Effect of Digital Adherence Tools on adherence to antiretroviral treatment among adults living with HIV in Kilimanjaro, Tanzania: a randomized controlled trial

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Running head: Digital adherence tools for PLHIV

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Abstract

**Background:** Lifelong adherence to antiretroviral treatment (ART) remains challenging for people living with HIV (PLHIV). The aim of this study was to investigate whether any of two digital adherence tools (DAT) could improve adherence among PLHIV in Kilimanjaro, Tanzania.

**Methods:** We performed a parallel three-arm non-blinded randomized controlled trial with 1:1:1-allocation. We included adults aged between 18 and 65 years, living in Kilimanjaro Region, and who were on ART for at least six months. Their adherence as judged by the study nurses had to be suboptimal. In one arm, participants received reminder short message service (SMS)-texts followed by a question-SMS. In the second arm, participants received a real-time medication monitoring (RTMM) device (Wisepill®) with SMS-reminders. In the third arm, participants received standard care only. The primary outcome of mean adherence over 48 weeks was compared between arms using between-group t-tests in a modified intention-to-treat analysis.

**Results:** In each arm, we randomized 83 participants: data of 82 participants in the RTMM arm, 80 in the SMS-arm and 81 in the standard care arm were analyzed. Mean average (over 48 weeks) adherence in the SMS, RTMM and control arm was 89.6%, 90.6% and 87.9% for pharmacy refill; 95.9%, 95.0% and 95.2% for self-report in the past week; and in the past month 97.5%, 96.6% and 96.9% (p-values not statistically significant).

**Conclusions:** Receiving reminder SMS or RTMM combined with feedback about adherence levels and discussion of strategies to overcome barriers to adherence did not improve adherence to treatment and treatment outcome in PLHIV.
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Keywords: PLHIV; Adherence to treatment; Digital Adherence Tools; Clinical Trials; Short Message Service; Real Time Medication Monitoring

Introduction

Human immunodeficiency virus (HIV) infection remains one of the largest global health problems with 37.9 million people living with HIV (PLHIV) in 2018 [1]. In Tanzania, 1.6 million people were living with HIV in 2018, with 71% of adults living with HIV being on treatment and 62% virologically suppressed [2]. High sustained levels of adherence (at least >85%) are needed to prevent virologic failure and the emergence of antiviral drug resistance, with newer antiretroviral regimens especially those including dolutegravir seeming to be more forgiving for non-adherence [3–5].

Adherence may be influenced by a variety of factors [6–10]. A previous study conducted among tuberculosis (TB) patients in our setting in Kilimanjaro, Tanzania led to a framework showing that adherence is influenced by the intention to adhere to TB treatment, which in turn is affected by knowledge and beliefs about TB-treatment, perceived facilitators and barriers to adherence to TB-treatment, and the motivation to have an improved health-status [11]. We believe similar factors may apply to PLHIV in our region and therefore interventions should focus on a
combination of these factors. In addition, barriers to HIV treatment adherence were previously found to include (1) patient factors, such as HIV stigma, disclosure concerns, substance abuse and food insecurity, (2) treatment factors, like complex regimens and side effects, (3) health system-related factors, including limited numbers of health care workers, drug stock outs and long waiting times at the health facilities and (4) an unsatisfying patient-doctor relationship [12,13]. Specifically, in our setting, facilitators of HIV treatment adherence include support from friends and family and the assistance of home-based care workers [12].

Digital Adherence Tools (DATs) that involve the use of mobile phones and short message service (SMS) are a promising means for improving adherence to treatment and retention in care. The number of mobile phone users in Tanzania is high, being 81% in 2018, and 25 billion SMS were sent in the second quarter of 2019[14]. Although several reviews have shown a positive effect of DATs on adherence and retention in care, the literature on benefit from such interventions is quite mixed and depends on factors such as the type and/or content of SMS that is used and the specific population that is studied [15-17]. Moreover, a recent review about digital interventions aimed at enhancing medication adherence pointed out that the design of such interventions needs to be adapted to make them suitable for application in lower income countries to prevent failure of such interventions [18]. Factors like technology accessibility, socioeconomic background of participants using the DAT interventions, and geographically based internet or cellular connectivity should be considered when designing interventions to be applied in lower income countries. A recent study reported that 44% of the published studies about digital health aimed at enhancing antiretroviral adherence yielded insignificant effects and advocated for longer follow-up studies with larger groups of patients [19]. Further, Lester already emphasized the need for an ‘Ask, don’t tell’-approach in 2013. Their randomized
controlled trial in Kenya showed that weekly interactive text messaging asking patients how they were doing, with follow-up phone calls to those reporting a problem, improved outcomes of HIV treatment, suggesting that the contents of SMS also matters [20]. Simply asking ‘How are you?’ instead of asking whether pills were taken may cause less unintended disclosure of the HIV status and consequential stigmatization.

Another DAT is the so-called real time medication monitor (RTMM), i.e. a pillbox that records opening of the box. One such RTMM device, Wisepill®, also sends reminder-SMS. This DAT can generate adherence reports, which could be used for feedback. Providing participants with feedback about their level of adherence derived from electronic medication dosing data was previously shown to improve adherence [21-23].

We believe that sending SMS to PLHIV or using RTMM with customized SMS-messages are attractive means to improve adherence, as they enable feedback, thereby targeting several adherence impeding factors. In our pilot studies in Kilimanjaro with PLHIV we have shown the feasibility and positive user experience of SMS-reminder cues and RTMM [24-26].

We investigated the effect of RTMM and SMS on adherence to ART. The primary objective of our study was to assess whether reminder cues and tailored feedback by using RTMM or SMS improve ART adherence among adult PLHIV in Kilimanjaro, Tanzania. The secondary objectives were (1) to examine the effect of our interventions on proportions of participants who reached cut-off values for sufficient adherence (i.e. >85%, >90% of doses taken) (2) the effect on
virological outcome. Our hypothesis was that both RTMM and SMS will improve ART adherence and virological suppression among PLHIV.

Methods

Study design

We performed a parallel randomized controlled three-arm trial in which adult PLHIV were randomized in a 1:1:1 ratio to (1) RTMM, (2) SMS or (3) standard care and followed for 48 weeks.

Study population

We recruited PLHIV between 1 December 2017 and 31 December 2018 and followed them till 28 February 2020 in Kilimanjaro Christian Medical Centre (KCMC), a referral hospital, and Majengo Health Centre, both located in urban Moshi. Inclusion criteria were adults aged between 18 and 65 years, living in Kilimanjaro Region, who were on ART for at least six months (i.e., they were in the adherence implementation phase) [27]. We used age 65 years as upper limit as we believe older PLHIV will have difficulties in dealing with the modern digital tools. In Tanzania, people with age 65 or above are considered elderly. Importantly, their adherence, as
judged by the study nurses, should was suboptimal adherent based on the following information: self-reported non-adherence; missed clinic visits; returning of excess leftover medication; or self-reporting other signs of nonadherence like not adhering to prescribed time of intake; having continuously high viral loads. Further, they needed to be willing to use an RTMM device and receive SMS. Finally, they had to be able to read and understand SMS. Excluded were PLHIV admitted to the hospitals, participants with co-morbidities who participated in other DAT trials, or who had participated in studies using DAT.

**Ethical considerations**

The study was approved by the College Research and Ethical Review Committee (CRERC) of Kilimanjaro Christian Medical University College (KCMUCo) and the National Health Research Ethics Sub-Committee (NatHREC) of the National Medical Research Institute (NIMR) of Tanzania.

We used a stringent informed consent procedure. The study nurse thoroughly explained the study to the study participants using a participant information sheet written in Kiswahili. The participant got ample time to decide to participate including the possibility of taking the sheet home to obtain more thinking time. Once, potential participants decided to participate, they were asked to complete an understanding test. The test contained questions about understanding the study (e.g. voluntary participation, possible withdrawal). Then, the participant was asked to sign the informed consent form.
Study procedures

Screening and enrolment

Study nurses pre-screened potential participants for eligibility based on judging them to be suboptimal adherent. After informed consent, participants were interviewed by the study-nurse on demographics and HIV history. We also recorded ART regimen, time of usual intake and self-reported adherence by asking how many pills were missed in the past week and past month. Furthermore, details on pharmacy refill counts were recorded, i.e. number of pills dispensed during the previous visit and leftover pills during the current visit. Participants who did not own a cell-phone were provided with one. Participants were subsequently randomized by using the randomization module in Redcap® whereby the data manager assigned participants to the interventions. One month later, during the enrolment visit with the study nurse, viral load was measured and participants allocated to the intervention-arms were provided with an explanation on how to use the DAT. The enrolment was done one month after randomization because (1) time was needed to prepare the intervention for each participant, (2) it allowed for having a baseline adherence measurement and (3) it limited the burden for our study participants by avoiding an extra visit to the clinic.

Follow-up and assessment of adherence
Follow-up was based on the 2017 Tanzanian HIV-care-and-treatment-guidelines with clinic visits each eight weeks [28]. Study visits were linked to those visits and performed at weeks 0 (enrolment), 8, 16, 24, 32, 40 and 48. During each visit, pharmacy refill counts and self-reported adherence were recorded. At 48 weeks, viral load measurement was repeated.

**Standard care**

In Tanzania, PLHIV who are suspected of having low levels of adherence receive minimal adherence counseling according to the current Tanzanian HIV treatment guidelines [28]. Nurses or pharmacists, depending on available staff, judge the level of adherence during consultations. Patients or their treatment supporters may visit the clinic for just a refill of drugs by passing by the pharmacy only. PLHIV coming at the pharmacy for a refill are asked whether they took all the pills from their previous refill and if they had any difficulties with adherence. A viral load measurement is performed annually. If the viral load is >1000 copies/ml, extensive adherence counselling is done monthly and viral load measurement is repeated after three months according to the HIV treatment guidelines.

**SMS-arm**
In the SMS-arm, participants received a reminder-SMS on three random days a week, 30 minutes before usual intake time. One hour after usual intake time, on the same days, a second SMS was sent with a question if medication had been taken. The participant had to reply with ‘Yes’, ‘No’ or ‘Not yet’. Days were different for each participant and each week in order to maintain a surprise effect and prevent SMS fatigue through which we prevented the patient getting used to SMS (Annex IA, http://links.lww.com/QAI/B650).

RTMM arm

Participants in the RTMM arm received the so-called Wisepill® device, an internet enabled medication dispenser. It can contain ART for a period of up to four weeks, depending on the regimen. Each opening is registered and a signal with information about time of opening plus battery-life is being sent immediately to a server using the General Package Radio Service (GPRS) network. At the server, the usual time of intake with a window period of three hours was registered. If participants had not opened the dispenser 15 minutes before the end of the three-hour window period, they received an SMS-reminder (Annex IB, http://links.lww.com/QAI/B650). During the enrolment visits, participants were shown how to use the device. They were instructed about how to open it, how to take medication from it, how to refill and charge it. In addition, they were being instructed to check carefully whether the indicator lights are lighting up during any action of the device and to report if the lights failed. Lastly, the participants were being told that opening the device is immediately visible by the study team.
Structured feedback on adherence in intervention arms

Through a web-based interface with authorized access, the study team could download adherence reports showing number of SMS which had been sent, delivered and replied to (SMS-arm) or showing the pillbox openings (RTMM-arm). Study nurses discussed adherence reports as described by Ngowi et al[29] using the stages of change model (annex II.http://links.lww.com/QAI/B650)[30]. During these discussions, participants went through the stages of precontemplation, contemplation, preparation, action and evaluation in each visit. Participants were asked about their opinion regarding their self-reported adherence since the previous visit (pre-contemplation), followed by showing an adherence report on which participants were asked to reflect (contemplation). A discussion followed on possible barriers for adherence and steps that can be taken, resulting in a target for the next visit (preparation). After the feedback, participants were expected to have increased intention to adhere, which should be followed by changing behavior (action). During the next visit the same process was repeated including evaluation of the preceding period (Annex IIIA.http://links.lww.com/QAI/B650). In the standard care arm, no additional procedures were instituted aside from asking about perceived adherence (annex IIIB.http://links.lww.com/QAI/B650).

Adherence measures and virological response
Levels of adherence at each visit were calculated based on pharmacy refill counts and participants’ self-report in the past week and past month as displayed in Annex IV, http://links.lww.com/QAI/B650. Virological suppression, measured at week 0 and 48, was defined as a viral load <20 copies/ml as per standard of care.

Data analyses

Study population description and differences between arms

A case report form (CRF) was used to collect data and Redcap® software was used for managing data[31]. Participants’ characteristics at time of enrolment were compared by chi-square for categorical data, by ANOVA for data that were normally distributed, and by Kruskal-Wallis test for data not normally distributed.

Analyses

A modified intention-to-treat approach was used for primary analyses [32]. We included only participants who came for a second visit after enrolment where outcome parameters on adherence data were collected the first time. We excluded patients who did not attend the second visit and for whom we were thus unable to collect the necessary data. Adherence is measured
over the previous period by counting leftover pills and days between visits and by asking how many pills were missed. Both could not be done for participants who did not return for a second visit. This meant that we could not include all those who were intended to receive the intervention. As such, this was a modified intention-to-treat analyses. In addition, a per-protocol analysis was performed on participants who remained for 48 weeks.

Primary objective: effect of intervention

To address the primary objective on the effect of the interventions, we performed t-tests to investigate whether mean adherence over the whole study period in the intervention arms was different from mean adherence in the control arm. Mean adherence was calculated for both self-reported adherence and pharmacy refill adherence. It was the mean of subsequent adherence measurements:

Self-reported adherence in the past week = (((7xpills to take per day) - (missed pills)) / (7xpills to take per day)) *100%

Self-reported adherence in the past month = (((Number of days in the past month x pills to take per day) - (missed pills)) / (number of days in the past month x pills to take per day)) *100%

Pharmacy-refill adherence: (((pills given in previous visit + returned pills at previous visit) - returned pills at current visit) / (number of days between visits * number of pills to take per day)) * 100%.
Annex IV describes in more detail how we calculated adherence and how we dealt with missing values of pharmacy refills.

The assumptions for the between-group t-test of having more than 30 participants in each arm and homogeneous variances between arms were met.

**Primary objective: effect of interventions over time**

To investigate the effect of the interventions over time, we conducted a generalized least squares (GLS) effects models analysis. Using the Hausman test, a random-effects model was chosen in preference to a fixed-effects model, whereby arm and time were fixed. We adjusted for several covariates including recruitment-site, sex, age, years since first positive HIV-test, years on current ART-regimen and virological status at study entry. For the latter we used a cut-off value of 1000 copies/ml which is the cut-off for distinguishing stable from unstable patients in the Tanzanian HIV-treatment guidelines of 2017 [28]. Any patient who is found to have a viral load of 1000 copies/ml or more at a single time-point is considered unstable and needs enhanced adherence counselling.

**Secondary objectives: effect on cut off values of adherence and on virological outcome**
To address the secondary objectives, we first examined the effect of our interventions on proportions of patients who reached different cut-off values of adherence, by performing chi-square analyses. As different studies have reported different needed levels of adherence to prevent treatment failure, we looked at proportions reaching 80%, 85%, 90%, 95% and 100%. We then examined the effect of the interventions on virological outcome (VL<20 copies/ml at week 48), conducting chi-square analyses.

Additional analyses

To better understand the underlying data, we firstly compared adherence rates between patients with the outcome of suppressed versus unsuppressed viral load at 48 weeks (irrespective of study arm) with Student’s t-tests. Secondly, we analyzed the relationship between different adherence assessment methods using Spearman correlation-coefficients whereby a correlation below 0.25 was considered little or no relationship, between 0.25 and 0.5 a fair degree of relationship and over 0.5 moderate to good[33]. For all above described analyses, a p-value of <0.05 was considered significant.

Sample size calculation
In order to answer our first objective, our sample size calculation was estimated based on a mean adherence to ART of 85.0% (SD: 28.6), as reported in a previous study by Lyimo et al. in which adherence was measured through so-called medication event monitoring systems in our setting in Kilimanjaro (MEMS)[34]. The study of Lyimo was performed over a period of 3 months, while our study would be following participants for 12 months. Therefore, we decided to use a slightly lower mean adherence levels for our calculation, which is 80%. We wanted to demonstrate a difference of at least 10% between either of the intervention arms and the control arm leading to an effect size of 0.52. With a power of 90% and a two-sided $\alpha=0.05$, 80 participants were required in each arm based on a difference between two independent means (calculation using G*Power 3.1 software). As we expected 10% loss-to-follow-up, we aimed to enroll 88 participants per arm for a total of 264 participants. We used stratified block randomization by recruitment site and sex whereby the data manager used Redcap® software to allocate subjects to different arms [31].
Results

Study population description and differences between arms

Two-hundred-sixty-five participants were screened and randomized; two-hundred-forty-nine returned for the enrolment visit. The majority (71%) were female. Mean age was 41.2 years. Median time since first known positive HIV-test was 7.2 years. Participants had used their current ART regimen for a median of 4.4 years. Adherence was self-reported as being suboptimal by 68% of participants, 76% had missed clinic visits and 70% returned excess pills to the clinic in the past six months (Table 1). There were no differences in participant characteristics amongst arms. Two-hundred-twenty-five participants completed the 48 weeks, 77 in the RTMM arm, 73 in the SMS arm and 75 in the control arm.

Primary objective: effect of intervention

Eighty-two participants in the RTMM arm, 80 in the SMS-arm and 81 in the standard care arm had a second study-visit (Table 2). Mean average (over 48 weeks) adherence in the SMS, RTMM and control arm was 89.6%, 90.6% and 87.9% for pharmacy refill; 95.9%, 95.0% and 95.2% for self-report in the past week; and in the past month 97.5%, 96.6% and 96.9% (p-values all not statistically significant; Table 2). Self-reported adherence in the past week and month was not significantly different between the SMS- and RTMM-arm and the control arm either.
Adjusting analyses for co-variates did not change the effect of the interventions except for site and viral load at study entry; whereby the difference between sites was caused by differences in percentage of participants with viral load <1000 copies/ml at study entry. Among participants with VL<1000 copies/ml at study entry (n=189), we found a significantly higher mean pharmacy refill adherence in the SMS-arm and RTMM-arm compared to the control arm (p=0.045; p=0.002, table 5). For self-reported adherence, we only found significantly higher mean adherence in the SMS-arm for self-report over the past month (p=0.045, annex V,http://links.lww.com/QAI/B650; table 1).

Primary objective: effect of interventions over time

In the repeated measurement analyses, we found no difference in change in adherence over time between the RTMM (–2.91; p= 0.309) and SMS (0.92; p = 0.75) arms compared with the control group. We found decreasing adherence based on pharmacy refill counts among patients in KCMC for RTMM with marginal significance (–6.73; p= 0.054). When we stratified analyses by viral load at study entry (1000 copies/ml), we found insignificant results.

Secondary objectives

Adherence at different percentages of doses taken across study arms
There was a significantly higher percentage of participants taking 85% of doses or more according to pharmacy refill counts in the RTMM-arm (80%) and SMS-arm (79%) compared to standard care (65%; p=0.05) and in participants taking 90% of doses or more with 68% in the RTMM-arm, 75% in the SMS-arm and 67% in the control arm (p=0.02) (table 2).

We did not find any difference in percentage doses taken in self-reported adherence in the past week. For self-reported adherence in the past month, we only found a borderline significant difference in proportion of participants reaching 100% adherence with 61% in the SMS-arm, 41% in the RTMM-arm and 52% in the control arm (p=0.05).

Effect of interventions on virological outcome

There was no significant difference between the three arms in participants who were virologically suppressed at week 48 (p=0.99, table 3). In the sub-analysis among patients with viral load of ≤1000 copies/ml at study entry, we also did not find a significant difference in virological suppression amongst arms (p=0.93).

Additional analyses
**Adherence in participants with suppressed and unsuppressed viral load**

Participants with viral load below 20 copies/mL at week 48 had a significantly higher mean adherence based on pharmacy refill counts compared to those with viral load over 20 copies/ml (table 4).

**Relationship between adherence measurements**

Median self-reported adherence was 100 percent in the past week (IQR: 97-100) as well in the past month (IQR: 98.2-100). Median adherence based on pharmacy refill counts was 93.3% (IQR: 22.3-100; table 6). There was a moderate correlation between self-reported adherence in the past week and pharmacy refill adherence (r=0.41) and between self-reported adherence in the past month and pharmacy refill adherence (r=0.42).
Discussion

Our results do not support the hypothesis that RTMM or SMS with reminder cues and tailored feedback improve adherence to treatment. However, we did find that RTMM and SMS increased the proportions of participants who reached adherence levels of 85% and 90% based on pharmacy refill data. RTMM and SMS based interventions did not have a significant effect on viral suppression.

Several studies have investigated the effect of RTMM and/or SMS on treatment adherence and virological outcome. A Ugandan study found that RTMM with SMS improved adherence [23] while in South Africa there was no effect, but treatment interruptions were shortened [35]. A study in Kenya showed increased communication about adherence due to SMS, but did not show improvement of clinical outcomes[36]. Further, a trial in Malawi did not show an effect of SMS on retention in care [37].

A possible explanation for the limited effect of our intervention could be the Hawthorne effect which means that being part of a study is influencing adherence positively, even in the control group.[38] Although we did not see an improvement in adherence over time, the average adherence might be higher in the control arm compared to actual standard care. Careful discussion with the study staff revealed that, despite following standard guidelines in the control group, attention to adherence during the study procedures was more extensive in the control arm than in actual standard care.
Another possible explanation for the lack of an effect may be that the barriers addressed during feedback may not be the barriers most impacting the participants (e.g., structural factors like low socio-economic status, health system accessibility). Although the intention of the intervention was to give an opportunity during the tailored feedback to discuss such barriers and to find strategies to overcome these or cope with them, we can imagine that the nurse counsellors may not always have done this sufficiently thoroughly. Other studies have shown benefit from mHealth interventions when the participants are new to ART and need support with habit formation, and/or with extra communication through phone-calls after no-intake to provide more robust support than a simple reminder [38]. Our SMS intervention did not include a follow up call to participants who indicated that they did not take their medication. In the Wel-Tel study such follow-up calls to participants turned out to be helpful in improving adherence. We chose not to include follow-up calls for feasibility reasons. With the current set-up of HIV care, there is limited time and capacity to conduct follow-up calls. Our intervention was meant to relieve the health staff from such extra burden of follow-up call duties while at the same time creating a venue for better communication on adherence during face-to-face clinic visits when needed. Further, the effect of interventions is highly dependent on study population under investigation, the study design and the study area in relation to network and power availability [15-20].

Although we did not find a difference in mean adherence, we did find that in the SMS- and RTMM-arms, the proportion of participants reaching 85% and 90% adherence based on pharmacy refill data was significantly higher. Unfortunately, studies are not consistent on the required levels of adherence as some report that 95% is needed but others report 90% or even 85%[3–5]. In our analysis adjusted for confounders, we found that adherence improved significantly among participants with viral load <1000 copies/mL at study entry. These results
raise the question whether RTMM and SMS may be useful in this subgroup of patients to keep adherence at high levels. Participants who had a viral load >1000 copies/ml at study entry may already have had limited intention to adhere to treatment, as suggested in van den Boogaard’s previous research[11], and this intention was probably not sufficiently influenced by our interventions. Formative research including mixed-methods research and observation could assist in adapting the feedback sessions. Results from such research may inform future interventions to increase intention to adhere by increasing knowledge and beliefs about ARV treatment, using perceived facilitators and overcoming barriers to adherence and increasing the motivation to have better health outcomes.

Our study has limitations. First, we encountered several bottlenecks affecting the delivery of the intervention. These were (1) technical issues including limited battery life of RTMM devices, limited network and a high number reminder-SMS not being sent by the provider, (2) stigma and related fear of disclosure due to others seeing the device or SMS and (3) limited time of nurses impeding tailored feedback according to instruction and lack of understanding of digital tools. These bottlenecks have been partly described in our case series report of participants participating in the current trial [29]. These factors may have led to suboptimal delivery of the interventions resulting in a limited effect. However, we believe these are difficult to avoid, and are real-life factors that may be present when such interventions are being implemented in routine clinical care.

A second limitation relates to selection bias. Our study with phones and messages is based on participants who can read and write. As such, those with low literacy have been excluded while they form a significant part of the PLHIV population, although in Kilimanjaro literacy is high.
Therefore, the current interventions are not applicable in less literate participants. This could be overcome by using so called interactive voice response calling in which SMS-texts are being replaced by actual phone calls. In addition, patients with co-morbidities were excluded. They might have a high pill burden that may affect adherence negatively. Also, we selected patients based on judgement of nurses of their adherence level as we had no other means to establish their adherence at screening. Looking at data on adherence and virological outcomes at study entry showed that a large percentage of participants had high levels of adherence and a high number of participants were virologically suppressed. This may have caused little room for adherence improvement and diluted the effect of the interventions.

A third limitation of our study is that we did not measure drug resistance at baseline. Drug resistance may have had a major effect on treatment outcome. In participants with a high viral load at time of enrolment and harboring drug resistant virus, even perfect levels of adherence would not be expected to improve virologic outcome.

A fourth limitation concerns the generalizability of our results. This study was conducted in two health care facilities in Moshi, Kilimanjaro. This is an urban area in a region with high literacy rates compared to other regions in Tanzania. We believe that the study findings are not generalizable to all adults living with HIV in Tanzania or East Africa due to differences in network availability and understanding of digital tools and ability to read SMS. Moreover, our findings are not generalizable to key populations such as pregnant and breastfeeding women, children and adolescents as these key populations may experience different barriers for adherence to treatment.
The current study focused on adults living with HIV in general, and as such we did not exclude pregnant and breastfeeding women. Since we did not collect specific information about gestational status, we do not know for sure whether pregnant and breastfeeding women were included. However, in our recruitment centers, pregnant women attend different departments. Therefore, we believe it is not likely that female participants known to be pregnant or breastfeeding were included.

A last limitation is that our study was powered to evaluate a difference in mean adherence between each of the intervention groups and the control group. The study was not powered to demonstrate differences in virological outcomes between the study arms.

Strengths of our study are that we based our interventions on a theoretical model of factors influencing adherence and on the stages of change model for the feedback session, leading to well-constructed interventions. Another strength is that we used two measures of adherence, pharmacy refill and self-report. The reason that we found differences for pharmacy refill counts, but not for self-report is probably due to social desirability, with patients in all arms over-reporting their pill intake. Lastly, we did not exclude participants who did not have a phone, i.e. those who are most likely participants from lower socio-economic levels, but provided them with a phone.

Conclusions
In conclusion, our results do not support the hypothesis that SMS and RTMM have a positive effect on adherence to HIV treatment. However, in patients who had a viral load below 1000 copies/ml at study entry, we found that adherence was significantly better in the intervention arms, suggesting that our interventions may have helped to ensure sustained adherence in these patients. More research is warranted to investigate how the intervention could be optimized to enhance adherence in different risk groups by adding more attention to intention to adhere for participants who have a high viral load. In addition, we advocate for more studies among key populations such as pregnant and breastfeeding women, children and adolescents as these key populations may experience different barriers for adherence to treatment.

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Disclaimer: N/A
Competing interests

No conflicts of interest have been reported.

Authors’ contributions

IMSDb: Dr. Sumari was involved from the inception of writing the research proposal till the writing up of this manuscript. She coordinated the data management including database and data verification. She did the analyses and wrote this manuscript.

KMN: Mr. Ngowi was involved from the inception of writing the research proposal till the writing up of this manuscript. He coordinated the study and data collection processes and wrote this manuscript.

TS: Dr. Sonda was involved in the analyses of the data.

FP: Mr. Pima was involved in the data collection processes.

LM: Miss. Masika was overseeing the data collection in the field and was playing a major role in data verification.

MAGS: Prof. Dr. Sprangers supervised KMN and contributed largely to writing up this manuscript.
PR: Prof. Dr. Reiss supervised KMN and contributed largely to writing up this manuscript.

BM: Dr. Mmbaga was overseeing the progress of the study in Kilimanjaro, Tanzania and contributed to writing up this manuscript.

PTN: Dr. Nieuwerk was involved from the inception of writing the research proposal till the writing up of this manuscript. She supervised KMN and contributed largely to this manuscript.

REA: Prof. Dr. Aarnoutse was mentoring IMSdB and was involved from the inception of writing the research proposal to the writing up of this manuscript. He contributed largely to the proposal and the manuscript.

Author information

No additional information

Additional files

Additional file 1: Annex I: Stages of Change Model

Information on file format. JPEG.

Additional file 2: Annex IIA: Template for tailored feedback
Information on file format. PDF.

Additional file 3: Annex IIB: Scheme for discussing adherence in standard care

Information on file format. PDF.

Additional file 4: Annex IIIA: SMS scheme

Information on file format. JPEG.

Additional file 5: Annex IIIB: RTMM

Information on file format. JPEG.

Additional file 6: Annex IV: Adherence calculations

Information on file format. PDF.

Additional file 7: Annex V: Results post hoc analyses

Information on file format. PDF.

List of abbreviations
ABC  Abacavir

ANOVA  Analysis of Variance

ART  Antiretroviral Treatment

AZT  Zidovudine

CRERC  College Research and Ethical Review Committee

CRF  Case Report Form

DAT  Digital Adherence Tool

FTC  Emtricitabine

GLS  Generalized Least Squares

GPRS  General Package Radio Service

HIV  Human Immunodeficiency Virus

IQR  Interquartile Range

KCMC  Kilimanjaro Christian Medical Center
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCMUCo</td>
<td>Kilimanjaro Christian Medical University College</td>
</tr>
<tr>
<td>MEMS</td>
<td>Medication Events Monitoring System</td>
</tr>
<tr>
<td>ml</td>
<td>Milliliter</td>
</tr>
<tr>
<td>NatHREC</td>
<td>National Health Research Ethics Sub-Committee</td>
</tr>
<tr>
<td>NIMR</td>
<td>National Medical Research Institute</td>
</tr>
<tr>
<td>PLHIV</td>
<td>People living with HIV</td>
</tr>
<tr>
<td>RTMM</td>
<td>Real Time Medication Monitoring</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SMS</td>
<td>Short Message Service</td>
</tr>
<tr>
<td>SR</td>
<td>Self-report</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>VL</td>
<td>Viral load</td>
</tr>
</tbody>
</table>
References


3TC Lamivudine


Table 1: Demographic and disease characteristics at enrolment (N=249)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>RTMM arm</th>
<th>SMS arm</th>
<th>Standard of Care</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%), mean (SD), median (IQR)</td>
<td></td>
<td>249(100)</td>
<td>83(33)</td>
<td>83(33)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>176(71)</td>
<td>57(68)</td>
<td>60(72)</td>
<td>59(71)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>41.2(11.10)</td>
<td>42.8(12)</td>
<td>39.6(12)</td>
<td>41.2(12)</td>
<td>0.22</td>
</tr>
<tr>
<td>Primary school (%)</td>
<td>152(61)</td>
<td>51(61)</td>
<td>50(60)</td>
<td>51(61)</td>
<td>0.36</td>
</tr>
<tr>
<td>Secondary school (%)</td>
<td>84(34)</td>
<td>29(35)</td>
<td>29(35)</td>
<td>26(31)</td>
<td></td>
</tr>
<tr>
<td>Tertiary School (%)</td>
<td>11(4)</td>
<td>3(4)</td>
<td>2(2)</td>
<td>6(2)</td>
<td></td>
</tr>
<tr>
<td>Reported suboptimal adherence(%)</td>
<td>169(68)</td>
<td>50(60)</td>
<td>57(69)</td>
<td>62(75)</td>
<td>0.19</td>
</tr>
<tr>
<td>Missed visits(%)</td>
<td>188(76)</td>
<td>65(78)</td>
<td>66(80)</td>
<td>57(69)</td>
<td>0.21</td>
</tr>
<tr>
<td>Had leftovers(%)</td>
<td>175(70)</td>
<td>57(69)</td>
<td>61(74)</td>
<td>57(69)</td>
<td>0.74</td>
</tr>
<tr>
<td>Median years HIV positive (IQR)</td>
<td>7.2(2.6-11.9)</td>
<td>6.7(2.2-11.2)</td>
<td>5.6(2.4-11.9)</td>
<td>8.1(3.3-12.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Median years on current ART (IQR)</td>
<td>4.4(1.8-7.7)</td>
<td>4.3(1.3-7.2)</td>
<td>4.1(1.9-7.5)</td>
<td>5.4(2.1-8.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>NVP+AZT+3TC-fixed dose, 2 times 1 pill (%)</td>
<td>55(22)</td>
<td>17(21)</td>
<td>16(19)</td>
<td>22(27)</td>
<td>0.28</td>
</tr>
<tr>
<td>EFV+TDF+3TC-fixed dose, 1 pill (%)</td>
<td>97(39)</td>
<td>33(40)</td>
<td>37(45)</td>
<td>27(33)</td>
<td></td>
</tr>
<tr>
<td>EFV+TDF+FTC-fixed dose, 1 pill (%)</td>
<td>21(8)</td>
<td>5(6)</td>
<td>8(10)</td>
<td>8(10)</td>
<td></td>
</tr>
<tr>
<td>EFV (1 pill) + AZT+3TC (2 times, 1 pill)</td>
<td>31(12)</td>
<td>11(13)</td>
<td>13(16)</td>
<td>7(8)</td>
<td></td>
</tr>
<tr>
<td>EFV + ABC+3TC (2 times 1 pill) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>NVP + AZT+3TC-2 times 1 pill (%)</td>
<td>ATV/r+AZT+3TC (2 times 1 pill)</td>
<td>ATV/r+TDF+FTC (2 times 1 pill)</td>
<td>ATV/r+ABC+3TC-2 times 1 pill (%)</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1(0.4)</td>
<td>20(8)</td>
<td>10(12)</td>
<td>3(4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r+AZT+3TC-1 time 3 pills, 1 time 2 pills</td>
<td>24(10)</td>
<td>7(8)</td>
<td>21(11)</td>
<td>12(15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load &lt;20 copies/mL* (%)</td>
<td>117(48)</td>
<td>42(51)</td>
<td>33(42)</td>
<td>42(52)</td>
<td></td>
</tr>
<tr>
<td>Viral load &lt;1000 copies/mL* (%)</td>
<td>189(78)</td>
<td>63(77)</td>
<td>65(82)</td>
<td>61(75)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, interquartile range

NPV=nevirapine, EFV=efavirenz, ATV=atazanavir, r=ritonavir, LPV=lopinavir, ABC=abacavir, AZT=zidovudine; 3TC=lamivudine; FTC=emtricitabine; TDF=tenofovir disoproxil fumarate

*N=242, for seven participants the results were not available
Table 2: Differences in mean adherence between arms (modified intention-to-treat analyses, n=243)

<table>
<thead>
<tr>
<th>Arm (N)</th>
<th>Control arm (81)</th>
<th>SMS arm (80)</th>
<th>RTMM arm (82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported mean adherence in past week³</td>
<td>95.2 (11.8)</td>
<td>95.9 (10.6)</td>
<td>95.0 (9.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Self-reported mean adherence in past month³</td>
<td>96.9 (7.4)</td>
<td>97.5 (7.2)</td>
<td>96.6 (7.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean pharmacy refill adherence</td>
<td>87.9(12.9)</td>
<td>89.6(12.9)</td>
<td>90.6(10.8)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Table 3: Differences in reaching adherence cut off values between arms (modified intention-to-treat analyses, n=243)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Control arm</th>
<th>SMS arm</th>
<th>RTMM arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Self-report</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past Week 100%³</td>
<td>151</td>
<td>62.9</td>
<td>51</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Week &gt;95%²</td>
<td>193</td>
<td>80.4</td>
<td>66</td>
<td>81</td>
<td>65</td>
</tr>
<tr>
<td>SR Week &gt;90%³</td>
<td>205</td>
<td>85.4</td>
<td>70</td>
<td>86</td>
<td>69</td>
</tr>
<tr>
<td>SR Week &gt;85%³</td>
<td>212</td>
<td>88.3</td>
<td>72</td>
<td>89</td>
<td>70</td>
</tr>
<tr>
<td>SR Week &gt;80%³</td>
<td>221</td>
<td>92.1</td>
<td>73</td>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>Past Month 100%²</td>
<td>123</td>
<td>51.2</td>
<td>42</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>SR Month &gt;95%³</td>
<td>209</td>
<td>87.1</td>
<td>70</td>
<td>86</td>
<td>71</td>
</tr>
<tr>
<td>SR Month &gt;90%³</td>
<td>214</td>
<td>89.2</td>
<td>72</td>
<td>89</td>
<td>72</td>
</tr>
<tr>
<td>SR Month &gt;85%³</td>
<td>221</td>
<td>92.1</td>
<td>74</td>
<td>91</td>
<td>73</td>
</tr>
<tr>
<td>SR Month &gt;80%³</td>
<td>229</td>
<td>95.4</td>
<td>76</td>
<td>94</td>
<td>77</td>
</tr>
<tr>
<td><strong>Pharmacy refill</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>11</td>
<td>4.5</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>95%</td>
<td>94</td>
<td>38.7</td>
<td>27</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>90%</td>
<td>160</td>
<td>65.8</td>
<td>54</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>85%</td>
<td>182</td>
<td>74.9</td>
<td>53</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>80%</td>
<td>205</td>
<td>84.4</td>
<td>66</td>
<td>81</td>
<td>67</td>
</tr>
</tbody>
</table>
Table 4: Differences in adherence and virological outcomes between arms (per protocol analyses, n=225)

<table>
<thead>
<tr>
<th></th>
<th>Total(%)</th>
<th>RTMM arm</th>
<th>SMS arm</th>
<th>Standard of Care</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>225</td>
<td>77</td>
<td>73</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Viral load &lt;20</td>
<td>156(69)</td>
<td>53(69)</td>
<td>51(70)</td>
<td>52(69)</td>
<td>0.99</td>
</tr>
<tr>
<td>copies/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load &gt;1000</td>
<td>28(12)</td>
<td>12(16)</td>
<td>9(12)</td>
<td>7(3)</td>
<td>0.51</td>
</tr>
<tr>
<td>copies/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Differences in mean adherence between arms in participants with VL <1000 copies at study entry

<table>
<thead>
<tr>
<th></th>
<th>Control arm N=62</th>
<th>RTMM arm N=64</th>
<th>p-value</th>
<th>SMS arm N=61</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported adherence in past week</td>
<td>93.9</td>
<td>95.8</td>
<td>0.31</td>
<td>97.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Self-reported adherence in past month</td>
<td>96.0</td>
<td>96.8</td>
<td>0.58</td>
<td>98.4</td>
<td>0.045</td>
</tr>
<tr>
<td>Pharmacy refill adherence</td>
<td>86.9</td>
<td>93.1</td>
<td>0.002</td>
<td>91.4</td>
<td>0.045</td>
</tr>
</tbody>
</table>
Table 6: Difference in adherence for participants who were virologically suppressed and participants who were not suppressed

<table>
<thead>
<tr>
<th></th>
<th>Viral Load&lt;20 copies/ml</th>
<th>Viral Load=&gt;20 copies/ml</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>156</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Mean self-reported adherence in past week (% of doses taken)</td>
<td>95.7</td>
<td>94.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean self-reported adherence in past month (% of doses taken)</td>
<td>95.9</td>
<td>92.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean pharmacy refill adherence (% of doses taken)</td>
<td>92.1</td>
<td>85.6</td>
<td>0.008</td>
</tr>
</tbody>
</table>