博士論文

Nurse-led mobile phone voice call reminder and on-time antiretroviral pills pick up in Nepal: a randomized controlled trial

ネパールにおける看護師主導の携帯電話音声コールリマインダーと期限内抗レトロウイルス薬受け取り行動：ランダム化比較試験

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Abbreviations

3TC: Lamivudine

AIDS: Acquired Immune Deficiency Syndrome

ART: Antiretroviral Therapy

ARV: Antiretroviral

CD4: Cluster of Differentiation 4

CIOMS: Council for International Organizations for Medical Sciences

CONSORT: Consolidated Standards of Reporting Trials

EFV: Efavirenz

GEE: Generalized Estimating Equations

HBV: Hepatitis B

HIV: Human Immuno Deficiency Virus

ICT: Information Communication Technology

ID: Identity Number

LMIC: Low-and Middle-Income Countries

SDGs: Sustainable Development Goals

SMS: Short Message Services

SSA: Sub-Saharan Africa

TB: Tuberculosis

TDF: Tenofovir

UNAIDS: Joint United Nations Program on AIDS

UTT: Universal Test and Treat

WHO: World Health Organization

Abstract

Background

A high number of HIV-positive individuals in resource-limited settings cannot collect their antiretroviral (ARV) pills on-time. I aimed to investigate the efficacy of a nurse-led mobile phone-based intervention on improving clinic attendance for on-time ARV pills collection in Nepal.

Methods

I conducted this randomized controlled trial in which the eligible HIV-positive individuals were randomly assigned (1:1) to the nurse-led mobile phone voice call reminder intervention or the voice call for health promotion messaging control condition. The primary outcome was assessed using the World Health Organization's definition of on-time ARV pick up (regular clinic attendance [100% on-time pick up], inconsistent clinic attendance [missing one or more on-time pick up] at baseline and six-month follow-up. I performed the primary analysis by intention to treat. I assessed the trial efficacy by generalized estimating equation models to determine intervention x time interactions.

Results

An independent researcher randomly assigned 468 HIV-positive individuals to the intervention (n=234) or control group (n=234). Forty-three individuals were lost to follow-up. After adjusting for covariates, HIV-positive individuals in the intervention group were more likely to attend their clinics regularly compared with the control group (intervention x time; adjusted odds ratio 2.02, 95% CI:1.15-3.55). Similarly, they were more likely to be adherent to ARV

medication compared with the control group (intervention x time, AOR: 2.51, 95% CI: 1.12-5.59) (p=0.024).

Conclusions

This nurse-led mobile phone voice call reminder intervention is efficacious to improve on-time ARV collection in resource-limited settings.

Key words: Antiretroviral, on-time ARV pills pick up, mobile phone intervention, HIV-positive individuals, Nepal

Chapter 1

Introduction

1.1 Antiretroviral therapy and HIV epidemic

Antiretroviral therapy (ART) is a combination of medications that treat Human Immunodeficiency Virus (HIV) infection. These medicines do not kill viruses or cure the disease, but when taken regularly can prevent the progression of HIV infection.[1] ART is considered one of the most effective interventions to improve health and well-being of HIV-positive individuals.[2-4] It has hugely reduced morbidity and mortality attributed to HIV infection. Such benefits are often attributed to increased ART coverage.[5]

Globally, ART coverage has expanded widely.[6-8] In 2001, it was available to only 2% of the eligible people.[9] With rapid scale-up, about 50% of the HIV-positive individuals accessed ART at the end of 2017.[5] This dramatic increase in coverage has had multiple advantages in the lives of HIV-positive individuals and public health — first, the reduction of premature mortality. From 2000 to 2017, it has been attributed to lessening more than 50% of global HIV infection-related deaths.[5, 10] Second, reduction in morbidity.[11] People on ART are more likely to have a better immune function and less likely to suffer from opportunistic infections, thus reducing morbidity due to HIV infection. Third, prevention of new HIV infections.[12] High adherence to ART is considered an effective way to prevent new HIV infections at the population level. Consequently, ART improves quality of life and longevity of HIV-positive individuals.[13]

Such benefits of ART and global success in HIV response have led to the formulation of several important global goals- the ultimate goal is to end AIDS as a public health problem by 2030.[14]

1.2 HIV epidemic and global goals

The global health community is determined to achieve two major goals associated with the HIV response. First one is 90-90-90 goals by 2020. It suggests 90% of all people living with HIV would know their HIV status, 90% of the HIV-positive individuals who know their status would be enrolled in ART and 90% of the people will have suppressed viral load.[5, 15] By 2016, UNAIDS estimated the global status to be 70%-77%-82%.[5] The second global goal is to end AIDS as a public health threat by 2030.[16]

However, tremendous efforts are necessary to achieve and sustain such ambitious global goals. Especially, in the resource-limited settings where the toll of HIV epidemic is the biggest. To achieve such global goals, the global community has committed to implement the universal test and treat (UTT) as one of the effective strategies.[7]

1.3 Universal test and treat strategy

In 2015, WHO recommended the UTT or treat all strategy to all countries. According to UTT, ART should be prescribed to all adults living with HIV, regardless of WHO clinical stage and CD4 cell count.[17]

Previously, not all individuals could initiate their treatment as soon as they were diagnosed with HIV infection. For instance, according to WHO 2013 guidelines, the following were the criteria to initiate ART:[8]

1) individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and CD4 count ≤350 cells/mm^3;
2) All individuals with HIV with CD4 count >350 cells/mm^3 and ≤ 500 cells/mm^3 regardless of WHO clinical stage; and
3) All individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:
    I) Individuals with active TB disease;
    II) Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease; and
    III) Partners with HIV in serodiscordant couples should be offered and ART to reduce HIV transmission to uninfected partners.

Although the global community is committed to achieving global goals through UTT, several challenges remain in HIV treatment such as improving adherence to HIV treatment.

1.4 Adherence to HIV treatment

HIV treatment adherence is defined as the extent to which HIV-positive individuals follow the instructions provided by their HIV-care providers regarding their HIV treatment and care.[18] It includes regular clinic attendance and uninterrupted lifelong medication intake.[19]

HIV-positive individuals must attend clinics for various purposes such as to collect their antiretroviral (ARV) pills, monitoring their treatment outcomes, and treating opportunistic infections. Among them, ARV pills pick up is the major reason for their clinic attendance.[17] Globally, improving clinic attendance for pills pick up remains one of the key challenges to ART programs.[20-22] Those who miss their clinic visits for pills pick up are more likely to be non-adherent to treatment, have higher mortality rates, and could develop HIV-drug resistance.[23, 24]

1.5 HIV treatment adherence in the era of UTT

Improving HIV treatment adherence is vital to achieving global goals related to HIV response. Treatment adherence mainly contributes by reducing viral suppression, improving quality of life, and ultimately decreasing morbidity and mortality associated with HIV infection.[6] However, a higher number of individuals are expected to be on ART with the implementation of UTT, and health systems in low-income countries are predicted to be further strained as global financing in HIV response has diminished.[25, 26] Further, fewer health care providers could end up delivering ART services to a higher number of individuals, thus negatively influencing the quality of delivered HIV treatment and care services.

Furthermore, in the context of UTT, HIV-positive individuals have lesser pre-treatment time compared to previous HIV treatment procedures. Previously, HIV-positive individuals had a few months to prepare for their treatment.[27, 28] This time was usually used to understand the diseases and importance of ART adherence. For many individuals, initial months of HIV

diagnosis brings psychological turmoil which negatively affects their treatment. HIV-positive individuals new on treatment are more likely to lost to follow up and have higher mortality rates.[29, 30] However, with the implementation of UTT, they have less time to prepare for the treatment and to cope with psychological distress. Among several other components of HIV treatment, on-time pills pick up, especially is a more important component among HIV-positive individuals on ART.

1.6 On-time ARV pills pick up and WHO target

Improving clinic attendance for on-time ARV pills pick up within two days of the run-out date,[20, 31] in particular, remains the key challenge to ART programs.[21, 22, 32] Inconsistent ARV pills pick up may lead to treatment failure and selection of drug-resistant HIV among HIV-positive individuals.[33, 34] For tackling HIV-drug resistance, WHO recommends >90% on-time ARV pills pick up among all individuals registered at ART clinics.[20] However, globally, over 30% of ART clinics did not achieve the WHO target in 2009,[32] which increased to 42% in 2014.[20] Factors such as forgetfulness, feeling healthier, treatment literacy, commuting time, travel costs, mental health issues, and substance use contribute to missed clinic visits in low- and middle-income countries (LMIC). [20-22, 35]

Achieving WHO's on-time pills pick up target is more challenging in LMIC. For example, among African countries, 59% to 83% of ART clinics did not meet this WHO target.[22] Among six Asian countries, none of the 1048 ART clinics in the study could meet the

target in 2009.[32] In 2014, about 35% of ART clinics in Southeast Asia did not meet the WHO target. [20]

On-time ARV pills pick up is also positively associated with medication adherence.[36] Individuals those who attend their clinics regularly have a higher likelihood of achieving optimal medication adherence than those who attend their clinics inconsistently.[36]

1.7 Responses to improve on-time ARV pills pick up

WHO has listed some of the important responses to improve on-time ARV pills pick up.[20] These include decentralization of ART services and behavioral interventions, such as cognitive behavioral therapy. Further responses are peer counseling, reminder devices, fixed-dose combinations, and once-daily regimens, reduction of HIV-associated stigma, provision of more than a one-month supply of ARV drugs, use of objective measures of adherence to counseling patients and electronic or paper-based pharmacy registers. However, these interventions involve multiple stakeholders, need a high cost, and are complex to implement, especially in the resource-limited settings.

1.8 Mobile phone-based interventions and on-time pills pick up

In LMIC, mobile phone-based interventions are promising, as they are cost-effective and simple to execute.[37] They are also highly feasible because of the exponential increase of mobile phone users in LMIC. For example, in sub-Saharan Africa, 94% adult population used mobile phones in 2015,[38] and South Asia, its coverage was over 100% in 2016.[39] In LMIC, this increased coverage has led to a variety of mobile phone-based interventions to improve

HIV treatment outcomes. However, only five randomized controlled trials have assessed the efficacy of mobile phone-based interventions in improving HIV-positive individuals' clinic attendance as identified by a meta-analysis.[40]

Of the five trials, three were conducted in LMIC,[37, 41, 42] and two in high-income countries.[43, 44] Four of those trials used either short message service (SMS) only[41, 42] or a combination of voice calls and SMS reminders,[37, 43] whereas one trial that focused on voice call only reminders was conducted at prevention of mother-to-child transmission clinics.[42] All three trials in LMIC effectively improved clinic attendance, but they focused on maternal[41, 42] or pediatric clinic attendance.[37] The two trials in the high-income countries did not effectively improve clinic attendance.[43, 44] Moreover, mobile phone voice call reminders could be more effective in improving ART outcomes among HIV-positive individuals in limited-literacy, resource-limited settings.[45] However, no trial has assessed the efficacy of mobile phone voice call reminders on clinic attendance for on-time ARV collection among the adult population. Therefore, the development of mobile phone-based interventions is urgently needed to effectively improve clinic attendance for on-time ARV pills pick up in LMIC.

1.9 WHO's recommendations on mobile phone-based interventions

Mobile health (mhealth) is defined as "the use of mobile and wireless technologies for health—aims to capitalize on the rapid uptake of information and communication technologies (ICT) to improve health system efficiency and health outcomes." [46] In the past decade (2010-18), mhealth approach has been extensively used to improve HIV care and

treatment. It has been utilized to improve uptake of HIV testing, receiving laboratory results, delivering health messages, clinical appointments reminder, and improving HIV treatment adherence.[45, 47]

WHO has recognized mhealth as one of the cost-effective strategies to improve population health outcomes. It reflects in WHO's policies and strategies to achieve health-related sustainable development goals (SDGs). WHO passed a resolution at the 71st world health assembly in 2018 to scale mhealth and digital health interventions in the era of SDGs. Moreover, WHO has classified mhealth and digital health interventions and recommends its use in improving HIV treatment adherence.[48]

WHO has categorized the different modes of digital and mobile technologies which supports health system needs. Classification of such interventions includes four categories: I) interventions for data services; II) interventions for healthcare providers; III) interventions for a health system or resource managers; IV) interventions for clients.[48]

Interventions for clients are directly aimed at improving patients' adherence to treatment procedures. Such interventions consist untargeted client communication, client to client communication, personal health tracking, citizen-based reporting, on-demand information services to clients and client financial transactions, and targeted client communication. Particularly, targeted client communication includes targeted alerts and reminders to the clients. These targeted mhealth interventions have the high potentiality to

produce positive health outcomes and improving ART adherence among HIV-positive individuals.[45, 47] They could particularly produce more impact in LMICs, where the mobile phone use has increased extensively.

1.10 Mobile phone use in LMIC and Nepal

Mobile phone use has dramatically increased in LMIC.[38] In 2000, only four percent people had access to mobile phones in LMIC. In 2015, that number exponentially rose to 94 percent.[38] This trend was observed even in the least developed regions of the world such as SSA,[38] and South-Asia.[39] In SSA, 76 mobile cellular subscriptions were present for every 100 people.[38] However, in South-Asia, it was much higher than in SSA, 107 subscriptions per 100 people.[39]

Nepal is a low-income country in South-Asia with total 28 million population.[49] Similar to its South-Asian counterparts; mobile subscription rate is higher in Nepal. It is even higher than the South-Asian average.[39] In 2016, 111 mobile cellular subscriptions were available for every 100-people compared to South-Asian average of 107 subscriptions against 100 people.[39] In Nepal, mobile phone users skyrocketed from 2008 to 2016. In 2008, only 16 subscriptions were there for 100 people, in 2017 this number rose to whopping 111 subscriptions for 100 people.[39]

Higher mobile phone use generates ample potential to improve HIV treatment adherence. Mobile phones can be effective mediums to deliver adherence related messages and assist HIV-positive individuals in multiple ways. The increasing use of mobile phones in

developing countries can further assist people to understand the disease, treatment and their progress in ART through various mobile phone applications.[50]

1.11 HIV epidemic in Asia-Pacific and Nepal

Asia and Pacific region is the home to the second largest HIV-epidemic in the world.[5] This also represents one of the fastest growing epidemics.[51] Unlike in SSA, HIV-epidemic in Asia and Pacific is concentrated among people who inject drugs, men who have sex with men, migrants, and sex workers.[51] In 2016, this region hosted 5.1 million people living with HIV. In the same year, 270, 000 new people were infected with HIV in the region and 170, 000 people died of AIDS-related illnesses.[5] Despite this, the treatment coverage was only 47% among people living with HIV. In total, an estimated 2.4 million people had access to antiretroviral therapy in 2016.[5, 51]

HIV-epidemic in Nepal mimics Asian epidemic.[52] HIV infection is more prevalent among high-risk populations such as people who inject drugs, men who have sex with men, migrants, and sex workers.[53] In 2017, about 30,000 people were estimated to be living with HIV; 12,000 of them were accessing ART throughout the country.[54] To increase the ART coverage and improve health outcomes, the government of Nepal implemented UTT from February 2017.[55] Despite of enormous efforts ART was accessed only by 40% of the eligible HIV-positive individuals in 2015.[56]

1.12 Research gaps

HIV treatment adherence is indispensable for successful ART.[1] This includes clinic

attendance for on-time ARV pills pick up and ARV medication adherence. However, limited successful interventions to improve on-time ARV pills pick up create a barrier to realize positive ART outcomes. Especially, in low-income settings such as Nepal, lack of interventions and poorly functional clinic appointment reminder system deters HIV-positive individuals to enhance on-time ARV pills pick up among HIV-positive individuals. Mobile phone-based interventions, however, have shown promises to improve clinic attendance for on-time ARV pills pick up in various settings.

Several mobile phone-based interventions exist to improve clinic attendance among HIV-positive individuals.[40] Most of them had been conducted in SSA,[37, 41, 57] and high-income countries with mixed effectiveness.[40, 43, 44] Moreover, they were implemented in pre-UTT context and universally accepted intervention is lacking to improve clinic attendance. Especially, no randomized controlled trials have been implemented to improve clinic attendance for on-time ARV pills pick up in LMIC.[40, 45] Also, an explosion in mobile phone use in Asia and Pacific region has provided tremendous opportunities for mobile phone-based interventions among HIV positive individuals in the era of UTT.

Mobile phone reminders have the high potentiality to improve clinic attendance, and follow-up appointments among HIV-positive individuals.[40] Such interventions have mainly focused on improving clinic appointment and medication intake reminders and receiving laboratory results. Those trials have used automated calls, SMS messages and voice call

reminders.[47, 58 59] A systematic review showed the high effectiveness of voice call reminders initiated by health care providers compared to automated messages and SMS messages to improve clinical appointments.[60] A qualitative study in India showed people are less likely to use SMS messages compared to voice calls.[61] A systematic review also showed high feasibility of voice calls compared with SMS messages especially in limited literacy, resource-limited settings.[45]

Furthermore, a high number of these interventions are conducted in SSA where countries are experiencing generalized HIV epidemic. Thus, to improve on-time ARV pills pick up in Nepal, I designed this mobile phone voice call reminder intervention among HIV-positive individuals and recruited nurses to deliver it. I chose voice call reminders because, in Nepal, one-third of HIV-positive individuals on ART have limited literacy.[35] Those with limited literacy cannot read SMS messages but could listen to voice calls.[45, 62] Health care provider-led mobile phone voice call reminders are likely to improve clinic attendance.[60] Among health care providers; nurses were selected in this study to assist women with HIV; in Nepal, over 50% of HIV-positive individuals on ART are women.[35] Similar to neighbor India, the majority of nurses in the country passively are women.[62] Thus, this study was conducted in low-income country Nepal to address the above-mentioned research gaps.

1.13 Objectives

This study has two objectives.

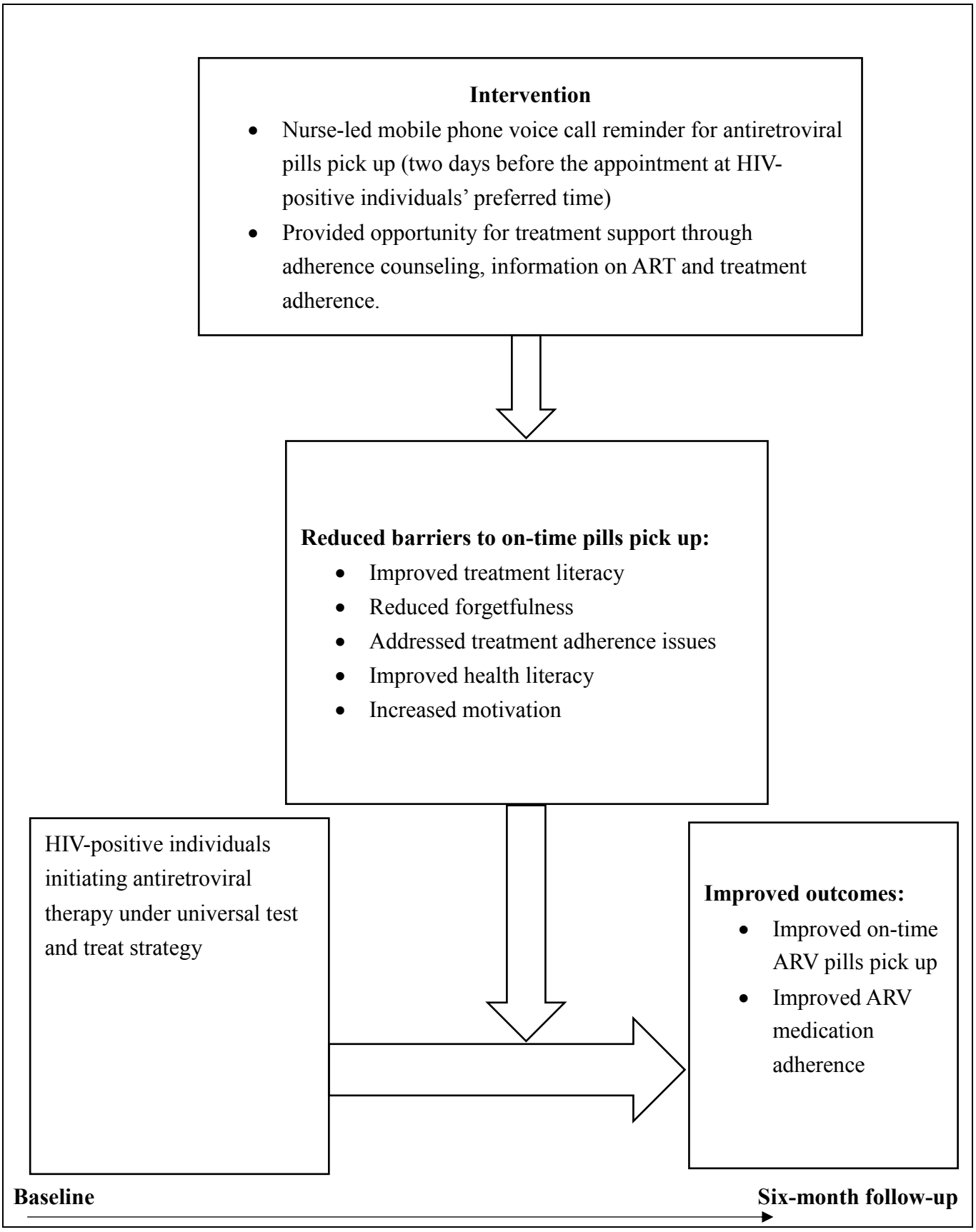
1) To investigate the efficacy of a nurse-led mobile phone voice call reminder intervention on improving clinic attendance for on-time ARV pills pick up among HIV-positive individuals in Nepal.

2) To investigate the efficacy of a nurse-led mobile phone voice call reminder intervention on improving ARV medication adherence among HIV-positive individuals in Nepal.

1.14 Study hypotheses

I had two hypotheses in this study. First, I hypothesized that the effect of the intervention on improving clinic attendance for on-time ARV pills pick up would be statistically higher among individuals in the intervention group compared to the control group. Second, I hypothesized that the ARV medication adherence would be statistically higher among individuals in the intervention group compared to the control group.

Figure 1: Conceptual framework: how the intervention would work?



1.15 Conceptual framework: how the intervention would work?

HIV-positive individuals face several barriers to pick up their ARV pills on-time.[63] Such barriers exist at different levels ranging from individual to health system.[64] The individual level barriers include lack of treatment literacy, forgetfulness, mental health issues, busy schedule, and self-rated better health.[20-22, 35] Especially, in Nepal about 40% of the HIV-positive individuals lack HIV treatment literacy which creates a major barrier for their on-time ARV pills pick up.[35]

I designed this intervention to tackle individual-level barriers to on-time pills pick up among those enrolled in ART under UTT strategy. In this study, I recruited nurses to deliver mobile phone voice call reminders to improve clinic attendance for on-time ARV pills pick up. I used voice calls because of three reasons. First, voice calls by health care providers are potentially more effective than automated messages such as SMS.[60] Voice calls enhance direct interaction and could reduce the forgetfulness of the individuals and motivate them to attend clinics. It could also provide an opportunity to avail HIV treatment-related information, discussing issues in medication adherence, and improve their treatment literacy. Additionally, nurses may counsel them on their health status, challenges in their treatment adherence, and make them aware of the importance of their on-time ARV pills pick up. Second, in Nepal, one-third of HIV-positive individuals on ART have limited literacy.[35] So, sending SMS messages would reduce the usability of intervention among them, as understanding SMS

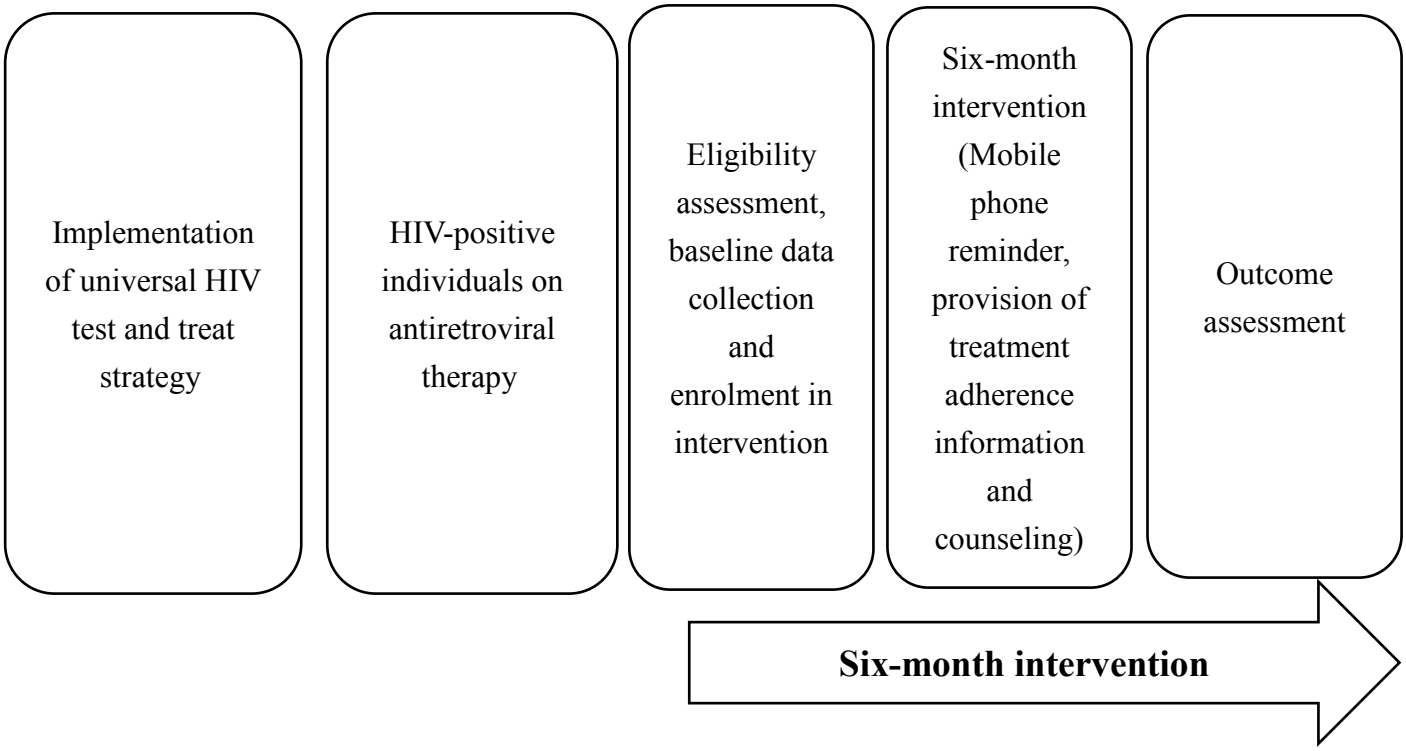
needs the reading capability, but individuals could listen to the voice calls.[45, 62] Finally, a high number of HIV-positive individuals on ART in Nepal are women and to assist those individuals, nurses were included in my study as in Nepal majority of Nurses are possibly women similar to neighbor India.[62] Thus, the intervention would significantly improve on-time ARV pills pick up and ARV medication adherence among HIV-positive individuals.

In this study, nurses reminded HIV-positive individuals about their medication pick up two days before their scheduled appointment at their preferred time. To increase the usability of the intervention, people were given a chance to choose their most feasible time of phone calls. The intervention was delivered for a period of six months. Data was collected at the baseline and six-month follow-up.

1.16 Study timeline

Figure 2 shows the timeline of this study. In this study, I included HIV-positive individuals who were on ART under UTT strategy in Nepal. This strategy was implemented in Nepal in February 2017. From October to December 2017, I assessed the eligibility of the individuals, collected their baseline data, and enrolled them in this study. HIV-positive individuals in the intervention and control groups received the intervention for six months. After the completion of the intervention, I conducted an outcome assessment.

Figure 2: Study timeline



Chapter 2
Methods

2.1. Trial design

This study is a multi-centered, two-arm randomized controlled trial with an HIV-positive individual as the unit of randomization. The allocation ratio of randomization was 1:1. HIV-positive individuals were randomized to either mobile phone voice call reminder intervention or healthy living messaging control groups.

2.2 Study area

I conducted this study in Nepal, a low-income country in South Asia. It had a total population of 28 million in 2017.[49] Nepal is administratively divided into seven provinces and 77 districts. In 2016, 63 ART clinics were functional in Nepal. Out of 63 clinics, 18 had a CD4 cell testing facility.[54] As of May 2017, about 12,000 HIV positive individuals accessed ART services.[54] This study's clinics were under the Nepalese Ministry of Health. By the end of May 2017, about 7000 HIV-positive individuals were accessing ART services at the study sites. I conducted this study at seven ART clinics located at seven hospitals representing four provinces and six districts. I conducted at ART clinics in Kathmandu (1), Lalitpur (1), Rupandehi (1), Banke (1), Kailali (2), and Kanchanpur (1) districts.

HIV infection was prevalent among different key populations in diverse study districts. For example, in Rupandehi, Banke, Kailali, and Kanchanpur districts, which are bordering India, HIV infection was prevalent among seasonal labor migrants. Whereas, in Kathmandu and Lalitpur districts, it was more prevalent among people who inject drugs.

2.3 Study participants

In this trial, HIV-positive individuals were eligible to participate if they were on first-line ART regimen under the UTT strategy, aged 18 years or over, and owned a mobile phone. Individuals were not eligible if they had severe physical and mental illnesses.

2.4 Enrolment procedure

I enrolled HIV-positive individuals in this study following three steps. First, HIV care providers screened individuals using anonymized data maintained at the study clinics. Second, HIV-positive volunteers, HIV care providers, peer supporters, or research staff (baseline assessors) approached potential individuals for further screening. Finally, the research staff explained in detail the study procedures to all of the HIV-positive individuals, obtained their written informed consent, and enrolled them in the study. Enrollment took place at the study ART clinics.

2.5 Randomization

Figure 3 shows the detailed process of participants' randomization. HIV-positive individuals were randomly assigned to the mobile phone voice call reminder intervention or the voice call for health promotion messaging control group. An independent researcher randomized HIV-positive individuals using a computer random number generator (1:1 randomization) using blocked randomization (block size = 4).

The research staff used ART number (unique patient ID) of each individual and then converted it into the trial identity number. An independent researcher assigned all the HIV-positive individuals to either an "intervention group" or a "control group" using computer-generated random numbers. HIV-positive individuals were not told whether they were in an intervention group or a control group.

2.6 Blinding

In this study, intervention and control groups received similar intervention strategies. Only the contents of the interventions were different. Both groups received standard HIV care per national HIV treatment and care guidelines. Further, they were not informed whether they received an intervention voice call or a control voice call. Therefore, it was difficult for HIV-positive individuals to identify if they were receiving the intervention or a control condition. However, due to the nature of the intervention, individuals could know what they were receiving under the study procedures and thus, they could not be completely blinded. The outcome assessors were masked to the allocation group of HIV-positive individuals, but the nurses who delivered the intervention could not be masked due to the nature of the intervention.

2.7 Intervention

2.7.1 Mobile phone voice calls

After the enrollment in this trial, HIV-positive individuals completed a baseline survey. This included information on demographics, depressive symptoms, HIV disclosure

status, alcohol use, and internalized stigma. The trained research staff administered the baseline survey using a pre-tested semi-structured questionnaire and interviewed HIV-positive individuals using a face-to-face technique in a confidential environment at the clinics. The research staff obtained the primary outcome (clinic attendance), ART regimen, and WHO clinical stage data from the medical records maintained at the clinics under the Nepalese Ministry of Health. After completing the baseline survey, an independent researcher randomly assigned HIV-positive individuals to either an intervention group or a control group.

Two trained female nurses delivered the intervention from two different locations: one nurse in the intervention group and one nurse in the control group. As per the intervention, mobile phone voice calls were made to HIV-positive individuals. If the first call was missed, a second call was made on the same day; if the second call was also missed, a final call was made the next day. Nurses called all individuals at their preferred time. HIV-positive individuals could choose the most feasible time for receiving their phone calls before taking part in the intervention.

In both intervention and control groups, HIV-positive individuals received the standard HIV care under the national HIV treatment guidelines.[55] Then, HIV-positive individuals received a paper with their scheduled clinic attendance date for their ARV pills pick up. At the time of each clinic visit, HIV-care providers scheduled a day for ARV pills pick up among the HIV-positive individuals. At the study sites, HIV-care providers

scheduled clinic attendance for ARV pills pick up once a month. The date was scheduled in a manner not to coincide with national holidays or Saturdays.

In this study, HIV-positive individuals in the intervention group received nurse-led mobile phone voice call reminders, which were made two days before their scheduled date for ARV pills pick up. Individuals were called two days prior to their scheduled date so that it would be easier for them to remember and prioritize their clinic visit. The nurse delivered the following message in the Nepali language: Namaste! Sanchai hunuhuncha? Hajurko asusadhi line jane din parsi ho. Kripaya samayamai aspatal janu hos. Dhanyaabad! This message translates to, "Hello! How are you? Please be reminded, your pills pick up date is the day after tomorrow. Please come to your clinic on time. Thank you." Moreover, during the phone calls, individuals had opportunities to talk with the nurse regarding issues in their treatment adherence; she also provided HIV treatment-related information; counseled them as needed, and motivated individuals to attend their clinics on-time. The nurse called them once a month as per their scheduled date for ARV pills pick up for six months expect on Saturdays or national holidays.

2.7.2 Control

In the control group, the nurse delivered the following messages to them in the Nepali language: Namaste! Sanchai hunuhuncha. Swastha rahanako lagi Nepal Sarkar le mero barsa manaudai cha tesaima aadharit kehi swastha sandesh haru dina chahanchau. Hanikarik madira sewan nagarau, churot ra surtijanya padartha sewan nagarua, niyamit wayam garua.

Dhanyabaad! This message translates to “Hello! How are you? The Nepal government is celebrating this year as “my year”. We would like to convey health-promoting messages based on that. First, avoid harmful alcohol. Second, avoid the use of tobacco products and quit smoking. Third, exercise daily and be physically active. Thank you.” The nurse called them once a month irrespective of their scheduled date for ARV pills pick up for six months.

2.7.3 Measures to enhance participation

In both groups, I used multiple methods to keep the participation of HIV-positive individuals. First, the research staff briefed HIV-positive volunteers and HIV care providers at the study clinics regarding the trial procedures. They explained HIV-positive individuals about the trial and motivated them to remain in the trial throughout the study. Second, the two nurses made additional phone calls to contact those who were not responding to the planned phone calls to assess their challenges; they provided counselling to individuals about their participation in the trial in both groups. Finally, a nurse provided health promotion messages through mobile phone voice calls to the control group HIV-positive individuals to improve their participation in the study.

2.7.4 Quality control, monitoring, and supervision

I adopted several measures to enhance the quality of intervention. First, I recruited 14 research staff (baseline assessors) with credentials in public health or nursing. They were provided with intensive training before their involvement in the study. The training focused

on conducting face-to-face interviews, ethical concerns, management issues, and respect for the confidentiality of HIV-positive individuals. Second, the two nurses were intensively trained in the delivery of mobile phone voice calls to individuals in intervention and control groups. They also learned about effective communication through phone calls, potential challenges, respect of confidentiality, psychosocial issues, mental health, the health status of HIV-positive individuals, reporting, and recording.

Additionally, the nurse was trained who called individuals in the intervention group. This intensive training focused on HIV-treatment adherence, adherence challenges faced by individuals, and HIV-treatment literacy. Both nurses reported daily to the trial coordinator. Third, to collect the data, I applied validated and pre-tested measures used in similar settings.[35] Finally, trial coordinator supervised the nurses and outcome assessors. The trial coordinator was based in the field.

Nurses who were involved in this study made mock phone calls to HIV-positive individuals who were not taking part in the main intervention. Based on their feedback, the contents of the intervention were further polished and articulated to suit HIV-positive individuals in this study.

Individuals were given full right to withdraw from this trial at any stage, but none of the HIV-positive individuals withdrew their participation from this study.

2.8 Trial registration

This trial was registered at clinicaltrials.gov, which is a clinical trials registry database. The trail identification number is NCT03367130. This study is reported following the CONSORT 2010 guidelines.

2.9 Measures

2.9.1. Primary outcome

The primary outcome of this study was clinic attendance for on-time ARV pills pick up at the baseline and after the intervention (six-month follow-up assessment). I defined on-time ARV pills pick up using WHO's definition,[20] which is also adopted by the Nepalese Ministry of Health.[28] WHO has defined on-time ARV pills pick up as collecting ARV pills within two days of a scheduled ARV pills pick up date.[20] In this study, I categorized an individual as "regular clinic attendee" if s/he had a 100% on-time ARV pills pick up, whereas I categorized an individual as an "inconsistent clinic attendee" if s/he missed any on-time ARV pills pick up during the study period. To collect on-time ARV pills pick up data, outcome assessors used a standardized measure in Nepal.[35]

2.9.2 Secondary outcome

This study's secondary outcome was ARV medication adherence. I assessed this at the baseline and six-month follow-up using a validated questionnaire adopted from AIDS Clinical Trials Group. I defined adherence as intake of >95% of the doses of prescribed medication and non-adherence as intake of ≤95% of the prescribed doses.[28] ARV medication adherence

was self-reported by the HIV-positive individuals, and I calculated it in the period of the last 30 days.

Research staff obtained clinic attendance for medication pick up data from the medical records of HIV-positive individuals maintained at the ART clinics. ARV medication adherence data was self-reported by HIV-positive individuals. Research staff used an interviewer-administered, pre-tested questionnaire to collect the data.

2.9.3 Covariates

I used several covariates in the analysis. I measured socio-demographic characteristics, namely, age, sex, formal education, employment status, marital status, place of residence, and ethnicity; and mental health and HIV-related characteristics, namely, HIV status disclosure to family members, depressive symptoms measured by Beck Depression Inventory Scale (validated for use in Nepal), alcohol use, internalized stigma measured by AIDS-related stigma scale, ART regimen, and WHO clinical stage.

Socio-demographic variables

Age

I used age as a continuous variable. Research staff asked HIV-positive individuals about their age in completed years.

Sex

I used sex as male, female, and other. None of the HIV-positive individuals were of other sex in this study. Thus, I categorized sex as male and female.

Formal education

I defined formal education as having been to a formal school ever in the lifetime. If HIV-positive individuals reported going to school they were categorized as "yes" if not "no".[35]

Employment status

For assessing the employment status, I used a dichotomous variable. Research staff asked HIV-positive individuals if they are in a work which provided them income. I categorized individuals as employed when they reported "yes" and unemployed when they reported "no".

Marital status

I used marital status as a categorical variable in this study. I categorized marital status as married, single, widow/widower, divorced, and living in a relation.

Place of residence

Place of residence was used as a categorical variable. I called it "urban" if people reported living in municipalities and I called it "rural" if they reported living in Village Development Committees.[35]

Ethnicity

I used ethnicity was a categorical variable. I categorized individuals' ethnicity namely Janajati, Chettri, Bhramin, Scheduled caste, Buddhist, Newar, Muslim, and Madheshi.

Depressive symptoms

I measured depressive symptoms by Beck Depression Inventory (BDI-la) scale validated for the use in Nepal.[65] This scale has also been translated in Nepali language.

Internalized stigma

I measured internalized stigma by a seven-item scale.[66] I computed the final scores by summing all items. Higher scores indicated higher internalized stigma. Each item had a

dichotomous response, 1 = Agree, 0 = Disagree. The total score ranged from 0 to 7.

HIV disclosure status

I used a single question measure to assess HIV status disclosure, are there people at your family you have not told you are HIV positive because you fear their reaction?*"*. Their responses were categorized into "Yes," when they report disclosure and "No" when they did not.[35]

ART regimen

This study consisted of first-line ART regimen. The ART regimen was a categorical variable and I categorized it as Tenofovir + Lamivudine + Efavirenz and others.

WHO clinical stage

I used WHO AIDS clinical staging criterion to collect the information on AIDS progression levels. Under this criterion, disease progression level ranges from stage I to IV. [67] Stage I is usually asymptomatic, and stage IV represents an advanced AIDS stage. A trained physician does clinical staging to each individual before initiating ART. The research staff obtained data on clinical staging from the medical records of HIV-positive individuals.

In addition, alcohol use information was also collected from individuals in an assumption that it could play a role in clinic attendance and ARV medication adherence.

Acceptability of the intervention

I measured the acceptability of the intervention by four questions among HIV-positive individuals in intervention group.[43] First, the research staff asked, how satisfied they were with the delivered intervention. A three-point Likert scale was used to categorize their

responses, ‘dissatisfied,’ ‘neither satisfied nor dissatisfied,’ and ‘satisfied.’ Second, the research staff asked, whether they were disturbed by the reminder; if they were disturbed by the reminder reasons for such disturbances were sought from them. Third, the research staff asked whether they considered the intervention useful to them or not. Finally, the research staff asked them whether they would recommend it to other people or not.

2.10 Sample size calculation

Based on a previous study in Nepal,[35] I assumed regular clinic attendance rate is 33% for on-time ARV pills pick up. Based on the previous studies,[60,68] I also assumed the intervention would increase the regular clinic attendance by 15 to 20 percentage points. In this scenario, about 370 HIV-positive individuals (185 in intervention and 185 in control), would be required to reject the null hypothesis. To counter for lost to follow-up and missing data, I recruited 468 HIV-positive individuals. I also assumed also 95% confidence interval and 80% power of the test. I used OpenEpi, an online platform to calculate the sample size.[69]

2.11 Ethical considerations

This study adhered all the ethical considerations as outlined in the guideline by Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO, international ethical guidelines for health-related research involving humans in resource-limited settings, involving vulnerable population, and community engagement.

I designed this research upon the findings of the previous study in Nepal among similar populations.[35] Further, before the implementation of this intervention individuals were

consulted who shared similar characteristics with this study's population. They provided the feedback and based on their suggestions the contents of the intervention were framed to suit better among HIV-positive individuals who took part in this study. Therefore, this intervention was derived from the existing need in the community which is consistent with the CIOMS and WHO guidelines on research in communities with limited resources. The research protocol of this study was approved by the Research Ethics Committees of the Graduate School of Medicine at the University of Tokyo (approval number 11711) and Nepal Health Research Council in Nepal (approval number 337/2017). National Center for AIDS and STD Control /Ministry of Health also granted written permission to conduct this study. Approval was also received from each participating hospital. Appendix 4 and 5, provide the detailed informed consent process.

Following the approval, the research team and I coordinated with the ART clinics. HIV-care providers, HIV-positive volunteers, and research staff contacted the HIV-positive individuals to assess their eligibility. During the interaction with HIV-positive individuals the research staff and personnel mentioned above shared the research plan and explained the intervention details. Consistent with the CIOMS and WHO guideline, the research team thoroughly explained about the importance of this study, potential harms, and how it could enhance HIV care and treatment among HIV-positive individuals.

As explained in the CIOMS and WHO guidelines on research involving vulnerable persons and groups, special protections were considered. This included no more than minimal risks for procedures that offer no potential individual benefits; safeguards designed to promote voluntary decision-making, and limited the potentiality for confidentiality breaches.

The research staff and I obtained written informed consent from each individual. Participation in this research was voluntary. Before participation, each HIV-positive individual was informed about the study objectives and procedures. HIV-positive individuals' anonymity was maintained throughout the study and their right to privacy was given utmost consideration. Furthermore, interviews and enrolment in the trial were conducted in a confidential environment. At any stage of the study, HIV-positive individuals could decide not to continue with the study and ensured that they will not be penalized in any manner for refusal to participate or if they wish to leave the study in between.

2.12 Data collection

The baseline data was collected between October, and December 2017 and follow-up assessement was conducted in June 2018. The research staff collected the data through a semi-structured questionnaire. I first trained research staff on data collection, ethical, and study procedures. The research staff then conducted face-to-face interviews at the confidential environment in the study clinics. The research staff took about 40 minutes to conduct the baseline interview.

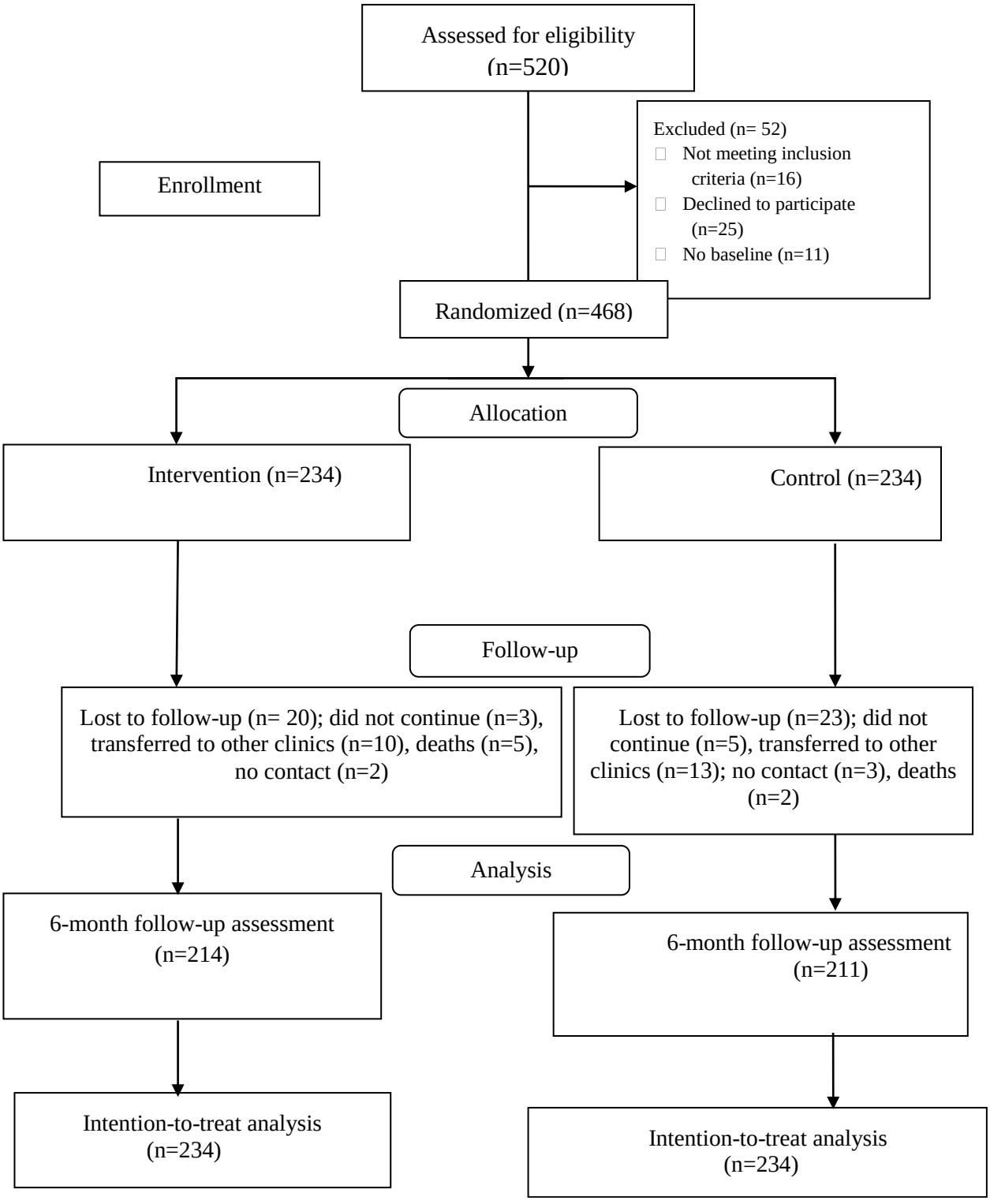
2.13 Data analyses

I collected data from 468 HIV-positive individuals at the baseline and 425 HIV-positive individuals at the six-month follow-up assessment. I performed all analyses according to the intention-to-treat principle.

I followed the following three steps for data analyses. First, I compared baseline characteristics between the intervention and control groups using descriptive statistics; I used χ^2 tests to compare lost to follow-up status. Second, I assessed the changes in primary and secondary outcomes at the six-month follow-up using χ^2 tests. Third, I evaluated the efficacy of the intervention using a generalized estimating equation (GEE) models. I assessed the primary (clinic attendance for on-time ARV pick up) and secondary (ARV medication adherence) outcomes to measure the efficacy of the intervention (intervention versus control), time (treated as a categorical variable; baseline and at six months), and intervention x time interaction. For all of the GEE models, I included the intervention as the exposure variable. I adjusted all of the GEE models for the covariates, which included age, sex, education, employment, WHO clinical stage, depressive symptoms, internalized stigma, and HIV disclosure status. I set the level of statistical significance at $p < 0.05$ and performed all analysis in STATA (R)13.1(StataCorp, College Station, Texas, USA).

Chapter 3
Results

Figure 3: Trial flow and randomization process



3.1 Trial flow and randomization process

A total of 520 HIV-positive individuals were screened for their inclusion in this trial. Of them, 16 (3%) did not meet the inclusion criteria, and 36 (7%) declined to participate or did not complete the baseline interview. Thus, a total of 468 individuals were enrolled, and randomly assigned: 234 to the mobile phone voice call reminder intervention and 234 to the health promotion messaging group (figure 3). In total, 425 (91%) individuals completed the six-month follow-up assessment (the last individual was assessed on June 30, 2018). Of the 234 HIV-positive individuals in the intervention group, 214 (91%) completed the six-month follow-up assessment, whereas 211 (90%) of the 234 individuals in the control group completed the six-month follow-up assessment. At enrollment, all HIV-positive individuals were on ART for at least two and a maximum of six months.

At the six-month follow-up assessment, 43 HIV-positive individuals (9%) were lost to follow-up (figure 3). Of them, 23 (53%) were transferred to other hospitals, eight (19%) did not continue the intervention, seven (16%) died, and five (12%) could not be contacted.

3.2 General characteristics of the HIV-positive individuals at baseline

Table 1 shows the general characteristics of all the HIV-positive individuals in the study (n=468). Out of the total, 55.6% were male. Their mean age was 36.9 years (SD 10.3), and 73.7% had formal education. Only 40% were employed, and 88.5% lived

in urban areas.

Table 1. General characteristics of HIV-positive individuals at baseline

		Total (n=468)	%
Age mean (SD)		36.9 (10.3)	
Sex			
	Male	260	55.6
	Female	208	44.4
Formal education			
	Yes	345	73.7
	No	123	26.3
Employment status			
	Unemployed	281	60.0
	Employed	187	40.0
Marital status	Married	324	69.3
	Single	65	13.9
	Widow/Widower	63	13.5
	Divorced	10	2.1
	Living in a relation	6	1.2
Place of residence			
	Urban	414	88.5
	Rural	54	11.5
Ethnicity			
	Janajati	169	36.1
	Chettri	107	22.9
	Bhramin	88	18.9
	Scheduled caste	35	7.5
	Buddhist	28	5.9
	Newar	16	3.4
	Muslim	15	3.2
	Madheshi	10	2.1

3.3 HIV and ART-related characteristics of HIV-positive individuals at baseline

Table 2 shows health and ART-related characteristics of the HIV-positive individuals (n=468). Of the total, 97.2% were on TDF+3TC+EFV ART regimen. About 80% were categorized as being at stage I and II, 61% were regularly attending clinics for their medication collection, and 84% had optimal medication adherence.

Table 2. Health and ART-related characteristics of the participants at the baseline

		Total (n=468)	%
ART regimen			
	TDF[a]+3TC[b]+EFV[c]	455	97.2
	Other	13	2.8
WHO clinical stage			
	Stage I	240	51.3
	Stage II	135	28.9
	Stage III	82	17.5
	Stage IV	11	2.3
Depressive symptoms			
	Absent	216	46.1
	Mild	136	29.1
	Moderate	96	20.5
	Severe	20	4.3
Internalized stigma score mean (SD) (range)		3.5 (2.2)	(0-7)
HIV disclosure status (family)			
	No	164	35.0
	Yes	304	65.0
Alcohol use			
	No	422	90.2
	Yes	46	9.8
Clinic attendance			
	Regular	285	60.9
	Inconsistent	183	39.1

ARV adherence			
	Adherent	394	84.2
	Non-adherent	74	15.8

[a]TDF-Tenofovir

[b] 3TC-Lamivudine

[c] EFV-Efavirenz

3.4 Comparison of general characteristics across intervention groups

Table 3 shows the comparison of general characteristics among individuals across intervention and control groups. Of total (n=468), 234 (50.0%) were in intervention group and 234 (50.0%) were in control group. Mean age of individuals in the intervention was 37.3 years (SD 10.7), it was similar in the control group 36.5 years (SD 9.9). About 73.5% HIV-positive individuals had formal education in the intervention group compared to 73.9% in the control group. About 40.0% were employed both in intervention and control groups, and 88.0% of the HIV-positive individuals in intervention and control groups lived in urban areas.

Table 3. Comparison of general characteristics across intervention groups

		Intervention n (%) 234 (100.0)	**Control n (%) 234 (100.0)**	**p-value**
n (%)				
Age mean (SD)		37.3(10.7)	36.5(9.9)	0.396
Sex	Male	125 (53.4)	135 (57.7)	0.352
	Female	109 (46.6)	99 (42.3)	
Formal education	Yes	172 (73.5)	173 (73.9)	0.916
	No	62 (26.5)	61 (26.1)	
Employment status	Employed	95 (40.6)	92 (39.3)	0.777
	Unemployed	139 (59.4)	142 (60.7)	

Marital status	Single	33 (14.1)	32 (13.7)	
	Married	164 (70.1)	160 (68.4)	0.822
	Living in a relation	2 (0.9)	4 (1.7)	
	Divorced	6 (2.6)	4 (1.7)	
	Widow/ Widower	29 (12.3)	34 (14.5)	
Place of residence	Urban	206 (88.0)	208 (88.9)	0.772
	Rural	28 (12.0)	26 (11.1)	
Ethnicity	Janajati	87 (37.2)	82 (35.0)	
	Chettri	52 (22.2)	55 (23.5)	0.490
	Bhramin	49 (20.9)	39 (16.7)	
	Scheduled caste	18 (7.7)	17 (7.3)	
	Buddhist	9 (3.8)	19 (8.1)	
	Newar	6 (2.6)	10 (4.3)	
	Muslim	7 (3.0)	8 (3.4)	
	Madheshi	6 (2.6)	4 (1.7)	

3.5 Comparison of health and ART status characteristics across intervention groups

Table 4 shows the comparison of health and ART-related characteristics of the HIV-positive individuals in this study stratified by their intervention groups. Of total in intervention group (n=234), 97.4% were on TDF+3TC+EFV ART regimen. About 78.0% were categorized as being at AIDS clinical stage I and II in intervention group which was slightly higher in control group (82.0%). HIV-positive individuals in both groups had similar rates of regular clinic attendance for their medication collection (60.0% vs 61.5%) at the baseline. ART medication adherence was slightly higher among individuals in the control group compared to intervention group (86.3% vs. 82.1%).

Table 4. Comparison of health and ART status-related characteristics across intervention groups

		Intervention n (%) 234 (100)	Control n (%) 234 (100)	p-value
ART regimen				
	TDF[a]+3TC[b]+EFV[c]	228 (97.4)	227 (97.0)	0.778
	Other	6 (2.6)	7 (3.0)	
WHO clinical stage				
	Stage I	117 (50.0)	123 (52.5)	0.425
	Stage II	66 (28.2)	69 (29.5)	
	Stage III	47 (20.0)	35 (15.0)	
	Stage IV	4 (1.8)	7(2.9)	
Depressive symptoms				
	Absent	118 (50.4)	98 (41.9)	0.012
	Mild	61 (26.1)	75 (32.1)	
	Moderate	51 (21.8)	45 (19.2)	
	Severe	4 (1.7)	16 (6.8)	
Internalized stigma score mean (SD)		3.5 (2.2)	3.5 (2.2)	0.787
HIV disclosure status				
	No	73 (31.2)	91 (38.9)	0.081
	Yes	161 (68.8)	143 (61.1)	
Alcohol use				
	No	206 (88.0)	216 (92.3)	0.120
	Yes	28 (12.0)	18 (7.7)	
Clinic attendance	Regular	141 (60.3)	144 (61.5)	0.776
	Inconsistent	93 (39.7)	90 (38.5)	
ARV adherence	Adherent	192 (82.1)	202 (86.3)	
	Non-adherent	42 (17.9)	32 (13.7)	0.205

3.6 Changes in clinic attendance for on-time ARV pills pick up and ARV medication adherence at six-month follow-up

Table 5 shows the changes in clinic attendance for on-time ARV pills pick up and ARV medication adherence between intervention and control groups at six-month after the intervention. At six-month follow-up, significantly higher individuals in the intervention group attended their clinics regularly for medication collection compared to the control group (p=0.001). Individuals in the intervention group also had significantly higher ARV medication adherence compared to HIV-positive individuals in the control group (p=0.024).

Table 5. Changes in clinic attendance for on-time ARV pills pick up and ARV medication adherence at six-month follow-up

	Total n (468) n (%)	**Intervention n (234) n (%)**	**Control n (234) n (%)**	**p-value**
Primary outcome				
Clinic attendance[a]*				
Six-month follow-up				
Regular	268 (63.1)	151 (70.6)	117 (55.5)	0.001
Inconsistent	157 (36.9)	63 (29.4)	94 (44.5)	
Missing[c]	43	20	23	
Secondary outcome				
Medication adherence[b]*				
Six-month follow-up				0.024
Adherent	372 (87.5)	195 (91.1)	177 (83.9)	
Non-adherent	53 (12.5)	19 (8.9)	34 (16.1)	
Missing	43	20	23	

[a] Achieving 100% on-time ARV pills pick up defined as regular clinic attendance, otherwise inconsistent clinic attendance, [b] Missing at least one ARV pill intake in the last 30 days was defined as non-adherent, otherwise adherent. * χ^2 p-values. [c] Missing includes 43 individuals lost to follow-up (23 transferred out, eight did not continue, seven died, and five could not be contacted)

3.7 GEE: Efficacy of nurse-led mobile phone reminder on improving clinic attendance for on-time antiretroviral pills pick up

Table 6 shows the efficacy of the mobile phone reminder intervention on improving clinic attendance for on-time antiretroviral pills pick up. After adjusting for covariates, HIV-positive individuals in the intervention group were more likely to attend clinics regularly for their ARV pick up compared with the control group (intervention x time, AOR: 2.02, 95% CI:1.15-3.55) (p=0.014).

Table 6: GEE: Efficacy of nurse-led mobile phone reminder on improving clinic attendance for on-time ARV pills pick up

Variable	Adjusted odds ratio	95% CI	p-value
Intervention x time[a]	2.02	1.15-3.55	0.014
Intervention			
Control	1.00		
Intervention	0.96	0.65-1.43	0.876
Time			
Baseline	1.00		
Six-month follow-up	0.78	0.53-1.16	0.226
Age	0.99	0.97-1.00	0.378
Sex			
Male	1.00		
Female	0.83	0.61-1.62	0.236
Formal education			
Yes	1.00		
No	0.81	0.57-1.16	0.265
Employment status			
Employed	1.00		
Unemployed	0.87	0.64-1.18	0.382
WHO clinical stage			
I and II	1.00		
III and IV	0.91	0.64-1.31	0.634
Depressive symptoms			
Absent	1.00		
Mild	0.88	0.62-1.23	0.462
Moderate	0.79	0.54-1.16	0.244
Severe	1.16	0.55-2.43	0.682
Internalized stigma	1.04	0.97-1.11	0.223
HIV status disclosure			

Yes	1.00		
No	0.84	0.62-1.14	0.285

[a] Intervention x time represents the status of the intervention group in comparison with the control group at the six-month follow-up assessment. The table shows the efficacy of mobile phone reminder intervention on improving clinic attendance for on-time ARV pills pick up (total 850 observations, the sum of observations of individuals with complete data at baseline (425) and 6-month follow-up assessment (425).

3.8 GEE: Efficacy of nurse-led mobile phone reminder intervention on improving ARV medication adherence

Table 7 shows the efficacy of nurse-led mobile phone reminder intervention on improving ARV medication adherence. After adjusting for covariates, HIV-positive individuals in the intervention group were more likely to be adherent to ARV medication compared with the control group (intervention x time, AOR: 2.51, 95% CI: 1.12-5.59) (p=0.024). Also, individuals who did not disclose their HIV status to family members were less likely to be adherent to ARV medication (AOR: 0.57, 95% CI: 0.38-0.86) (p=0.008).

Table 7: GEE: Efficacy of nurse-led mobile phone reminder on improving ARV medication adherence

Variable	Adjusted odds ratio	95% CI	P-value
Intervention x time[a]	2.51	1.12-5.59	0.024
Intervention			
Control	1.00		
Intervention	0.75	0.44-1.27	0.297
Time			
Baseline	1.00		
Six-month follow-up	0.90	0.52-1.54	0.705
Age	1.00	0.98-1.02	0.823
Sex			
Male	1.00		
Female	1.15	0.75-1.75	0.512

Formal education			
Yes	1.00		
No	1.06	0.64-1.76	0.806
Employment status			
Employed	1.00		
Unemployed	1.16	0.75-1.77	0.491
WHO clinical stage			
I and II	1.00		
III and IV	1.38	0.81-2.37	0.232
Depressive symptoms			
Absent	1.00		
Mild	1.10	0.67-1.79	0.690
Moderate	0.74	0.45-1.23	0.256
Severe	0.85	0.33-2.21	0.750
Internalized stigma	1.07	0.98-1.18	0.121
HIV status disclosure			
Yes	1.00		
No	0.57	0.38-0.86	0.008

[a] Intervention x time represents the status of the intervention group in comparison with the control group at the six-month follow-up assessment. The table shows the efficacy of mobile phone reminder intervention on improving medication adherence (total 850 observations, the sum of observations of individuals with complete data at baseline (425) and 6-month follow-up assessment (425).

3.9 Acceptability of the intervention

Table 8 shows the acceptability of the intervention among individuals in the intervention group. I identified high acceptability of the intervention. In the intervention group, 91% of the individuals were satisfied with the mobile phone voice call reminders, and 96% found the intervention to be useful. Moreover, 95% of the individuals would recommend the intervention to others, and only 3% felt disturbed by the mobile phone voice call reminder.

Table 8: Acceptability of the intervention

Variable	Intervention n (%)
n (%)	n (214)
Satisfaction with intervention	
Satisfied	194 (90.7)
Neither satisfied nor dissatisfied	17 (7.9)
Dissatisfied	3 (1.4)
Usefulness of intervention	
Yes	205 (95.8)
No	9 (4.2)
Will recommend intervention to others	
Yes	204 (95.3)
No	10 (4.7)
Disturbance by phone calls	
Yes	7 (3.3)
No	207 (97.7)
Reason for disturbance*	
Scared of my HIV status disclosure	7 (100.0)
*n=7 (only among those who were disturbed).	

Chapter 4

Discussion, conclusions, policy implications, and recommendations

4.1 Discussion

Nurse-led mobile phone voice call reminders effectively improved clinic attendance for on-time ARV pills pick up among HIV-positive individuals on ART in a low-income setting. In this study, HIV-positive individuals who received mobile phone voice call reminders were more likely to attend their clinics regularly compared with those who received health promotion messages control condition. The intervention also significantly improved the ARV medication adherence in the intervention group compared with the control group. This is the first randomized controlled trial to show that nurse-led mobile phone voice call reminder intervention can significantly improve on-time ARV pills pick up in the context of universal HIV treatment. Additionally, this study found the high acceptability of the intervention, as indicated by the high user satisfaction, reported usefulness by the majority of the individuals, and willingness to recommend it to others.

Findings of this study are unique in that the intervention included bi-directional, nurse-led mobile phone voice call reminders and was performed among HIV-positive individuals in a low-income Asian country that started ART under UTT strategy. Majority of previous studies on the use of mobile phones used SMS reminders and were conducted in sub-Saharan Africa[37, 41, 57] and high-income countries.[43, 44] None of these studies focused on health care worker-led, bi-directional

mobile phone voice calls reminders or targeted improving clinic attendance for on-time ARV pills pick up.[40]

In this trial, HIV-positive individuals in the intervention group were more likely to attend clinics regularly for their ARV pills pick up compared with the control group. This outcome could be attributed to several reasons. First, mobile phone reminders could have motivated HIV-positive individuals to attend clinics regularly and reduced their forgetfulness.[70] Second, having nurses send mobile phone voice call reminders provided opportunities for patient health care provider interaction,[60] which is conventionally not possible in SMS reminders.[37] During the phone call, individuals could make queries to the nurse regarding their treatment and the challenges they face in treatment adherence. They may have felt cared for, valued, and supported in their treatment.[61] Additionally, the interaction may have improved the treatment literacy among HIV-positive individuals, which is an important determinant for on-time ARV pills pick up in Nepal.[35] Third, HIV-positive individuals could choose their feasible time for receiving the phone calls. This feature may have increased the usability of the intervention. Fourth, direct voice call reminders enabled the nurses to determine instantly whether the person received their appointment reminder or not. Finally, individuals with limited literacy benefitted from the voice calls compared with SMS, which requires reading capability.[62]

HIV-positive individuals in the intervention group were also more likely to achieve optimal ARV medication adherence. This could be attributed to two reasons. First, their regular clinic visits for medication collection encouraged adherence. As already highlighted, HIV-positive individuals are more likely to achieve medication adherence when they visit clinics regularly for their ARV pills collection.[36] Regular clinic visits ensure an adequate amount of medicines; thus, they are less likely to run out of drugs and also more likely to receive adherence support and counseling by health care providers at the health centers.[68] Second, the reminders might have increased their awareness of and priority for regular medication intake, as they received opportunities to interact with nurses, discuss issues in adherence, and explore potential solutions.

In this study, HIV-positive individuals who did not disclose their HIV status to family members were less likely to achieve medication adherence; it was despite the efficacy of the intervention. Disclosure of HIV status to family members could assist HIV-positive individuals in HIV treatment, and support them in multiple ways. This includes medication intake reminder by family members, provision of psychological, and physical support required for medication adherence. Also, disclosure makes individuals live their lives normally, but non-disclosure could increase anxiety and result in fear of stigma and discrimination by the family members. Individuals may

want to hide their treatment information such as their intake of ARV drugs and their treatment procedures, which could interrupt their medication adherence.[64]

Moreover, this study revealed high acceptability of the intervention among HIV-positive individuals in this study. I measured acceptability by assessing satisfaction with the reminders, usefulness of the intervention, disturbance owing to phone calls, and recommendation of the intervention to others. Over 90% of the individuals in the intervention group were satisfied with the intervention and reported its usefulness. Almost all individuals were willing to recommend the intervention to others.

This intervention has a high potential for scalability in LMIC. Mobile phones are commonly used in many resource-limited settings. They can be an effective medium to deliver HIV treatment adherence-related messages and assist individuals in multiple ways. Especially, mobile phone voice call functionality can be effective among populations with limited literacy. Meanwhile, cost per mobile phone call is affordable even in LMIC.[37] Mobile phone voice calls alone are considered highly cost-effective compared with SMS or a combination of calls and SMS.[37] Therefore, mobile phone-based interventions can play a pivotal role in improving HIV treatment in the UTT era.

These important findings should, however, be considered in light of several

limitations. First, study hospitals and districts were purposively selected. This was because, in Nepal, HIV-epidemic is concentrated among some high-risk groups and it is more prevalent in some regions compared to other regions. For example, Kathmandu, the capital city hosted about 20% of the total HIV-positive individuals in the country.[65] Moreover, seasonal migrants constitute the majority of HIV-positive individuals in province seven.[71] On the other hand, it is highly prevalent among people who inject drugs in province three. Therefore, it was not feasible to randomly choose the study hospitals and districts. However, participating hospitals account for more than 50% of the total HIV-positive individuals enrolled on ART throughout the country. This makes the study representative of the national scenario. Second, this study might be prone to contamination given the nature of the trial. However, it was less likely because individuals lived in scattered communities and they were not told whether they received an intervention voice call or a control voice call. Also, to avoid potential contamination this study provided health messages to control group as suggested by a systematic review.[72] Finally, the study consisted of about 90% of HIV-positive individuals who lived in urban areas. Therefore, it may not represent the rural regions.

Despite these limitations, this study has several unique strengths. First, this trial is the first to report the efficacy of a nurse-led mobile phone-based intervention

for improving the engagement of HIV-positive individuals in the context of UTT in a low-income country. Second, the randomized controlled and longitudinal design of this study provides strong causal findings. Third, the high acceptability of this intervention suggests high usability of the intervention. Phone calls are relatively cheaper in low-income countries such as Nepal, which shows that the intervention is potentially less expensive to implement in LMIC.[37] However, further cost-effective analysis is necessary including cost of salary of the nurses during the phone call.

4.2 Conclusions

In conclusion, this simple and low-intensity intervention was efficacious to improve on-time ARV pills pick up and ARV medication adherence among HIV-positive individuals on ART under UTT strategy. The intervention was also positively evaluated by HIV-positive individuals. This trial highlights the importance of scaling up mobile phone-based interventions in addition to ongoing efforts to improve the engagement of HIV-positive individuals on ART in resource-limited settings in the era of universal treatment. In this trial, improvement in on-time ARV pills pick up might represent clinically meaningful treatment outcomes for HIV-positive individuals on ART. Finally, a clinical trial is imperative with a longer follow-up, to incorporate secular trends as well as to confirm the effect of the intervention on improving viral suppression and optimizing HIV drug resistance outcomes.

4.3 Policy implications and recommendations

Findings from this study highlight scaling up of mobile phone voice call reminders to improve regular clinic attendance and adherence to antiretroviral medication in the era of UTT. Mobile phone voice call reminders and other mhealth interventions could play a pivotal role in achieving global goals related to the HIV epidemic. In low-income countries such as Nepal, similar interventions have the potential to play a critical role in realizing person-centered HIV care. Regular access and availability of mobile technologies in such countries present enormous opportunities for improving HIV care.

Additionally, continuous efforts are needed to increase HIV disclosure status among HIV-positive individuals. Such programs are direly required to improve ARV medication adherence among individuals and should be targeted among individuals who are on ART. HIV status disclosure should be integral to any ongoing efforts to improve HIV treatment outcomes in resource-limited settings.

Results of this study could be useful to support the burgeoning global mhealth and digital health movement in the context of HIV treatment and care. Also, it could contribute to achieving the ultimate global goal of ending AIDS as a public health

threat as a part of sustainable development goals. Finally, a clinical trial is imperative with a longer follow-up period (12 months or over) and larger sample size to incorporate secular as well as seasonal trends and also to confirm the efficacy of the intervention on improving treatment outcomes such as viral suppression and optimizing HIV-drug resistance indicators.

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References

1. IAPAC. What is antiretroviral therapy? International Association of Providers in AIDS Care. 2014. Available from: http://www.aidsinfonet.org/fact_sheets/view/403 [Accessed August 30, 2018].

2. Medland NA, McMahon JH, Chow EP, Elliott JH, Hoy JF, Fairley CK. The HIV care cascade: a systematic review of data sources, methodology and comparability. J Int AIDS Soc. 2015;18:20634.

3. Havlir D, Beyrer C. The beginning of the end of AIDS? N Eng J Med. 2012;367(8):685-7.

4. Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? Lancet. 2013;382(9903):1515-24.

5. UNAIDS. Data 2017. Joint United Nations Programme on AIDS. 2017. Available from: http://www.unaids.org/en/resources/documents/2017/2017_data_book [Accessed August 10, 2018].

6. Ford N, Ball A, Baggaley R, Vitoria M, Low-Beer D, Penazzato M, et al. The WHO public health approach to HIV treatment and care: looking back and looking ahead. Lancet Infect Dis. 2018;18(3):e76-e86.

7. WHO. Treat all people living with HIV, offer antiretrovirals as additional prevention choice for people at "substantial" risk. World Health Organization. 2015. Available from: http://www.who.int/mediacentre/news/releases/2015/hiv-treat-all-recommendation/en/ [Accessed October 20, 2015].

8. WHO. Consolidated guidelines on the use of ART drugs for treating and preventing HIV infection. 2013. World Health Organization. Available from: www.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf [Accessed April 6 2015].

9. UNAIDS. "15 by 15" a global target achieved. Joint United Nations Programme on AIDS. 2015. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_15by15_en.pdf

[Accessed September 21, 2015].

10. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014.

11. Mayer KH, Venkatesh KK. Antiretroviral therapy as HIV prevention: status and prospects. Am J Public Health. 2010;100(10):1867-76.

12. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Eng J Med. 2011;365(6):493-505.

13. Tomita A, Garrett N, Werner L, Burns JK, Ngcobo N, Zuma N, et al. Impact of antiretroviral therapy on health-related quality of life among South African women in the CAPRISA 002 acute infection study. AIDS Behav. 2014;18(9):1801-7.

14. UNAIDS. 90-90-90: treatment for all. Joint United Nations Programme on AIDS. 2014 .Available from: http://www.unaids.org/en/resources/909090 [Accessed August 15, 2018].

15. Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. BMJ Glob Health. 2016;1(2):e000010.

16. UN. Sustainable development goal 3 ensure healthy lives and promote well-being for all at all ages. United Nations. 2016. Available from: https://sustainabledevelopment.un.org/sdg3 [Accessed September 20, 2018].

17. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. recommendations for a public health approach. Second edition. 2016. Geneva, Switzerland, World Health Organization. 2016.

18. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014(11).

19. Mugavero MJ, Davila JA, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. AIDS Patient Care STDs. 2010;24(10):607-13.

20. WHO. Global report on early warning indicators of HIV drug resistance. World Health Organization. 2016. Available from: http://www.who.int/hiv/pub/drugresistance/ewi-hivdr-2016/en/ [Accessed May 10, 2017].

21. Do TN, Nguyen TM, Do MH, Masaya K, Dang TB, Pham TL, et al. Combining cohort analysis and monitoring of HIV early-warning indicators of drug resistance to assess antiretroviral therapy services in Vietnam. Clin Infect Dis. 2012;54 Suppl 4:S306-12.

22. Fokam J, Billong SC, Bissek AC, Kembou E, Milenge P, Abessouguie I, et al. Declining trends in early warning indicators for HIV drug resistance in Cameroon from 2008-2010: lessons and challenges for low-resource settings. BMC Public Health. 2013;13:308.

23. Jiamsakul A, Kerr SJ, Kiertiburanakul S, Azwa I, Zhang F, Chaiwarith R, et al. Early suboptimal ART adherence was associated with missed clinical visits in HIV-infected patients in Asia. AIDS Care. 2018:1-7.

24. Armstrong WS, Del Rio C. Editorial commentary: Falling through the cracks and dying: missed clinic visits and mortality among HIV-infected patients in care. Clin Infect Dis. 2014;59(10):1480-2.

25. Hontelez JAC, Chang AY, Ogbuoji O, De Vlas SJ, Bärnighausen T, Atun R. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. AIDS. 2016;30(15):2341-50.

26. AVERT. Funding for HIV and AIDS. 2018. Available from: https://www.avert.org/professionals/hiv-around-world/global-response/funding [Accessed August 10, 2018].

27. NCASC. National antiretroviral therapy guidelines. Nepal Ministry of Health/

National Center for AIDS and STD control. Kathmandu, Nepal. 2012.

28. NCASC. National consolidated guidelines for treating and preventing HIV in Nepal. Nepal Ministry of Health/ National Center for AIDS and STD Control. Kathmandu, Nepal. 2014.

29. Oo Mm, Gupta V, Aung TK, Kyaw NT, Oo HN, Kumar AM. Alarming attrition rates among HIV-infected individuals in pre-antiretroviral therapy care in Myanmar, 2011-2014. Glob Health Action. 2016;9:31280.

30. Kumarasamy N, Venkatesh KK, Devaleenol B, Poongulali S, Yephthomi T, Pradeep A, et al. Factors associated with mortality among HIV-infected patients in the era of highly active antiretroviral therapy in southern India. I J Infect Dis 2010;14(2):e127-31.

31. WHO. Assessment of world health organization HIV drug resistance early warning indicators.World Health Organization. Geneva, Switzerland. 2011. Available from: http://apps.who.int/iris/bitstream/10665/75186/1/9789241503945_eng.pdf [Accessed October 4, 2015].

32. Bennett DE, Jordan MR, Bertagnolio S, Hong SY, Ravasi G, McMahon JH, et al. HIV drug resistance early warning indicators in cohorts of individuals starting antiretroviral therapy between 2004 and 2009: World Health Organization global report from 50 countries. Clin Infect Dis. 2012;54 Suppl 4:S280-9.

33. Oyugi JH, Byakika-Tusiime J, Ragland K, Laeyendecker O, Mugerwa R, Kityo C, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. AIDS. 2007;21(8):965-71.

34. Parienti JJ, Massari V, Descamps D, Vabret A, Bouvet E, Larouze B, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis. 2004;38(9):1311-6.

35. Ayer R, Kikuchi K, Ghimire M, Shibanuma A, Pant MR, Poudel KC, et al. Clinic attendance for antiretroviral pills pick-up among HIV-positive people in Nepal: roles

of perceived family support and associated factors. PloS One. 2016;11(7):e0159382.

36. Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, et al. Clinic attendance for medication refills and medication adherence amongst an antiretroviral treatment cohort in Uganda: a prospective study. AIDS Res Treat. 2010;2010:872396.

37. Bigna JJR, Noubiap JJN, Kouanfack C, Plottel CS, Koulla-Shiro S. Effect of mobile phone reminders on follow-up medical care of children exposed to or infected with HIV in Cameroon (MORE CARE): a multicentre, single-blind, factorial, randomised controlled trial. Lancet Infect Dis. 2014;14(7):600-8.

38. US Global Leadership Coalition. The technology that's making a difference in the developing world. 2017. Available from: http://www.usglc.org/blog/the-technology-thats-making-a-difference-in-the-developing-world/ [Accessed August 15, 2018].

39. The World Bank. Mobile cellular subscriptions (per 100 people). 2016. Available from: https://data.worldbank.org/indicator/IT.CEL.SETS.P2 [Acessed August 15, 2018].

40. Jong SS, Thompson LM. Meta-analysis of mobile phone reminders on HIV patients' retention to care. J Mob Technol Med. 2017;6(1):5-18.

41. Odeny TA, Bukusi EA, Cohen CR, Yuhas K, Camlin CS, McClelland RS. Texting improves testing: a randomized trial of two-way SMS to increase postpartum prevention of mother-to-child transmission retention and infant HIV testing. AIDS. 2014;28(15):2307-12.

42. Kebaya L, Nduati R, Wamalwa D, Kariuki N, Bashir A. PO-0260a efficacy of mobile phone use on adherence to Nevirapine prophylaxis and retention in care among the HIV-exposed infants in PMTCT: a randomised controlled trial. Arch Dis Child. 2014;99(Suppl 2):A329-A.

43. Perron NJ, Dao MD, Kossovsky MP, Miserez V, Chuard C, Calmy A, et al. Reduction of missed appointments at an urban primary care clinic: a randomised controlled study. BMC Fam Pract. 2010;11:79.

44. Norton BL, Person AK, Castillo C, Pastrana C, Subramanian M, Stout JE. Barriers to using text message appointment reminders in an HIV clinic. Telemed J E Health. 2014;20(1):86-9.

45. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: a systematic review and meta-analysis. PloS One. 2018;13(9):e0204091.

46. Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, et al. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. BMJ. 2016;352:i1174.

47. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010;376(9755):1838-45.

48. WHO. Classification of digital health interventions v1.0: a shared language to describe the uses of digital technology for health. World Health Organization. Geneva, Switzerland. 2018 Available from: http://www.who.int/reproductivehealth/publications/mhealth/classification-digital-health-interventions/en/ [Accessed September 20, 2018].

49. The World Bank. Nepal: country at glance. 2015 Available from: http://www.worldbank.org/en/country/nepal [Accessed December 24, 2015].

50. Pew Research Center. Smartphone ownership and internet usage continues to climb in emerging economies. 2016. Available from: http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/ [Accessed August 15, 2018].

51. AVERT. HIV and AIDS in Asia & the Pacific regional overview. 2018. Available from: https://www.avert.org/professionals/hiv-around-world/asia-pacific/overview [Accessed August 20, 2018]

52. NCASC. Factsheet 1: HIV epidemic update of Nepal, as of December 2015. 2016. Ministry of Health/National Center for AIDS and STD Control. Available from:

http://ncasc.gov.np/index1.php?option=YnvuhyOVnuqVPWQ4vf7Jrmfb6GgaBOWesXQtjB7REWs&id=5zl0bzut2SW_PNi9Z3YU9gTGUQzcsfgbqElBIg5AYPE [Accessed May 10, 2017].

53. NCASC. National HIV/AIDS Srategy 2011-2016. Nepal Ministry of Health/National Center for AIDS and STD Control. Kathmandu, Nepal. 2011.

54. NCASC. Factsheet 6: HIV care and antiretroviral therapy services in Nepal, as of July 2016. Nepal Ministry of Health/ National Center for AIDS and STD Control. 2016. .Available from: http://ncasc.gov.np/index1.php?option=YnvuhyOVnuqVPWQ4vf7Jrmfb6GgaBOWesXQtjB7REWs&id=5zl0bzut2SW_PNi9Z3YU9gTGUQzcsfgbqElBIg5AYPE [Accessed May 10, 2017].

55. NCASC. National HIV testing and treatment guidelines. Nepal Ministry of Health/ National Center for AIDS and STD Control. 2017.Kathmandu, Nepal.

56. NCASC. Factsheet 6: Antiretroviral therapy(ART) and care services in Nepal,as of July 2014. Nepal Ministry of Health/ National Center for AIDS and STD Control. Available from: http://ncasc.gov.np/index1.php?option=e6r5wlVM8od_u8Y0CdwsDiTfg0cohLLpEcNS8hphu-0&id=tpiM0-3jQJSgbwyGzyMu6MqZg7II7SNbuuLWYvy03pI [Accessed May 10, 2017].

57. Kebaya L, Nduati R, Wamalwa D, Kariuki N, Bashir A. PO-0260a efficacy Of mobile phone use on adherence to nevirapine prophylaxis and retention in care among the HIV-exposed infants in PMTCT: a randomised controlled trial. Arch Dis Child. 2014;99(Suppl 2):A329.

58. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS. 2011;25(6):825-34.

59. Shet A, Costa AD, Kumarasamy N, Rodrigues R, Rewari BB, Ashorn P, et al. Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India. BMJ. 2014;349.

60. Hasvold PE, Wootton R. Use of telephone and SMS reminders to improve attendance at hospital appointments: a systematic review. J Telemed Telecare. 2011;17(7):358-64.

61. Rodrigues R, Poongulali S, Balaji K, Atkins S, Ashorn P, De Costa A. 'The phone reminder is important, but will others get to know about my illness?' patient perceptions of an mHealth antiretroviral treatment support intervention in the HIVIND trial in South India. BMJ Open. 2015;5(11):e007574.

62. Duggal M, Chakrapani V, Liberti L, Satyanarayna V, Varghese M, Singh P, et al. Acceptability of mobile phone-based nurse-delivered counseling intervention to improve HIV treatment adherence and self-care behaviors among HIV-positive women in India. AIDS Patient Care STDS. 2018;32(9):349-59.

63. Wasti SP, van Teijlingen E, Simkhada P, Randall J, Baxter S, Kirkpatrick P, et al. Factors influencing adherence to antiretroviral treatment in Asian developing countries: a systematic review. Trop Med Int Health. 2012;17(1):71-81.

64. Wasti SP, Simkhada P, Randall J, Freeman JV, van Teijlingen E. Factors influencing adherence to antiretroviral treatment in Nepal: a mixed-methods study. PloS One. 2012;7(5):e35547.

65. Amiya RM, Poudel KC, Poudel-Tandukar K, Pandey BD, Jimba M. Perceived family support, depression, and suicidal ideation among people living with HIV/AIDS: a cross-sectional study in the Kathmandu Valley, Nepal. PloS One. 2014;9(3):e90959.

66. Simbayi LC, Kalichman S, Strebel A, Cloete A, Henda N, Mqeketo A. Internalized stigma, discrimination, and depression among men and women living with HIV/AIDS in Cape Town, South Africa. Soc Sci Med. 2007;64(9):1823-31.

67. NCASC. National consolidated guidelines for treating and preventing HIV in Nepal. Kathmandu, Nepal. Nepal Ministry of Health/National Center for AIDS and STD Control. 2014. Kathmandu, Nepal.

68. Abdulrahman SA, Rampal L, Ibrahim F, Radhakrishnan AP, Kadir Shahar H, Othman N. Mobile phone reminders and peer counseling improve adherence and

treatment outcomes of patients on ART in Malaysia: A randomized clinical trial. PloS One. 2017;12(5):e0177698.

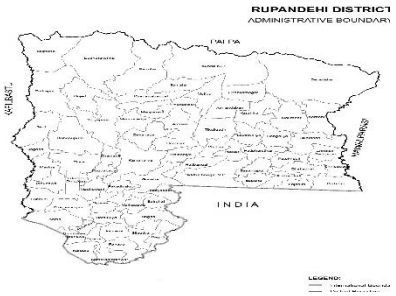
69. OpenEpi. Open source epidemiologic statistics in public health. 2013. Available from www.openepi.com/Menu/OE_Menu. [Accessed May 10, 2017].

70. Crutchfield TM, Kistler CE. Getting patients in the door: medical appointment reminder preferences. Patient Prefer Adherence. 2017;11:141-50.

71. Bam K, Thapa R, Newman MS, Bhatt LP, Bhatta SK. Sexual behavior and condom use among seasonal dalit migrant laborers to India from far-west, Nepal: a qualitative study. PLoS One. 2013. 8(9): e74903.

72. Steins Bisschop CN, Courneya KS, Velthuis MJ, Monninkhof EM, Jones LW, Friedenreich C, et al. Control group design, contamination and drop-out in exercise oncology trials: a systematic review. PloS One. 2015;10(3):e0120996.

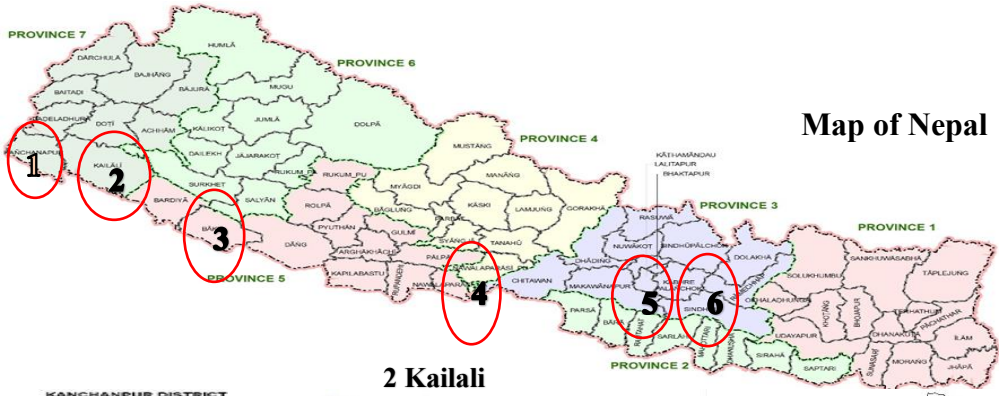
Appendix 1: Map of Nepal and study districts



4 Rupandehi

5 Kathmandu

6 Lalitpur



Map of Nepal

1 Kanchanpur

2 Kailali

3 Banke

Appendix 2: Research questionnaire (English)

Section 1: General information

No	Questions and filters	Coding categories	Skip
101	How old are you? (In completed years)	☐☐	
102	Sex	Man……..…..1 Woman…….....2 Third gender…….…...3	
103	Have you ever attended a school?	Yes……1 No…….0	**If "NO" go 104**
104	If yes, what is the highest grade you completed?	☐☐	
105	Which ethnic/caste group do you belong to?	Bhramin……..….1 Chettri ……2 Newar……..3 Janajati……4 Muslim……5 Others……(specify)	
106	Where do you presently live? (Central Bureau of Statistics Nepal definition)	Urban……...1…….. (Specify municipality name) Rural…….0……. (Specify VDC name)	
107	What is your current relationship status?	Single……...1 Married……2 Living with partner…..3 Divorced……..4 Widowed…….5 Others……(specify)	
108	What is your current occupation?	Unemployed……..1 Agriculture……..…..2 Government employee……..3 Business……4 Student……..5 Others……(specify)	
109	Do you currently own a mobile phone? If yes, could you please provide your mobile number?	Yes…….1 No……..0 _ _ _ _ _ _ _ _ _ _	
110	If yes, what type of mobile phone do you own?	Smartphone……1 Normal……...2 Others……..(specify)	
111	At what time would you like to be called?	In the morning ……..1 In the afternoon…….2 In the evening……...3 Anytime……4	
112	HIV clinical staging (Please refer to medical record)	WHO Stage 1……1 WHO Stage 2……2 WHO Stage 3……3 WHO stage 4……4	

Section 2: Internalized stigma

No	Questions and filters	Coding categories	Skip
	Internalized stigma		
201	It is difficult to tell other people about my HIV infection.	Agree……..1 Disagree……..0	
202	Being HIV positive makes me feel dirty.	Agree…….....1 Disagree……..0	
203	I feel guilty that I am HIV positive.	Agree…….....1 Disagree…….0	
204	I am ashamed that I am HIV positive	Agree…….....1 Disagree……..0	
205	I sometimes feel worthless because I am HIV positive.	Agree…….....1 Disagree……..0	
206	It is my own fault that I am HIV positive.	Agree…….....1 Disagree……..0	
207	I hide my HIV status from others	Agree…….....1 Disagree……..0	

Section 3: HIV disclosure status

No	Questions and filters	Coding categories	Skip
301	Are there people at your family you have not told you are HIV positive because you fear their reaction?	Yes……...1 No…….2	

Section 4: ARV medication adherence

NO	Questions and filters	Coding categories	Skip
401	In the month (30 days) did you miss taking your medication?	Yes……1 No……..0	
402	When was the last time you missed taking any of your medications? Check one	Within the past week……..5 1-2 weeks ago…….4 2-4 weeks ago…...……..3 1-3 months ago……...2 More than 3 months ago…….....1 Never skip medications or not applicable……...0	

Section 5: Beck Depression Inventory (BDI)

NO	Questions and filters During the past two weeks, including today, have you been feeling…	Coding categories	Skip
501	Sadness?	(0) I don't feel sad (1) I feel sad much of the time (2) I am sad all the time (3) I am so sad or unhappy that I can't stand it	

502	Pessimism?	(0) I am not discouraged about my future (1) I feel more discouraged about my future than I used to be (2) I do not expect things to work out for me (3) I feel that my future is hopeless and will only get worse	
503	Past failure?	(0) I do not feel like a failure (1) I have failed more than I should have (2) As I look back, I see a lot of failures (3) I feel I am a total failure as a person	
504	Loss of satisfaction?	(0) I am not particularly dissatisfied (1) I am often dissatisfied (2) I am usually dissatisfied with most aspects of my life (3) I am dissatisfied with every single aspect of my life	
505	Guilty feelings?	(0) I don't feel particularly guilty (1) I feel guilty over many things (2) I feel quite guilty most of the time (3) I feel guilty all of the time	
506	Punishment feelings?	(0) I don't feel I am being punished (1) I feel I may be punished (2) I expect to be punished (3) I feel I am being punished	
507	Self-dislike?	(1) I feel the same about myself as ever (2) I have lost confidence in myself (3) I am disappointed in myself (4) I dislike myself	
508	Self-criticalness?	(0) I don't criticize or blame myself more than usual (1) I am more critical of myself than I used to be (2) I criticize myself for all my faults (3) I blame myself for everything bad that happens	

509	Suicidal thoughts or wishes? (During the past 2 weeks, have you thought about ending your life?)	(0) I don't have any thoughts of killing myself (1) I have thoughts of killing myself, but I would not carry them out (2) I would like to kill myself (3) I would kill myself if I had the	
510	Crying?	(1) I don't cry any more than I used to (2) I cry more than I used to (3) I cry over every little thing (4) I feel like crying, but I can't	
511	Irritability?	(0) I am no more irritable than usual (1) I am more irritable than usual (2) I am more irritable than usual (3) I am irritable all the time	
512	Loss of interest?	(1) I have not lost interest in other (2) I am less interested in other people or things than before (3) I have lost most of my interest in other people or things (4) It's hard to get interested in anything	
513	Indecisiveness?	(1) I make decisions about as well as ever (2) I find it more difficult to make decisions than usual (3) I have much greater difficulty in making decisions than I used to (4) I have trouble making any decisions	
514	Work inhibition?	(1) I work as well as usual (2) I feel that I do not work as well as I used to (3) Work for me is very difficult I cannot do any work at all	
515	Change in sleeping pattern?	(1) I have not experienced any change in my sleeping pattern (2) I can't sleep well as well as I used to (3) I wake earlier than I used to (4) I wake very early and it's impossible to fall back asleep	
516	Body image	(1) I don't feel I look any worse than I used to (2) I am worried that I am looking worse than I used to (3) I feel that usually look unattractive	

		I feel that I am ugly or repulsive-looking	
517	Weight loss?	(0) My weight has not changed (1) I have lost about 5 kilos (2) I have lost about 10 kilos (3) I have lost more than 15 kilos	
518	Change in appetite?	(0) I have not experienced any change in my appetite (1) My appetite is somewhat less than usual (2) My appetite is much less than before (3) I have no appetite at all	
519	Somatic preoccupation?	(0) I am no more worried (1) I am more concerned about my health than I used to be (2) I am so concerned about my health that it is hard to think about anything else (3) The only thing I can think about is my health and nothing else	
520	Tiredness or fatigue?	(0) I am no more tired or fatigued than usual (1) I get tired or fatigued more easily than usual (2) I am too tired or fatigued to do a lot of the things I used to do (3) I am too tired or fatigued to do most of the things I used to do	
521	Loss of interest in sex?	(0) I have not noticed any recent change in my interest in sex (1) I am less interested in sex than I used to be (2) I am much less interested in sex now (3) I have lost interest in sex completely	

Section 6: Alcohol use

NO	Questions and filters	Coding categories	Skip
601	Do you current consume alcoholic drinks?	Yes……1 No…….2	

Section 7: Acceptability of the intervention

	Questions	Coding categories	Skip
701	How satisfied are you with the phone calls?	Very dissatisfied……..….1 Dissatisfied……...2 Neither satisfied nor dissatisfied……....3 Satisfied……4 Very satisfied……5	
702	Was the phone reminder useful to you?	No…….....0 Yes…….....1	
703	Will you recommend this phone reminder to other people?	No…….....…...0 Yes……..……1	
704	Were you disturbed by the mobile phone reminder?	No…….....0 Yes……1	
705	If yes, reasons for disturbance.	Annoyed……...1 Fear of disclosure…….2 Others…… (Specify)	

Section 8 : Clinic attendance for ARV pills pick up

SN	Scheduled day (Day/Month/Year)	Outcome of scheduled day "Adhered" or "Missed"	Remarks

I) Date of HIV diagnosis ……

II) Date of linkage to HIV care ……..

III) Date of ART start……

IV) Last date of follow up: ……

V) Client status

- Missing Yes…….1 No……..2
  - If yes, date of missing DD/MM/YY ……

- ✓ Active on ART Yes……..1 No……..2

VI) WHO clinical staging:

WHO stage I ……..1

WHO stage II ……..2

WHO stage III ……..3

WHO stage IV ……..4

VII) Current ART regimen : ……

Appendix 3: Research questionnaire (in Nepali)

	भाग 1: सहभागीको पृष्ठभुमिका बिशेषताहरु			
सं	**बिशेषताहरु**		**कोडिंग वर्गहरु**	**जानुहोस्**
101	तपाई कति बर्ष को हुनुभयो ? (पुरा भएको वर्ष लेख्नुहोस्)	☐☐		
102	लिंग	पुरुष.....1 महिला.....2 तेस्रोलिंगी.....3		
103	तपाइ कहीले विद्यालय जानु भएको थियो ?	थियो .....1 थिएन.....2		
104	यदि जानुभएको थियो भने तपाइले हासील गरेको उच्चतम शिक्षा कति हो?	☐☐		
105	तपाई कुन जातको मान्छे हो?	ब्राह्मण.....1 छेत्रि.....2 बौद्ध धर्म.....3 नेवार.....4 जनजाती.....5 मुस्लिम.....6 अन्य..... (खुलाउनु होस्)		
106	तपाई अहिले कहाँ बस्नुहुन्छ ?	जिल्ला..... नगरपालिका.....1 गाविस.....0		
107	तपाइको अहिलेको बैबाहिक स्थिति के हो ?	एक्लो (अबिबाहित).....1 बिबाहित.....2 पार्टनरसंग बसेको.....3 सम्बन्ध बिच्छेद भएको.....4 एकल.....5 अन्य..... (खुलौनुहोस्)		
108	तपाईको हालको ब्यबसाय के हो?	बेरोजगार.....1 कृषि.....2 सरकारी जागिरे.....3 व्यापार/ब्यबसाय.....4 बिद्यार्थी.....5 अन्य..... (खुलाउनुहोस्)		
109	के तपाईसंग मोबाइल फोन छ ? यदी तपाईसंग मोबाइल फोन छ भने तपाइको नम्बर कती हो ?	छ.....1 छैन.....2 _____		
110	यदी तपाईसंग मोबाइल फोन छ भने तपाइको फोन कस्तो प्रकारको हो?	स्मार्ट फोन.....1 साधारण फोन.....2 अन्य..... (खुलाउनुहोस्)		

111	यदि तपाई फोन कल सेवा लिन इचुक्क हुनुहुन्छ भने तपाइलाई कुन समयमा कल गर्दा राम्रो हुन्छ?	विहान.....1 समय ( ) दीउसो.....2 समय ( ) बेलुकी.....3 समय ( ) जुनसुकै बेला पन.....		
112	HIV clinical staging (कृपया मेडिकल रेकोर्डमा हेर्नुहोस्)	WHO stage 1.....1 WHO stage 2.....2 WHO stage 3.....3 WHO stage 4.....4		

	भाग 2: Internalized stigma **(तलका प्रश्नहरुमा तपाई सहमत वा असहमत के हुनुहुन्छ बताईदिनु होस्।)**		
सं	**बिशेषताहरु**	**कोडिंग वर्गहरु**	**जानुहोस्**
201	अरु मानिसलाई आफु HIV संक्रमित भएको कुरा भन्न गाह्रो हुन्छ ।	सहमत .....1 असहमत.....0	
202	म HIV संक्रमित भएको कारणले आफु अपवित्र भएको महसुस हुन्छ ।	सहमत .....1 असहमत.....0	
203	मलाई HIV संक्रमित भएकोमा पश्चाताप महसुस हुन्छ ।	सहमत .....1 असहमत.....0	
204	HIV संक्रमित भएको कारणले म लज्जीत छु ।	सहमत .....1 असहमत.....0	
205	म HIV संक्रमित भएको कारण कहिलेकाही मेरो कुनै मूल्य छैन जस्तो महसुस हुन्छ।	सहमत.....1 असहमत.....0	
206	आफ्नो गल्तीको कारणले म HIV संक्रमित भए ।	सहमत .....1 असहमत.....0	
207	म HIV संक्रमित भएको कुरा अरु संग लुकाउछु ।	सहमत .....1 असहमत.....0	

	भाग 3: HIV disclosure status	**कोडिंग वर्गहरु**	**जानुहोस्**
301	के तपाइले आफ्नो घरका कुनै सदश्यहरुलाई उहाहरुको प्रतिक्रियाको डरले आफ्नो HIVको अवस्थाबारे भन्नुभएको छैन?	हो.....1 होइन.....0	

	भाग 4: एन्टी रेट्रोभाइरल थेरापीको प्रयोग	**कोडिंग वर्गहरु**	**जानुहोस्**
401	गएको महिना मा (30 दिन तपाईं ले विभिन्न कारण ले पिल्स हरु सेबन गर्न छुटाउनुभएको थियो ?	हो.....1 होइन.....0	
402	तपाईं ले अन्तिम पटक कहिले औषधि सेवन गर्न छुटाउनुभएको थियो ?	कहिल्यै छुटाइन.....1 ३ महिना भन्दा पहिले.....2 १ देखि ३ महिना भन्दा पहिले.....3 २ देखि ४ हप्ता पहिले.....4 १ देखि २ हप्ता पहिले.....5	

	भाग 5: Beck Depression Inventory (BDI)	
	तलका लक्षणहरुले तपाइलाई गएको २ हप्तामा कत्तीको पिरोल्यो सोचेर जबाफ दिनु होला।	
501	गएको दुई हप्तामा तपाई कत्तीको उदास हुनुहुन्थियो?	(1) कहिल्यै भईन (2) प्राय भए (3) सधै जसो भए (4) असह्य भएको थियो
502	गएको दुई हप्तामा तपाई कत्तीको निराश हुनु भयो? जस्तै) आफ्नो भविष्यको बारेमा सम्झेर(	(1) कहिल्यै भईन (2) प्राय भए (3) सधै जसो भए (4) असह्य भएको थियो
503	गएको दुई हप्तामा तपाईलाई आफ्नो जीवनमा कत्तीको असफल भएजस्तो लग्यो?	(1) कहिल्यै लागेन (2) प्राय लग्यो (3) सधै जसो लग्यो (4) पूर्णरुपले असफल भए जस्तो लग्यो
504	गएको दुई हप्तामा तपाई आफ्नो जीवनदेखि कत्तिको असन्तुष्ट हुनुभयो?	(1) कहिल्यै भईन (2) प्राय भए (3) सधै जसो भए (4) जीवनको हरेक कुरामा असन्तुष्ट भए
505	गएको दुई हप्तामा तपाईले आफ्नो जिन्दगिको लागि आफुलाई कत्तिको दोषी ठान्नुभयो?	(1) कहिल्यै ठानिन (2) प्राय ठाने (3) सधै जसो ठाने (4) जीवनको हरेक कुरामा दोषी ठाने
506	गएको दुई हप्तामा तपाईले आफ्नो जिन्दगिमा कत्तिको दुख या सास्ती भोग्नु भयो?	(1) कहिल्यै भोगिन (2) प्राय भोगे (3) सधै जसो भोगे (4) जीवनको हरेक कुरामा सास्ती भोगे
507	गएको दुई हप्तामा तपाईलाई, आफुदेखि आफुलाई कत्तिको वाक्क लग्यो?	(1) कहिल्यै लागेन (2) धेरैजसो लग्यो (3) सधै लग्यो (4) आफुलाई नै घृणा लग्यो
508	गएको दुई हप्तामा तपाई आफ्नो गल्तीहरु प्रति कत्तिको जिम्मेवार हुनुभयो?	(1) जिम्मेवार भईन (2) गल्ती र कमजोरीको लागि जवाफदेही भए (3) कमजोरीहरुको निन्दा गरेको थिए (4) हरेक नरामा कुराप्रति जिम्मेवार भए
509	गएको दुई हप्तामा तपाईले आफुलाई कत्तिको हानी पुर्याउन चाहनु भयो?	(1) आफुलाई कुनै पनि हानी पुराउन चाहिन (2) हानी पुराउन चाहे तर केहि गर्न सकिन (3) म आफुलाई नै मार्न चाहन्थे (4) मैले मौका पाएको भए आत्महत्या गर्थे
510	गएको दुई हप्तामा कत्तिको रुनु भयो?	(1) पहिले भन्दा बडी रोईन (2) पहिले भन्दा बडी रोए (3) हप्तै भरी रोए (4) चाहेर पनि रुन सकिन

511	गएको दुई हप्तामा तपाईलाई कत्तिको झर्को लग्यो?	(1) कहिले लागेन (2) प्राय लग्यो (3) सधै जसो लग्यो (4) असहय भएको थियो
512	गएको दुई हप्तामा तपाईलाई अरुसंग कत्तिको हासखेल गर्न मन लग्यो?	(1) हासखेल गर्न मन लग्यो (2) पहिले जस्तो गर्न मन लाग्दैन (3) अरुप्रति मेरो इच्छा हराएर गयो (4) कसैको कुनै वास्ता राक्न मन लागेन
513	गएको दुई हप्तामा तपाईले आफ्नो जीवनमा कत्तिको निर्णय लिन सक्नुभयो?	(1) सके (2) पहिले जस्तै सकिन (3) निकै गाह्रो भयो (4) कुनै पनि निर्णय लिन सकिन
514	गएको दुई हप्तामा तपाईलाई तपाई आफु कत्तिको राम्रो भए जस्तो लग्यो?	(1) पहिले भन्दा नराम्रो भइन (2) म नराम्रो हुदै गैरहेको जस्तो लग्यो (3) म सधै नराम्रो नै भैरहे (4) म कुरूप वा घिन लाग्दो देखिएको थिए
515	गएको दुई हप्तामा तपाईले कत्तिको काम गर्न सक्नुभयो?	(1) पहिले जत्तिको सके (2) पहिले जत्तिको सकिन (3) एकदम गाह्रो भयो (4) केहिपनि काम गर्न सकिन
516	गएको दुई हप्तामा तपाई कत्तिको सुत्नु भयो?	(1) पहिले जत्तिकै सुते (2) पहिले जस्तो सकिन (3) पहिले भन्दा अगाडी बिउझंथे र निदाउन सकिन (4) एकदमै चाडै बिउझंथे र निदाइन
517	गएको दुई हप्तामा तपाई कत्तिको थाक्नु भयो?	(1) थाकिन (2) पहिले जस्तो थाकिन (3) जे गर्दा पनि थाक्दथे (4) एकदमै थाकेर केहि पनि गर्न सकिन
518	गएको दुई हप्तामा तपाई खाना कत्तिको रुचीभयो?	(1) पहिले जत्तिकै रुची भयो (2) पहिले जति रुची भएन (3) एकदमै कम रुची भयो (4) पटक्कै रुची भएन
519	गएको दुई हप्तामा तपाईको तौल कत्तिको घटेको थियो?	(1) घटेको थिएन (2) ५ के जी भन्दा बडी घट्यो (3) १० के जी भन्दा बडी घट्यो (4) १५ के जी भन्दा बडी घट्यो
520	गएको दुई हप्तामा तपाईलाई आफ्नो स्वास्थको चिन्ता कत्तिको लग्यो?	(1) पहिला भन्दा बडी चिन्ता लागेन (2) ढुखाई र पीडाले गर्दा चिन्तित थिए (3) स्वास्थको कारणले गर्दा अरु केहि सोच्न सकिन (4) स्वास्थको कारणले केहि होश नै भएन
521	गएको दुई हप्तामा तपाईले आफ्नो जीवन साथीको बारेमा कत्तिको सोच्नु भयो?	(1) पहिला जत्तिकै सोचे (2) पहिला जत्तिकै सोचीन (3) त्यति वास्ता नै भएन

		(4) वास्ता नै भएन

	भाग 6: Alcohol use	कोडिंग वर्गहरु	जानुहोस्
601	के तपाई आजभोलि मदिरा सेवन गर्नु हुन्छ ?	हो.....1 होइन.....0	

	भाग 7: Acceptability of the intervention		
	प्रश्नहरु	कोड बर्गहरु	जानुहोस्
701	तपाइले प्राप्त गरेको मोवाइल फोन कल सेवा प्रति कत्तिको सन्तुस्ट हुनुहुन्छ?	धेरै असन्तुस्ट.....1 असन्तुस्ट.....2 न सन्तुस्ट न असन्तुस्ट.....3 सन्तुस्ट.....4 धेरै असन्तुस्ट.....5	
702	के फोन सेवा तपाइलाई उपयोगी लग्यो?	लग्यो .....1 लागेन 0	
703	के तपाई यो फोन सेवा अरुलाई पनि प्रयोग गर्नु भन्नु हुन्छ?	भन्छु .....1 भन्दिन.....0	
704	के तपाइलाई फोन सेवाले कुनै बाधा पुर्याएको थियो?	थिएन.....0 थियो 1	
705	यदि बाधा पुर्याएको थियो भने कस्तो बाधा पुर्याएको थियो?	झर्को लागेको थियो .....1 मेरो HIV को बारेमा अरुलाई थाहा हुन्छ भन्ने डर लागेको थियो .....2 अन्य ..... (खुलाउनुहोस्)	

भाग 8: Clinic attendance for ARV pills pick up

Use treatment and care register to assess the following information.

NO	Scheduled day (Day/Month/Year)	Outcome of scheduled day "Adhered" or "Missed"	Remarks

१. HIV पत्ता लागेको मिती:

२. ART सुरु गरेको मितीः

३. HIV भएको समयः .....(महिना, वर्ष)

४. अहिलेको ART केन्द्रमा भर्ना हुदाको उमेर (महिना, वर्ष): .....

५. HIV staging at diagnosis of HIV :

क . WHO स्टेज 4

ख WHO .स्टेज 3

ग WHO .स्टेज 2

घ WHO .स्टेज 1

अन्य .....

६. Treatment regimen currently in

a. 1st line regimen
b. Substituted 1st line regimen
c. 2nd line regimen
d. Others.....(Specify

७. Regimen name :.....

********** End of questionnaire**********

Appendix 4: Information sheet (in English)

For participants

Introduction:

This study is conducted by the Department of Community and Global Health, Graduate School of Medicine, The University of Tokyo, Japan. The principal investigators are Rakesh Ayer and Professor Masamine Jimba. This is the part of the larger study which will be conducted from October, 2017 to June, 2018.

This document explains the details of the study mentioned above. We humbly request for your voluntary participation in this study. Therefore, please read this information sheet so that you are fully aware of the research process. If you have any questions regarding this study, please feel free to ask the persons listed below.

Objective of the study:

The objective of our study is to evaluate the effectiveness of the mobile phone reminder intervention to improve clinic attendance for antiretroviral pills pick up.

Research Procedure:

If you decide for the participation in this study, you will first take part in face to face interview which will take about 30-45 minutes and then you will be enrolled in the main study. In the questionnaire, you will be requested to answer the questions about your socio-demographic characteristics, mental health, and medication adherence. In the main study you will receive phone calls monthly for the period of 6 months. We will randomly select you to either receive one or the other type of phone calls. We assure you the confidentiality of all the information you give.

Possible risks and benefits:

Some of the questions that we ask might make you uncomfortable. However, the information you provide us will be helpful to improve HIV care in Nepal and other developing countries. You are free to skip such questions or also withdraw the participation from the study before the submission of the completed questionnaire. We will provide a pen to you for your participation.

Confidentiality:

All the information collected during the study will remain confidential. Your name will not be recorded, and it will not be included in any of the reports we make or publish out

of this study. Only the code numbers will be used in the questionnaire. The questionnaire will be kept securely by the concerned researchers and discarded using shredder after 5 years i.e. by August 2022.

Withdrawal from participation:

We assure your participation in this study is entirely voluntary. It is guaranteed that you have rights to withdraw from the study before the submission of the completed questionnaire without any consequences. If you wish, you also have the right to withdraw from receiving phone calls under this study.

Voluntary agreement:

If you understand what this study involves and agree to participate, you can join this study as a participant. If you do not agree to participate, you are free to do so and you do not need to give any information and you do not need to put your signature at any places.

Please sign on the attached informed consent sheet for if you would like to participate in the study. Thank you for your kind cooperation and participation.

Appendix 5: Information sheet (in Nepali)

अनुसन्धानको शिर्षक: "नेपालमा मोवाईल फोन कल कार्यक्रम मार्फत औषधी लिन आउने HIV संक्रमितहरुको नियमीत क्लिनिक उपस्थितिमा सुधार"

प्रमुख सोधकर्ताहरु : राकेश ऐर (टोक्यो विश्वविधालय, जापान); माशामीने जिम्बा (टोक्यो विश्वविधालय, जापान)

महिला तथा सज्जन ब्रिन्द,

यस अध्ययनमा तपाईंको सहभागिताको लागि धेरै धेरै धन्यवाद। यस अध्ययनको उद्देश्य नेपालमा एन्टिरेटोभिरल औसधि लिनका लागि क्लिनिक उपस्थिति सुधार गर्न मोबाइल फोन रिमाइन्डरको प्रभावकारिता निर्धारण गर्ने हो।

हामी यस अध्ययनमा संरचित प्रश्नावली प्रयोग गरेर सहभागीहरूलाई प्रस्न गर्न चाहन्छौं। हामी सहभागीहरूको नाम सोध्दैनौं। त्यसैले सहभागीहरूको पहिचानको खुलासा हुनेछैन।

यदि तपाईं यस अध्ययनको उद्देश्यसँग सहमत हुनुहुन्छ र अध्ययनमा भाग लिन चाहानुहुन्छ भने, तपाइँलाई तपाइँको औषधिको सेवन, मानसिक स्वास्थ्य र सामाजिक आर्थिक जानकारीका-बारेमाप्रश्नहरू सोधिनेछ।

यो कार्यलाई टोक्यो विश्वबिधालयको रिसर्च ऐथिक्स् कमिटी र नेपाल स्वास्थ अनुसन्धान परिषदले अनुमति दिएको छ । यस अध्ययनको लागि अनुदान एशियालि विकास बैंक जापान छात्रवृत्ति-कार्यक्रम द्वारा प्रदान गरिएको छ।

यस अध्ययनको लागि तपाईंको सहभागिता पूर्णतया स्वैच्छिक हो र तपाईले कुनै पनि प्रश्नको उत्तर दिन अस्विकार गर्न सक्नुहुनेछ। तपाईलाई यो कार्यबाट आफ्नो सहभागिता फिर्ता लिने

पूर्ण अधिकार छ। सहभागिता फिर्ता लिनका लागि तपाईंले "शोध फारम को त्याग" हस्ताक्षर गर्न भने पर्छ।

तपाइ आफ्नो गोपनियता बारे निर्धक्क भए हुन्छ। तपाईंको जवाफ अन्य एचआईभी सकारात्मक-व्यक्तिकासाथ राखिने भएकाले **गोपनियता** सुनिश्चित हुन्छ। हामीले प्राप्त गरेका सबै जानकारी सख्त गोपनीय रहनेछ र तपाईंको जवाफ कहिल्यै चिन्न सकिने छैन। यहाँ कुनै गलत वा सही जवाफ छैन। तपाईंको खुलापन र ईमानदारिता अत्यन्त महत्त्वपूर्ण छन्। यद्यपि, तपाईंले जवाफ दिन नचाहेका प्रश्न छोड्न सक्नुहुन्छ ।

तपाइको केहि प्रश्नहरु छन् भने तल दिएको व्यक्ति र ठेगानामा सम्पर्क गर्न सक्नुहुन्छ;

श्री राकेश ऐर र प्राध्यापक माशामाने जिम्बा

समुदाय तथा बिश्व स्वास्थ भीभाग, टोक्यो विश्वबिधालय, ७१-३-, होंगो, बुन्क्योकु-, टोक्यो ११३-००३३

Appendix 6: Ethical approval from the University of Tokyo

Graduate School of Medicine and Faculty of Medicine
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Ethics Committee

Date: 19 October, 2017

Serial Number: 11711

Title of research: Improving clinic attendance for antiretroviral pills pick up among HIV positive individuals in Nepal through a mobile phone reminder intervention: a randomized controlled trial

Name of applicant: Masamine Jimba, Professor, Department of Community and Global Health, Graduate school of Medicine, The University of Tokyo

This is to certify that a plan for the research project identified above was reviewed, and was approved by the Ethics Committee on October 2nd, 2017.

THE UNIVERSITY OF TOKYO

Kohei Miyazono, Dean
Graduate School of Medicine and
Faculty of Medicine
The University of Tokyo

KM/ya

東京大学
THE UNIVERSITY OF TOKYO

Appendix 7: Ethical approval from Nepal Health Research Council

Government of Nepal

Nepal Health Research Council (NHRC)

Ref. No.: 761

12 October 2017

Mr. Rakesh Ayer
Principal Investigator
University of Tokyo, Japan

Ref: **Approval of thesis proposal** entitled **Improving Clinic Attendance for Antiretroviral Pills Pick up Among HIV Positive Individuals in Nepal through a Mobile Phone Reminder Intervention: A Randomized Controlled Trial**

Dear Mr. Ayer,

It is my pleasure to inform you that the above-mentioned proposal submitted on **26 August 2017** (**Reg. no. 337/2017** please use this Reg. No. during further correspondence) has been approved by Nepal Health Research Council (NHRC) Ethical review board on **11 October 2017**.

As per NHRC rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol. Expiration date of this proposal is **April 2018.**

If the researcher requires transfer of the bio samples to other countries, the investigator should apply to the NHRC for the permission. The researchers will not be allowed to ship any raw/crude human biomaterial outside the country; only extracted and amplified samples can be taken to labs outside of Nepal for further study, as per the protocol submitted and approved by the NHRC. The remaining samples of the lab should be destroyed as per standard operating procedure, the process documented, and the NHRC informed.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of their project proposal and **submit progress report in between and full or summary report upon completion.**

As per your thesis proposal, the total research amount is **NRs. 8, 00,000.00** and accordingly the processing fee amounts to **NRs 10,000.00**. It is acknowledged that the above-mentioned processing fee has been received at NHRC.

If you have any questions, please contact the Ethical Review M & E Section at NHRC.

Thanking you,

Prof. Dr. Anjani Kumar Jha
Executive Chairman

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