

# Mobile phone text messages for improving adherence to antiretroviral therapy (ART): a protocol for an individual patient data meta-analysis of randomised trials

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## ABSTRACT

**Introduction:** Mobile phone text messaging is emerging as an important tool in the care of people living with HIV; however, reports diverge on its efficacy in improving adherence to antiretroviral therapy (ART), and little is known about which patient groups may benefit most from phone-based adherence interventions. We will conduct an individual patient data meta-analysis to investigate the overall and subgroup effects of text messaging in three recently published text-messaging randomised controlled trials.

**Methods and analysis:** Data from two Kenyan and one Cameroonian trial will be verified, reformatted and merged. We will determine pooled effect sizes for text messaging versus standard care for improving adherence to ART using individual patient random-effects meta-analysis. We will test for the interaction effects of age, gender, level of education and duration on ART. Sensitivity analyses will be conducted with regard to thresholds for adherence, methods of handling missing data and fixed-effects meta-analysis. Only anonymised data will be collected from the individual studies.

**Ethics and dissemination:** Ethical approval was obtained for the individual studies. The results of this paper will be disseminated as peer-reviewed publications, at conferences and as part of a doctoral thesis. This individual patient data meta-analysis may provide important insights into the effects of text messaging on ART adherence in different subpopulations, with important implications for programme implementation involving such interventions and future research.

## INTRODUCTION

More than 30 million people are living with HIV worldwide.<sup>1</sup> Over the past few years, considerable progress has been made in the

## ARTICLE SUMMARY

### Article focus

- To outline the analytic plan for a collaborative individual patient data meta-analysis of randomised trials of text messaging to improve adherence to antiretroviral therapy.

### Key message

- Individual patient data meta-analysis can provide insight into the patient groups most likely to benefit from text messaging and the most effective kinds of messages.

### Strengths and limitations of this study

- Robust analytical methods that take into account within-study and between-study differences.
- No systematic search for other studies will be carried out.

treatment of HIV infection. Key among the developments to control HIV is the advent of antiretroviral therapy (ART). ART has been shown to slow down disease progression, prevent transmission and boost immunity; however, its success depends on patients achieving high levels of medication adherence.<sup>2</sup> Even though some evidence suggests that patients with lower levels of adherence can still achieve viral suppression,<sup>3 4</sup> optimal adherence is desirable since it is correlated with improved clinical, immunological and virological outcomes.<sup>2 5 6</sup> On the other hand, poor adherence can lead to progression to AIDS, the development of resistant strains, increased transmissibility, more hospitalisations and longer stays.<sup>2 7</sup> ART adherence can be influenced by a number of factors broadly categorised into patient-related factors, medication characteristics,

health system characteristics and disease characteristics.<sup>8–13</sup> More specifically, females, people aged above 50 years and the more educated are more likely to be adherent to ART.<sup>9 14</sup> Adherence to ART may wane over time.<sup>15 16</sup>

There is an emerging evidence that mobile phones can play an important role in healthcare delivery, especially in resource-limited settings.<sup>17</sup> The appeal of using phones to promote adherence has grown as phone ownership rates continue to rise in sub-Saharan Africa and elsewhere.<sup>18</sup> Short message service (SMS) is a particularly useful application that can be used to collect or share information and to enhance communication between health personnel and patients in a low-cost manner.<sup>19</sup> With regard to patient management, mobile phone text messages have been demonstrated to induce positive behaviour changes in domains such as smoking cessation, physical activity and self management of high blood pressure, diabetes and asthma.<sup>20</sup> Other studies report high levels of satisfaction among participants.<sup>21 22</sup> In light of these, one can expect SMS texting to serve as reminders to take medication, provide greater connectedness with a provider or provide encouragement to remain adherent to ART.

A recent Cochrane systematic review synthesising data from two trials conducted in Kenya showed that text messaging is efficacious in improving adherence.<sup>22–24</sup> A third trial conducted in Cameroon reported no improvements in adherence.<sup>25</sup> Yet, to the best of our knowledge, there are no individual patient data meta-analyses for this type of intervention. We will use individual patient data to aggregate the findings from these three randomised controlled trials.

The WHO recognises mobile health (mHealth) as a potential resource for improving outcomes in low resources settings.<sup>26</sup> This paper will provide the best available evidence for the use of text messages in improving adherence to ART. It will also provide the most accurate estimation of the extent to which, and the subpopulations in whom, we can expect text messages to improve adherence.

## Objectives

Our primary objective is to determine the overall effect of mobile phone text messages versus usual care for improving adherence to ART using individual level data.

Our secondary objective is to investigate the effects of mobile phone text messages in subgroups known to have different adherence behaviours: gender, age, level of education and duration on ART.

## METHODS AND ANALYSIS

### Overview of the trials and data sources

We have obtained individual patient data from three trials: the CAMPS trial,<sup>25</sup> the WelTel trial Kenya 1<sup>22</sup> and one other in Kenya.<sup>23</sup> The CAMPS trial (n=200) investigated the use of weekly motivational text messages

versus usual care to improve adherence to ART in Yaounde, Cameroon.<sup>25</sup> The WelTel trial was a multisite trial of weekly messages inquiring about participants' status involving 538 participants in Kenya.<sup>22</sup> Pop-Eleches *et al* investigated short daily messages, long daily messages, short weekly messages and long weekly messages compared to standard care in 431 participants in Kenya.<sup>23</sup> These studies were included based on the following criteria: they are all randomised controlled trials of a text messaging intervention in people living with HIV to improve their adherence to ART. The characteristics of these studies are reported in detail in [table 1](#). To our knowledge, there are no other published randomised controlled trials (RCTs) of text-messaging interventions designed to improve ART adherence in resource-limited settings.

### Data management

To promote collaboration with the authors of these reports, we will adhere to the highest levels of confidentiality and ensure professionalism by providing regular updates on data handling and analysis.

We will collect baseline covariates, endpoint data and coding information from each study. Data will be stored on a controlled-access computer with backup and treated confidentially. Data will be stored in its original form, but copied for conversion into SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, V.20.0. Armonk, New York: IBM Corp). We will check for the missing data and compare it with published trial reports. Any discrepancies will be resolved by contacting the original authors. Data will also be checked for appropriate ranges, for example, an age less than 10 years would be implausible, since only adults were included in the parent studies. Finally, all common variables will be allotted new unified names and an identifier variable will be added to participants from the same trial.

### Data merging procedures

Only variables that are available in all three data sets will be used. The categories reported in the individual studies will be reformatted into new uniform categories for the individual patient data meta-analysis. The final data set will include the following baseline covariates: age (years), gender (male/female), level of education (none, primary, secondary or higher) and duration on ART (months). The intervention variable will be text messaging (short daily, long daily, short weekly or long weekly modalities) versus no text messaging. The primary outcome will be adherence > 95% with respect to measures used in the three studies (by a visual analogue scale at 6 months<sup>25</sup>; by medication event monitoring system from week 12 through week 48<sup>23</sup>; and as a percentage of pills taken at 6 and 12 months<sup>22</sup>). Secondary outcomes include mortality, study withdrawal, lost to follow-up and transfers. [Table 2](#) describes the original format of the data and how they will be reformatted for use in the individual patient data meta-analysis.

**Table 1** Characteristics of included studies

	<i>Lester et al</i>	<i>Pop-Eleches et al</i>	<i>Mbuagbaw et al</i>
Design	A multisite two-arm randomised controlled trial	A single site five-arm randomised controlled trial	A single site two-arm randomised controlled trial
Inclusion criteria	≥18-years-old, initiating ART for the first time, and able to access a mobile phone on a near-daily basis and communicate via SMS	≥18 age who had initiated ART less than 3 months prior to enrolment	≥21 years who owned mobile phones, could read text messages and had been on ART for at least 1 month
Baseline characteristics reported	Gender, age, CD4 count, WHO stage, clinic, viral load, literacy, level of education, monthly income, mobile phone access and residence	Marital status, religion, language, roofing, education, gender and age	Age, gender, education, family awareness of HIV status, presence of OI, BMI, CDC stage, regimen, duration on ART, CD4 count and VAS adherence
Sample size	538 (intervention=273; control=265)	431 (Short daily message=70; Short weekly message=73; Long daily message=72; Long weekly message=74; Control=139)	200 (intervention=101; control=99)
Interventions	Weekly text message inquiring about status- Participants required to respond in 48 h	Short daily message Short weekly message Long daily message Long weekly message	Varied weekly motivational text message with response number provided
Control	Standard care	Standard care	Standard care
Primary outcomes	Self reported adherence (in preceding month), viral load	MEMS adherence	VAS adherence, number of missed doses (in preceding week), PRD
Secondary outcomes	Attrition (loss to follow-up, mortality, transfers, withdrawals)	Treatment interruptions	Weight, BMI, opportunistic infections, CD4 count, viral load, QOL, all cause mortality, retention in care
Duration of follow-up	12 months	48 weeks (12 months)	6 months
Overall findings	Improved adherence and reduced viral load	Improved adherence and reduced treatment interruptions	No improvements in adherence

ART, antiretroviral therapy; BMI, body mass index; CD4 count, CD4-positive-T-lymphocyte count; CDC, Centres for Disease Control and Prevention; MEMS, Medication Event Monitoring System; OI, opportunistic infection; PRD, pharmacy refill data; QOL, quality of life; SMS, short message service; VAS, visual analogue scale.

## Statistical methods

Analyses will include all study participants irrespective of whether they received the allocated intervention (intention-to-treat). Summary statistics will be presented as mean (SD) or median (IQR) for continuous variables and number (percent) for categorical variables. The primary outcome will be adherence to ART. All three studies have sufficient data to dichotomise adherence at 95%, defining adequate adherence (greater than 95%) and poor adherence (95% or less). Effect sizes will be computed for comparisons between the various text messaging modalities versus no text messaging, and for all forms of text messaging versus no text messaging. We will report ORs and corresponding 95% CIs. The level of statistical significance,  $\alpha$ , will be set at 0.05. Forest plots will be graphed for all pooled effects.

An individual patient random-effect meta-analysis will be conducted to determine the overall effect of text messaging on adherence, with 'study' as a random effect, to model variation across studies and to account for clustering within a study.<sup>27</sup> This analysis will be

repeated for secondary outcomes. In an adjusted analysis, adherence to ART, our primary outcome and dependent variable will be modelled as a function of the intervention (text message/no text message) and baseline characteristics (age, gender, duration on ART and level of education) as fixed effects.

Model fit will be tested using maximum likelihood estimations. Multicollinearity will be assessed using the variance inflation factor (VIF), with a VIF of 4 or more considered as evidence of substantial multi-collinearity. Data will be analysed using SPSS V.20.0 (SPSS, Inc, 2009, Chicago, Illinois, USA). The data analysis plan is illustrated in figure 1.

## Sensitivity analysis

We will also test the sensitivity of our results to a 90% cut-off point for adherence, imputation of missing data using multiple imputation<sup>28</sup> and method of analysis (fixed-effect vs random-effect meta-analysis). For the individual patient fixed-effect meta-analysis, generalised estimation equations (GEE) will be used to obtain the

**Table 2** Data merging procedures

Variable	Lester <i>et al</i>	Pop-Eleches <i>et al</i>	Mbuagbaw <i>et al</i>	IPD* Meta-analysis
Age	Years	Years	Years	Years
Gender	Male/female	Male/female	Male/female	Male/female
Level of education	No formal education	None	None	None
	Lower primary	Completed primary	Primary	Primary
	Upper primary			
	Lower secondary	Completed secondary	Secondary	Secondary or higher
	Upper secondary			
	High school			
	Middle college and University		University	
Duration on ART	Months	Months	Months	Months
Intervention	SMS short weekly	SMS short daily SMS short weekly SMS long daily SMS long weekly	SMS Long weekly	SMS short daily SMS short weekly SMS long daily SMS long weekly
Control	No SMS	No SMS	No SMS	No SMS
Adherence	Yes (>95 at 6 & 12 months)	Yes (≥95% from 12 to 48 weeks)	Yes (>95% at 6 months)	Yes (as reported in studies)
Final outcome	Lost to follow-up	Lost to follow-up	Lost to follow-up	Lost to follow-up
	Death	Death	Death	Death
	Withdrew	Withdrew	Withdrew	Withdrew
	Transferred out	Transferred out	Transferred out	Transferred out

\*Individual patient data.  
SMS, short message service.

average response over the population.<sup>29</sup> An exchangeable correlation structure will be assumed for this analysis—individuals within the same study are equally correlated. We will also report estimates of effects based on aggregate data from the individual studies.

### Subgroup analysis

The findings from the included studies raise the possibility that text messaging may be more effective at improving adherence among individuals whose adherence is likely to be lower in the absence of any intervention, such as in males and individuals with higher levels of education.<sup>22 25</sup> For these subgroups, we will add the interaction terms (subgroup-by-intervention interaction) to the models. *p* Values for the interaction terms will be reported.

### Assessment of heterogeneity

For the pooled estimates of effect, heterogeneity between studies will be measured using the  $\tau^2$  statistic (an estimate of the between-study variance in the random-effects model). The  $\chi^2$  test of homogeneity (level of significance— $\alpha=0.10$ ) and the  $I^2$  test (the percentage of the overall variation due to heterogeneity) will be used in the fixed-effects models. The intraclass correlation coefficients from the GEE will be reported.

### Risk of bias

Risk of bias will be assessed using the Cochrane Risk of Bias tool for randomised controlled trials.<sup>30</sup>

### ETHICS AND DISSEMINATION

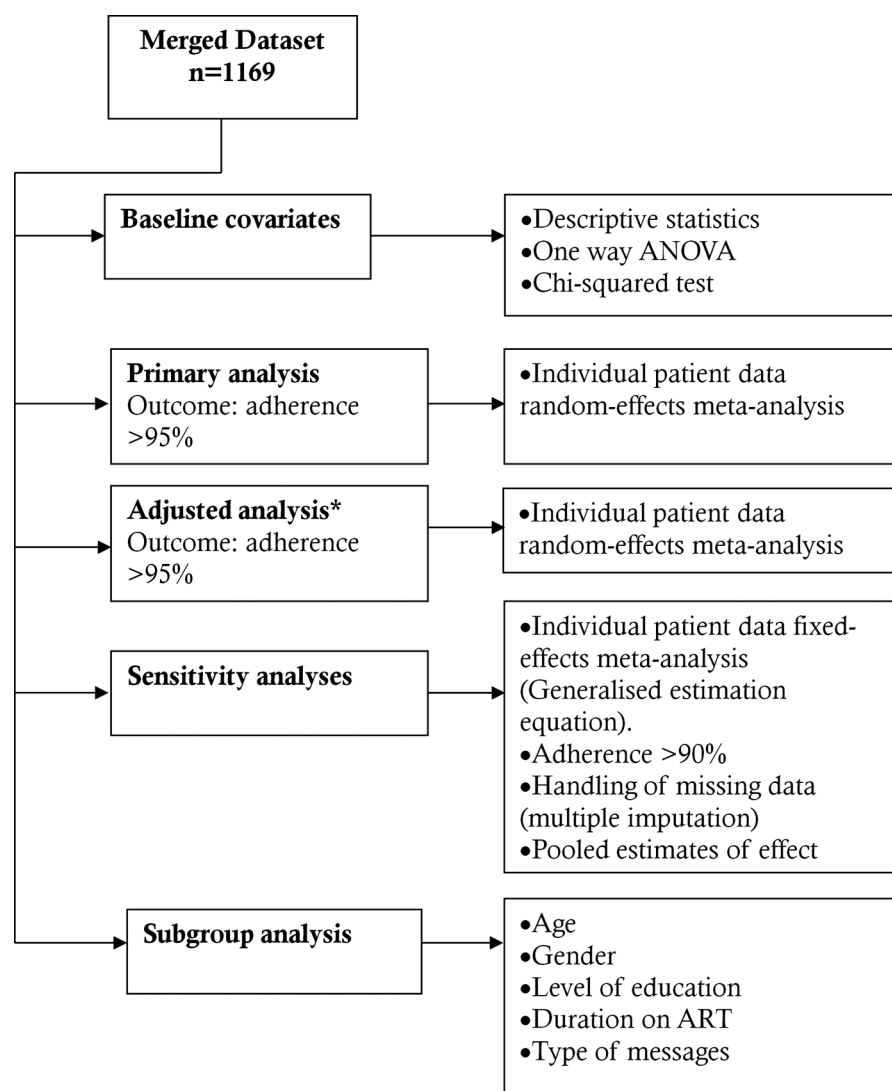
This individual patient data meta-analysis was exempt from ethics approval by the Hamilton Integrated Research Ethics Board, as it involves only anonymised precollected data. Ethical clearance and informed consent were obtained for each of the individual studies.<sup>22 23 25</sup> Only anonymised data will be collected from the individual studies. We plan to disseminate our results at international meetings and in peer-reviewed journals. Our findings will also be publicly presented and defended as part of a doctoral thesis.

### DISCUSSION

We recognise the considerable resources and international cooperation required to perform a meta-analysis based on individual patient data and will build on already existing relationships<sup>31</sup> to produce a high quality meta-analysis.

The two Kenyan trials we included in this individual patient data meta-analysis reported significant improvements in adherence, while the third trial did not. However, the populations and interventions in these three trials, though similar in broad terms (adults living with HIV receiving text messages to improve adherence), are sufficiently different to warrant further investigation. Other differences include the settings, interventions, measures of adherence and duration of the trials.

The CAMPS trial used a variety of motivational text messages developed based on the health belief theory of



\*Adjustment for age, gender, level of education and duration on ART as fixed effects

**Figure 1** Analysis plan for individual patient data.

behaviour change.<sup>25</sup> Responses to these messages were optional. The WelTel trial used a simple “How are you?” to which participants were required to respond within 24 h.<sup>22</sup> Pop-Eleches *et al* used messages designed to address forgetfulness (short message) and lack of social support (long message).<sup>23</sup> Participants in this trial were given Nokia mobile phones. All other studies ran for 12 months except the CAMPS trial which ended at 6 months. These differences may have consequences on the effects of the interventions depending on participant preference for a specific kind of message and the length of time required to measure a significant effect.

Some limitations worth noting include the differences between the studies which limit the generalisability of the findings, notably the different interventions and measures of adherence. However, the availability of high-quality data from three well-conducted studies and our use of multilevel models to account for between-study differences will provide reliable estimates of the effects

of text messaging on adherence to ART. Moreover, we did not conduct any systematic search for other relevant trials. Only these three trials were invited to participate in the review.

Individual patient data meta-analysis holds several advantages over aggregate meta-analysis including the possibility of checking, exploring and reanalysing the data in a consistent way. We can also perform more complex analysis with regard to the associations between interventions and patient characteristics. On the other hand, individual patient data meta-analysis cannot deal with bias originating from study design and conduct.<sup>32</sup> It may also be subject to publication bias.<sup>33</sup>

By identifying the subpopulations in which the intervention is likely to be most beneficial, this paper will address important clinical and operational questions regarding the use of text messaging to improve adherence to ART. Even though current guidelines encourage the use of text messaging,<sup>34</sup> additional knowledge can

be gained from pooling and comparing data from individual studies. Text messaging and other phone-based interventions are unlikely to resolve adherence problems for all patients. This paper will provide valuable guidance on patient groups that may be targeted to receive such interventions, thereby increasing cost-effectiveness and freeing up resources to target other patients with more intensive adherence interventions.

This paper will highlight the key characteristics that are associated with a better response to text messaging for the improvement of adherence to ART. Our findings will inform future research and implementation programmes.

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**Contributions** All authors participated in the planning of the study. LM and LT conceived the idea. LM wrote the first draft of this manuscript. MLK, RTL, HT, CPE, MS, LD and EJM revised several versions of the manuscript. All authors approved the final version.

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