation

Decision analytic modeling will be used to assess WelTel from a health care payer/donor perspective. An incremental analysis will evaluate the intervention compared to standard care. Direct costs of text messaging, infrastructure maintenance and technical support will be collected through trial reports and electronic reports generated by the WelTel platform. Estimates of labour costs will be derived using the activity based costing method.[20] The WHO-CHOICE database will be utilized to price labour and other resources used.[21] Participant questionnaire data will include patient-specific costs and time missed from work that will be used in a secondary societal analysis.

Relative risk of loss to care within one year of diagnosis will describe the benefit of WelTel compared to standard care over a short time horizon. Modeling will extend the time horizon to life-long due to the chronic nature of HIV disease. The model will be populated using parameters identified from the literature such as rates of transmission, opportunistic infection and complications. Incremental improvements in retention will be transformed into disability-adjusted life-years (DALY) averted.

We will report the incremental cost-effectiveness ratio (ICER), in this case the ratio of the incremental cost to provide WelTel over usual care and the effect of DALY averted. The summary measure will be the incremental cost per patient retained over one year. The ICER will also be determined for cost per DALY averted, so that we may compare WelTel to other global health strategies and programs.[21] In accordance with WHO guidelines, we

will use a discount rate of 3%.[21] Probabilistic sensitivity analyses will be conducted on the discount rate, retention rates, costs of WelTel, costs of resources such as ART and other pertinent variables. We will perform scenario analyses including lifetime projections assuming consistent effects of WelTel over time, diminishing effects, and no effect beyond one year. Consistent with WHO-CHOICE standards, the threshold for cost-effectiveness is three times per capita gross domestic product (GDP) per DALY averted.[21] A very cost-effective intervention is less than one times GDP per DALY averted.[21] These thresholds will be shown on an incremental cost-effectiveness plane that will be constructed from the probabilistic analysis.

Ancillary studies

1. Participant engagement with the WelTel intervention

To better understand participant engagement with the intervention, a detailed descriptive analysis of cell phone communication will be conducted. This will include a summary of problems identified through the intervention and reasons why patients did not respond to the messages. Factors associated with responding with a problem and non-response will also be examined. Several mobile health (mHealth) interventions have experienced significant declines in participant response rates over time,[22-24] bringing into question the long-term sustainability of these interventions. Response rates remained stable during the 12-month study period of the WelTel Kenya1 trial,[25] this trial will confirm whether response rates to the WelTel service are equally durable in among patients in an earlier stage of HIV care. Patient-perceived benefits of and barriers to the intervention will also be examined.

2. Retention during the first year of HIV care and factors associated with loss to care

In their systematic review, Rosen and Fox indicate that studies adequately quantifying loss to care are scarce.[1] To this end, we will conduct a prospective cohort study alongside the RCT to evaluate participant retention in the early stages of HIV care. Participants involved in the trial will be included in the cohort. To increase the generalizability of study findings, in addition to trial participants, patients ineligible for the trial, e.g. because they do not have cell phone access, will also be eligible to participate in the cohort study. Participants will be followed-up for 12-months. Objectives of the cohort study are to quantify loss to care in the first year after diagnosis and to determine risk factors associated with loss to care.

ETHICS AND DISSEMINATION

Research ethics approval

The original study protocol, information and consent form, and baseline questionnaire were approved by the University of British Columbia Clinical Research Ethics Board (H12-00563) and the African Medical and Research Foundation Ethics and Scientific Review Committee (P40/12). Modifications to the original trial protocol have been submitted as amendments to the IRBs, and approval has been obtained. Ethical approval will be renewed on an annual basis.

Consent

After a clinic staff member introduces the trial, a trained research nurse will provide the potential participant with further details. If the participant would like to enrol, the research nurse will discuss the information in the consent form with them in the language in which the potential participant is most comfortable, English or Kiswahili. Participants will be given the opportunity to ask questions before providing written consent. Once signed, each participant will be provided with a copy of the information and consent form. Illiterate

patients who wish to participate will provide consent in the presence of a literate witness; the participant's thumb print will be used in lieu of their signature.

Confidentiality

To maintain participant confidentiality, all personally identifying information will be removed from questionnaires and study documents where possible. Participants will be identified on these forms by a unique study identification number (ID). Study documents containing personal information e.g. locator form, informed consent forms, etc. will be kept off-site and separate from other study data. Completed questionnaires and study documents will be stored in locked filing cabinets with limited access. All personally identifying information will be removed from interview transcriptions. The risk of breach of confidentiality resulting from the text messaging intervention will be minimized since the content of the text message will not include language related to HIV. Data stored on computer databases will be password-protected and access to files will be limited.

Dissemination

Regardless of the significance, direction or magnitude of effect, we will publish our primary findings and ancillary studies in peer-reviewed journals. We will also report study findings through conference abstracts, relevant websites, at workshops and to the participating clinic staff and patients. Once all of the data has been collected and cleaned, we will aim to submit the trial results for publication within three months.

CONCLUSION

This trial provides the opportunity to test whether the WelTel intervention is effective in earlier stages of HIV care, even before individuals start treatment. The clinic involved in the trial has several measures in place to ameliorate loss to care; however, retention in care

is still identified as a major issue and barrier to the maximum success of their HIV care and treatment program. Through this trial, we will be able to determine whether the WelTel text-messaging intervention, by engaging patients with the clinic on a weekly basis, is a cost-effective way to help promote retention in this critical stage of HIV care.

Table 1 Outcomes, measures and methods of analysis

Outcome/Variable	Hypothesis	Outcome measure	Method of analysis
1.Primary outcome:			
a) 12-month retention in care	intervention>control	Attends12-month clinic appointment (10-14 month timeframe)	Chi-squared test
2. Key secondary outcomes:			
a) Retention in Stage 1 HIV care	intervention>control	Attends clinic to receive CD4 results (within 3 weeks of positive HIV test)	Chi-squared test
b) Incremental cost-effectiveness ratio	intervention>control	Cost per disability adjusted life year averted	Decision analytic model
3. Additional secondary outcomes:			
a) Timely initiation of ART	intervention>control	Starts ART within 3 months of eligibility (for those eligible at baseline)	Chi-squared test
b) Time to ART initiation	intervention>control	ART initiation after eligible (at baseline)	Kaplan-Meier survival analysis
c) 6-month retention in care	intervention>control	Attends 6-month clinic appointment (5-7 month timeframe)	Chi-squared test
d) Level of engagement	intervention>control		
e) Proportion of scheduled appointments kept	intervention>control	Mean proportion of scheduled appointments attended	T-test
f) Satisfaction with care	intervention>control	5-point Likert scale item	Kruskal-Wallis test
g) Level of social support	intervention>control	5-point Likert scale item	Kruskal-Wallis test
h) Quality of life	intervention>control	SF-12 PCS and MCS scores	T-test
i) Death (all-cause)	intervention>control	All-cause mortality (binary)	Chi-squared test
4. Subgroup analyses			Regression methods with appropriate interaction term
a) female vs. male	female>male		
b) age	younger>older		
c) shared vs. own phone	own phone>shared phone		
d) distance from clinic	≤1 hour > >1 hour		
e) ART-eligible vs. ineligible	ART eligible>ineligible		

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COMPETING INTERESTS

Richard T Lester is the founder of WelTel, a non-profit non-governmental mHealth organization with the goal of scaling up evidence-based mHealth solutions; he has no financial stake in or salary from the organization. For the remaining authors no conflicts of interest were declared.

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CONTRIBUTORSHIP

MVDK and RTL conceived the study. RTL, MVDK, DO, LB, KK, LT, CM, and EM secured funding. MVDK, RTL, DO, LB, KK, EM, CM, AE, PA, AP, KS, and LT contributed to the study design. LT provided statistical expertise. MVDK and SK designed the data collection tools. MVDK drafted and revised the manuscript; KS and AP drafted and revised the qualitative and cost-effectiveness sections respectively. All authors contributed critical intellectual input and approved the final manuscript.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	☑
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	☑
	2b	All items from the World Health Organization Trial Registration Data Set - most elements included	☐
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (author list)	☑
	5b	✓ Name and contact information for the trial sponsor	☐
	5c	× Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	☑
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) - many items not applicable	☐
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	☑
	6b	Explanation for choice of comparators	☐
Objectives	7	Specific objectives or hypotheses	☑
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	☑

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	☑
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	☑
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	☑
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	☑
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	☑
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	☑
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	☑
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	☑
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	☑
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	☐

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	☑

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	☑
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	☑
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	☑
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	☑
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	☑
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	☑
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	☑
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	☑
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	☑
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	☑

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	☑
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	☑
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	☐
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	☑
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	☐
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	☑
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	☐
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	☑
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	☑
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	☐
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	☐
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	☑
	31b	Authorship eligibility guidelines and any intended use of professional writers	☐
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	☐

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	☐
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	☐ n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Figure 1 HIV cascade of care

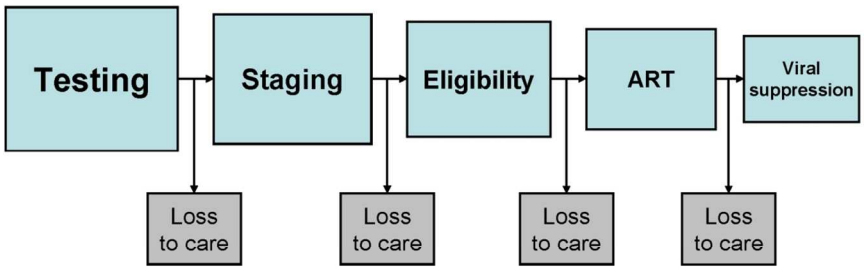

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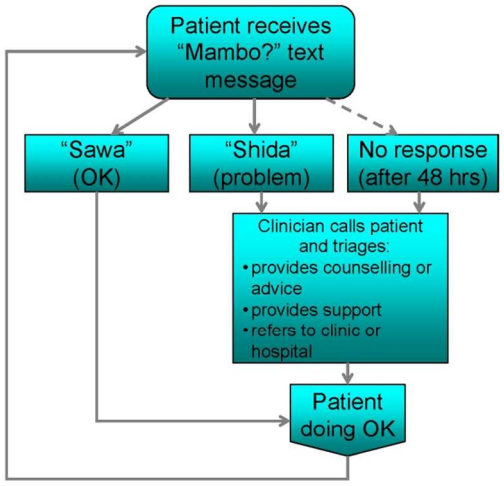
Figure 2 The WelTel intervention



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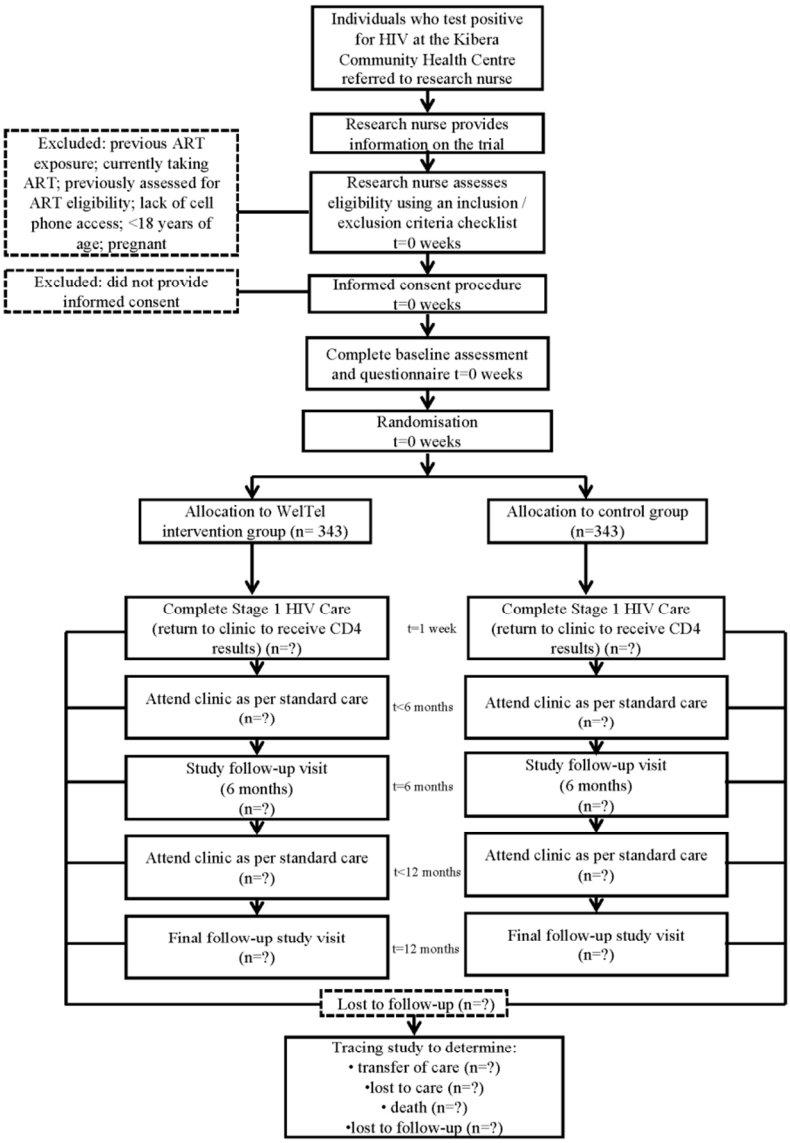

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