論文の内容の要旨

論文題目　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）

氏名 ラケシュ アエアル
Rakesh Ayer

Abstract

Background

Antiretroviral therapy is considered one of the most effective interventions to treat HIV infection and improve the health and well-being of HIV-positive individuals. To accelerate its benefits globally, countries have implemented universal test and treat (UTT) strategy to improve HIV treatment. On-time antiretroviral pills pick up is key to successful HIV treatment and a high number of individuals especially in the resource-limited settings do not pick up their pills on-time. Several consequences are reported owing to inconsistent antiretroviral pills pick up, such as HIV-drug resistance, treatment failure, and higher mortality. Individual level barriers to on-time pills pick up include forgetfulness, mental health problems, lack of HIV treatment literacy, and self-rated better health status. On-time antiretroviral pills pick up has also been associated with medication adherence among the HIV-positive individuals. Several responses have been reported to enhance on-time antiretroviral pills pick up, but they have not been scaled up in many resource limited settings because of their high cost and involvement of multiple stakeholders to implement them. Efficacy of the interventions to improve on-time pills pick up barely remains unknown and studies are lacking on evaluation of such interventions using randomized trial design. Mobile phone-based interventions, however are promising, particularly in resource - limited settings where the use of mobile phone technologies has skyrocketed. Additionally, mobile phone-based interventions are simple to execute and cost-effective even in low- and middle-income countries. Therefore, I designed this randomized controlled trial to achieve two objectives. First, to investigate the efficacy of the nurse-led mobile phone-based intervention on improving clinic attendance for on-time antiretroviral pills pick up in a low-income country Nepal. Second, to investigate the efficacy of the nurse-led mobile phone call reminder to enhance medication adherence among HIV-positive individuals in Nepal.

Methods

I conducted this randomized controlled trial in Nepal. I recruited HIV-positive individuals from seven hospitals representing six districts in Nepal. They were eligible to participate if they were on antiretroviral therapy under UTT; aged 18 years or older; owned a mobile phone and were under the first line antiretroviral

therapy regimen. Individuals were randomly assigned (1:1) to the nurse-led mobile phone voice call reminder intervention (clinic appointment for antiretroviral pills pick up) or the voice call for health promotion messaging control condition. Randomization was done by a computer random number generator using blocked randomization (block size=4). Outcome assessors were masked to the allocation group. I assessed the primary outcome using the World Health Organisation's definition of on-time antiretroviral pills pick up (regular clinic attendance [100% on-time pills pick up], inconsistent clinic attendance [missing one or more on-time pills pick up] at the six-month follow-up assessment.

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. 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. In both intervention and control groups, HIV-positive individuals received the standard HIV care under the national HIV treatment guidelines.

Intervention group

In the intervention group of this study, HIV-positive individuals received nurse-led mobile phone voice call reminders, which were made two days prior to their scheduled date for ARV pills pick up. 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 the period of six months expect on Saturdays or national holidays.

Control group

In the control group, the nurse delivered health promoting messages. The nurse called individuals once a month irrespective of their scheduled date for ARV pills pick up for the period of six months.

Based on a previous study in Nepal, I assumed 33% regular clinic attendance for on-time ARV pills pick up. If the intervention increased the on-time ARV pills pick up from 33% to 48%, then about 370 HIV-positive individuals, 185 in the intervention and 185 in the 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 Open Epi, an online platform to calculate the sample size.

This study adhered all the ethical considerations as outlined in the guideline by Council for International Organizations of Medical Sciences in collaboration with WHO, international ethical guidelines for

health-related research involving humans in resource limited settings, involving vulnerable population, and community engagement.

The research protocol of this study was approved by the Research Ethics Committees of the Graduate School of Medicine at the University of Tokyo and Nepal Health Research Council in Nepal. 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. 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. Participants' anonymity was maintained throughout the study and their right to privacy was given utmost consideration.

I performed the primary analysis by intention-to-treat principle. I evaluated the efficacy of the trial by Generalised Estimating Equation models to determine intervention x time interactions (differences between intervention groups from baseline to six-month follow-up assessment) for the primary outcome. This trial is registered with the Clinicaltrials.gov, number NCT03367130; the trial has been completed.

Results

An independent researcher randomly assigned 468 HIV-positive individuals to the intervention group (n=234) or the health promotion messaging group (n=234). Of these, 23 participants were transferred to other health facilities, eight did not continue with intervention, seven participants died and five participants could not be contacted. 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 group 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 intervention group compared to 73.9% in 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. 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. ARV medication adherence was slightly higher among individuals in the control group compared to intervention group (86.3% vs 82.1%). At baseline, 141 (60%) attended their clinics regularly for pills pick up in the intervention group compared to 144 (62%) in the control group. At the six-month follow-up assessment, 151 (71%) attended their clinics regularly for pills pick up in the intervention group compared to 117 (56%) in the control group. After adjusting for covariates, participants in the intervention group were significantly more likely to attend their clinics regularly for antiretroviral pills pick up compared to the control group (intervention x time; adjusted odds ratio 2.02, 95% CI 1.15 to 3.55). Similarly, at baseline, 192 (82%) were adherent to their medication compared to 202 (86%) in the intervention and control groups, respectively. At the six-month follow-up assessment, 195 (91%) attained medication adherence compared to 177 (84%) in the intervention and control

groups, respectively. After adjusting for covariates, HIV-positive individuals in the intervention group were significantly more likely to achieve ARV medication adherence compared to the control group (intervention x time; adjusted odds ratio 2.51, 95% CI 1.12 to 5.59). No adverse events related to study participation were reported.

Conclusions

This nurse-led mobile phone voice call reminder intervention can be efficacious to improve on-time antiretroviral pills pick up and ARV medication adherence in resource-limited settings. Future research in low-and-middle-income countries should focus on the longer-term efficacy of the mobile phone-based intervention on improving viral suppression and optimizing HIV drug resistance outcomes.