A MOBILE PHONE SHORT MESSAGE SERVICE INTERVENTION TO INCREASE RETENTION IN HIV CARE AMONG HIV-POSITIVE MEN WHO HAVE SEX WITH MEN (MSM) IN PERU

WELTEL PERU

SUMMARY

Retention in care (or in care) for HIV is associated with increased survival and viral suppression, and with less transmission of the virus. HIV disproportionately affects men who have sex with men (MSM). In Peru, the HIV epidemic is concentrated in them (prevalence of 12.2%), while only 0.4% of the general population is HIV+. What is concerning is that MSM tend to have lower rates of retention in HIV care. Studies with text messages (SMS) have been reported to be effective in promoting testing for HIV and other sexually transmitted infections in MSM. Two-way text messaging (2-way, ie when the patient can reply) can provide a higher level of real-time support to patients. WelTel was the first randomized controlled trial to use this interactive approach and reported a significant increase in adherence and viral suppression. WelTel has been used successfully for HIV, asthma and tuberculosis. However, further studies are needed to evaluate the use of this strategy to increase retention in HIV care in resource-limited settings, such as in Latin America. The hypothesis is that an adapted version of WelTel can be used to implement a 2-way text message-based intervention, and to increase retention in care among HIV+ MSM in Peru.

To address the low retention in HIV care among MSM in Lima, we will use the WelTel system and its strategy managed by health providers consisting of sending reminder and informative SMS and differentiated follow-up. We will assess the efficacy of the intervention with a randomized controlled trial comparing the proportion of HIV+ MSM retained in HIV care among those who received the intervention versus the standard care arm, up to one year after enrollment. We will recruit 208 participants who will be randomly assigned (1:1) to an intervention group (receives the intervention with WelTel) and a control group (standard of care). Delivery of the intervention will take place over 6 months, and the main outcome to be measured will be retention in HIV care up to 1 year after enrollment.

ACRONYM

PLWHA: people living with HIV/AIDS.
MSM: men who have sex with men.
ART: antiretroviral therapy.
SMS: short message service (short text message).
CD4: CD4 T lymphocyte cell.
CV: viral load.
RR: relative risk.
MINSA: Ministry of Health.
PS: health provider.
STIs: sexually transmitted infections.

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INTRODUCTION

23.3 million people living with HIV/AIDS (PLWHA) are now receiving antiretroviral therapy (ART) and it is estimated that there will be 2.8 million more per year in the next 3 years (19). For continued access to ART and monitoring of clinical and virological progress, PLWHA must be maintained in high-quality care. **Retention in HIV care is associated with increased survival, viral suppression; and reduced HIV transmission and viral resistance** (20,21). Missing more than two HIV care visits increased mortality risk in a multicenter cohort study (HR = 3.61; 95% CI, 2.35-5.55) (21). Low retention in HIV care is a critical barrier to achieving optimal individual and community outcomes. Continuum of HIV care includes testing for exclusion, linkage to care, initiation of ART, retention, and adherence to therapy to achieve and maintain viral suppression. Since 2010, the number of new HIV infections in Latin America has remained stable, without significant decreases as observed in all other regions of the world (19). Viral suppression remains low in some regions: 22% in the Middle East and North Africa; 40% in the Caribbean; and 52% in Latin America (19). **With the expansion of ART, urgent efforts are needed to retain PLWHA in care and thus reduce morbidity, mortality, and the incidence of new HIV-related infections** (22-24).

HIV disproportionately affects men who have sex with men (MSM). MSM represent 41% of new infections in the region (19). In fact, MSM have a 27-fold higher risk of HIV infection than the general population (25). In Peru, the epidemic is concentrated among them (prevalence 12.2%), while only 0.4% of the general population is HIV+ (19,26). The incidence among MSM aged 18 to 29 years has increased substantially and 60% of new infections occur in this group (27,28). **Of concern, HIV-positive MSM are less likely to remain in care than other population groups** (29-33). In the United States, 54.3% retention in HIV care and 50.8% viral suppression were reported among MSM aged 20-24 years (32). In Peru, less than 50% of MSM have been tested for HIV and it is estimated that only 24% of those infected know their status (28). The Ministry of Health reported that retention in HIV care after the first year is 55%, which drops significantly during the second year (26). National viral suppression is only 36% (26).

Based on multiple studies that have shown efficacy, the World Health Organization (WHO) strongly recommends the use of text messages (mobile health) to improve adherence to ART (34-38). **However, evidence on the impact of mobile health for retention in HIV care is scarce** (39,40). Some studies in Africa concluded that short message service reminders (SMS or text messages) are effective in improving retention in HIV care in the general population (39). Until now, no controlled study has done the same with MSM, one of the populations most affected by HIV. Studies with MSM have reported good efficacy of SMS reminders to promote testing for HIV

and other sexually transmitted infections (STIs) (41-43). More trials with this key population are needed to evaluate the use of SMS to increase retention in HIV care in resource-limited settings, such as in Latin America (39).

Two-way communication (between patient and healthcare provider) with text messages (SMS) has the potential to provide comprehensive care through improved communication. A meta-analysis comparing one-way versus two-way SMS found that two-way SMS is the main driver for improving treatment adherence, while one-way messages have little or no benefit (44). Two-way messaging can provide a higher level of real-time support to patients. An evaluation of this strategy using the "behavior change wheel" suggested that the flow of support after an initial SMS is a key contributor to improving ART adherence (45). Health providers need appropriate tools to optimize the delivery of two-way text-based interventions and make them feasible and easy to deliver (38). An existing tool supported by evidence from previous studies can be adapted for use with MSM in Peru, with the aim of optimizing the delivery of a two-way text message intervention to increase retention in HIV care (38).

WelTel was the first randomized controlled trial using an interactive two-way text messaging approach that reported a significant increase in adherence and viral suppression in Kenya (RR for non-adherence: 0.81, 95% CI: 0.69 -0.94; RR for virologic failure 0.84, 95% CI: 0.71-0.99), as well as among HIV+ women in Vancouver, BC (38,46). WelTel is based on a well-structured platform that connects healthcare providers with patients through regular text messages. It uses a web-based program (software) (accessed through the Internet) with intuitive functionalities that allow providers to monitor, track and support large numbers of people (47). The platform allows addressing multiple morbidities, as well as different health services. The system has been tested in Kenya, Rwanda, South Africa, the United States, and Canada and has been used for other diseases such as tuberculosis and asthma (46,48,49). A recent study with WelTel in Kenya significantly improved Quality of Life scores ("the 4th 90") (40). HIV+ MSM in Peru may benefit from receiving an SMS-based intervention delivered through the WelTel platform to increase low retention in HIV care (retention = 50% at study site).

JUSTIFICATION

Peru is a relevant place to test an SMS intervention to increase retention in HIV care based on existing WelTel technology. The country has a high number of cell phone subscriptions (121 per 100 people), and smartphone use is also very common and constantly growing (50-52). Our preliminary data shows that Peruvian MSM are interested in receiving HIV prevention information via SMS (2,3,50,53). Other studies report that HIV+ MSM are interested in interacting with health providers to discuss HIV-related issues that may positively affect their retention in care (55). The proposed study will develop, implement, and evaluate an adapted version of WelTel to deliver a two-way interactive SMS intervention to increase retention among HIV+ MSM. WelTel has been used extensively in other resource-limited settings, and there is preliminary information in Peru to help tailor the content of such an intervention (3,4,12,40,43,49,55).

The use of a two-way SMS intervention to improve retention in HIV care among MSM is innovative. Globally, there are no published controlled studies on improving retention among HIV+ MSM that have used this approach and this study will be the first to evaluate this type of mHealth intervention in Peru. This study will provide evidence on the use of mobile health to improve retention in HIV care, where retention is currently very low. Retention has been the focus of fewer interventions compared to other steps of the HIV care continuum, and it is a crucial step because it involves multiple visits over time (35,57-59). This is the first study that will test the WelTel system in Latin America, specifically in Peru, where there are promising characteristics to carry out the intervention. We will adapt and validate the system for use in Spanish. We will test an already developed system that has the flexibility to add new features to improve patient follow-up.

OBJECTIVES

General Objective:

To assess the efficacy of a text message (SMS)-based strategy delivered with the support of a web tool (WelTel) to increase retention in HIV care in Peru.

Specific Objective:

To determine the efficacy of SMS-based intervention delivered through the WelTel system in increasing retention in HIV care compared to standard care.

Hypothesis:

An SMS-based intervention delivered through the WelTel system will increase retention in HIV care among MSM. We hope to increase retention in HIV care from 50% to 70%.

METHODS

Study Overview:

To address the low retention in HIV care among MSM in Lima, we will use the WelTel system and its strategy managed by health providers that consists of sending reminder and informative SMS and with differentiated follow-up. We will assess the efficacy of the intervention with a randomized controlled trial comparing the proportion of HIV+ MSM retained in HIV care versus the standard care arm up to one year after enrollment. Table 1 summarizes the exposures, results, and design.

Behavior Theory:

The *behavior change wheel framework* has been used to explain how WelTel can promote adherence to ART. The Capability, Opportunity, Motivation, and Behavior model is at the core of the theory (45). According to this model, the achievement of a behavior requires the presence of capacity, opportunity and motivation. To perform in a behavior, a person needs psychological (knowledge and skills) and physical capacity. Opportunity (physical and social) refers to factors that promote behavior. Physical opportunities are those that occur in the external environment, such as a physical reminder (SMS) to take medication. Social opportunities refer to non-physical factors, such as social norms and interpersonal influences. Motivation includes automatic and

reflexive processes that elicit behaviors such as emotions, habits, beliefs, and plans. Automatic processes are those that involve emotional responses, impulses, desires, and reflex responses, while reflective processes involve conscious planning and evaluation. This framework advocates identifying behavior change techniques as components of the intervention.

Only 1 behavior change technique has been identified for the automated text messaging component of the intervention: requesting/indicating the behavior. The behavior change techniques identified in WelTel were mainly related to its personalized communication component delivered to patients who reported a problem or query. These techniques were: a) eliciting/indicating the behavior, b) unspecified social support, c) reducing negative emotions, d) communication from a credible source, e) information about health consequences, f) social emotional support, g) practical social support, eh) instructions on how to perform a behavior. At WelTel, such behavior change techniques were linked to 5 intervention functions: environmental restructuring, empowerment, education, persuasion, and training.

Finally, to specify possible mechanisms of action to promote a behavior, such techniques and functions must be connected to influences on behavior following this model. The proposed mechanisms of action to facilitate adherence behavior in WelTel were: a) the delivery of an external trigger (SMS reminder to complete a behavior) and social support, to influence opportunities and automatic motivation through restructuring and environmental clearance; b) delivery of health-related information and social support to influence ability, opportunity, and motivation through education, persuasion, and training. We believe that retention in HIV care will be similarly influenced in our intervention.

General description:

This intervention will be designed for MSM who are HIV positive. We will recruit subjects 18 years of age or older. The intervention will begin one day after enrollment. The two-way SMS intervention will have four components: 1) an automated weekly SMS sent to ask how they are doing (basic follow-up); 2) phone calls from a health provider to participants who respond that they have a problem, or that they need support or some information that cannot be resolved by text message; 3) SMS reminder 1 week before an appointment for HIV care.

Design:

Randomized controlled trial.

Main result:

The primary outcome will be retention in HIV care for up to 1 year after enrollment. Participants will be classified as retained in care if they attend three HIV care appointments that are separated by 90 days or more within a one-year period (at the study HIV center) (64). Otherwise, they will be classified as not retained. The delivery of the intervention will last 6 months and the follow-up period to verify retention will last up to 12 months.

Main exposure:

Text message (SMS) based intervention delivered through the WelTel system by trained health providers.

Procedures:

1. ***Recruitment and eligibility criteria***. We will identify and recruit 208 HIV+ MSM in the Cayetano Heredia Hospital HIV service for a period of up to 12 months. *Eligible participants* will be 1) men who have sex with men; 2) 18 years or older; 3) has been diagnosed HIV positive; 4) own a cell phone that can send and receive SMS; 5) resides in Lima; and 6) not be enrolled in another study that uses text messaging.

2. ***Enrollment and randomization***: During enrollment, the recruiter will be blinded to assignment to the intervention group. The recruiter will obtain informed consent and instruct the participant on how he should interact if he starts receiving text messages (see appendix 1). Participants will be randomly assigned after providing their cell phone number and brief general information (first name, date of diagnosis, email). They will be assigned a study ID and randomly divided into intervention or control arm (1:1 ratio) using computer generated random numbers. Arm assignments will be in sequentially numbered sealed envelopes. Healthcare providers trained to administer the intervention will be informed by the research team when a new participant is enrolled in the intervention arm. Due to the nature of the study, healthcare providers and participants will not be blinded to group assignment. The participants assigned to the intervention arm will have their telephone numbers registered on the platform.

3. ***Intervention***. We will use the WelTel platform. For 6 months, every Monday the system will send automatic SMS with the question "How are you?" or similar questions (How are you?; How are you doing?). Participants will be instructed to respond if they are okay ("All OK") or if they have a problem ("I want support"; "I'm not okay"). The provider will send a return SMS to participants who have a problem or query; or they will call those who need it. The WelTel program has a customizable dictionary that identifies the words (or phrases) that the administrator indicates; thus, the answers of the participants are automatically ordered to indicate who needs follow-up through a reply SMS or call. One week before each appointment for HIV care, health providers will send an SMS reminder (Table 1).

4. ***Standard care arm***. In 2018, the government published new national guidelines for HIV care (65). After pre-test counseling, the diagnosis of HIV is made with two rapid tests. Those who test positive for both tests receive post-test counselling, including emotional support, and are linked to an ART initiation center, ideally within the same week. During the first medical appointment after diagnosis, laboratory tests including CD4 and viral load (VL) are requested. In most cases, initiation of antiretroviral treatment (ART) occurs at the second medical appointment when basic laboratory results are available. Currently, it is not mandatory to have CD4/CV results available to start ART. ART, viral load and CD4

lab tests are provided free of charge. It is recommended that patients have CD4 counts and viral load testing twice during the first year. A one-month supply of ART is initially provided. If patients are adherent, nurses dispense ART every 3 months and also assess adherence.

Table 1. Summary of the study: exposures, results and design.

Component	Sub-component	Description
Intervention arm (exposure)	Basic follow-up SMS (check-in)	Weekly automatic SMS with the question "How are you?" or similar messages. This will be shipped for 6 months.
	Calls	The provider can call participants who have a problem.
	Appointment reminders	SMS reminder one week before each appointment for HIV care.
Results	Primary	Retention in HIV care up to 1 year after enrollment, defined as attending 3 appointments that are 90 days apart within a 1-year period.
Design	Desing	Randomized controlled trial with a parallel group.
	Sample size	We aim to increase retention in HIV care from 50% to 70%. With 104 participants in each arm, we will have 80% power to detect this difference.
	Follow-up	6 months (intervention); 12 months (retention measure).
	Theory	The behavior change wheel framework and its model of Capability, Opportunity, Motivation and Behavior.
Control arm	Standard of care	Post-test counselling, including emotional support and linkage to ART initiation, ideally within a week. ART, CD4, and viral load laboratory tests are provided free of charge in Peru.

Analysis plan:

1. ***Data sources for the main result***. The main outcome to be measured will be retention in HIV care during the first year after enrollment. Retention in care will be considered if they attend 3 HIV care appointments that are at least 90 days apart within a one-year period (64). We will verify retention in HIV care with: study registration (enrollment) sheets, physical medical records from the HIV service, reception appointment notebooks, and with a final follow-up survey.

   Health providers will enter the data from the enrollment registration sheets into a database that will be stored in a password-protected computer file. The data from the final follow-up online survey completed by the participants will be exported to the physical database and will be periodically deleted from the online survey system server. All data resulting from the interaction between providers and participants will be stored on the WelTel platform that has high security standards: encrypted, password protected and HIPAA compliant (*The Health Insurance Portability and Accountability Act*).

2. ***Statistic analysis***. for the main outcome, we will compare the proportion of MSM who were retained in care in both groups, as a cumulative incidence rate. If any variable of interest is not balanced between intervention and control arms, we will calculate Mantel

Haenszel-adjusted relative risks (RR). For secondary outcomes, we will also assess differences in the proportion of participants.

3. ***Calculation of the sample size***. We hope to increase retention in HIV care from 50% to 70% one year after enrollment in the study clinic among HIV+ MSM. With 104 participants in each arm, we will have 80% power to detect this difference.

   Our main outcome is the degree of loss to follow-up. Retention in care at the study HIV service (as opposed to being lost to follow-up) is the primary outcome, and retention in any HIV clinic will be a secondary measure. Participants lost to follow-up will be considered as not retained. We will measure the retention in an establishment of the Ministry of Health (MINSA). MINSA provides care to more than 60% of Peruvians (73). Since retaining subjects in our public health system is an important goal, we have not adjusted the sample size calculation based on the potential loss of subjects to follow-up.

OPERATIONALIZATION OF VARIABLES

Table 2. Operationalization of variables.

Variable	Type	Options	Source
Age	Continuous	> 18	Online follow-up survey
Education	Categorical	Secondary, Technical, Superior,	Online follow-up survey
Civil status	Categorical	Single, Married, Outgoing, Coupled	Online follow-up survey
Employment situation	Categorical	Unemployed, Employed	Online follow-up survey
Nationality	Categorical	Peruvian, Foreign	Online follow-up survey
sexual orientation	Categorical	Gay, Bisexual, Straight	Online follow-up survey
Diagnosis date	Date	Day month Year	Clinic history; dating record
Treatment start date	Date	Day month Year	Clinic history; dating record
Attended appointment dates	Date	Day month Year	Clinic history; dating record
Viral load	Continuous		Clinic history
CD4	Continuous		Clinic history
alcohol use	numeric		Online follow-up survey
Condom use, last encounter	Categorical	Yes, No	Online follow-up survey
Email	Text		enrollment sheet
Cell phone number	Numeric	NA	enrollment sheet
Arm	Categorical	Control, Intervention	Study Database
Retention in HIV care	Categorical	If not; Attend three appointments for HIV care that are 90 days or more apart within a one-year period (at the study HIV center)	Clinic history; dating record; online follow-up survey; WelTel system

TIMELINE

Actividades	Year 1				Year 2				Year 3				Year 4			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Recruitment/Enrollment																
Delivery of intervention																
Monitoring and analysis																
Manuscript development																

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APPENDIX 1
INFORMED CONSENT FORM

Study Title:
A mobile phone short message service intervention to increase retention in HIV care among HIV-positive men who have sex with men in Peru.

Investigators:
Luis Menacho, Giovani Díaz, Magaly Blas, Elsa Gonzáles

Institution:
Universidad Peruana Cayetano Heredia

Purpose of the study:
We are inviting you to participate in a study to see the usefulness of a new text message follow-up strategy to help you keep appointments at this care service, and to provide you with ongoing support. This is a study developed by researchers from the Universidad Peruana Cayetano Heredia and the Alexander Von Humboldt Institute of Tropical Medicine.
We have seen that as time goes by, many patients receiving antiretroviral treatment stop coming for some controls. As a consequence, their health status cannot be assessed, they do not collect their medications, and they run the risk that the therapy will no longer work as well. The objective of this study is to evaluate a new strategy to motivate them and remind them not to stop coming to their controls.

Procedures:
If you decide to participate in this study, the following will be done:

1. You will need to provide your cell phone number and email address.

2. You will need to complete an online survey at the beginning, middle (at 6 months) and at the end of the study (at 12 months). We will send this survey to you by mail or cell phone. It will last 30 minutes (32 short items) and you will be asked for brief demographic information, sexual behavior, attendance at check-ups, and about some of your physical and mental health habits.

3. Some participants will receive text messages from a health provider approximately once a week for 6 months. They will be informative messages, reminders and also motivating. For confidentiality, a neutral language will be used and some messages will be private: you will be able to see them only if you enter the password that you will be given at the beginning. You can reply to messages if you have any questions, or a member of the team will call you back if you need them.

Risks:
There is a possibility of a breach in confidentiality if someone else reads your cell phone. We will minimize this risk by sending text messages with neutral language that does not contain words directly related to HIV to anticipate if someone else reads the text messages on your cell phone. In addition, text messages with additional information will be protected by a password that only

you will know. We recommend having the cell phone with a password, which is very common now. There is a possibility that some of the questions in the follow-up online surveys may cause you some discomfort, you are free to answer them or not.

Benefits:
You may benefit from receiving informative, reminder and also motivational text messages to help you keep appointments, stay in care which will help maintain good health. Likewise, you could receive logistical and emotional support from health providers.

Costs and compensation
You will not have to pay anything to participate in the study. Likewise, you will not receive any economic or other incentive.

Confidentiality:
We will store your information with codes and not with names. Only researchers will have access to the databases. If the results of this study are published, no information will be shown that allows the identification of the people who participated in this study.

Participant rights:
If you decide to participate in the study, you may withdraw from the study at any time, or not participate in part of the study without harm. If you have any further questions, please ask the study staff or call Dr. Luis Menacho at 991671979.

If you have questions about the ethical aspects of the study, or believe that you have been treated unfairly, you can contact Dr. Frine Samalvides Cuba, president of the Institutional Research Ethics Committee of the Universidad Peruana Cayetano Heredia at telephone 01-3190000 annex 201355, the which will be enabled soon so, in the meantime, you can send an email to: duict.cieh@oficinas-upch.pe

A copy of this informed consent will be provided to you.

DECLARATION AND/OR CONSENT
I voluntarily agree to participate in this study, I understand the activities I will participate in if I decide to enter the study, I also understand that I can decide not to participate and that I can withdraw from the study at any time.

Name (participant):
Date and time:

Name (investigator):
Date and time: