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Do Short Message Reminders Improve ART Adherence? Randomized Control Trial among HIV Clients - Kadoma (Zimbabwe) - KAMP Study Protocol

Article by D. Chirundu[1], S. Tapesana[2], P.N. Magande[3], G. Madzingaidzo[4], T. Mduluza[5]
[1, 4] *Health Dept, Kadoma*
[2, 3] *Dept. of Community Medicine, University of Zimbabwe, Zimbabwe*
[5] *Dept. of Biochemistry, University of Zimbabwe, Zimbabwe*
E-mail: [1]dchirundu@me.com, [2]drstanelytaps@gmail.com, [3] pmagande@gmail.com, [4]geshemma08@gmail.com, [5]tmduluza@medic.ac.zw

Abstract

Background: Adherence to antiretroviral therapy among clients seeking care at Kadoma City Integrated TB and HIV Care Site has been documented to be 86% as opposed to the expected adherence of 95%. The Zimbabwe 2015 survey for Early Warning Indicators for HIV drug resistance identified Kadoma as a hotspot. Low level adherence to antiretroviral therapy is associated with poor clinical outcomes. We set out to evaluate the efficacy of cell phone –supported short message reminders compared to standard care on adherence among clients receiving antiretroviral therapy at Kadoma, Zimbabwe.

Methods: The study design is a randomized controlled trial. Patients on ART at Rimuka Integrated TB and HIV Care Site will be randomized to receive either a structured weekly text message in addition to standard care (the intervention) or standard care support alone (the control). Respondents will be evaluated at baseline, six months and 12 months after recruitment into the study. Primary outcomes are self-reported adherence to ART and CD4 cell counts at twelve months scheduled follow-up. Secondary outcomes will be opportunistic infections, weight, body mass index (BMI) and retention on ART. Primary analysis will be by 'intention-to-treat'.

Discussion: The mHealth concept could be an innovative method in prompting adherence to anti-retroviral therapy in poor resource settings. The trial will evaluate the efficacy of a weekly personalized SMS reminder on adherence among clients on ART at Rimuka Integrated Tuberculosis and HIV clinic Kadoma, Zimbabwe.

Keywords: *Adherence, ART, HIV, Kadoma, SMS, RCT*

Introduction

Human immunodeficiency virus (HIV) continues to be a global public health problem, having claimed more than 39 million lives so far[1]. There were approximately 36.7 million people living with HIV at the end of 2015, with 2.1 million people becoming newly infected with HIV globally. Sub-Saharan Africa is the most affected region, with 25.5 million people living with HIV in 2015. More so, sub-Saharan Africa also accounts for almost 70% of the global total of new HIV infections.[2]

Antiretroviral (ARV) medications are long-term treatments whose aim is to drive viral load below the current detection limit. Viral suppression in turn reduces immune suppression and slows disease progression. Improvements in access to effective ART has resulted in the clinical and public health benefits; shown by the greatly reduced number of HIV infected people progressing to AIDs and reduced hospital occupancy rates. The age adjusted death rates from HIV/AIDS has drastically declined more than 70% since the wide accessibility of ART.[3, 4, 5]

Compliance to ART is critical to the survival of HIV infected people. However, successful antiretroviral treatment is reliant on sustaining high rates of adherence. The optimal level of

adherence required for anti- retroviral (ARVs) medication to work effectively is 95%.[6, 7] This level of adherence demands taking the correct dose of drugs at the right time, and observing any dietary restrictions. Anything less than this level of adherence leads to viral resistance and ultimately treatment failure.

Whilst adherence to ART has emerged as a major determinant of the success of antiretroviral therapy, other determinants of antiretroviral therapy outcomes have been documented.[8]Genetic differences in drug metabolism, severe baseline immune suppression, prior drug resistance and concurrent opportunistic infections have been shown to determine the clinical outcomes of antiretroviral therapy.[16]Among the determinants of clinical outcomes, adherence to ART is one of the few modifiable factors determining outcomes for patients on ART. [9, 10, 11]

A number of *m*Health interventions have been tested in Africa and beyond as a behavioral intervention to improve adherence. In a parallel RCT study in Cameroon 2007,adults 21 years and older clients received weekly standardized motivational text message versus normal care.[12]The primary outcome was adherence measured as per visual analogue scale (VAS), number of missed doses a week preceding the interview and pharmacy refill data. The follow up period in this study was six months. The study did not demonstrate a significant difference in adherence by VAS and reported missed doses on comparing the intervention and non-intervention groups. It was concluded that standard motivational mobile phone message did not improve adherence. Whist the duration of the study could have been an issue other researchers have reported positive results with fewer respondents.

Two clinical trials in Kenya have evaluated the benefits of using phone text message reminders to improve adherence. The Weltel trial (2009) was a multisite parallel arm RCT that compared SMS and standard care among ART clinic attendees.[13] Weekly SMSs that were supposed to be responded to in 48hrs were send to 273 respondents each in the intervention and non-intervention arm. The intervention group had more than 95% adherence compared to 50% in the non-intervention group. This study showed that those who received SMS had improved ART adherence and rate of viral suppression compared to controls.

In a factorial design randomized control trial in Kenya 2011. Cristian Pop-Eleches *et. al*. evaluated the efficacy of SMS reminders against standard care.[14]In this study, 70 received short messages daily, 72 received long messages daily, 73 received short messages weekly and 74 long messages weekly. It is reported that weekly SMS reminders increased the participant's adherences by 13%-16% thereby achieving a 90% overall adherence compared to those who did not receive reminders. Pop Eleches *et. al.* concluded that SMS reminders may be an important tool to achieve optimal adherence to antiretroviral therapy in resource limited settings. The findings by Pop Eleches *et. al.* were consistent with Maduka *et.al.* (2012) in Nigeria who found an increased adherence among participants who received SMS reminders compared to the non-interventional group.

There are still many gaps and the quality of some of the trials leaves a lot to be desired. The proposed study will test the efficacy of SMS in an urban setting in Zimbabwe and this is the first time such a study will be done in the country. The results of the study will be used primarily by HIV/AIDS control programs to improve adherence. This will, in turn, have an effect on virological failures, clinical outcomes and ultimately health related quality of life of the infected. The objective of the study is to investigate the efficacy of cell phone short message reminders on adherence to anti-retroviral therapy among clients seeking HIV care at Rimuka Integrated HIV/TB clinic.

Methodology

Description of study site

Rimuka Integrated HIV and TB Clinic is the trial setting. This is a primary health care center at Kadoma (Zimbabwe). The center provides HIV and TB collaborative services. It was established in 2012. In terms of HIV workloads in the City, Rimuka has the highest workload of 7300 clients compared to 2600 managed at Kadoma general hospital a

government referral center. The catchment area for Rimuka Integrated HIV and TB center is primarily Rimuka high density suburb with a population of 52000.

Study design

A randomized controlled trial will be conducted to investigate the efficacy of weekly short message service (SMS)reminders on improving adherence to ART. In the intervention group, participants will receive a weekly SMS reminder for the duration of the trial. This will be in addition to the usual care offered to clients. The SMS will comprise of a different motivational message each week. Those randomized into the non-intervention group will receive usual HIV care as prescribed by the Zimbabwe ART guidelines. This comprises of CD4+ cell counts, adherence classes and follow up.[16]

Randomization

The generation and sequential numbering of the sampling frame will be done by a data capture clerk. Generation of the random numbers will be done by a health information officer. The centre manager will compile a list of the respondents using the randomly generated numbers. Group allocations will be done by a nurse by assigning opaque envelopes sequentially as they appear in the box for those recruited into the study. The procedure for concealment will be as described by Gordon S. Doig.[17] In this study, there will be no allocation concealment and no blinding as it is neither possible to blind respondents nor investigators. To prevent intervention contamination, one person will be selected from each household. However, due to the increased attention on the respondents – Hawthorne effect cannot be ruled out.[31]Theconsort diagram is presented in figure 1.

Outcomes

The primary outcome will be adherence to ART as measured by a combination of self-reported adherence, pill counts, visual analogue scale (VAS), and pill identification tests (PIT). Adherence will be measured at baseline, six months and 12 months. The secondary outcomes will be Cluster of Differentiation 4+ (CD4+) count, viral load, opportunistic infection, weight, and body mass index.

Intervention

In the intervention group, participants will receive a motivational SMS reminder on a weekly basis for the duration of the trial. This will be in addition to the usual care offered to clients as defined by the Zimbabwe ART guidelines. Motivational messages that will be sent on a weekly basis will include *'Time for your life'* and '*Do not forget to take your medication'* among others. The message will change on a weekly basis.

Non intervention

Those randomized into the non-intervention group will receive standard HIV care that comprises of CD4+ cell counts, adherence classes and follow up.

Duration

The duration of the study will be 52 weeks, with measurement of outcomes at baseline, 26 weeks and 52 weeks.

Sample size

The sample size calculated using Open Epi Version 3.03a™ was 306 assuming a 1:1 allocation ratio. The study will be set at 80% power to yield a statistically significant result using a chi-square test (assuming an intention-to-treat principle for the analysis) at alpha = 0.05/2 (*i.e.* using Fleiss formula and statistical methods for rates and proportions) with a continuity correction. The sample size calculation is based on the comparison between proportions of patients with adherence rates (measured as percent with adherence >95%). The proportion of respondents in each arm of the study who have more than 95% adherence will

be compared because this is the variable with the largest sample size. A two tailed test will be used and effect in either direction will be interpreted. Assuming an attrition rate of 10% we intend to enroll 168 participants in the intervention and 168 participants in the control group.[18]

Analysis plan

The analysis and reporting of the results with follow the CONSORT, Consort e-health and SPIRIT 2013 guidelines.[19, 20, 21, 22] the process of patient selection and flow throughout the study will be summarized using a flow-diagram, figure 1. Patient demographics and baseline outcome variables (both primary and secondary) will be summarized using descriptive summary measures and expressed as means or medians. The intention-to-treat principle will be used to analyze all outcomes. [23] We will also use multiple-imputation to handle missing data.[24]The*t-test*will be used for comparing groups on continuous outcomes and the *chi*-squared test for binary outcomes. All statistical tests will be two-sided and at the 5% level of significance.

Ethical considerations

The study will be guided by the Belmont and Helsinki reports.[25, 26, 27] the study will be reviewed by an ethical review committee (Zimbabwe Medical Research Council). Participation will be voluntary and participants can withdraw from the study at any time. Written informed consent will be obtained from all participants and confidentiality maintained at all stages of the study. The intervention will be a motivational message that will generally talk about health and medicine so that confidentiality of respondent is not compromised.

Discussion

Human Immunodeficiency Virus has continued to be a global public health problem.[1]Low adherence among clients in Kadoma as report by Muringazuva et. al (Year) is a threat the HIV control program in general and ART in particular. The World Health Organization has also prioritized the use of ICT/*m*health in health.[28] It is against this background that this randomized controlled trial to evaluate the efficacy of weekly SMS on anti-retroviral therapy adherence is being conducted. It is hoped that the study design will provide quality evidence to support or dispute the use of ICT/*m*Health among clients on ART in Kadoma.

Elsewhere, Lester *et. al*. (2009) compared the effectiveness of cell phone supported SMS messaging to standard care, quality of life and retention in an adult population.[13]Mbuagbaw*et. al.* (2011) in a study in Cameron reported no difference in adherence between the intervention and non-intervention group at three and six months.[12]In our study, we will be assessing the clinical outcomes for a duration of 12 months at six monthly intervals. Batya *et. al.* (2014) carried out a combination strategy for enhancing linkages to and return to HIV care among newly diagnosed adults in Mozambique.[29]Unlike Batya whose study was looking at ART naïve respondents, our study will primarily look at the effect of SMS on adherence among those who have been on ART for at least four weeks. Engle *et. al.* (2015) in Ghana developed a study protocol with an objective to evaluate *m*health intervention on patient adherence and doing a cost benefit analysis.[30] However; our study will differ from this as we will not do a cost benefit analysis.

The results of this trial are expected to provide evidence on the effect of mobile phone reminders on adherence to ART in a Zimbabwean primary health care context. The intervention is also expected to improve immunological and virologic outcomes. The results will highlight key implications for other low-income settings in sub-Saharan Africa.

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KAMPS consort diagram

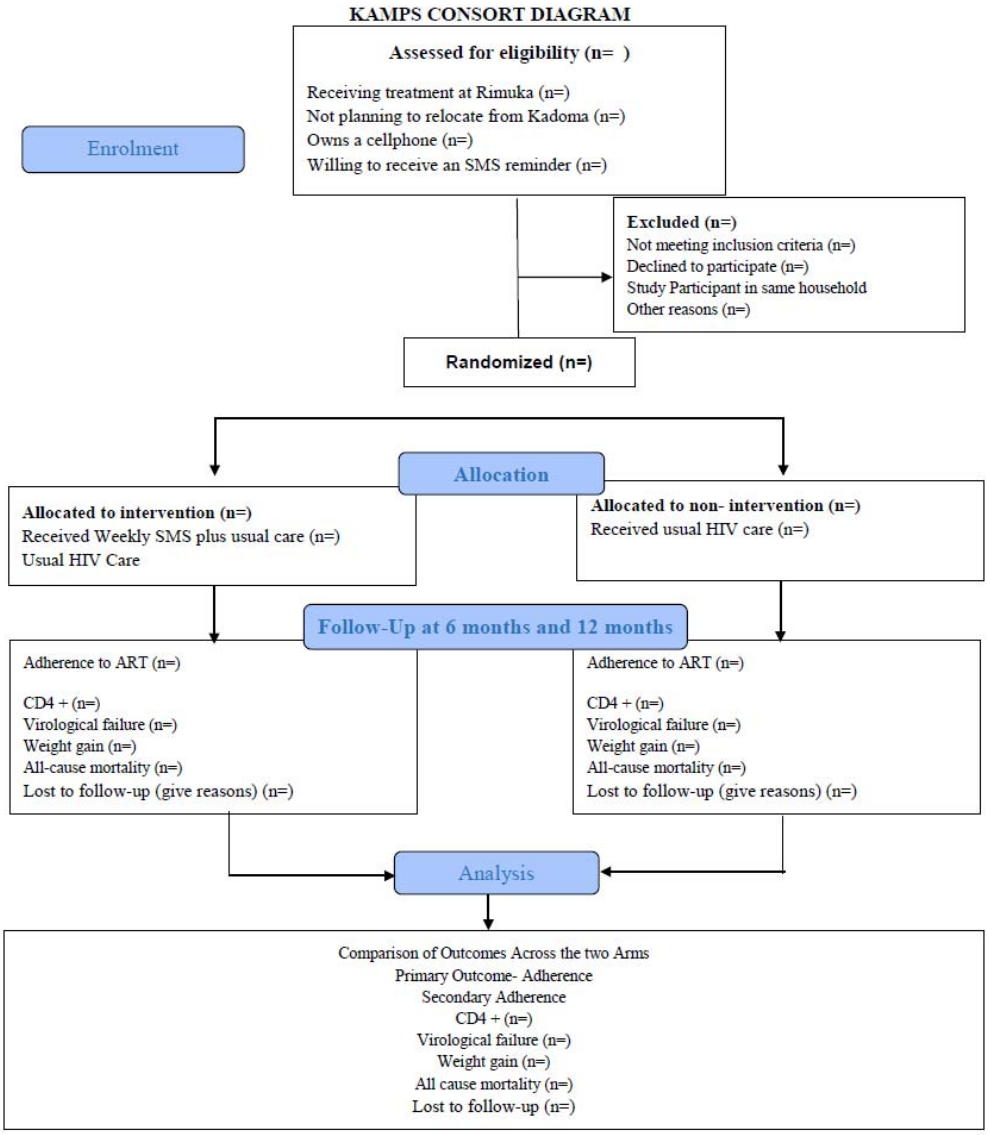

Figure 1. KAMPS Study Consort Diagram

Table 1. Plan for Data Analysis

Variable Outcome	Hypothesis	Outcome Measure	Method of Analysis
Primary	Intervention improved outcome from baseline to 6months		
Adherence to ART at 6 months		Percentage adherence in previous 30days>95% [binary]	Chi-squared
Secondary	Improvement occurred		
Adherence % at 12 months	Improvement occurred		
Immune reconstitution at 6 months	Improvement occurred	CD4 T-cells/mm3 (continuous)	T-test
Weight gain and BMI	Improvement occurred	Change in Weight (continuous)	T-test
Occurrence of Opportunistic Infections	Improvement occurred	Presence of AIDS defining opportunistic infection (binary)	Chi-square
Deaths (all cause)	Improvement occurred	All-cause mortality (binary)	
Rand 360	Improvement occurred	Quality of life questionnaire	T-test
Satisfaction with Care provided	Improvement occurred	Questionnaire	
Level of Disclosure HIV Status	Improvement occurred	Questionnaire	Chi-square
Impression of Stigma	Improvement occurred	Questionnaire	T-test
Family Dynamics	Improvement occurred	Questionnaire	T-test
Variable Outcome	Hypothesis	Outcome Measure	Method of Analysis
Cellphones /lost Stolen	Improvement occurred	Presence of cellphone	T-test
Stopped Taking ART	Improvement occurred	Self-report	T-test
Required Active tracing	Improvement occurred	Field officer binary	Chi-square test
Subgroup Analysis			
Female Vs. Male	Sex (gender affects adherence)		
Area of Residents	Distance to HC		

	affects adherence	
Level of Education	Low education affects adherence	
Employed vs. unemployed	Employment status affects adherence	
4. Sensitivity Analysis	Improvement occurs	
Per protocol analysis		Chi-square /T test
Adjusting for baseline		Multivariate analysis
Clustering		