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Potential tools for promoting adherence to antiretroviral therapy among people living with HIV in Tanzania

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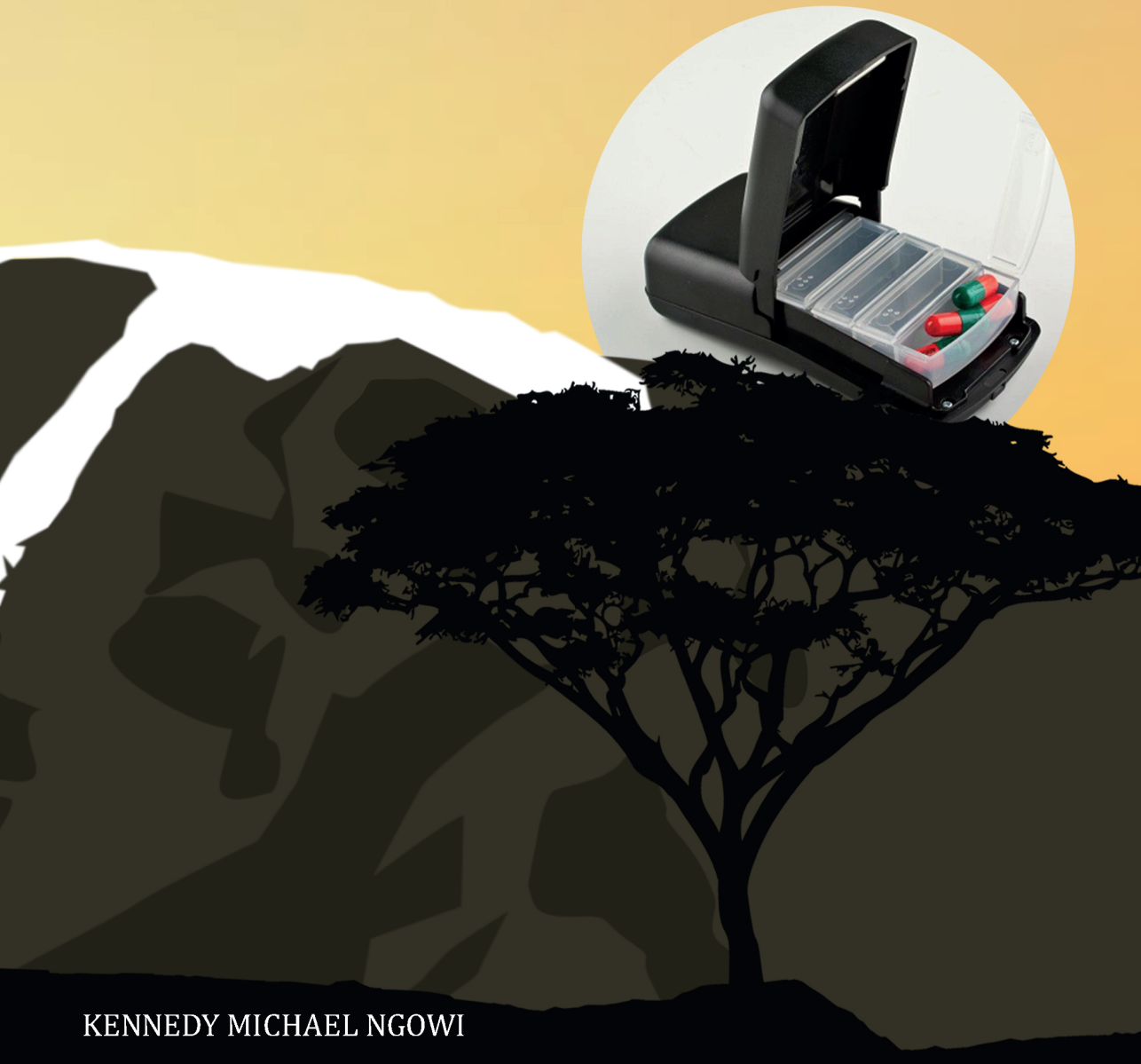

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Digital Health Technologies: Potential Tools for Promoting Adherence to Antiretroviral Therapy Among People Living With HIV In Tanzania

Kennedy Michael Ngowi

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Digital Health Technologies: Potential Tools for Promoting Adherence to Antiretroviral Therapy Among People Living With HIV In Tanzania

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TABLE OF CONTENTS

Chapter One

General introduction and outline of the thesis

GENERAL INTRODUCTION

HIV is a major global health problem. An estimated 54% of the world's population affected by HIV lives in sub-Saharan Africa (SSA), making HIV/AIDS a serious community health threat in this area.[1] In 2017, more than 300,000 deaths recorded in Africa were due to AIDS-related diseases.[2] In this thesis, we focus specifically on Tanzania where nearly 1.6 million persons have been reported to live with HIV in 2017.[3] Of those, 71% were adults receiving antiretroviral treatment (ART). However, only 58% of these adults had suppressed viral loads.[4] Sufficiently high levels of adherence to ART are needed to achieve and maintain suppressed viral load. Despite the vast majority of people living with HIV(PLHIV) in Tanzania have access to ART, maintaining adherence to lifelong treatment thus seems to be a major challenge.[4]

Adherence to HIV Treatment

Adherence is defined as the whole process around taking medication and the extent to which patients comply with treatment guidance and medical advice.[5] This includes taking all the pills that have been prescribed on time and attending all the clinic appointments.[6] In the context of HIV, adherence is effective when medication intake of ART is more than 95% over a given period. The same percentage has been recommended by the World Health Organization (WHO) as the optimal rate for ensuring viral suppression.[7] Failure to reach that threshold will increase the chance of treatment failure, which increases the likelihood of developing drug resistance, HIV disease progression, and ultimately death. Several factors have been found to be associated with poor adherence. These can be divided into patient-related factors, treatment-related factors, and health-system-related factors each of which will be further elaborated in the next sections.

Patient-related factors

Patient-related factors largely relate to the barriers perceived by patients, including availability of food, fear of experiencing stigma and unwanted disclosure of HIV status, lack of social support, and alcohol abuse. These barriers may cause patients to experience anxiety, depression, and distress which may result in poor adherence to ART. Another factor related to cultural and religious aspects pertains to the majority of African communities believing that HIV causes shame to the family.[8–10] Patients may also feel reluctant to access ART care as they believe that HIV is a punishment for their sins.[11] In addition, fear of stigmatization and discrimination were also found to limit PLHIV's ability to make use of the social support

offered. As a result, PLHIV have difficulties disclosing their status to others, including family members, partners, and friends.[6,9,12,13] Studies have recommended adherence-enhancing strategies to address all these factors to ensure that the causes of non-adherence are identified and where possible remedied. Several strategies have been shown to be effective in addressing the mentioned adherence barriers, including mobile technology interventions, adherence counselling, provision of social support and community education.[14]

Treatment-related factors

Studies have indicated that patients may stop their medication due to medication side effects such as delusions, vomiting, faintness, weakness and skin-rashes.[15] Other studies described that due to the limited availability of HIV care, including poor counselling and limited stock of medication, patients tend to discontinue HIV treatment.[16,17] Poor patient-doctor communication has also been found to be associated with non-adherence as it hampers patients to engage in a trustworthy dialogue regarding their health condition. Effective communication improves patients' understanding and adherence to proposed treatment plans.[15,18] Similarly, strong patient-nurse relationships within health facilities contribute to continuity of HIV care.[10]

Health system-related factors

In SSA, particularly in remote areas, health systems have been struggling to provide comprehensive HIV care to PLIHV.[6,19] Several key barriers within the health system have been identified such as insufficient human resources to provide efficient HIV counselling, inadequate knowledge about HIV treatment guidelines by health care staff, unreliable and inaccurate tools to monitor adherence, drugs stock-out, and long traveling distance to reach the health facility.[20–23] Additionally, delay of HIV treatment due to high costs of viral load testing in most of SSA countries[24] and lack of tailored adherence strategies and interventions have also been mentioned as possible barriers of the HIV health care system.[25]

Adherence Measures

A number of adherence measurement methods exist to monitor adherence. In the context of clinical care, self-reported adherence and pill counts are among the tools often used to record medication adherence.[26–28] These methods are relatively simple and affordable as part of regular clinic routine. Moreover, they may support meaningful communication about adherence between health care providers and patients.[15] However, due to recall and social

desirability bias, self-reported adherence tends to overestimate patients' adherence levels.[19] Another intrinsic limitation of self-report and pill counts is that missed doses are only detected with a delay of several weeks or months.

A study has described this challenge for pharmacy refill based adherence measures, mostly because of clinicians delaying initiation of medication adherence interventions in the absence of viral rebound.[29] In addition, another study found self-reported adherence to have a low sensitivity in predicting viral load rebound.[19] However, the same study recommended frequent viral load testing as crucial for monitoring and enabling the early detection of antiretroviral treatment failure.[19] According to the WHO, viral load measurement is reliable and is the gold standard for actual medication adherence.[24] Furthermore, some HIV treatment guidelines have defined cut-off points by which patients who have plasma HIV-RNA < 20 copies/ml are considered virologically suppressed, between 20 and 1000 copies/ml are considered to be virologically stable and those with HIV-RNA > 1000 copies/ml are considered to be virologically failing.[4] However, in practice the main challenge is that viral load testing is mostly not, or only infrequently, available as it is too expensive in most low-income countries.[30] In addition, turnaround time of viral load testing results is unfavourable, with time to receiving results reaching three months or more after sample taking due to a centralized system of testing.[11]

Another technique to measure and monitor adherence is electronic medication monitoring by which a medication-containing bottle (MEMS) embedded with a microelectronic chip can record daily-detailed data of medication adherence, each time it is opened. Compared with self-report measures of adherence, MEMS avoids recall bias. However, an intrinsic limitation is that opening the bottle does not necessarily equate to actual medication intake.[31] The relatively high costs of the MEMS device renders it unaffordable for routine clinical use in limited resource settings. An additional limitation of the MEMS device is the fact that patients may forget to bring the device with them when attending the clinic.

Opportunities for using Digital Adherence Tools (DAT)

The majority of the population in SSA has access to mobile phones.[32] This high penetration of mobile phones has been driven by the huge demand for mobile money by the financial sector. This has also made mobile phone use affordable thereby allowing users to transfer cash and buy items through the mobile network.[33] The health sector has benefited enormously from mobile technology particularly in improving treatment outcomes of patients.[33–35]

In areas with high prevalence of HIV, several DATs may be useful, including (1) "short messaging service (SMS) texts" and (2) real-time medication monitoring (RTMM), also called "internet enabled digital pillboxes", as they have been explored for monitoring and improving antiretroviral treatment outcome.[36] Moreover, the use of telecommunication enables interactive HIV care consultation and sending clinic reminders without the need to travel a long distance to the rural communities, as has been practiced in Botswana.[37] Also, the acceleration of increased internet coverage in urban settings and the availability of affordable smartphones, has provided a platform to develop mobile apps for supporting directly observed "video" therapy among patients with HIV and tuberculosis (TB).[38] However, the Tanzanian technological infrastructure does not yet allow for such advanced systems which require affordable high speed internet in order to support video calling or mobile apps. Therefore, in this thesis we only focus on SMS and RTMM.

Short Messaging System (SMS)

Short Messaging System (SMS) has been described as the most efficient and promising mobile technology to improve ART adherence in SSA. The Joint United Nations Programme on HIV/AIDS (UNAIDS) advocates for SMS technology as a potential tool to transform HIV care in limited-resource settings.[39] Similarly, the WHO describes SMS services to have a high impact on delivering health care services in settings where the penetration of internet access is limited.[7,40] Considering its potential for improving adherence to ART, several studies have investigated the feasibility and acceptability of SMS in resource-limited settings. The aim of these studies was to investigate the effects of sending SMS to remind patients, amongst others, to take ART medication and to attend the clinic, and to ask their perceptions on using the interventions. For instance, in Kenya, a Randomized Clinical Trial (RCT) found that weekly SMS-reminders were highly acceptable among PLHIV and increased their clinic attendance rate.[41,42] Similarly, the WelTel trial reported improvements regarding ART adherence and the potential to suppress viral load among PLHIV through sending SMS reminders.[43] In

South Africa, SMS reminders improved communication between nurses and patients, particularly with respect to improving adherence.[44,45] Other studies conducted in other countries in SSA, such as Cameroon, Uganda, and Botswana, have also reported beneficial effects of using SMS reminders on ART adherence.[37,46–48] A meta-analysis of several RCT's reported that participants randomized to an SMS intervention had better adherence compared to patients receiving standard care.[35,49–51] While SMS is the preferred and most promising intervention to remind and improve medication intake, it remains difficult to identify and track non-adherent patients in real-time.

Real-Time Medication Monitoring (RTMM)

Interventions employing real-time medication monitoring (RTMM) have been suggested as another potential effective strategy to improve medication adherence. RTMM is a mobile technology comprised of a pillbox which contains (HIV) medication that records each opening.[16,29–31] RTMM can monitor and record the time the pillbox is opened and the medication supposedly taken, and transfer this information to a web-based platform. The platform records the data and generates automated reports.[52] These reports provide vital information such as date, time and percentage of adherence based on pillbox openings, thereby providing insight into the patient's adherence. The clinic nurse may use such reports as an intervention to discuss with patients about adherence patterns and possible related factors and decide together on an action plan.

Several studies have already investigated the feasibility and acceptability of RTMM in resource-limited settings.[31,46,53,54] However, to our knowledge, no RCT has been conducted in Tanzania which compared the use of SMS and RTMM with standard care to improve adherence among PLHIV. Such a trial therefore is an important component of the studies reported in this thesis.

Challenges of Digital Adherence Tools

Despite the advantages of using DATs, several challenges associated with the use of such technologies have also been encountered. Unreliable network connections, high costs of maintaining telemedicine infrastructure, and understaffing of technical experts have each been described as limitations.[55] Furthermore, a systematic review investigating the sustainability of mobile interventions also described the high costs of internet bundles which are cost-

prohibitive for the majority of users, and are therefore a key barrier to using a mobile app.[25,38]

Objectives of the Thesis

Therefore, the overall aim of this thesis is to investigate the impact of digital health technology as a potential tool to primarily support ART adherence and secondarily improve clinical outcomes among PLHIV in Tanzania. The first objective is to compare the effectiveness of two DATs, SMS and RTMM, with standard care in promoting treatment adherence, using a randomized clinical trial, the so-called REMIND-HIV trial. The second objective is to examine the barriers and challenges participants encounter when using the DAT strategies. The final objective is to examine to what extent the adherence measures, including pharmacy refill counts, self-reported adherence and RTMM, predict virologic suppression.

Outline of the Thesis

In chapter two, we describe a pilot study that investigated the acceptability and feasibility of sending SMS reminders to help remind pregnant and breastfeeding women living with HIV (WLHIV) in Kilimanjaro, Tanzania to take their medication. Such women often have difficulties in maintaining adequate levels of ART adherence. Therefore, we decided to conduct this pilot study using SMS in this particular group. This was a 6-months observational pilot-study among WLHIV attending antenatal and postnatal care. Participants received a SMS reminder before actual time of intake. Then later, a follow-up SMS was sent, asking participants whether medication was taken or not.

In **chapter three,** we describe the main results of the 48 week REMIND-HIV trial investigating the effect of the use of DATs on adherence to ART among adults living with HIV in Kilimanjaro. Participants were randomized to standard care, or to standard care in combination with either receiving reminder SMS-texts, or using a real-time medication monitoring (RTMM) device (Wisepill®) which stores antiretroviral medication and records the opening of the device as proxy for medication intake. Adherence to ART measured through self-report and pharmacy refill count served as the primary outcome, and viral load suppression rates as secondary outcome.

Whilst the REMIND-HIV trial was underway and the participants discussed their level of adherence in clinic visits with study nurses, several discrepancies came to light between self-

reported adherence and adherence recorded by SMS text messaging or RTMM among some trial participants. This led us to set up a qualitative study, including short face-to-face in-depth interviews with these participants to systematically explore possible reasons for these observed discrepancies, the results of which are described in **chapter four**.

In **chapter five** we describe the case of a REMIND-HIV trial participant randomized to use RTMM, who consistently had an adherence level of >95% by self-report, pharmacy refill and RTMM at all study visits, but died shortly after completing the trial. The details of this case illustrate well the possible caveats of the use of RTMM for monitoring adherence.

In **chapter six**, we describe a mixed-methods sub-study of the REMIND-HIV trial, conducted after all participants had completed the trial, to assess the post-implementation acceptability of the intervention in the context of end-user experience. The Theoretical Framework of Acceptability developed by Sekhon et al.[56] was used in which seven domains of acceptability of the intervention were assessed: affective attitude, perceived effectiveness, ethicality, perceived burden, self-efficacy, intervention coherence and opportunity costs of the interventions.

Chapter seven describes the analysis of the sensitivity, specificity, negative predictive value and positive predictive value of self-reported adherence, pharmacy refill counts, and RTMM for predicting virological failure in the REMIND-HIV trial. The analyses were repeated using different adherence cut-off levels, including 80%, 85%, 90%, 95% and 100%, to determine at which cut-off, which adherence measure best predicted a viral load of >20 copies/mL.

Chapter eight discusses the main findings of the thesis, also in the context of the existing literature. We additionally list the limitations of these studies and provide recommendations for future studies on how to overcome those limitations. Lastly, we discuss the lessons learned and how to engage key stakeholders to scale-up DATs.

Chapter nine provides a summary in both English and Dutch of the main findings of each of the studies described in each chapter.

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Chapter Two

Feasibility of SMS to remind pregnant and breastfeeding women living with HIV to take antiretroviral treatment in Kilimanjaro region, Tanzania: a pilot study

Authors

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ABSTRACT

Background: Pregnant and breastfeeding Women Living with HIV (WLHIV) often have difficulties in reaching adequate levels of adherence (>95%) to Antiretroviral treatment. "Forgetting" is the most commonly mentioned reason. Sending reminders via SMS is expected to improve adherence. We conducted a pilot study to investigate acceptability, user experience and technical feasibility of sending reminder-SMS to WLHIV.

Methods: This was a 6-months observational pilot-study among WLHIV attending antenatal and postnatal care at Kilimanjaro Christian Medical Centre in Moshi, Tanzania. Women received a reminder-SMS 30 minutes before usual time of intake. One hour later, they received an SMS asking whether they took medication to which they could reply with 'Yes' or 'No'. Messages were sent 3 times a week on randomly chosen days to prevent reliance on daily messages. We calculated the percentage of number of SMS delivered, failed to be delivered, and replied to. We analysed feedback from exit-interviews about experience with the SMS-reminders.

Results: 25 women were enrolled (age 18-45), 2 were lost to follow up. 5,054 messages were sent of which 53 failed to be delivered (1%). 1,880 SMS were sent with a question if medication was taken; 1,012 (54%) messages were replied to, of which 1,003 (99%) were replied with 'YES' and closely to 'YES', and a total of 9 (1%) with 'NO' and 'closely to NO'. 868 messages (46%) were not responded to due to either dropout, change of phone number, loss of phone or network failure. Results from 18 interviews showed that 16 (89%) women were satisfied with SMS reminders. 2 (11%) were concerned about unwanted disclosure because of the content 'don't forget to take medication' and one reported other privacy issues (6%). 3 (17%) women experienced stigma.

Conclusion: 99% of SMS being delivered indicates that SMS reminders in this resource-limited setting are technically feasible. However, concerns regarding privacy were noted, specifically the risk of unwanted disclosure and the experience of stigma. Participants indicated that being made aware of their adherence, motivated them to adhere better. However, personalised and more neutral content of the SMS might be a way to improving the intervention.

BACKGROUND

Infants are still being born with HIV in Sub Saharan Africa (SSA), despite significant increases in treatment coverage and implementation of programs to reduce vertical transmission of HIV.[1] In East African countries, the coverage of Prevention of Mother-To-Child Transmission (PMTCT) programmes varied between countries from for example 77% in Kenya to 95% in Uganda in 2016.[2,3] In Tanzania, there were 77,200 pregnant women living with HIV (WLHIV) in 2016.[4] Of them, only 84% received free effective Antiretroviral Treatment (ART), resulting in a high mother-to-child transmission rate of 11%. The transmission rates of HIV from mother to child during pregnancy, delivery and breastfeeding vary from 15% to 45% in the absence of PMTCT programmes. According to the World Health Organization (WHO) guidelines, initiation of lifetime Antiretroviral Therapy (ART) by WLHIV under the recommended Option B+ programme has the potential to reduce the transmission of HIV to the newborn to below 5%.[6] In addition, their infants should receive nevirapine syrup till 6 weeks postpartum and exclusive breastfeeding up to month 6, preferably continuing breastfeeding up to 24 months in addition to solid foods.[7] In a prospective cohort study conducted in the Kilimanjaro region in 2016, out of 200 pregnant women enrolled, 4.8% were found to be HIV positive while only 41% were in PMTC care.[5] Sustaining a high level of adherence to ART during pregnancy, postpartum and during breastfeeding are, however, a prerequisite to prevent HIV-transmission from mother to child.[8]

Achieving optimal levels of adherence (>95%) is still a major challenge due to several factors including drug shortages and forgetting to take medication.[9] Adherence to ART entails that medication is taken at the right time and exactly as prescribed without missing a dose. Poor adherence to ART may not only lead to virological failure and HIV-transmission from mother to child but also to creation of resistant HIV strains.

A meta-analysis among a large sample of People Living with HIV (PLHIV) outlined that worrying about disclosing the HIV status and forgetting to take medication on time were major barriers to adherence in Sub Saharan African countries.[10] Achieving and maintaining high levels of adherence to ART is particularly challenging for pregnant and breast-feeding women. It was shown that pregnant women using ARV tend to forget taking doses of ART more often than non-pregnant women. They also may have more difficulties in incorporating medication intake into their busy schedule than non-pregnant women.[11] Furthermore, it was shown that pregnant women may quit taking medication due to side-effects of ARV. Breastfeeding women

may also feel more healthy after delivery leading to reduced motivation to continue taking medication.[1]

Nowadays, more than 80% of the population in Tanzania has access to mobile phones.[12] Out of those, 60% own a basic phone without internet access and 20% a smartphone. Short Message Service (SMS) has emerged as one of the leading mobile services.[12] This provides a potential platform to support HIV treatment adherence by sending reminder cues through texting.

Several studies conducted in resource-limited settings examined the potential of mobile phone use in enhancing adherence to HIV medication. In a study conducted in Kwazulu Natal, South Africa, participants received an SMS once a week to remind them to take their HIV medication.[13,14] A total of 98% of the participants reported that the SMS helped them to remember taking their medication. Two Randomised Clinical Trials (RCT) undertaken in Kenya indicated that weekly SMS reminders led to improved ART adherence.[15,16] In Botswana, the adoption of SMS reminders has improved adherence to ART and also the relationship between patients and health care providers. In addition, results from that study showed that 93% of participants responded to the SMS reminders indicating it had helped them to take medication on time.[17] WLHIV were satisfied about SMS reminders as indicated in both studies in South Africa and Kenya.[13,15] A 6 month pilot study conducted in South India, compared 2 to 3 times weekly SMS reminders with reminders via Interactive Voice Response (IVR). Adherence improved in both groups from 85% to 91%. However, all enrolled study participants would prefer automated IVR.[18]

Although previous studies showed that it is technically feasible to enhance adherence by sending SMS reminders and that this improved self-reported adherence, several challenges remain. In the studies in South Africa and Kenya, 10% of sent messages did not reach study participants due to loss of their phones and change of phone numbers during the study period. Also, they reported that participants who received daily SMS texts responded less often to these messages compared to participants who received weekly SMS texts.[15] Participants reported concerns about privacy in studies in Kenya, South Africa and Botswana.[14,15,17] Drop-out rates as high as 35% were reported in an RCT in Uganda.[19] In this RCT, the reminder and a question asking about adherence were included in a single SMS. This combined question was not found to motivate participants to take their medication. Language illiteracy was noted to be a challenge in studies in Cameroon[20] and Uganda[19] as participants preferred SMS text messages in their native language instead of English. A systematic review of 35 studies about SMS applications in Africa found that only 5 studies evaluated the level of acceptance through

exit interviews, showing that 94% of participants were highly satisfied. This review also indicated that network failure was a concern for 14% of enrolled participants causing them to sometimes miss the reminder SMS. Battery power was a problem to participants as well.[21]

Whereas SMS reminders are a promising method to enhance adherence to ART, challenges remain with respect to technical feasibility, acceptability, timing and content of the messages. In the present pilot study, we aim to investigate the acceptability and technical feasibility of using short text messages for enhancing adherence to ART among pregnant and breastfeeding WLHIV in Kilimanjaro, Tanzania.

METHODS

Study Design

This was a prospective, single-arm, 6-months observational pilot-study among HIV-positive pregnant and breastfeeding women. The study was approved by the Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC) No. 829 and the National Health Research Ethics Sub-Committee (NathRec) of Tanzania NIMR/HQ/R.8a/Vol.1X/2432.

Study Participants

From May 2017 to July 2017, we recruited pregnant and breastfeeding women who were attending either antenatal or postnatal care at Kilimanjaro Christian Medical Center (KCMC) in Moshi, Tanzania. KCMC is a tertiary referral hospital in the Northern zone of Tanzania with 450 beds and provides service to approximately 250 to 300 pregnant and breastfeeding WLHIV annually. The centre includes a special Child Centred Family Care Clinic (CCFCC), which provides care and treatment to children living with HIV/AIDS and their families. Women were eligible for the study if they (1) were HIV positive and pregnant or breastfeeding, (2) were aged between 18 and 50 years, (3) were attending Kilimanjaro Christian Medical Centre, (4) were on ART since at least 6 months, (5) had no foreseen changes in ART in the subsequent 3 months, (6) owned a mobile phone with operational SIM card, (7) lived in rural or urban areas of the Kilimanjaro Region, (8) were willing to receive SMS reminding them to take ART, (9) were able to read and reply to SMS, (10) were willing to come to the clinic at least once a month and (11) provided written informed consent to participate in the study. We excluded WLHIV who were either on co-medication for other (chronic) diseases such as tuberculosis (TB), diabetes and chronic hypertension; or who were admitted to a hospital or were participating in concurrent SMS reminder studies. As this was a pilot study investigating the

feasibility of a newly developed intervention, a sample size of 25 WLHIV was considered sufficient to meet our aims.

Study Procedures

Recruitment and Monitoring of WLHIV

We used convenience sampling to recruit women. Potential participants were identified by a clinic nurse who informed the research doctor. The doctor determined whether a candidate fulfilled the eligibility criteria. The study nurses explained the study in detail to the eligible participant using a participant information leaflet. The participant was given time to read and understand the leaflet. Written informed consent was requested from participants before any study procedure. Following that, the nurse invited all women who agreed to participate. Subsequently, baseline information about the participants was collected through a short structured questionnaire asking about demographics, mobile phone number and usual time of medication intake according to the physician's prescription. We entered the participant's phone number into the SMS program and subscribed the participant's phone number to an unlimited monthly SMS bundle.

After enrolment, participants were followed for 6 months. The participants attended the clinic monthly for medication refill and antenatal follow-up. After 3 months, the study doctor asked a general question "*What is your general experience with the SMS messages?"* The answer was written down verbatim.

After 6 months, participants were interviewed about their experience with receiving SMS by using a semi-structured questionnaire. The interview was conducted in Swahili by the study doctor. Data from the enrolment questionnaire and the exit-interviews were entered in REDCap® (Research Electronic Data Capture) 9.3.5, Vanderbilt University, Tennessee USA, an open-source web-based system which has features for query generating, auditing and data validation.[22]

The Intervention

SMS Content

The SMS were grouped into 4 categories. We designed the SMS in Swahili and only those were sent to our participants. Figure 1 shows the SMS scheme translated into English for the purpose of general readability of this manuscript. First, an introduction SMS was sent once on the day of enrolment to welcome the participant. Second, a reminder message to alert the

participant to not forget to take their medication was sent 30 minutes before usual time of medication intake. Thirdly, a question SMS was sent one hour after usual time of intake to ask the participants if they took the medication according to the doctor's instruction. The participant had to reply with any of the options 'N' (Ndiyo, meaning YES) - I took my medication, 'H' (Hapana, meaning NO) - I did not take my medication or 'B' (Bado, meaning NOT YET). If the reply was YES or NO, an acknowledgement SMS was sent saying "Thank you and have good day" and the SMS flow was terminated. If the reply was "NOT YET", one hour later, a question SMS was sent again to ask if medication was taken.

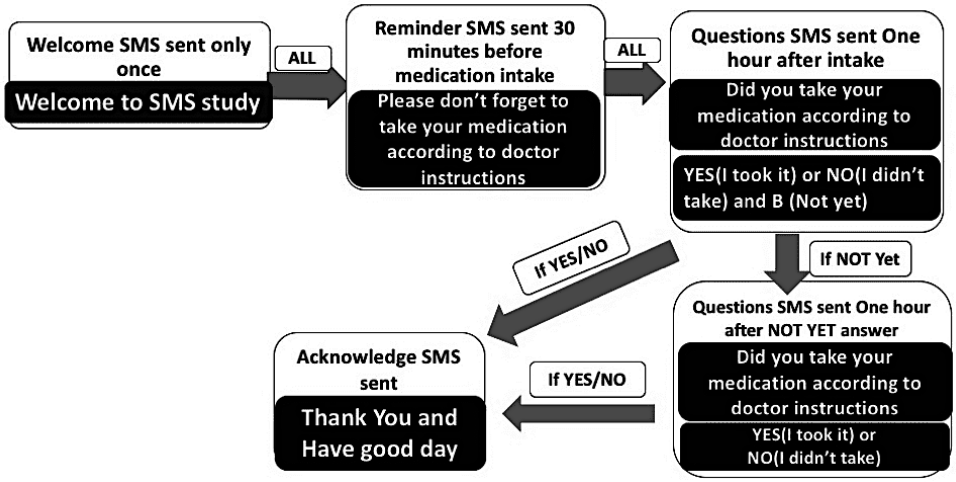

Figure 1: Flow of SMS messages sent to participants

The timing of the SMS reminders was scheduled individually and processed automatically by the SMS system. The SMS system sent messages 3 times a week on randomly chosen days. The days were different for each participant. We used the permutations formula:

$$ {}_nP_r = \frac{n!}{(n-r)!} $$

for calculation of the number of possible combinations of 3 days in a week of 7 days. 35 combinations of days were possible (i.e. Mon-Tues-Wed, Mon-Tues-Thurs, Mon-Tues-Fri, Mon-Tues-Sat etc.).

The SMS Program

The SMS program was developed using open-source software Telerivet® (San Francisco, California, United States).[23] The software has a standard platform that integrates most of the

existing mobile phone technologies. Telerivet allows routing of messages to and from any number of mobile devices with a basic internet connection. With a cloud-based management system, it supports the developer to adapt an external Application Platform Interface (API) using other platforms for monitoring and tracking activities. The system is only accessible through password authorisation.

Keywords

Keywords are pre-defined words that women could respond to by typing an SMS reply. Once the SMS from a participant is received, the SMS program scans the message content and matches it with our pre-defined keywords such as 'YES' and 'NO'. When keywords were recognised, the program automatically sent a reply to the participant based on the specified conditions and algorithm that we programmed in the system.

Outcome measures

Technical Feasibility of the SMS Program

Technical feasibility was based on the degree of performance and success of the system operation. Performance was determined by tracking the total number of SMS messages sent and delivered per participant; specifically, the number of SMS reminders and SMS questions. The success of the SMS system was based on scheduling of SMS messages, which includes the time of intake and date of SMS sent, failed and delivered. The outcome of feasibility was measured through calculating percentages. The numerator was the total number of SMS delivered and the denominator was the total number of SMS sent.

Acceptability of Receiving SMS Reminders and Questions

Acceptability was evaluated in terms of satisfaction with receiving SMS reminders and questions by participants. This was evaluated using a questionnaire containing 18 questions. Each question had closed-ended response options to be answered by "yes" or "no" or “good” or not “good” followed by open-ended questions to solicit explanations. The open-ended questions provided more narrative explanations of the answers selected in the closed questions. The questionnaire was developed by the study team based on feedback given during consultations and on previous research.[16] The topics were on general experience with receiving the SMS reminders and questions, difficulties in receiving SMS, timing of SMS, contents of the SMS, problems with network connectivity, travelling, advantages of the SMS, potential stigma and loss of confidentiality by receiving SMS, ability to reply to SMS, impact on adherence, taking medication on days without SMS and ideas about adherence promoting interventions. Descriptive analyses (frequencies and percentages) of the outcomes were conducted to measure the acceptability. The numerator was the frequency calculated from closed-ended question. The denominator was the total number of participants that participated in the exit- interview.

Adherence to Medication

To obtain an indication about the extent to which SMS can be used for adherence monitoring, we calculated adherence based on SMS replies. ‘Yes’ answers were seen as an indication (“proxy”) for medication intake. We calculated an adherence percentage for each participant based on the number of responses that contained the keyword ‘YES’ or similar to ‘YES’ and ‘NO’ or similar to ‘NO’ (numerator). This was divided by the total number of question SMS sent to the participants one hour after usual time of medication intake (denominator). SMS with responses similar to ‘YES’ were ‘I TOOK MY PILLS’, ‘I REMEMBERED TO TAKE MY PILLS’, ‘THANKS FOR REMINDING ME’. These responses were considered “similar to Yes” and we assumed that these responses indicated that women took their medication. The responses determined to be similar to ‘NO’ where ‘I DIDN’T TAKE IT’, ‘I FORGOT TO TAKE IT’ and ‘I COULD NOT TAKE IT’.

Data Analyses

We used IBM SPSS software® version 24 (New York, US) for statistical analyses to determine the frequencies of answers to the SMS messages. Responses to the questions of the exit-interview were presented as frequencies and percentages. Narratives from feedback during consultation and from the exit-interviews were used to illustrate the frequencies. We calculated

adherence based on the SMS messages ('YES' meaning medication was taken) as stated in the previous paragraph for each woman who participated. From there we calculated median adherence for all included women.

RESULTS

25 women participated in our study. Their overall characteristics and variables related to HIV are shown in Table 1. 2 women dropped out before the end of the study and could not be traced for the exit interview. Data for all 25 participants are included in Table 1. 8 women (32%) were pregnant at the time of inclusion and 17(68%) were breastfeeding. The median duration on ART was 4 years (range: 0.5-12) and median age of participants was 36 (range 23-43). 22 (88%) women were on first-line ART and 3 (12%) were on second-line ART.

Table 1: Characteristics of pregnant and breastfeeding women

Characteristics	**(%) or Median [IQR*]**
Pregnant women	8 (32%)
Breastfeeding women	17(68%)
Age (Years)	10[range 30-40]
Duration on ART before the study(years)	2 [range: 6-8]
On first line ART (TLE) (DUOVIR-N)	22(88%)
On second line ART (LPV/r + TDF +FTC) OR (ATV/r + ABC + 3TC)	3(12%)

TLE: Tenofovir+Lamivudine+Efavirenz

ATV/r + ABC + 3TC: Atazanavir/Ritonavir (ATV/r) + Abacavir/Lamivudine (ABC/3TC)

LPV/r + TDF +FTC: Tenofovir +Emtricitabine (Truvada) + Lopinavir-ritonavir (LPV/r)

*IQR=Interquartile Range

Technical Feasibility of Sending and Receiving Messages

In total, 5,054 SMS were scheduled and sent of which 5,001 (99%) were delivered. 53 (1%) were not delivered. (Table 2). 4 participants occasionally received SMS messages too late despite having been sent at the scheduled time, which appeared to be due to participants switching off their phone during the night or network failures. SMS messages were resent the next day. A total of 1,845 (99.6% of total sent) SMS reminders were delivered 30 minutes before medication intake and 1,880 (99.5% of total sent) SMS questions were delivered one

hour after scheduled intake to ask the participants whether they took their medication or not. More question SMSs were sent than reminders, since the question was repeated after one hour if the reply was 'Not yet'.

Table 2: Overview of SMS delivered

Variables	**Number of SMS(%)**
Total SMS scheduled and sent for 25 participants • Delivered • Failed	5054 5001(99%) 53 (1%)
Reminder SMS that were delivered "Please don't forget to take your medication according to Doctor's instruction"	1845 (99.6%)
Question SMS that were delivered "Have you taken your medication according to Doctor's instructions?"	1880 (99.5%)*

Table 3: Overview of SMS sent and delivered per woman.

		Before cleaning Yes							After cleaning						
Number	**Reminder**	**Question**	**Yes**	**No**	**Total Answers**	**% Answered**	**Adherence Yes/ Messages Sent**	**Adherence Based On Answers**	**Question**	**Yes**	**No**	**Total Answers**	**%Answered**	**Adherence Yes/ Messages Sent**	**Adherence**
587	36	35	26	1	27	77%	74%	96%	35	26	1	27	77%	74%	96%
349	77	79	67	0	67	85%	85%	100%	79	67	0	67	85%	85%	100%
506	78	78	5	0	5	6%	6%	100%	78	67	0	67	86%	86%	100%
812	78	81	28	0	28	35%	35%	100%	81	28	0	28	35%	35%	100%
561	78	83	16	1	17	20%	19%	94%	83	17	1	18	22%	20%	94%
046	78	79	5	0	5	6%	6%	100%	79	5	0	5	6%	6%	100%
941	78	83	46	0	46	55%	55%	100%	83	48	0	48	58%	58%	100%
001	78	78	46	1	47	60%	59%	98%	78	46	1	47	60%	59%	98%
170	78	78	43	0	43	55%	55%	100%	78	44	0	44	56%	56%	100%
126	78	80	64	2	66	83%	80%	97%	80	64	2	66	83%	80%	97%
414	78	87	7	0	7	8%	8%	100%	87	60	0	60	69%	69%	100%
266	81	81	5	0	5	6%	6%	100%	81	17	0	17	21%	21%	100%
028	78	78	36	0	36	46%	46%	100%	78	66	0	66	85%	85%	100%
086	78	78	27	0	27	35%	35%	100%	78	27	0	27	35%	35%	100%
446	78	78	42	0	42	54%	54%	100%	78	43	0	43	55%	55%	100%
556	78	79	40	2	42	53%	51%	95%	79	41	2	43	54%	52%	95%
911	78	78	57	0	57	73%	73%	100%	78	57	0	57	73%	73%	100%
299	78	78	51	2	53	68%	65%	96%	78	51	2	53	68%	65%	96%
221	78	79	54	0	54	68%	68%	100%	79	54	0	54	68%	68%	100%
179	78	78	44	0	44	56%	56%	100%	78	52	0	52	67%	67%	100%
195	78	78	0	0	0	0%	0%		78	0	0	0	0%	0%	
977	78	82	12	0	12	15%	15%	100%	82	17	0	17	21%	21%	100%
455	13	13	0	0	0	0%	0%		13	0	0	0	0%	0%	
248	78	80	30	0	30	38%	38%	100%	80	37	0	37	46%	46%	100%
811	78	79	67	0	67	85%	85%	100%	79	69	0	69	87%	87%	100%
TOTAL	1845	1880	818	9	827	44%	44%	99%	1880	1003	9	1012	54%	53%	99%
MEDIA						53%	51%	100%					58%	58%	100%
MEAN						44%	43%	99%					53%	52%	99%

*before cleaning: analysis included only the keyword "YES, NO"
*after cleaning" analysis included keyword "YES, NO, Similar with YES and Similar with NO "

Acceptability of SMS Reminders and Questions

18 (72%) participants were reached and willing to participate in the exit interviews whereas 5 participants could not be reached for follow-up (Table 4). 2 of 25 participants asked to be removed from the study before the end of the 6 months follow up due to the SMS content mentioning the word "medication". These participants proposed the SMS content to contain neutral or customised words. Other participants also mentioned the concern of limited confidentiality which might lead to disclosure of their HIV status. This was explained by one participant saying *"For instance the reminder question 'Did you take your medication' may lead to lack of confidentiality or disclosure of my status to my friends or partner"*. Another comment was *"The SMS as they come in, sometimes I am not with my phone, therefore I'm worried someone else could see that SMS"*. Most participants (75%) reported to be satisfied with receiving SMS reminders and questions. For example, one participant acknowledged that *"the reminder SMS was very supportive to me to remind me to take medication because several times I am busy with my usual activities"*. Others described the desire for continuing to receive reminder messages after the end of the study. 4 of the 18 participants (22%) expressed having difficulties in receiving the reminder SMS. The feedbacks from those participants were*, "The SMS were coming late, most of the times about 30 minutes later"*, *"Sometimes I find the SMS the next morning"*, *"Sometimes the SMS delays up to one day"*.

Adherence to Responding to SMS Questions

Out of 1,880 SMS sent with the question "Did you take medication?", a total of 1,012 (54%) were replied to. 818(44%) SMS were replied to with the keyword 'YES' and a total of 185 (10%) were replied to with similar to 'YES' indicating that medication was taken. A total of 864 SMS (46%) were not replied to. 9 SMS (1%) replied with 'NO' and similar to 'NO' (see table 5). The median adherence based on YES-replies was 51% (range 0-85). The median adherence based on YES and similar-to-YES-replies was 58% (range 0-87).

Table 4: Feedback on receiving SMS reminders and messages

Participants feedback	**N 18(72%)**
General experience with receiving SMS	
Not good at all	1 (5.6)
Not good	1 (5.6)
Good	2 (11.1)
Very good	14 (77.8)
Experience with SMS system not good at all (n=2)	
Lack of confidentiality – disclosure	
I don't like, it is not safe on my side	
SMS came on time	
Yes	15 (83.3)
No	3 (16.7)
SMS did not come on time (n=3)	
SMS delivered 30mins later	
SMS delivered on the following morning	
SMS delivered one day later	
Difficulties with receiving SMS	
Yes	4 (22.2)
No	14 (77.8)
Difficulties (n=4)	
Some days there were no SMS received	
Delay in receiving SMS	
Missing	
Opinion about content	
Not good at all	3 (16.7)
Not good	1 (5.6)
Good	2 (11.1)
Very good	12 (66.7)
Content is not good or not good at all (n=4)	
The words 'you are reminded to take medication' was not good to me	
It breaks the confidentiality	
The word 'kumeza dawa' (take medication) is not good. It breaches confidentiality	
The SMS which say 'kumeza dawa (take medication)' is a bit not good if someone else sees it	

Table 5: Adherence based on SMS replies

Variables	**Number of SMS (%) or Median [IQR]**
Total SMS sent with question "Have you taken your medication according to Doctor's instructions"	1880
Total Replied (YES, closely to YES, NO, closely to NO, NOT YET)	1012 (54%)
• Replied with YES	818 (81%)
• Total Replied YES and Closely to YES	1003 (99%)
• Replied with NO or closely to NO	9 (<1%)
Total not replied	864(46%)

DISCUSSION

In this pilot study, we investigated the acceptability and feasibility of sending SMS reminders to pregnant and breastfeeding WLHIV in Kilimanjaro (Tanzania) to take their antiretroviral medication. Almost all SMS that were sent, i.e. 99%, were actually delivered, supporting its technical feasibility. 54% of all monitoring SMS were replied to. The majority of participants found it acceptable to receive SMS that reminded them to take their medication and were satisfied with the content. However, there were also participants who expressed concerns about their privacy and were afraid that receiving the SMS could disclose their HIV status to others.

Only 1% of SMS was not delivered. Although we do not have data about each individual reason, they are most likely related to network failure, loss of phone and change of phone number.

The finding that 46% of the question-SMS were not replied to was unexpected and disappointing. We were uncertain about the underlying reasons. Our primary thought was that participants did not understand or were annoyed by the messages. Also, there could have been changes of phone numbers, network failures, or participants could have been non-adherent. In the exit-interviews, the main reasons mentioned by participants were sharing of phones and network issue. Also, the adherence percentage of 58% is rather low, but as this was based on 'YES'-replies only this rather represents adherence to the SMS. In general, studies have shown that the mean adherence to ART among pregnant women in sub-Saharan Africa countries

ranges from 35% to 93.5%.[24] For instance, a study in the Eastern Cape, South Africa showed an adherence level of 69% among pregnant women.[25] Some participants mentioned that they did not have an SMS bundle enabling them to reply, despite the fact that we sent them a monthly bundle. The fact that a few participants experienced stigma and had disclosure concerns, was expected. This finding is consistent with studies in South Africa, Kenya and Uganda that showed that some participants had concerns about the privacy of SMS.[14,26,27] 2 participants withdrew consent during follow-up and 5 others could not be traced anymore at the end of the study. This is a common problem in resource-limited settings where there are challenges of retaining pregnant and breastfeeding women in care.[24,28,29] Many pregnant women discover their positive HIV status during pregnancy and are worried to disclose their status to their husbands or others.[27]

Our findings are in line with other studies showing that receiving SMS reminders might be intrusive. For example, Rashmi et al. in South India have recommended that weekly SMS should be sent at a time that is convenient for participants to reduce intrusion.[11] In this study, participants indicated that being aware that their adherence to medication was monitored, motivated them to adhere better. Similar to our study, participants mentioned that knowing someone caring for them by reminding them of the intakes, helped them to be adherent. The study of Mushamiri et al [30] found high response rates to reminder and question SMS in the first 3 months, but a clear decline in response rates thereafter. This suggests that participants may get used to SMS messages and ignore responding to the text despite being adherent.

This study has several limitations. First, the focus of the study was on technical feasibility and experience of users which both showed positive results. This means we cannot draw any formal conclusions regarding adherence to treatment. Also, the level of adherence was based on the reply-SMSs, which is indirect and self-reported. We are not sure if the percentages of 'Yes'-answers are a true representation of adherence, as we did not measure accuracy through pill counts, questionnaires, direct measurements of drug concentrations, or with virological outcome. Despite our study design not being optimal to relate "Yes responses" to true drug adherence, the study may provide some indication of self-reported adherence. As such SMS may, to a certain extent allow monitoring of adherence, although adaptations to the program is likely needed. Another limitation is that only women who own a mobile phone were enrolled. This means that WLHIV without a mobile phone were excluded. Therefore, the results cannot be generalised to WLHIV without a phone, who may have different characteristics such as

living in rural areas, low socio-economic status and high illiteracy. In future studies, mobile phones may be supplied by adherence programmes.

One strength of our study is that it included so called interactive 2-way text messaging which encompasses receiving replies from participants and automated SMS sent back to participants. Another strength is that we were able to send the SMS content in local language that is understood and spoken by the vast majority of participants in contrast to several previous studies. Furthermore, the costs of the SMS program in terms of infrastructure investment were low. The sending of automated reminder SMS to 25 participants cost less than 2 US dollars per month. Also, being automated, we managed to decrease the burden on nurses by not having to involve them to send SMS to participants.

Based on our study, we recommend examining whether more neutral messages will trigger medication intake while not disclosing the HIV status. For instance, instead of the standard message 'Did you take your medication', we could ask 'did you do as recommended?' Furthermore, it is important to investigate whether the SMS program will really improve adherence in our setting. Therefore, clinical trials are needed to investigate the effect on adherence and implementation studies are needed to examine the effectiveness of the program in a real-world setting. WLHIV who will use the SMS program, whether it is in the context of a study or as part of regular care, should receive proper explanation about the SMS and its contents. Only in that way, they can make a well-informed decision whether to make use of the SMS reminders. WLHIV who are worried about unwanted disclosure can decline using it.

CONCLUSION

We found that it is technically feasible and acceptable to the majority of pregnant and breastfeeding women living with HIV to receive SMS to remind them to take their medication. There were a few women who expressed concerns about their privacy and were afraid that receiving the messages could lead to unwanted disclosure of their HIV status. Understanding and addressing such potential barriers and challenges will be crucial for researchers and policy makers to improve the design of future studies involving SMS and their successful implementation in practice. Moreover, further investigation of the impact of SMS on adherence to ART in other groups living with HIV is recommended.

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AUTHOR CONTRIBUTION

K.N. was involved from the inception of writing the research proposal to the writing up of this manuscript. He coordinated the study and data collection processes and wrote this manuscript.

E.M. was involved as a study doctor and contributed to data interpretation

R.A. was mentoring I.M. Sumari-de Boer and was involved in all stages of the project starting from the initial concept of the proposal idea till critically reviewing several versions of this manuscript.

B.T.M. was managing the progress and data of the study and contributed to writing up of this manuscript.

M.A.S. was involved as the main supervisor of K.M. Ngowi and critically reviewed several versions of this manuscript on language and contents

P.R. supervised K.M. Ngowi and critically reviewed several versions of this manuscript on technical aspects and contents

P. T. N. was involved in daily supervision of K.N., contributed largely in research proposal writing and critically reviewing of several versions of this manuscript.

I. M. S. was the principal investigator of the project and largely involved on conceptualizing the research ideas and supervising the team during all stages of the project and critically reviewing all versions of the manuscript.

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Chapter Three

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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ABSTRACT

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

Setting: Kilimanjaro Region, 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, on ART for at least six months. Importantly, their adherence, as judged by the study nurses, had to be suboptimal. They also had to be able to read and understand SMS. 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®). If intake was not on time, participants received an SMS-reminder. In the third arm, participants received standard care only. The primary outcome of mean adherence over 48 weeks based on pharmacy refill data and self-report was compared between arms using between-group t-tests in a modified intention-to-treat analysis.

Results: In each arm, we randomized on 83 participants; Eighty-two participants in the RTMM arm, 80 in the SMS-arm and 81 in the standard care arm were part of analysis. 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).

Conclusions: DATs did not improve adherence to treatment and treatment outcome in PLHIV. A Hawthorne effect leading to improved adherence in the control group as compared to actual standard care and limited intervention coherence may have led to this finding.

Clinical Trial Number: PACTR201712002844286

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 (>85%) are needed to prevent virologic failure and the emergence of antiviral drug resistance, with newer antiretroviral regimens especially those including dolutegravir seem 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 Kilimanjaro in Tanzania showed 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 and therefore interventions should focus on a combination of these same factors. In addition, barriers to good adherence are (1) patient factors, which include stigmatization and substance abuse, (2) treatment factors, like complex regimens and side effects, (3) health system-related factors, including limited numbers of health care workers, drugs 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 adherence were from friends and family and assistance of home-based care workers. Barriers were use of alcohol, unavailability of food, stigma and disclosure concerns and clinics dispensing too few pills.[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 such as 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] Furthermore, Lester already emphasized the need for an “Ask, don't tell” approach in 2013. His 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 monitoring (RTMM), that is, 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 because 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 antiretroviral treatment (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 to examine (1) the effect of our interventions on proportions of participants who reached cutoff values for sufficient adherence (ie, >85%, >90% of doses taken) and (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, 3-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 up for 48 weeks.

Study Population

We recruited PLHIV between December 1, 2017, and December 31, 2018, and followed them till February 28, 2020, in Kilimanjaro Christian Medical Centre, 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, and who were on ART for at least 6 months (ie, they were in the adherence implementation phase). We used an age of 65 years as upper limit because we believed older PLHIV will have difficulties in dealing with the modern digital tools. In Tanzania, people aged 65 years or older are considered elderly population. Importantly, their adherence, as judged by the study nurses, had to be suboptimal adherent based on the following information: self-reported nonadherence; missed clinic visits; returning of excess leftover medication; or self-reporting other signs of nonadherence such as not adhering to prescribed time of intake; and having continuously high viral loads. Furthermore, 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 comorbidities who participated in other DAT trials, or people who had participated in studies using DAT.

Ethical Considerations

The study was approved by the College Research and Ethical Review Committee of Kilimanjaro Christian Medical University College and the National Health Research Ethics Subcommittee of the National Medical Research Institute 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 (eg, voluntary participation and possible withdrawal). Then the participant was asked to sign the informed consent form.

Study Procedures

Screening and Enrolment

Study nurses prescreened 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, that is, 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 performed 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 8 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 alone. PLHIV coming to the pharmacy for a refill are asked whether they took all the pills from their previous refill and whether they had any difficulties with adherence. A viral load measurement is performed annually. If the viral load is >1000 copies/mL, extensive adherence counseling is performed monthly, and viral load measurement is repeated after 3 months according to the HIV treatment guidelines

SMS-arm

In the SMS arm, participants received a reminder SMS on 3 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 whether medication had been taken. The participant had to reply with "yes," "no," or "not yet." Days were different for each participant and each week to maintain a surprise effect and prevent SMS fatigue through which we prevented the patient getting used to SMS (*Annex IA*).

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 4 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 packet radio service network. At the server, the usual time of intake with a window period of 3 hours was registered. If participants had not opened the dispenser 15 minutes before the end of the 3-hour window period, they received an SMS reminder (*Annex IB*). 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, and 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 whether the lights failed. Finally, 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 the number of SMS that 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,[24] using the stages of change model (*Annex III*).[29] 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 previous visit (precontemplation), 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 II*). In the standard care arm, no additional procedures were instituted aside from asking about perceived adherence (*Annex IIIB*).

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, Virological suppression, measured at weeks 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 was used to collect data, and Redcap software was used for managing data.[30] Participants' characteristics at the time of enrolment were compared by Chi test for categorical data, by analysis of variance 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.[31] 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 performed 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 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. We calculated the adherence as follows:

*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.[26] 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), 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 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.[30] For all above described analyses, a p-value of <0.05 was considered significant.

Sample Size Calculation

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 [33] in which adherence was measured through the so-called medication event monitoring systems in our setting in Kilimanjaro. The study of Lyimo et al was performed over a period of 3 months, whereas the participants were followed up in our study for 12 months. Therefore, we decided to use a slightly lower mean adherence level for our calculation, which was 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 2-sided $\alpha = 0.05$, 80 participants were required in each arm based on a difference between 2 independent means (calculation using G*Power 3.1 software). Because 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.[30]

RESULTS

Study population description and differences between arms

Two hundred sixty-five participants were screened and randomized; 249 returned for the enrolment visit. Most (71%) were women. The 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 6 months (Table 1). There were no differences in participant characteristics among 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). The average (over 48 weeks) adherence in the SMS, RTMM, and control arms 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% for self-report

in the past month, respectively (all P values were not statistically significant; Table 2). Self-reported adherence in the past week and month was not significantly different between the SMS and RTMM arms and the control arm either.

Adjusting analyses for covariates 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 and RTMM arms compared with that in the control arm (P = 0.045 and P = 0.002, respectively, Table 3). For self-reported adherence, we found significantly higher mean adherence only in the SMS arm for self-report over the past month (P = 0.045; Annex V, Table 3).

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 that in the control group. We found decreasing adherence based on pharmacy refill counts among patients in Kilimanjaro Christian Medical Centre 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 (80%) and SMS arms (79%) compared with that in the 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 4).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 found only 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 3 arms in participants who were virologically suppressed at week 48 (P = 0.99, Table 5). In the subanalysis among patients with viral load of

<1000 copies/mL at study entry, we did not find a significant difference in virological suppression also among the arms (P = 0.93).

Additional analyses

Adherence in Participants With Suppressed and Unsuppressed Viral Load

Participants with viral load less than 20 copies/mL at week 48 had a significantly higher mean adherence based on pharmacy refill counts compared with those with viral load more than 20 copies/mL (Table 6).

Relationship Between Adherence Measurements

The median self-reported adherence was 100 percent in the past week [interquartile range (IQR): 97–100] and in the past month (IQR: 98.2–100). The median adherence based on pharmacy refill counts was 93.3% (IQR: 22.3–100). 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).

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

	Total		**RTMM arm**		**SMS arm**		**Standard of Care**		**P**
	N, mean, median	**SD/IQR /%**	N, mean, median	**SD/IQR/ %**	N, mean, median	**SD/IQR /%**	N, mean, median	**SD/IQR /%**	
	249		83		83		83		
Female	176	71%	57	68%	60	72%	59	71%	0.87
Mean Age	41.2	11.10	42.8	11.6	39.6	12.3	41.2	11.9	0.22
Primary school	152	61.0%	51	61%	50	60%	51	61%	0.36
Secondary school	84	33.7%	29	35%	29	35%	26	31%	
Tertiary School	11	4.4%	3	4%	2	2%	6	2%	
Reported suboptimal adherence	169	67.9%	50	60%	57	69%	62	75%	0.19
Missed visits	188	75.5%	65	78%	66	80%	57	69%	0.21
Had leftovers	175	70.3%	57	69%	61	74%	57	69%	0.74
Median years HIV positive	7.2	2.6-11.9	6.7	2.2-11.2	5.6	2.4-11.9	8.1	3.3-12.5	0.43
Median years on current ART	4.4	1.8-7.7	4.3	1.3-7.2	4.1	1.9-7.5	5.4	2.1-8.0	0.48
NVP+AZT+3TC	55	22.1%	17	21%	16	19%	22	27%	0.28
EFV+TDF+3TC	97	39.0%	33	40%	37	45%	27	33%	
EFV+TDF+FTC	21	8.4%	5	6%	8	10%	8	10%	
EFV + AZT+3TC EFV + ATV EFV + ABC+3TC	31	12.4%	11	13%	13	16%	7	8%	
NVP + AZT+3TC	1	0.4%	0	0%	1	1%	0	0%	
ATV/r+AZT+3TC ATV/r+TDF+FTC ATV/r+ABC+3TC	20	8.0%	10	12%	3	4%	7	8%	
LPV/r+AZT+3TC LPV/r+TDF+FTC LPV/r+ABC+3TC	24	9.6%	7	8%	5	6%	12	15%	
Viral load <20 copies/mL*	117	48%	42	51%	33	42%	42	52%	0.36
Viral load <1000 copies/mL*	189	78%	63	77%	65	82%	61	75%	0.54

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)

Arm (N)	**Control arm** *(81)*	**SMS arm** *(80)*	**RTMM arm***(82)*	**p-value**
Self-reported mean adherence in past week	95.2 (11.8)	95.9 (10.6)	95.0 (9.5)	0.84
Self-reported mean adherence in past month	96.9 (7.4)	97.5 (7.2)	96.6 (7.2)	0.72
Mean pharmacy refill adherence	87.9(12.9)	89.6(12.9)	90.6(10.8)	0.36

**p<0.05*

Table 3: Differences in mean adherence between arms in participants with VL <1000 copies at study entry

	Control arm	**RTMM arm**	**SMS arm**	**P-value**
Self-reported adherence in past week	93.9	95.8	97.1	0.12
Self-reported adherence in past month	96.0	96.8	98.4*	0.045
Pharmacy refill adherence	86.9	93.1**	91.4*	0.045

*P<0.05

**p<0.01

Table 4: Differences in adherence cut off values between arms (modified intention-to-treat analyses, n=243)

	Total		**Control arm**		***SMS arm***		***RTMM arm***		***P-value***
	N	*%*	N	*%*	N	*%*	N	*%*	
Self-report									
Past Week 100%	151	*62.9*	51	*63*	56	*71*	44	*55*	*0.12*
Week >95%	193	*80.4*	66	*81*	65	*82*	62	*78*	*0.72*
SR Week >90%	205	*85.4*	70	*86*	69	*87*	66	*83*	*0.66*
SR Week >85%	212	*88.3*	72	*89*	70	*89*	70	*88*	*0.96*
SR Week>80%	221	*92.1*	73	*90*	74	*94*	74	*93*	*0.70*
Past Month 100%	123	*51.2*	42	*52**	48	*61**	33	*41**	*0.05*
SR Month >95%	209	*87.1*	70	*86*	71	*90*	68	*85*	*0.64*
SR Month >90%	214	*89.2*	72	*89*	72	*91*	70	*88*	*0.76*
SR Month >85%	221	*92.1*	74	*91*	73	*92*	72	*91*	*0.82*
SR Month >80%	229	*95.4*	76	*94*	77	*97*	76	*95*	*0.53*
Pharmacy refill									
100%	11	*4.5*	3	*4*	5	*6*	3	*4*	*0.66*
95%	94	*38.7*	27	*33*	32	*40*	35	*43*	*0.45*
90%	160	*65.8*	54	*67**	60	*75**	56	*68**	*0.02*
85%	182	*74.9*	53	*65**	63	*79**	66	*80**	*0.05*
80%	205	*84.4*	66	*81*	67	*84*	72	*88*	*0.53*

*p<0.05

Table 5: Differences in adherence and virological outcomes between arms (per protocol analyses, n=225)

	Total		**RTMM arm**		**SMS arm**		**Standard of Care**		**p-value**
	225		77		73		75		
Viral load <20 copies/ml	156	*69%*	53	*69%*	51	*70%*	52	*69%*	*0.99*
Viral load>1000 copies/ml	28	*12%*	12	*16%*	9	*12%*	7	*3%*	*0.51*

NB: all results were not significant using Student's t-test (p>0.05)

Table 6: Difference in adherence for participants who were virologically suppressed and participants who were not suppressed

	Viral Load<20 copies/ml	**Viral Load=>20 copies/ml**	**P**
N	156	69	
Mean self-reported adherence in past week (% of doses taken)	95.7	94.5	0.45
Mean self-reported adherence in past month (% of doses taken)	95.9	92.2	0.2
Mean pharmacy refill adherence (% of doses taken)	92.1	85.6	***0.008***

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-based 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] whereas in South Africa, there was no effect, but treatment interruptions were shortened.[34] A study in Kenya showed increased communication about adherence due to SMS but did not show improvement of clinical outcomes.[35] Furthermore, a trial in Malawi did not show an effect of SMS on retention in care.[36]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 with that in the 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 (eg, structural factors such as low socioeconomic status and 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 counselors may not always have performed 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 WelTel 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 setup 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 creating a venue for better communication on adherence during face-to-face clinic visits when needed. Furthermore, 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 because 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 the previous research by van den Boogaard et al,[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 antiretroviral 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 as follows: (1) technical issues including limited battery life of RTMM devices, limited network, and a high number of reminder SMS not being sent by the provider, (2) stigma and related fear of disclosure because of 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 this 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.

The 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, whereas 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 the so-called interactive voice response calling in which SMS texts are being replaced by actual phone calls. In addition, patients with comorbidities were excluded. They might have a high pill burden that may affect adherence negatively. In addition, we selected patients based on judgment of nurses of their adherence level because 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.

The 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 the time of enrolment and harboring drug-resistant virus, even perfect levels of adherence would not be expected to improve virological outcome.

The 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 with other regions in Tanzania. We believe that the study findings are not generalizable to all adults living with HIV in Tanzania or East Africa because of 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 because these key populations may experience different barriers for adherence to treatment.

This study focused on adults living with HIV in general, and as such, we did not exclude pregnant and breastfeeding women. Because 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.

The 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.

The 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 overreporting their pill intake. Finally, we did not exclude participants who did not have a phone, that is, those who are most likely from lower socioeconomic 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 less than 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 because these key populations may experience different barriers for adherence to treatment.

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AUTHORS CONTRIBUTIONS

M.S.B and K.N have contributed equally to the work.

M.S.B was involved from the inception of writing the research proposal to writing up of this manuscript. She oversaw the study including data management including database and data verification. She did the analyses and wrote this manuscript.

K.N was involved from the inception of writing the research proposal to writing up of this manuscript. He coordinated the study and data collection processes and wrote this manuscript.

T.S was involved in the analyses of the data, specifically the multilevel data analyses.

F.P was involved in the data collection process.

L.M was overseeing the data collection in the field and was playing a major role in data verification.

M.S supervised K.M. Ngowi and contributed largely to the writing up of this manuscript by critically reviewing several versions of the manuscript.

P.R supervised K. M. Ngowi and contributed largely to the writing up of this manuscript by critically reviewing several versions of the manuscript..

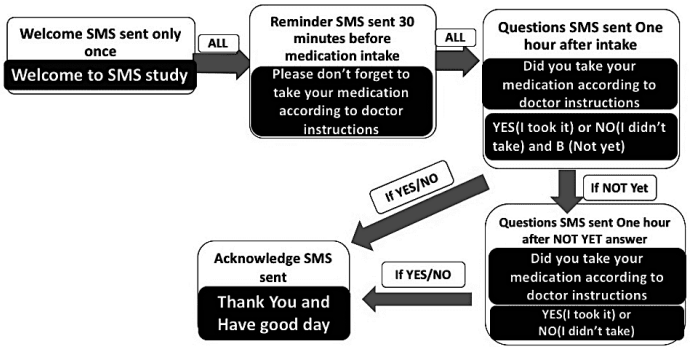
B.T.M was monitoring the progress of the study in Kilimanjaro, Tanzania, and contributed to the final version of the manuscript.

P.N was involved from the inception of writing the research proposal to writing up of this manuscript. She supervised K. M. Ngowi on a daily basis and contributed largely to this manuscript.

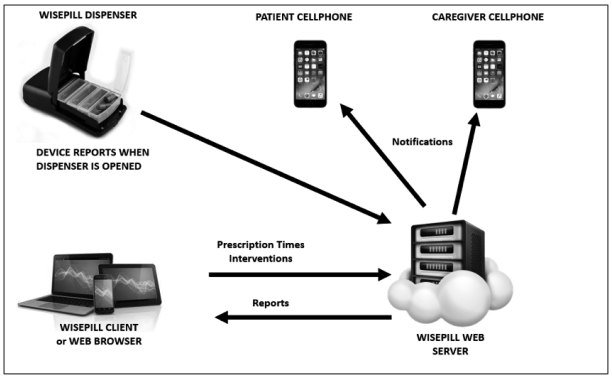
R. E.A was mentoring I. M. Sumari-de Boer and was involved from the inception of writing the research proposal to writing up of this manuscript. He contributed largely to the proposal and the manuscript by critically reviewing several versions of the manuscript on contents.

ANNEXES

Annex IA: SMS scheme

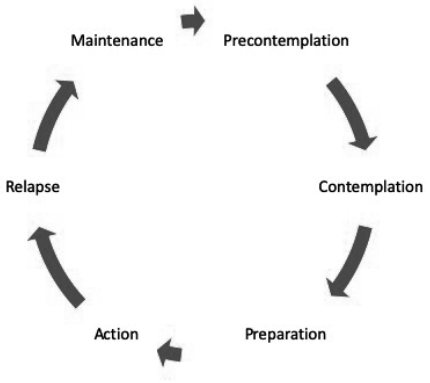


Annex IB: RTMM



Source: Wisepill

Annex II: Stages of Change Model



Annex IIIA: Template for tailored feedback

In general

The feedback conversation has to take place in a way that the patient feels accepted and feels treated with respect:

- Listen carefully, let the patient finish his/her story
- Show interest in the patient / try to empathize / show understanding, respect / Get confirmation
- Give your opinion about statements and opinions of the patient, so a discussion may emerge
- Emphasize that the counsellor and patient are one team

Note statements and opinions of the patient as much as possible on the dotted lines. If necessary, use another sheet of paper

A. Awareness of the problem

Goal of this stage: to help the patient to understand that inadequate adherence may lead to major problems. Creating awareness is done through discussion about the own objectively determined adherence data (RTMM-data) and by risk communication.

A1. Ask the patient about his/her estimation about his/her own adherence to treatment

"In this study we measure how you take your pills. Since some weeks you are using the RTMM device. As you know, this device registers when it is opened. The data are now known to me through the database that registers the data. These data are about this and this period (see overview adherence)."

1. "To what extent did you manage to take all pills in this period?"

…….....
…….....
…….....
…….....

Taking the pills was (mention all options):

☐ adequate/ good/ very good
☐ moderate

☐ bad / very bad
☐ other /don't know"

"How many pills do you think you took in terms of percentages?"

……
……
……
……

2. "Do you think you took the pills worse in the morning, afternoon or evening (depending on the patient) than other intake-times or were there no difference?"

……
……
……
……

3. "How strictly did you adhere to the intake-times?
The intake of pills was ☐ always / mostly on time
☐ sometimes yes / sometimes not on time
☐ mostly not on time"

……
……
……
……

4. How well did you adhere to food prescriptions, by taking the pills with or actually without food?
The intake of the pills was
☐ always / mostly according to food prescriptions
☐ sometimes yes / sometimes not according to food prescriptions
☐ mostly not according to food prescriptions
☐ not applicable, no food prescriptions

……
……
……
……

A2. Discuss overview adherence data*: to mirror*

Go through all parts of the "overview adherence" together with the patient.
Present the conclusions of the pharmacist. Try to separate the presentation of the data from the discussion about it (see A3).

- Number of doses taken Percentage of doses taken ☐
  Percentage of doses taken/ dosing moment ☐
  Percentage of days with correct intake ☐
  Number of doses
- Intake on time Percentage prescribed doses on time ☐
  Percentage prescribed doses on time/ ☐
  Dosing moment ☐
  Time between doses (minimal – maximal) ☐
- Combination number + time Percentage time with effective blood concentration ☐
- Conclusion pharmacist ☐

A3. *Discuss with the patient based on the "Overview Adherence". See also A4.*

Start de discussion with the question on the experience of the patient:
"What do you yourself think about the data that we just went through? Do you think you take the pills correctly? What do you think could be the consequences?"

…….....
…….....
…….....
…….....

A4. P*rovide education about the importance of adherence and the risks of inadequate adherence during the discussion.*

"It is very important that you take your pills on time and with or without food, like prescribed. It is known that you should take at least 95% of the pills to expect an adequate effect. We call that high adherence to treatment. If you don't take your pills or you take fewer pills

- The concentrations of the medication in the blood will become too low. The amount of virus in the blood can increase and the virus can become resistant. The medication will not work against the virus anymore.
- It may mean you will have to use another medication. Unfortunately, there are only few "spare" medications. After a certain time, there are no medications for you anymore. The stock of mediations will then be exhausted.
- You may acquire serious, life-threatening infections. ".

A5. Determine awareness

"We have to agree that the way you take your pills is not adequate. Do you agree with me that the way you take your pills will eventually lead to problems?"

If the patient acknowledges the nonadherence as a problem, you can go to next stage (B).

If the patient does not acknowledge the nonadherence as problematic, and so does not judge more attention as credible or meaningful, the counsellor should state his/her opinion again:
"If you would ask my opinion, I think that the adherence is not adequate to expect a good effect of the pills on the longer term. Because this can have such detrimental consequences for you, I would like to discuss further with you, to see what the reasons are for not taking the pills well and to see if we can improve it step-by-step. ".
Go to stage B.

B. Consideration

Goal of this stage: to support the patient in coming to intention to improve adherence to treatment.

B1. Mention the advantages and ask for possible disadvantages or barriers in improving adherence:

Mention advantages:
"If you could improve the intake of the pills it will probably have the advantage that

- The amount of virus in the blood will stay as it is now or will go down more
- And that you won't get a resistant virus
- That you don't have to start other medication, so that medications for you will not get exhausted. We will still have medication available.
- That no life-threatening infections will occur "

Make an inventory of possible barriers for good adherence to treatment.
"Maybe there are disadvantages of taking the pills or problems that hinder you in taking the pills well. Why do you think you did not take the pills well?"
…….....
…….....
…….....
…….....

If necessary, mention the following possible barriers, discuss them and give possibilities for support:

- psychosocial / behavioural characteristics: keeping the HIV infection a secret to others, little social

support, little intention or personal efficacy

Show confidence in the patient, emphasize the strong characteristics of the patient, predict and discuss the expected problems, mention possibilities to ask support from the environment.

- Perception of disease symptoms: opinions about the severity of the disease and the importance of adherence may ask may deserve attention again

- Characteristics of the medication
  - A complicated regimen: provide information about the importance of intake times, food prescriptions. *Consider using a facilitator (pills scheme, alarm clock, vibrator(phone), link intake to activities)*
  - Anxiety for side effects: try to put the anxiety in perspective*, by accurate support from a physical and by comparing them with the risk of nonadherence*

- Relation with health care workers

B2. *Discuss with the patient about possible effective interventions:*
"In what way can we help to improve the intake?"
…….....
…….....
…….....
…….....

C. Decision and preparation.

Goal of this stage: take a decision with the patient about improving adherence and register techniques that may help.

C1. "Would you, considering what we discussed, try with me to improve taking the pills?"
…….....
…….....
…….....
…….....

C2. Formulate a clear treatment goal:

"The final goal should be that you will take at least 95% of your pills and on time. Only than problems in the future will be prevented.
I would like to agree with you that will try your level best to improve your adherence to treatment as much as possible. This means that large efforts from your side are needed.
The final goal is to take 95% of the pills on time. For next time you should manage to at least take ....% of your pill well (judgement of the counsellor).
If I compare this with the RTMM data this agreement should be manageable. What do you think of this agreement?"
…….....
…….....
…….....
…….....

C3. To help you to take your pills well, we agree on the following:
…….....
…….....
…….....
…….....

(Description of facilitator or behavioural instructions)

C4. Write the agreements on a hospital card.

C5. Decision. "Your special RTMM device registers when you take your pills. You will come back after one month. Then we can look again at the data of the RTMM Device and discuss those data."

Annex IIIB: Scheme for discussing adherence in standard care

- *adherence:*

5.1 In relation to number of taken pills ☐
5.2 In relation to time (correct time, dosing interval) ☐
5.3 In relation to food prescriptions (if applicable) ☐

5.4 Use of facilitators for adherence? ☐ Yes ☐ No

Mention eventual facilitators:

_____
_____
_____

5.5 Attention physical on adherence in consultation? ☐ Yes ☐ No

Explanation:

_____
_____
_____

-*Side effects:*

5.6 General question: are there side effects? ☐
5.7 If necessary, targeted questions on known side effects ☐

Comments:

_____
_____
_____
_____

Annex IV: Adherence calculations

Adherence to treatment: Self-report and pharmacy refill counts

Adherence to treatment was calculated for the pills that contained the core-component of the antiretroviral regimen only, which was either efavirenz, nevirapine, ritonavir boosted atazanavir, ritonavir boosted lopinavir, or dolutegravir. As such, these could be single-component pills (i.e. efavirenz, nevirapine, ritonavir boosted lopinavir) or fixed-dose combinations of any of these with their backbone (i.e. efavirenz + tenofovir + lamivudine, nevirapine + zidovudine +lamivudine). In each visit, we asked the participants which regimen they were using, how many pills they should take per day according to their prescription and how many pills they missed in the past week and in the past month. This information was confirmed with the information in their medical files and pharmacy records. From there we calculated self-reported adherence as follows:

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%

At each visit, we also recorded type and number of dispensed pills in the previous visit and number of pills returned at the current visit. If the participant did not return pills, we asked if they knew how many pills were left at home. If this was not known, we assumed that the participant had taken all pills dispensed in the previous visit if the number of dispensed pills was lower than or equal to the number of prescribed pills for the period between the previous and current visit. For example, if a participant was dispensed 30 pills in the previous visit and he/she came back after 35 days, we assumed that adherence was 30 divided by 35. If the number of pills was more than the number of prescribed pills, we assumed that pills were taken according to prescription and that the number of returned pills would be the excess leftover. For example, if the participant came back after 25 days, we assumed the participant took 25 pills and adherence was 25/25 and 5 pills were leftover for the next period. We calculated an adherence percentage between two visits as follows:

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%. We truncated adherence at 100% assuming that levels higher than 100% were

actually representing 100%. For both self-reported adherence and pharmacy refill adherence, we calculated different cut-off levels of doses taken of 100%, 95%, 90%, 85% and 80%.

Average adherence percentages for self-reported adherence were calculated by summing the self-reported adherence percentages for each visit and dividing that by the number of visits done.

Average self-reported adherence = (((Adh period 1) +(Adh period 2) +(Adh period N) +…)/ (no visits)) *100%

Average adherence percentages for pharmacy refill adherence were calculated by multiplying each adherence percentage between visits with the number of days between those visits. Then these were each summed and divided by the total number of days that the participant was in the study.

Average adherence = (((Adh period 1 * no days period 1) +(Adh period 2* no days period 2) +(adh period N* no days period n) +…)/ (no days period 1+no days period 2+ no days period n+…)) *100%

Based on these average adherence levels, we calculated proportions of participants who reached 85%, 90%, 95% and 100% average adherence.

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Chapter Four

Technical and psychosocial challenges of mobile health usage for antiretroviral therapy (ART) adherence among people living with HIV in a resource limited setting: Case series.

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ABSTRACT

Introduction: Mobile communication has been found to improve ART-adherence among people living with HIV (PLHIV). In an ongoing randomized clinical trial, are currently investigating two mobile communication strategies i.e, sending SMS and real-time medication monitoring (RTMM), to improve adherence to ART among PLHIV in Tanzania. We noticed remarkable discrepancies between self-reported adherence and adherence recorded by SMS or RTMM among some of the first trial participants.

Objective: To describe these cases and the observed discrepancies in more detail, to serve as a useful illustration of some of the challenges in using mHealth in resource-limited settings.

Methods: In an ongoing randomized ,trial we are currently conducting adult PLHIV from two HIV treatment centers in Tanzania who are suspected of low levels of adherence, are they randomly assigned in a 1:1:1 ratio to receive: SMS reminders, RTMM, or no additional intervention to standard HIV care. During bi-monthly study visits PLHIV self-report their level of adherence, receive feedback about their level of adherence based on SMS or RTMM monitoring, and with HIV nurses discuss strategies to overcome problems with adherence. For the purpose of this report, we selected PLHIV who had completed five follow-up visits and consistently reported more than 95% adherence while SMS or RTMM recorded lower than 75% adherence. These PLHIV were invited for a face-to-face short in-depth interview to explore reasons for this discrepancy.

Results: At the time of this analysis, a total of 26 participants had completed follow-up. Six of these evidenced had evidence of the abovementioned discrepancies, with an average adherence of 46% based on SMS/RTMM monitoring, whilst self-reported adherence was 98%. Five of these six participants insisted that their adherence to ART was good, with four of them reporting that their adherence to properly using the monitoring device was low. Three participants mentioned concerns about involuntary disclosure of HIV status as a main reason for low adherence to using the device. Two participants were still depending on other reminder cues despite receiving SMS or RTMM reminders. Poor network coverage caused low adherence in one participant.

Conclusion: Psychosocial barriers were reported as importantly contributing to low adherence, both with respect to use of ART and proper use of the adherence monitoring device. This case

series illustrates that when introducing a new digital adherence monitoring technology, researchers should consider psychosocial barriers and distinguish between adherence to device use and adherence to treatment.

INTRODUCTION

The Kilimanjaro region in Tanzania has an HIV prevalence rate of 2.6%, which is lower than the country's national prevalence of 4.5%.[1,2] However, in this region, of those who receive antiretroviral treatment (ART), only 47% of people living with HIV have viral load suppression.[1] This suggests that adherence to ART is often not optimal. Due to limited resources, viral load is not routinely monitored, and consequently, timely information about potential poor adherence to ART is not available to HIV health care providers. Therefore, alternative means of providing information about and interventions to improve adherence to ART among people living with HIV are needed.[3] Mobile phone technology can potentially help to fill this need by using digital tools.

Several digital tools exist to monitor and intervene on adherence to treatment. Real-time medication monitoring (RTMM) records the date and time of every opening of a pillbox, a so-called event. It sends this information in real time to a web platform via the mobile network and is one of the existing technologies for monitoring adherence. Reminder SMS text messages may be sent to people living with HIV if the pillbox is not opened on time.[4] Text messaging can also be used on its own as another mobile phone technology to monitor and improve adherence. The feasibility of text messages was found to have mixed results, especially in rural areas.[5,6] Previous studies have described several challenges of delivering RTMM and SMS text messaging in resource-limited settings, such as poor network coverage, power failure, and lack of interoperability among network providers.[5,7] However, previous studies did not describe in detail how such challenges affect the delivery and use of mobile health (mHealth) strategies for treatment adherence. Furthermore, despite these technical challenges, we found that it was feasible and acceptable to monitor ART adherence using RTMM among people living with HIV who reside in the Kilimanjaro region.[8]

Currently, we are conducting a randomized trial in which we investigate the effect of mHealth strategies to improve adherence to treatment among people living with HIV in the Kilimanjaro region. People living with HIV are randomly assigned in a 1:1:1 ratio to receive (1) SMS text message reminders, (2) an RTMM device, or (3) no additional intervention to standard HIV

care. During the trial, we encountered major discrepancies between self-reported adherence and adherence reports generated by the assigned mHealth intervention in several of our trial participants. The objective of this report is to describe these cases and the observed discrepancies in more detail to serve as a useful illustration of some of the challenges researchers and health care providers need to consider when intending to use mHealth interventions to enhance adherence to ART in resource-limited settings.

METHODS

Patients enrolled in the RCT

We first describe the trial and the interventions from where we selected our patients. Our ongoing, parallel-group three-armed randomized controlled trial (REMIND study) has enrolled adult PLHIV from the Kilimanjaro Christian Medical Center and Majengo Health Centre, two specialized HIV care and treatment centers (CTC) in Moshi, Tanzania. By 2018, KCMC served a total of 2800 PLHIV, while Majengo served 1200. In our larger RCT study, 264 PLHIV were screened from both health centers. The study nurses played a vital role in ensuring that potential participants would understand the study. Written informed consent was requested from participants. They were subsequently randomized equally to the study arms which are the SMS, RTMM and control groups. The study was approved by the Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC) and the National Health Research Ethics Sub-Committee (NatHRec) of Tanzania. The main eligibility criteria for enrolment in the trial were that the participant must currently receive ART and that there is a suspicion of low adherence levels. The suspicion of low adherence was based on the following criteria as subjectively judged by nurse counselors and was based on (1) self-reported limited adherence, (2) missed medication refill visit, (3) return of leftover medication or (4) other signs of non-adherence including continuous high viral loads. Exclusion criteria are participants being admitted to the hospital or participation in other trials.

Intervention Arms

SMS

All participants who were enrolled in the SMS arm received three-weekly messages on random days. The messages were in Swahili and similar for all patients. Thirty minutes before the usual time of intake, an SMS was sent to remind them to take their medications. One hour after the usual time of intake another SMS was sent with the question “Did you take your medication?”.

The participant had to reply choosing from three options: (1) I took medication, (2) I did not take medication (3) Not yet. The flow of SMS messages is depicted in figure 1.

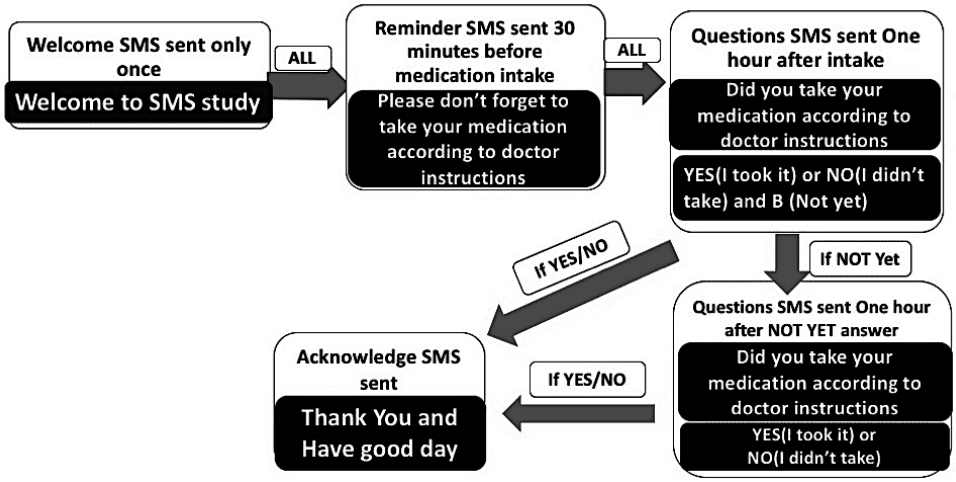

Figure 1: Flow of SMS messages.

RTMM-device

All participants enrolled in the RTMM arm received a Wisepill device containing a 3G SIM card that sends signals to a central server each time the device is opened, a so-called medication event and proxy for medication intake. The signal contains information about the time of opening, identification number of the device and technical information about the battery and strength of the signal. If the device was not opened within one hour and fifteen minutes after usual time of intake, the participant received an SMS text with a question whether they took their medication. The respondent could not respond to the SMS because the device does not have a function to support incoming SMS from user. Authorized members of the study team could access the adherence report generated by the device by signing in through the protected Web portal. Figure 2 presents the flow of communication between pill box, central server and patients' phone.

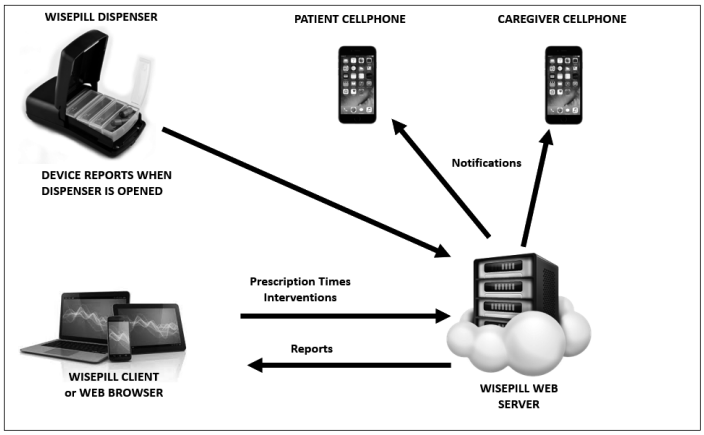

Fig 2: Wisepill device architecture (source: Wisepill)

Feedback session procedure

Participants attended the Care and Treatment Clinic (CTC) clinics every two months to receive standard HIV care and ART medication refills, as per Tanzanian HIV treatment guidelines.[9] During the visit, participants in the two intervention arms (SMS/RTMM) received tailored feedback from the HIV nurse counselor about their medication adherence according to SMS/RTMM monitoring. First, nurses asked participants if they skipped any doses of ART and to what extent they had been able to take all doses of their ART in the past period. Next, the nurse provided participants with a graph (generated from SMS/RTMM) showing their level of adherence in percentages. Participants were asked to comment on their adherence behavior displayed in the graphs. Participants' responses to the questions, their answers, comments and any explanations for potential discrepancies between reported adherence and adherence based on SMS/RTMM were registered. The feedback was obtained using semi-structured questionnaires and recorded on Case Report Forms (CRF).

Viral load was measured at enrolment in all study participants. The lower detection limit of the viral load test was 20 copies/ml. According to Tanzanian HIV treatment guidelines, viral loads above 1000 copies/ml have to be repeated after three months of intensified counseling on adherence to treatment and those below 1000 copies/ml will be repeated after a year. In participants defined as "cases", we retrieved their viral load from their medical records at trial entry and at the end of the follow-up period of the trial.

Case selection and Interview

For the present report, we define cases as trial participants in whom there was a major discrepancy between self-reported adherence by the participant at the bi-monthly study visit with the nurse and adherence according to SMS/RTMM monitoring, (i.e. patients reporting good adherence, 95% or higher to the nurse based on standard self-report question while SMS/RTMM indicated poor adherence,, i.e., around 75% or lower). All participants defined as "cases" were invited to an in-depth interview to explore whether they had encountered any technical or practical problems with using SMS or RTMM. The interviews were conducted by the study investigator with a topic guideline including (1) perceptions of being monitored, (2) technical issues and (3) any privacy concerns, (i.e., concerns that others would see the RTMM device or read the content of SMS which could disclose participants' HIV status). The topic list was prepared by the study team.

Analysis

For each of the participants defined as "case", we calculated their average level of adherence reported to the nurse at bi-monthly study visits and their level of adherence according to SMS/RTMM over the five visits in the follow-up period. For self-reported adherence, we directly asked how many doses were missed and from there we could calculate their adherence level. For adherence according to the SMS/RTMM, we calculated the number of correct intakes (measured by correct openings of the pillbox or by the number of 'YES'-replies to SMS) divided by the number of prescribed intakes. We report the participants' comments on discrepancies between self-reported and SMS/RTMM based adherence, the explanations that they gave for discrepancies and possible technical problems, privacy concerns, or other issues that emerged during the interviews.

RESULTS

Case study participants

By November 2018, a total of 26 participants out of 249 who started with the clinical trial had completed all five study clinic visits. Out of 26, twelve were enrolled from Majengo sites and 14 from KCMC. Twenty participants had adherence rates higher than 75% adherence as recorded by RTMM/SMS. 6Six of them had adherence rates lower than 75% but self-reported adherence rates of 95% or higher and were thus considered to have major discrepancies between self-reported- and SMS/RTMM-based adherence at each of the five study visits. A median of 46% adherence based on SMS/RTMM was recorded for all cases. Three (female) of

these eligible participants were enrolled in the SMS-arm and three (one female and two men) in the RTMM arm. All participants were on a twice daily ART regimen. Two participants in RTMM and one in SMS had suppressed viral loads (Table 1: Appendix 1).

Case One

The first case was a single mother living in Moshi-urban who responded to 73 (43%) of 168 SMS with the question whether she took her medication. Within study visits 1 to 5, the participant confirmed she received SMS reminders on time but she often did not respond to them because: "*I think I lacked commitment in responding to SMS*". She felt depressed because she was separated from her family. She had expected that the nurses would not find out that she was not responding to SMS. After she was confronted by the nurses with her low response rate to SMS she tried to reply to SMS more often. She mentioned that she had no difficulties taking her pills, despite not replying to the SMS. To improve adherence to ART, she mentioned *"I will set my phone alarm as extra reminder and involve the caregiver as well'.*

She did not have a concern about privacy and answered "*I have a smartphone and it's easy to disable SMS notification as well as put a password. So, no one can see or have access to my SMS*."

So, this participant reported high levels of adherence to ART despite a low response rate to SMS and this low response rate appeared to be related with feelings of depression.

Case Two

Case two was a Moshi urban resident who acquired HIV through mother to child transmission. Throughout visit 1 to 5, 186 SMS were sent and delivered with the question "did you take your medication?" However, only 95 (51%) SMS were responded to with "YES I took medication" and 91 (49%) SMS were not responded to.

When confronted by the nurses with her low response rate to SMS during the feedback sessions, she mentioned that the main challenge that hindered her replying to SMS were her friends who normally spent a lot of time with her especially in the evening. She explained that *"my friends are always in my room especially in the evening; therefore, I am not feeling comfortable to respond to SMS."* When she was asked whether she had disclosed her HIV status to them, she said *"I'm scared to tell them and with my age I still need them around. Also, none of my friends will believe I acquired HIV when I was born."* Of interest, she said that *"despite not responding to the SMS, I still take my medication.*"

So, this participant reported high levels of adherence to ART despite a low response rate to SMS. The main reason for the low response rate to SMS was related to fear of unwanted disclosure of her HIV status.

Case Three

In 2012, this 29-year old woman living in Moshi urban started ART. In the period of visit 1 to visit 5, a total of 186 SMS asking whether she took her medication were sent and received. She only replied to 53 (28%) SMS and she did not respond to 133 (72%) SMS.

During the feedback sessions with the nurses she insisted that *"I never missed the medication intakes and I replied to the SMS"* and she said that *"I am surprised to see that I did not reply to all SMS. I am wondering whether you are missing something as I believe that I managed to take about 80% of my pills."*

However, in the interview with the study coordinator she confessed that *"I was not honest during the feedback sessions with the nurses. The reason for that is that I was depressed because my sister found out I was receiving SMS to remind me to take medication for HIV and then it became even worse when she started telling my neighbors that I will die soon."* We asked her if the content of SMS should be changed, she said that *"I don't have a problem with the content, nowadays I delete the SMS once I have replied to it so that no one will read them in case they gain access to my phone.*"

So, the main reason for this participant for not replying to SMS is related to unwanted disclosure of HIV status and stigma surrounding HIV.

Case Four

Case four is a 58-year-old female living in Moshi rural who started ART in 2012 and was enrolled in the RTMM arm. According to RTMM, her level of adherence during the first two study months was 47%. After the HIV nurses showed her this level of adherence according to RTMM during the feedback session she said: "*I never missed the medication intakes. I think the RTMM was not working properly. Therefore, I want to be provided with a new device*." The study nurse exchanged the old device with a new one. In the next feedback session, her level of adherence according to RTMM was still low with 20% despite her insistence that she never missed a medication intake.

During the interview with the study investigator the participant mentioned that the device was easy to use but charging the device was a challenge because the device did not have an alarm for low battery. At the beginning of the study, this participant lived in a rural area at the time where her adherence level according to RTMM was low. After ten months she moved to town

and the device started to send daily signals showing device openings indicative of a high levels of adherence. The participant explained that *"I have never missed my medication intakes; therefore, I was surprised why the device was not recording the openings. After I moved from my old house in the village, the device started to record the openings so I thought the problem was network coverage."* The participant was happy to be monitored in real time as she felt being cared for. Privacy concerns were not an issue for this participant as she had disclosed her HIV status to her family.

So, for this participant, the main reason for the discrepancy between self-reported adherence and adherence generated by the device seemed to be related to adequate power/charging and availability of network coverage.

Case Five

This is a 33-year-old man who lives in Moshi urban who has been enrolled in the RTMM arm and had started ART in 2013. According to RTMM, his level of adherence to ART was on average 57% during the follow-up period of the study. This participant explained that his main problem using the RTMM device were concerns about disclosure of his HIV status: "*I* have *no problem with using the device except that I did not disclose my HIV status to my children and my co-workers. So sometimes it is difficult to open the device when I am with them. However, I always take my pills which I kept outside the device."* This participant further explained that *"I had difficulties carrying the device to my work place and since I'm working late sometimes, I sometimes missed my evening dose of medication."*

So, the main problems for this participant are related to unwanted disclosure of HIV status and difficulties to incorporate use of the device in daily activities.

Case Six

The sixth case is a 21-year-old man who acquired HIV infection through mother to child transmission. With an average of 60% ART adherence during the follow-up of the study, he acknowledged missing his medication due to lack of an alarm on the RTMM device. He explained that *"when I'm home with the device, I normally forget to open it."* He added that *"sometimes I wish the device should have an alarm to notify me to open it for my medication intake."* He also mentioned that *"currently I depend on other reminders such as news time hours and the alarm of the wall clock."* Before this participant enrolled in the study, he used to set an alarm with his mobile phone as reminder to take his medication. Now he says that "*since the device does not give an alarm, sometimes I missed my medication intakes as there*

is nothing to ring as alarm. However, as soon I receive the SMS-reminder, I take my medication."

So, for this participant the main reason for poor adherence recorded by the device was that the normal strategy that he used to remind himself to take his medication was interrupted when entering the study and he needed to adopt a new strategy. As the SMS reminder comes late, the participant might indeed be adherent but not on time.

DISCUSSION

This case series explored, in detail, 6 participants who had major discrepancies between their self-reported and digitally monitored adherence. This paper illustrates the challenges in using mHealth, which emerged during an intervention trial using SMS text message reminders and RTMM to improve adherence to ART among people living with HIV in the Kilimanjaro region in Tanzania. Interviews were conducted to determine whether the discrepancies were triggered by difficulties in using the interventions, poor network, power failures, potential stigma, or other reasons.

One remarkable observation was that it is important to distinguish between adherence to proper use of the digital adherence monitoring device and adherence to treatment. Patients enrolled in the SMS arm were expected to respond to each question they received by SMS text message. However, of all the SMS text messages that were delivered, on average, only 46% post intake text messages were responded to. The results showed that the post intake SMS text message was not triggering the trial participants to respond well to the messages. This finding seems to be in line with a previous study reporting that implementation of mHealth interventions in low-income countries can be complicated if end users have difficulties adapting to new technologies due to lack of experience or psychosocial barriers, which may lead to inadequate use of the technology (ie, limited responding to messages or incorrect use of the device for medication intake).[9]

Another remarkable finding was that several participants considered using additional ways to remind themselves to take their medication, such as using a phone alarm. We found this striking, as sending electronic reminders to participants was part of both intervention arms, yet participants needed additional tools to help them remember to take their medicine on time.

One participant insisted that she took her medication even when the RTMM device was replaced with a new one, but the new device continued to indicate poor adherence. This discrepancy turned out to be caused by the device not finding a network, and it was therefore unable to properly transmit the signal to indicate the medication intake event. As such, each time the device was opened, it was not recorded in the system. However, after the participant moved to an area with a network, the device was able to send the signal on a daily basis. This underlines that adequate network coverage is a prerequisite for the feasibility of mHealth.

In our previous study in the Kilimanjaro region [8], we also encountered the problem of network instability due to bad coverage that led to delays and failures in delivering reminder SMS text messages among participants residing in several remote villages. Despite the technical challenges that were addressed by interviewing participants, we believe that using mHealth and integrating it with the existing health system is possible, but it would require stability of several factors such as network coverage and power supply.[9,10] We therefore suggest that future studies on mHealth interventions in resource-limited settings may benefit from involving other stakeholders, especially mobile network providers, since they have a vital role in providing stable network coverage necessary for delivering such interventions.

Psychosocial barriers including lack of social support and mental health issues have shown to influence poor use of interventions due to fear of HIV-disclosure within the family or at work places. Findings from a previous study in Kenya have shown that SMS had better effect on treatment adherence for those who received SMS and reported a high level of social support.[11] Therefore, it is important to take into account mental health issues when applying digital tools by for example creating support through messages or use the tool to increase communication about mental health issues during clinic visits.

Privacy was a main issue for participants who did not disclose their HIV status to others. This finding is consistent with that of studies in South Africa and a study in Kenya that showed that some participants had concerns that monitoring was intruding on their privacy.[12,13] The use of neutral messages that do not refer to topics related to sickness or medication could overcome the problem of unwanted disclosure. In addition, participants in the South African study had concerns that the size and design of the pillbox would reveal their HIV status to the community, especially when they needed to open it in the vicinity of others. However, our pilot study in

Kilimanjaro [8] showed a different result, as most participants were happy with the color and size of the device.

Case 6 illustrates the importance of ensuring that an intervention intended to improve adherence does not interfere with a person's strategy to enhance their level of adherence. Despite that we told our participants to keep using their normal ways of reminding themselves to take their medication, this participant decided to quit using his phone alarm. Although he declared that the reminder SMS text message served as an alarm to him, it did not lead to improved medication intake according to the device. We cannot say that using the device hampered medication intake, as this participant was judged to be nonadherent at enrollment. Unfortunately, it was not clear why this patient was not adherent. It is possible that the participant was still not willing to disclose to the interviewer that he was not taking his medication or not taking it on time.

Two participants had suppressed viral loads after being exposed to the intervention for several months, despite having low levels of adherence as indicated by responses to text messages or by recorded RTMM device openings. It remains unclear whether these participants were adherent to taking their medication but nonadherent to the proper use of the intervention (ie, responding to SMS text messages or opening the RTMM device). This difficulty in distinguishing between adherence to treatment and adherence to proper use of an intervention or device is not unique to the 2 mHealth interventions that were used in this study. Similar findings have been reported in 2 studies conducted in Kenya.[11,12] Another explanation for the suppressed viral loads might be that levels of adherence were incorrectly recorded due to technical problems. To be able to distinguish between true low adherence to treatment and low adherence to the intervention combined with technical problems, drug levels in the blood could give more insight. Because it was not possible to measure plasma concentrations of antiretroviral drugs in this study, we could not verify whether these participants were nonadherent to their medication intake or nonadherent to using their device.

CONCLUSION & RECOMMENDATIONS

This case series explored the reasons underlying major discrepancies between self-reported adherence and digitally monitored adherence that occurred in 6 participants in our mHealth intervention trial. Based on our findings, we can make a number of recommendations. First, network coverage at the participant's home must be ensured before implementation. Second,

neutral messages (eg, “Hello, this is your friend from the REMIND Study. I hope you are doing well.”) should be used to avoid unwanted disclosure of HIV status. Third, participants should be advised to continue using their usual reminder cues. Fourth, a triage system could be developed to determine whether a patient is ready to use such mobile interventions to prevent the paradoxical situation that an intervention intended to improve treatment adherence actually worsens adherence. Fifth, researchers should attempt to distinguish between adherence to the use of a monitoring device and adherence to treatment. Last, our findings serve as a reminder of the paramount importance of psychosocial support in the context of providing HIV treatment and care.

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AUTHOR CONTRIBUTIONS

K.N. was involved in the project as study coordinator and developed the study protocol. He was responsible for designing and writing the whole manuscript including compiling of inputs from the listed authors and responding to the queries. Also, he was involved in data collection, analysis and interpretation and identifying relevant literature.

F.L. was involved as a study doctor seeing the participants in case of medical occurrences as well interpreting the clinic data during manuscript writing.

Z.H. was involved in the study as study nurse. She was engaged in the follow-up process of enrolled participants and interviewing them. Also, she participated in data collection and interpretation of the data.

E.M. was involved as the Principal pharmacist of the study and accountable for interpreting the adherence data.

B.T.M. was supporting the study team in project management and administrative issues relating to the study. Furthermore, she reviewed of the manuscript before submission.

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R.E.A. was involved in development of the study protocol, provided support during the entire study and critically reviewed several versions of the manuscript before submission.

P.R. Critically Reviewed the final manuscript before submission.

M.S.B. developed the study protocol and oversaw the study procedures as principal investigator. Also, she organized the manuscript methodology. She was involved in critically reviewing the initial and final drafts of the manuscript.

ANNEX 1. *Summary of Case characteristics*

Case	mHealth intervention	Age, gender	ART regimen	Self-reported adherence	Adherence according to SMS/RTMM	Viral load (copies/mL)		
						Enrollment	Month 3 to 6	Month 12
1	SMS	20-year-old female	On 2nd line regimen Started ART in 2011	95	43%	1927	2627	129
2	SMS	19-year-old female	On 1st line regimen Started ART in 2008	97	51%	47587	Not assessed due to missed clinic visit	6679
3	SMS	29-year-old female	On 1st line regimen Started ART in 2012	100	28%	367	No test done as VL was <1000	Not detectable
4	RTMM	58-year-old female	On 1st line regimen Started ART in 2012	100	33%	16106	<20	Not detectable
5	RTMM	33-year-old male	On 1st line regimen Started ART in 2013	97	57%	2863	67	12447
6	RTMM	21-year-old male	On 1st line regimen Started ART in 2005	100	60%	739	<20	Not detectable

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Chapter Five

Case report: Returning of antiretroviral medication dispensed over a period of 8 months suggests non-adherence despite full adherence according to Real Time Medication Monitoring.

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ABSTRACT

Real-time medication monitoring (RTMM) may potentially enhance adherence to antiretroviral treatment (ART). We describe a participant in an ongoing trial who, shortly after completing trial participation, died of cryptococcal meningitis despite high levels of adherence according to self-report, pill-counts and RTMM (> 99%). However, she evidenced consistently high HIV viral load throughout the 48-week study follow-up. Subsequently, her relatives unsolicitedly returned eight months' dispensed ART medication that she was supposed to have taken. This brief report illustrates the challenges of adherence measurements including RTMM, and reinforces the need to combine adherence assessments with viral load monitoring in HIV care.

INTRODUCTION

Sustained adherence to antiretroviral treatment (ART) at levels over 95% among people living with HIV (PLHIV) is required in order to prevent treatment failure and the emergence of drug resistance.[1] Therefore, monitoring of adherence is of paramount importance in the management of PLHIV. In resource-limited settings, self-reported adherence and adherence calculations based on pharmacy refill counts are often used, but have been shown to overestimate actual adherence rates.[2] Several reasons for such over-reporting have been found, including: (1) fear of being expelled from the study and losing the benefits provided by study participation, (2) social distance between study nurses and participants causing mistrust, (3) nursing staff that is perceived as condemning being non-adherent, and (4) counselling provided by study staff that may discourage openness, or alternatively, may be too permissive making misreporting easy.[3,4] Electronic monitoring devices consisting of either pill bottle caps or pillboxes that record and store the date and time of each opening of the cap or box are generally considered to be the most accurate and reliable adherence assessment method. The assumption underlying electronic medication monitoring is that each pill bottle or pill box opening represents ingestion of medication.[5,6,7] Here we present the case of a woman living with HIV that challenges this assumption. We first describe the ongoing randomized clinical trial in which the subject had participated.

TRIAL

The trial aims to investigate the effect of two mobile health (mHealth) strategies, real time medication monitoring (RTMM) and use of short message service (SMS), on adherence to treatment among PLHIV in Kilimanjaro, Tanzania. A total of 249 adults on ART who were subjectively judged to be non-adherent by nurse counsellors were recruited from two health centres. The judgement was based on missed clinic visits, reported non-adherence and

returning of leftover pills to the clinic. Participants were randomized equally in a ratio of 1:1:1 to receive SMS, RTMM or standard care and followed for 48 weeks. The study was approved by the Kilimanjaro Christian Medical College Research Ethics and Committee (CRERC) and the National Health Research Ethics Committee (NatHRec) of Tanzania.

Our case was randomized to the RTMM arm in which participants use an RTMM-device, the so-called Wisepill device, to take their medication. Each opening of the box is recorded, including the time stamp and status of the battery. This information is instantly sent through mobile data using General Packet Radio Service (GPRS) to a central database which has a secure web-based interface where the usual time of intake (agreed time between patient and healthcare provider) is stored. If the box is not opened on time, the participant receives a short message service (SMS) text on their mobile phone which acts as a reminder to take medication. The RTMM system generates a report that shows pill box openings. This report is then used during bi-monthly consultations with study nurses to discuss adherence and strategies for improvement, if needed. In the trial, adherence in all arms is measured through self-reporting by asking about the number of missed pills during the past month and through pharmacy refill counts by counting the number of leftover pills at each visit. In the RTMM arm, it is also measured through RTMM, in which pill-box openings are considered to indicate medication intakes.

CASE

A 38-year old single woman was first diagnosed with HIV in April 2017 and started on ART (tenofovir + lamivudine + efavirenz) in June 2017. Her medical file showed that she had a viral load of 423,000 copies/ml in April 2017 and a CD4-count of 276 cells/µL in June 2017. She was enrolled in our study in February 2018 and at that time was still on the first-line antiretroviral regimen of efavirenz, lamivudine and tenofovir. At enrolment, she had a high viral load of over 200,000 copies/ml, indicating virological failure possibly as a result of treatment non-adherence. As part of participating in the trial (RTMM arm), she reported detailed information about her adherence to treatment during clinic visits. She consistently reported to take all her antiretroviral pills except for one visit where she mentioned to have missed a few pills in the previous month. Her viral load continued to be high (> 200,000 copies/ml) for more than a year during follow-up in our trial despite extensive adherence counselling during study visits. From January 2019 onward, her health gradually deteriorated. She started feeling sick and cryptococcal meningitis was diagnosed. At her last 48 weeks study follow-up visit in February 2019, she looked fatigued and weak. As part of the trial, an exit-

interview was scheduled to obtain information about her experience on the usage of RTMM. She did not attend this interview. The patient died of cryptococcal meningitis in July 2019, in spite of having been switched to a second-line antiretroviral regimen of atazanavir, abacavir and lamivudine.

Virological and immunological outcomes

The participant had a viral load of 231,037 copies/ml at enrolment in February 2018. Three months later in May 2018, her CD4 cell count was 56 cells/µL. When the viral load measurement was repeated in August 2018, it remained high at 262,000 copies/mL and again in January 2019 (232,352 copies/mL) and February 2019 (245,932 copies/mL). At the last study visit in February 2019, her CD4-count had decreased to 16 cells/µL. In May 2019, her viral load had decreased to 44 copies/mL and her CD4 count increased to 160 cells/µL.

Adherence to treatment

The participant's adherence rates according to self-reporting, pharmacy refill monitoring, and RTMM were recorded at clinic visits during the study period. She reported to only have missed 2 pills in the total follow up of 355 days, which corresponds to an adherence rate of 99%. This was confirmed by pharmacy refill counts, according to which adherence over the total period was likewise above 99%. The high adherence rate of 99% was further confirmed by RTMM. Figure 1 shows the monthly adherence graphs that were generated by the RTMM device. The graphs show that most of the time, the patient consistently opened the RTMM device around 8 pm. In the feedback sessions where she received tailored feedback on her adherence reports, she always confirmed that she took all her medication adequately. Only at one visit in July 2018, she mentioned that her intake was not adequate. In addition, she explained that she used her phone alarm as an extra reminder and that her mother also helped reminding her to take medication. She confirmed that she experienced no problems in taking medication. After finishing her last study visit (end of study follow-up), she was invited for an exit-interview which she was not able to attend (Fig. 2).

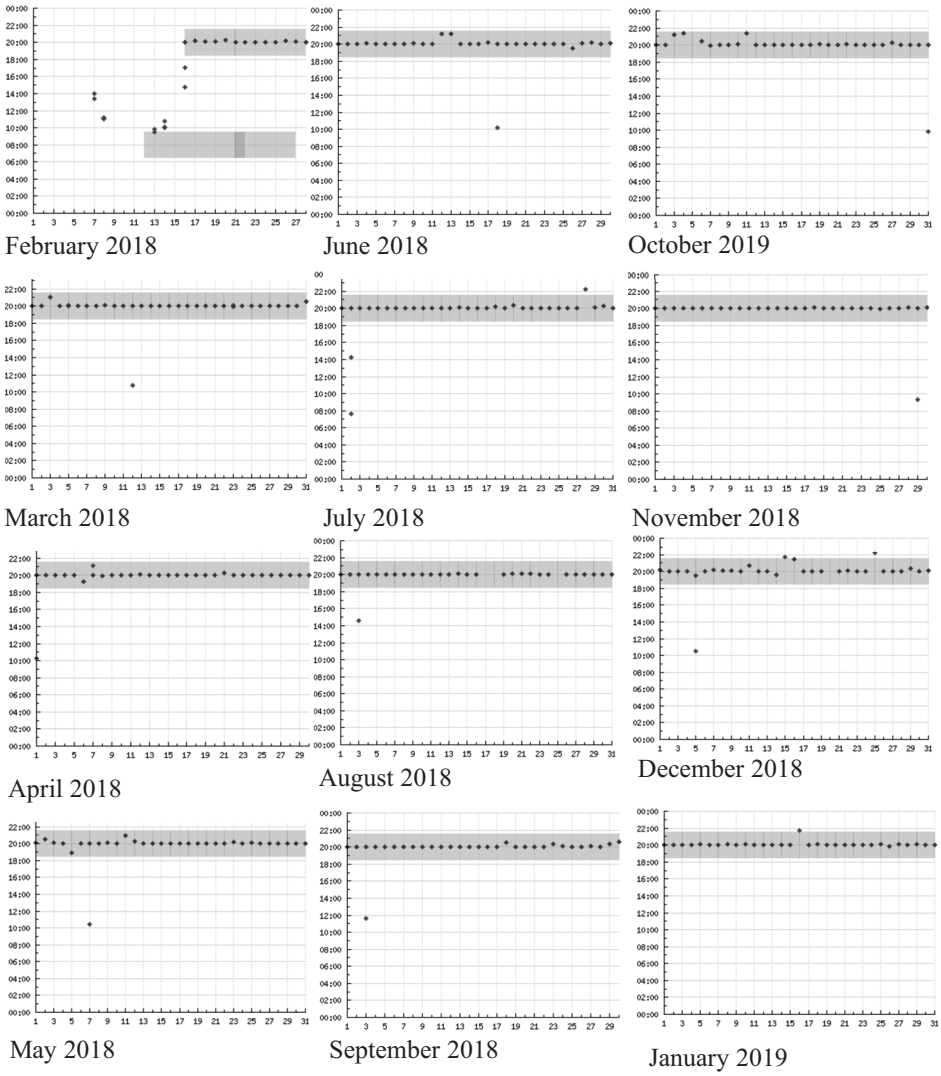

Figure 1: Adherence graphs (X-axis is the day of the month, Y-axis is the time of intake whereby the dots display the opening of the pillbox and the bars show the agreed time of intake)

*Figure 2:**a** First-line Medication that was returned by relatives of our trial participant. **b** Second-line Medication that was returned by relatives of our trial participant.*

Leftover pills

After our participant had died, her relatives came unsolicited to bring back leftover medication. In total, pills dispensed for 151 days (45% of the study period) for the first-line regimen were returned, and pills dispensed for 60 days for the second-line regimen were returned (43% of second-line regimen duration). The production dates of the returned first-line pills ranged from March 2017 to March 2018, indicating that those were the pills she had been supposed to be taking during the study. We had to conclude that despite the excellent adherence rates according to all three measures, i.e. self-report, pharmacy refill monitoring, and RTMM, her adherence had actually been low.

DISCUSSION

This case report describes a woman living with HIV whose adherence indicators showed excellent adherence but were in sharp contrast with her actual health indices. This case report illustrates that opening of the pillbox, the so-called medication event, does not necessarily mean actual pill intake. We can only speculate what made her open the pillboxes but not ingest the medication. Perhaps she wanted to please the researchers and study nurses, or prevent receiving an SMS reminder post-intake-time, or possibly avoid adverse reactions from those close to her. Despite extensive counselling and discussions on her clinical outcomes and adherence as part of the study, the nurse counsellors who provided feedback on the adherence reports were not aware of signals or information of her non-adherence. In addition, she had

disclosed her status to relatives, and reported not to have experienced stigmatization but rather received a lot of social support.

Previous studies have shown that opening the device is a good proxy of real intake of pills at the group level [3,7], but our case clearly illustrates that exceptions exist at the individual level. The question arises under what circumstances real-time monitoring is most useful. A study in Uganda found that real-time monitoring was only effective in the early stages of ART treatment, or if patients show medication side-effects.[8] Another study from Botswana also showed that RTMM is more effective in improving adherence for patients novel to ART, compared to experienced and knowledgeable patients.[9] A third study showed that using real-time monitoring alone had a less positive impact than when an SMS reminder was sent before the actual time of intake.[10] Such an SMS is particularly helpful if it contains educational and/or motivational information to stimulate medication intake (Table 1).
Various studies have shown benefits of adherence-enhancing interventions based on electronic medication monitoring (6–8). However, this case helps to remind us that despite high levels of electronically monitored and self-reported adherence, actual adherence may be poor for some individuals. The VOICE-D trial, which is a post-trial study asking participants why their actual product use was lower than they had reported, is worth mentioning. The results suggest that participants, acknowledged the importance of daily monitoring and honest reporting, and yet still over-reported their adherence due to fear of being expelled from the study and worry to be misjudged by nurses for criticizing the interventions.[3] Apparently, our participant refused to take ART but was unwilling or felt uncomfortable to communicate this to her health care providers. It serves as a reminder of the importance of making patients feel free to discuss their concerns and wishes with their healthcare providers, without the fear of being judged or blamed for being non-adherent or refusing medication.

CONCLUSION

In conclusion, this report illustrates that a valid and accurate measurement of medication adherence remains challenging, and reinforces the importance of combining the assessment of adherence with viral load monitoring as part of HIV care.

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AUTHORS CONTRIBUTIONS

K.N. was involved in the project as study coordinator and developed the study protocol. He was responsible on designing and writing the whole manuscript include compiling inputs from the listed authors and responding the queries. Also, he was involved in data collection, analysis and interpretation and identify relevant literature.

L.M. was involved in the study as study pharmacist. She was engaged in follow-up process of the enrolled participants and interviewed them. Also, she participated in data collection and interpretation of the data.

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ANNEX 1. *Table 1 Visit dates, adherence measures, virological, immunological and clinical findings*

Visits	Date	Self-report (%)	Pharmacy Refill (%)	RTMM (%)	Viral load (copies/mL)	CD4 count (cells/µL)	Signs and symptoms
Screening	15-1-2018						NR
Enrolment	16-2-2018	100	90	N/A	231,037	NM	NR
Extra visit	12-3-2018	100	100	100		NM	NR
Visit 2	7-5-2018		161	100	NM	56	No any complaints
Visit 3	2-7-2018	100	100	100	NM	NM	Healthy looking
Visit 4	9-8-2018	100	100	100	NM	NM	Good condition
Extra visit	29-8-2018		90	85	262,000	NM	NR
Visit 5	3-10-2018	93	137	100	NM	NM	Active and healthy
Extra visit	31-10-2018	100	146	96			NR
Visit 6	5-12-2018		111	100	NM	NM	Healthy looking
Extra visit	9-1-2019		100	100	232,352	NM	NR
Visit 7	6-2-2019	100	96	97	245,932	16	Looks sick (weak and fatigue)
Extra visit	29-5-2019				44	160	

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Chapter Six

"I wish to continue receiving the reminder Short Messaging Service": A mixed methods study on the acceptability of digital adherence tools among adults living with HIV on antiretroviral treatment in Tanzania

Authors

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ABSTRACT

Introduction: Digital Adherence Tools (DAT) to promote adherence to antiretroviral treatment (ART) for HIV are being increasingly adopted globally, however their effectiveness and acceptability in limited resource settings has been challenging. In this study, we examine the acceptability of DATs to improve adherence to ART.

Method: This study was part of a three-arm randomized controlled trial (REMIND) which investigated the effect of two different DAT's: SMS text messages (SMS) or real-time medication monitoring (RTMM) on treatment adherence; compared to standard of care. Exit interviews and in-depth interviews were conducted at 48 weeks follow-up, to collect data on their experiences (successes, challenges, and barriers) and behaviours regarding the implementation of the interventions. Translated transcripts, memos and field notes were imported to NVivo software version 12. We used a thematic framework analysis which drew from Sekhon's theoretical framework of acceptability (TFA), which comprises of seven constructs (affective attitude, perceived burden, perceived effectiveness, ethicality, self-efficacy, intervention coherence and opportunity costs).

Result: Of the 166 participants enrolled, 143 (86%) were interviewed (68 in the SMS arm and 75 in the RTMM arm). Participants were highly satisfied (98%) with the DAT system and the majority of them reported it motivated them to take their medication (99%). The majority of participants reported they were confident in their ability to comply with the intervention and understood how the intervention worked (97%). Very few reported negatively about the devices(carrying the device), with only 6% reporting that they did not feel comfortable and 8% had ethical concerns with the SMS-content A few participants reported challenges with their connectivity/network and that the visits were too time-consuming. A few participants reported that they incurred extra cost for the sake of the study.

Conclusion: Overall, the acceptability of these DATs was high. However, several factors may hamper their acceptability including the content and number of SMS, carrying the devices and the network availability.

INTRODUCTION

In Tanzania, the national HIV prevalence reported in 2018 was 4.6% and adults aged 15-49 years accounted for 81% of the people living with HIV (PLHIV).[1] Of those adults, 72% were on antiretroviral therapy (ART). Sustained adherence to ART can be challenging. Adherence is defined as the degree to which patients comply with treatment guidelines and medical advice.(2) In the context of HIV, good adherence means that patients should take at least 95% of their antiretroviral medication per given period,[3] although other studies have shown lower levels to be adequate.[4] Barriers to good adherence can be categorized into: (1) patient characteristics, which include illiteracy, non-disclosure of HIV status, and alcohol abuse, (2) treatment characteristics, such as complex dosing schemes and adverse effects, (3) health system-related factors, including limited numbers of health care workers, inadequate supply of drugs and long distance to the health facilities and (4) an unsatisfying patient-doctor relationship resulting in poor treatment service.[5,6] Identifying strategies to overcome these barriers is critical to ensuring adherence to ART for optimal health outcomes.

How to best support PLHIV to adhere to ART is a recurrent and clinically important question. In 2020, there were 48 million mobile subscriptions recorded in Sub Saharan Africa, representing 80% of the total population.[7] This rapid increase in the use of mobile phones across sub Saharan Africa over the past years have opened the door to the use of Digital adherence tools (DATs), which have formed the basis of many recent interventions.. There are different types of DATs; some use Short Messaging Service (SMS) texts as reminders and others use Real Time Medication Monitoring (RTMM). RTMM makes use of a pillbox that records every opening of the box as a moment of presumed drug intake. It provides real-time medication management of a patient through mobile networks by direct signal-sending of medication events (opening of the pillbox) and real-time intervening by sending SMS reminder texts.[8] Both DATs have been studied in sub Saharan Africa to assess their effectiveness at improving ART adherence, viral load suppression and clinic attendance.[9–13] In Uganda, trials that included RTMM technology linked to SMS reminders showed high acceptability and increased positive habits towards ART adherence.[14] A study conducted in South Africa found that being monitored in real time, motivated 80% of participants to take their ART.[15] These studies suggest a promising shift in how to leverage technology to support adherence among PLHIV.

However, unfavorable results have been reported from digital health interventions. Studies in Kenya, Uganda, India, Tanzania and Botswana reported that some participants were concerned

about unwanted HIV disclosure, others reported anticipated stigma arising from SMS content, which may mention the words medication and HIV.[10,16,17] A systematic review showed that unreliable internet connections and high purchase and maintenance costs of smart phones resulted in unsuccessful mHealth interventions in resource-limited settings.[18] Others have also reported logistical challenges; including the fact that family members often share mobile phones, the unreliable access to electricity, and issues of mobile phones breaking.[19–21] All the above-mentioned factors may limit the acceptability of DATs by both end-users and clinic staff. Given the inherent and published challenges reported in the implementation of DAT, further studies are required to explore and overcome barriers that could limit the acceptability of interventions in real world settings.

Sekhon et al. have developed a framework to guide the assessment of acceptability of innovative health interventions.[22] The Theoretical Framework of Acceptability (TFA) includes seven domains of acceptability of an intervention to be examined at three different stages. These are (1) pre-acceptability, prior an intervention's implementation, (2) concurrent acceptability, assessed during use of the intervention and (3) post-intervention after having used the intervention. We adapted the TFA to conduct a mixed-methods study among PLHIV on ART who had participated in a randomized controlled trial in Tanzania (called the REMIND-trial) to assess the post-intervention acceptability. The REMIND-trial aimed to investigate the effectiveness of RTMM and SMS on ART adherence compared to standard of care.[23] In this paper we report on the post intervention acceptability of DAT amongst trial participants.

METHOD

Study Design

This was a cross sectional mixed-methods sub study nested within the REMIND trial (PACTR201712002844286; https://tinyurl.com/y98q4p3l,). The study was approved by the Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC) and the National Health Research Ethics Sub-Committee (NatHREC) of Tanzania. The study was conducted accordance with the Declaration of Helsinki.

REMIND-trial

PLHIV from two specialized HIV care and treatment centers (CTC) in Moshi, Tanzania were included in this 48-week trial. The study was conducted between December 2017 and February 2020 in Moshi, Tanzania and has been reported in detail elsewhere.[23] In brief, eligible

participants were adults 18-65 years of age who were on ART for at least six months, had no foreseen need to change treatment, were subjectively judged to be poorly adherent according to the study nurse, were willing to use an RTMM device and/or receive SMS, were able to read and reply to SMS, were able to come to the clinic every two months, owned an operational SIM card, lived in Kilimanjaro Region, and consented to be in the study. PLHIV were excluded if they were on co-medication for other (chronic) diseases such as tuberculosis (TB) or diabetes, were admitted to hospital, or were participating in a concurrent SMS reminder study. Enrolled participants were randomized 1:1:1 to one of three study arms: RTMM arm, SMS arm, or a standard of care control arm. In the SMS arm, participants received SMS texts on three random days each week. One SMS text message to remind patients to take their medication was sent thirty minutes before the usual time of ART intake. Another SMS text message was sent with the question "Did you take your medication? one hour after the usual time of intake. The participant was asked to reply (1) Yes, I took it, (2) No, I did not take it, or (3) Not yet. The responses were displayed automatically on graphs for tailored feedback during consultation with a study nurse. Details about this feedback have been described elsewhere.[17] Participants enrolled in the RTMM arm received a Wisepill device RT2000 (Wisepill Technologies®) which serves as a pillbox for ART.[24] If the device is not opened at the allocated time, which serves as proxy for no medication intake, the participant received an SMS text message with a reminder to take the medication. Adherence reports generated by the device (accessible only to authorised members of the study team) were used to tailor feedback during consultation with a study nurse. In a previous study, we have reported the flow of communication between the pillbox, central server, and the patient's phone.[25]

In both intervention arms, participants received tailored adherence counselling from the study staff as supported by the adherence reports generated from the interventions. Study nurses showed the reports to participants and discussed their adherence patterns using the stages of the model for behaviour change.[26] The contents of the tailored feedback have been described elsewhere.[17] PLHIV randomized to the standard of care arm did not receive device /SMS and were not included in this study on DAT acceptability.

Mixed-Method Study on Acceptability of RTMM and SMS

Study procedures

Participants from both intervention arms who completed all 48 weeks of the trial were called or seen face-to-face for an exit-interview. In addition, we randomly selected ten participants from each intervention arm and invited them for an in-depth interview (IDI; n=20). This

number was deemed adequate to reach data saturation.[27,28] Informed consent was obtained for all participants to take part in this acceptability study, and that this informed consent included consent to publish the participant's anonymized responses.

Data Collection

In these interviews we asked study participants to share their experience (successes, challenges and barriers) and behaviour regarding the interventions throughout the study. The interviews were conducted in Swahili in private settings based on participant 's preference and lasted approximately 45 to 60 minutes.

We used seven constructs of TFA to design the interviews to assess all seven domains (Figure A1: affective attitude, perceived effectiveness, ethicality, perceived burden, self-efficacy, intervention coherence and opportunity costs.

Exit Interviews

Exit interviews were conducted by trained research assistants (RA) as participants completed their routine clinic visits. Interviews were face to face, unless the participant preferred a phone interview. A semi-structured questionnaire was used, which was based on our previous pilot study [29], and included issues emerging during the trial related to acceptability and adopting the TFA constructs. Closed questions were first asked to capture the participant's general perceptions, followed by an open-ended question for each item to allow further explanation**.** The questions were read out loud by RA, together with the response options. Data were entered in real time using RedCap, an open-source secure web application for building and managing online surveys and databases, which includes features for data quality assurance.

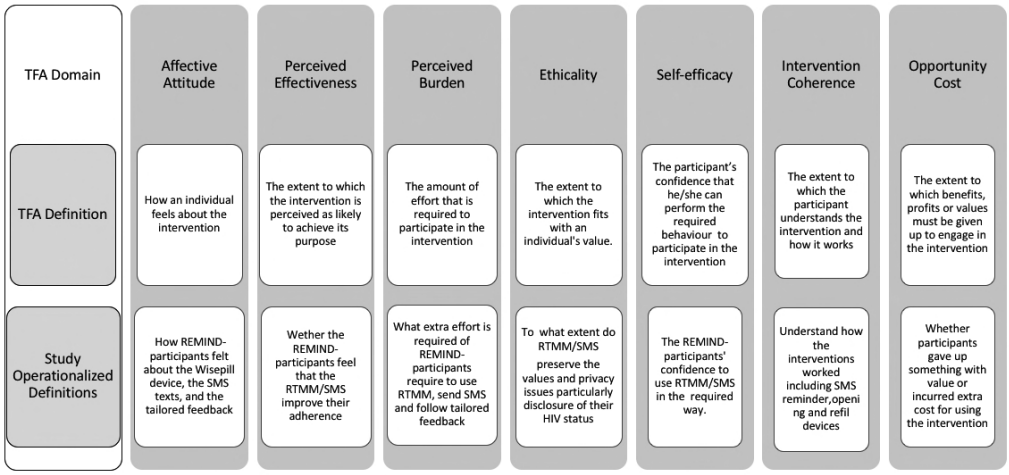

Figure A1. Seven constructs of TFA

In-depth Interviews

The in-depth interviews were conducted at an agreed upon time and space that was convenient for the participant. All interviews were conducted by the first author (KN) who is trained to conduct qualitative research including data collection and analyses. The interview guide was semi-structured and operationalized themes related to the seven mentioned constructs of acceptability in order to gain detailed insight than achieved in the more structured exit interviews. The discussion started with open-ended questions "please tell me what comes in your mind when you think back about the intervention". The participants could elaborate on the answers based on their knowledge and experience. The researcher asked follow-up questions and open probes to invite further explanation. All interviews were audio-recorded and transcribed verbatim by trained research assistants from Swahili into English. Notes and memos were also taken.

Analysis

The quantitative responses from exit-interviews were descriptively analysed using SPSSv.22 to give an overview of the frequency and percentages. Narrative explanations of the exit-interviews were listed to get better understanding of the underlying context of the quantitative answers. The qualitative responses were coded. During the process of coding, 20% of the transcripts were independently read by two authors (MSB and KN) and a list of subthemes was created based on those interviews. The interviews were discussed and agreement was achieved about the most common subthemes. A coding framework was developed based on the subthemes. Translated transcripts, memos and field notes from the IDIs were imported to

NVivo software version 12 for organizing the data and coding. Narratives were then coded based on the subthemes of the coding framework. We conducted thematic framework analysis of the coded data from the transcripts. A report of coded data based on subthemes was generated and exported into Word from NVivo. The two lead authors reviewed the report and discussed and interpreted the data in regular meetings to ensure the coded data corresponded to the framework.

RESULTS

Participant characteristics

Of the 166 participants enrolled in the two intervention arms, 150 (90%) completed the last study visit in the 48th week. Of those, 143 were interviewed (68 participants in the SMS arm and 75 in the RTMM arm; Table A1. The median age was 43 years. Two-third of participants were female. Twenty-three participants were lost to follow up after the final study visit and could not be interviewed. Results of the exit-interview are shown in Table A2, with numbers of participants reporting the answers, including their narrative explanations. Of the 20 participants invited for an in-depth interview, 19(95%) participated. The twentieth participant could not be reached due to nationally imposed restrictions on research as a result of the COVID-19 pandemic. Characteristics of these 19 interviewees are shown in **Table A3**. There is considerable variability in demographic characteristics and adherence rates, making this a heterogeneous group of participants. The themes and Quotes are shown in **Table A4.**

Table A1. Participant characteristics

Variable	**N (%)**
RTMM N (%)	75(52%)
SMS N (%)	68 (48%)
Sex (RTMM/SMS) N (%)	
Male	43(30%)
Female	100(70%)
Education level(RTMM/SMS) N (%)	
Non-at all	2(1.4)
Primary(1 to 7 grade)	89(62.2)
Secondary(8 -11 grade)	49(34.3)
Tertiary(above 12 grade)	3(2.1)
Marital status(RTMM/SMS) N (%)	
Single	49(34)
Married	59(41)
Living as married	4(3)
Separated	12(8)
Divorced	5(4)
Widowed	14(10)
Age Median (IRQ)	43(50-34)

Acceptability of the intervention

We present the results according to the seven constructs of the TFA

Affective Attitude

In the Exit interviews, 97% of RTMM and 98% of SMS participants indicated that their general experience with the devices was either good or very good. Ninety five percent reported that the way graphs displayed their adherence level was either good or very good. In addition, 98% indicated they were happy with the interventions.

Similar results were found in the in-depth interviews in which participants indicated to feel happy with the intervention, particularly concerning the reminders to take the medication. Nearly all the IDI participants were satisfied with the graphs showing their adherence status. Participants were happy to see the adherence percentages of opening the devices as well as the number of SMS that they had replied to. Those whose graphs showed a low adherence, indicated they were pleased to discuss their findings with the nurses and to explore how best they could improve their adherence in the coming clinic visits. When they were asked how they felt after completing their last 48-week study-visit, the majority indicated to be disappointed that the study was over.

Additionally, respondents elaborated that they will miss the extensive counselling and support received from study nurses during the clinic visits. At the end of the trial, patients preferred not to return the device nor to stop receiving SMS despite being informed that this was part of the study protocol at the beginning of the study. The size and appearance of the device were positively valued. Participants said it was easy to carry, and to keep in their pocket and it was not easily identifiable as a pill box containing ART.

> "For me to be enrolled in the project, it was something that made me feel very happy and I would say it was a good opportunity for me…especially when I was given the device which helped me to store my medications, which I could open at any place and take my medications without any stress*"* **, 35-year-old female participant**

> "What I would request is for the project to put…or continue with the system of reminding people, even after the project has ended, messages could remain on the phone so that people could still be reminded." **39-year-old male participant**

> "I wished they [read SMS] were coming every day because they motivated me to remember taking medications." **40-year-old female participant**

> "I was keeping the device in my pocket, and sometimes I could hold it in my hands and nobody could ask me because it almost resembles my phone handset"… "I found the device was very useful to me because I could be taking it anywhere I went. It was easy to store my medicines in there, more than keeping into a container whereby when you open it, you draw everybody's attention.
> If I travel, I put it into my bag also. I used to store it in a can container, but if I travel that container makes noises, so different from device. I do refill my medicines in the device nobody knows what I am carrying" **54-year-old-male participant**

Perceived effectiveness

Several participants agreed that the interventions had increased their motivation to take their medication every day. In the exit interviews, 142(99%) mentioned the intervention improved their adherence to treatment, 90% appreciated the SMS content and 80% reported they wished to receive the more than one messages every day.

IDI participants suggested that before the intervention, they had difficulties adhering to treatment especially in front of people. Many appreciated the SMS content "don't forget medication". Participants whose clinic files indicated a high viral load prior to the study, felt the study had assisted to reduce their viral load, with some mentioning how it fit within their regular lifestyle.

> "I was given the device, it was very helpful which gave me a motivation to remember that I had not taken my medication" **50-year-old female**

> "Before, it was very difficult for me to take my medications in the place with many people, but with the device, I could just open it, take my medications without anybody noticing what I have just done." **45-year old female**

> "The messages rescued me as I have already opened a red card by nurses at the clinic [meaning having bad treatment outcomes], but after the project, I was removed from the red card and opened another file." **45-old-female**

Perceived Burden

In the exit interviews, a number of patients reported to have difficulties using the intervention; nine (6%) responded it was not appropriate to receive the SMS, 23% responded to experience related HIV stigma, 2% reported the device was difficult to use, 5% considered it was a burden to keep the device at home, and 22% mentioned the SMS did not arrive on time.

IDI participants reported facing difficulties in having the device or replying to the SMS during the intervention period. They reported to be concerned with several aspects of the intervention. One participant found the feedback session during clinic visits too long (average of one hour per session). Another participant felt that there were too many SMS coming per week and preferred to be sent less often or weekly. One participant preferred the SMS reminders to be sent without any questions that required a response. Some participants were worried about losing the device or having it stolen and one respondent felt the device was too big to fit in his trouser pocket.

> "The interview with nurses at the clinic was too long until I get tired. May be the interview should be made shorter in future studies. Also, that nurse's tablet was somehow giving trouble to operate." **45-year old female**

> "Yes, it is big, and if I travelled, I used to put it into my bag because to put it in my pockets, its size is bigger than the touch phone. So, to carry this device in my pockets plus the phone, really looks a big load in my trouser pockets. That is why many times I carried it in my bag." **33-year old female**

Some participants also raised the issue of stigma; stigma which was primarily based on their own HIV status rather than taking part in the interventions. However, a few participants did raise the concern that taking part in the intervention may have increased the risk of their HIV status being inadvertently disclosed owing to the appearance of the device or because they may receive an SMS with the word "medication" included in the text.

> "I try to hide it, my mother forced me to give it [the phone] to her to read, saying she must see the message, I told her it is the message regarding the medications, then she was asking me what kind of medications….if the word medicine could be removed it should be replaced with another word. Let's say the message could be saying DO YOU REMEMBER? And I could reply saying 'yes I remember'." **23-year old female**

One client mentioned that the sound of the message alerting them to the reminder SMS during working hours was becoming a concern to his colleagues,

> "They did not see the SMS but were hearing the message delivery tone which came at 08.30 and 09.00 am and then asked me why so often messages every day on the same time. I told them they were the lottery messages, then they never asked me again." **38-year old male**

Ethicality

During the exit interviews, participants in both intervention arms, indicated that the intervention was consistent with their values and preserved their privacy, particularly regarding disclosure of their HIV status. However, the living arrangements of a few participants increased their risk of someone seeing the SMS content. This was reflected in the exit interviews where 8% reported that the content of the message was "not good" or "not good at all" and recommended the word "medication" should be removed from the reminder SMS "don't forget to take medication".

During the in-depth interview, patients did not report ethical issues; those who lived with family members, mentioned that they could comfortably accommodate the intervention within their life. Some reported that family members who had seen the devices, provided moral support for medication adherence. Furthermore, respondents who shared phones with their spouses mentioned that the intervention did not bring any domestic dispute when receiving the reminder SMS, but rather, motivated them to take their medication. No participants raised any ethical issues related to religion, tribe or culture.

> "My children know about my situation and were happy that I got that device to help me because they knew it would help me to not forget when it was time for me to take my medication or to lose any tablets. That is what made them very happy about the device." **45-year old female**

> "For my daughter to be aware of my situation, receiving the SMS was a great opportunity for me and helped me to not feel having HIV was my punishment for misbehaving. So, my daughter knows well that if I will leave the study I die." **38-year old male**

> "I share my phone with my husband, so when the message comes in, he just tells me the KCMC doctors have asked you to take your medications" **47 years old female**

Self-Efficacy

In the exit interviews, participants did not mention being unable to use the intervention. Participants described a certain level of determination to overcome any obstacles that would interfere with their engagement with the intervention. Participants also described how the interventions influenced them to set better health goals for themselves. Therefore, no subtheme emerged that was related to self-efficacy. However, the in-depth interview participants described how the intervention influenced their behaviour and promoted positive changes to ensure they adhere well with treatment.

> "Before the project I was drinking alcohol extensively. So, when I came home at night it was difficult for me to take medications at that time while my wife adhered to the medications. I had to pretend in front of her I took medication while I didn't. Now since I know I'm being monitored, I have stopped drinking alcohol and decided to stick on my medications as usual." **45-year-old of male**

Intervention Coherence

The majority of participants claimed to understand how the interventions worked. In the exit interviews 91% of respondents indicated that they were able to reply to the SMS, 85% mentioned they had no difficulty charging the device, 97% indicated it was easy to refill medication, and 95% reported to understand how the graph works.

The in-depth interviews participants were able to explain how the device worked and were familiar with how the device communicated about their adherence, how the SMS reminders were being sent, how the report shows adherence data on the tablets and how to open and refill the device.

> "When the message comes "Did you take your medications on time," I knew it was the time for my medications. Sometimes it was written "Do you take your medication as per the doctor's prescription?" After that I knew it was almost my time for medication, so even though I was busy , I prepared myself for taking my medication**." 54-year old male**

For many, this intervention was the first exposure to the use of digital tools in the generation of real time reports, however this was well understood and appreciated.

> "When she was asking me about my health status and the improvement of my medication intakes, she opened her big telephone and read the progress of how I replied the messages. She showed me the messages that I did not reply to and those I had replied to**." 45-year old female**

Opportunity Costs

Very few participants mentioned that they had to incur personal costs in order to take part in the study. Out of all those who participated in the exit interviews; 91% reported to have incurred no additional costs for the sake of the study. However one participant in the in-depth interviews described how she gave up her house in the village and had to move closer to town in order for the device to work. Another reported having to pay to charge the device so that she did not miss any messages or prevent reports being sent.

> "The reason I moved from the village to town was because my device was not communicating and the report was showing I was not opening the device even though I had". **42-year old female**

"I stayed with the device for six months before it lost charge, and because at home we did not have electricity, I had to take it to a young man who was educated, I told him not to open it but just to charge it and he charged me 1USD." **45-year-old female**

DISCUSSION

This mixed-methods study describes the findings of a post-intervention evaluation conducted to measure the acceptability of RTMM and SMS interventions aimed to improve adherence to ART among PLHIV. We found a high level of intervention satisfaction, with 98% of participants expressing that they would like to continue using the interventions. Moreover, 99.5% of participants who received the RTMM intervention found that it was easy to manage, including opening of the device, refilling the pills, and recharging the box. This finding was comparable to that in the SMS arm, where only 6% of participants reported to have experienced difficulties in responding to the SMS-reminders. Both of these DATs were found to be acceptable among PLHIV in this ART adherence trial in Tanzania.

Our study supports several other studies in finding that patients are happy and satisfied with DAT-based interventions.[30,31] In our study some participants mentioned various psychological barriers that could have impacted on uptake and satisfaction, including: stigma and worry of exposure.[17] A study in Kenya reported that high levels of satisfaction with the digital health intervention was associated with high levels of social support and quality of life.[19] Similar findings were noted in another study in which those who disclosed their HIV status appeared to find the SMS interventions worthwhile as they felt to be cared for and supported by others.[28]

Our study was embedded within a larger trial to assess the effectiveness of DATs to improve adherence. Despite other studies finding RTMM and SMS being effective in improving adherence, we were not able to show such an effect.[23] The interventions were only effective in participants who had a viral load <1000 copies/ml at study entry. So, despite the interventions being acceptable, they did not lead to the desired effect. Our mixed method study findings suggest that the intervention could be improved by overcoming certain barriers. For example, it was suggested by some of the participants to tailor interventions, taking user preferences into account, including personalized SMS contents (e.g. not to use the word take "medication"), receiving SMS more frequently for some participants (e.g. everyday SMS reminder) or less often for others (e.g. weekly SMS). Using tailored interventions with

personalized SMS was also reported to be preferred by participants of studies conducted in Kenya and Uganda[14,32] and may be considered in future research.

There are several limitations of our study. First, we could not conduct a pre-intervention evaluation to assess previous experiences and expectations. Studies have recommended that a pre-evaluation may examine the appropriateness of the intervention and suitability before being implemented.[33] Second, the implementation of the intervention by the study nurses may have been suboptimal, hampering the acceptability of the intervention. During conversations with the study nurses, we found they had struggled with the intervention due to high workloads, high social desirability rates despite extensive training and participants not showing up for clinic visits. Unfortunately, we do not have details about the exact conduct of the intervention by study nurses. Studies have shown that better understanding of implementation of the interventions by health care staff would result in more positive patient experiences.[34–36] Observations during instruction of the interventions and during feedback sessions could have given better insight on whether the interventions were conducted by study nurses as intended[33], and thus more acceptable to participants. Finally, we were not able to interview those participants who were lost-to-follow-up during the study. Those participants may report more negative ideas and opinions on the acceptability such as experienced stigma, less perceived effectiveness, and limited ethicality. Fortunately, the number of lost-to-follow-up was low with 13.9%.

The major strength of the study is the mixed-method design which provided both a quantification of acceptability and more detailed information about the different aspects of acceptability. With that information, we will be able to design future studies investigating the implementation and effectiveness of tailored SMS, using a pragmatic cluster trial. Another strength is the application of the TFA framework which offered comprehensive insight in the study participants' perceptions of acceptability that can be considered for future research.

CONCLUSION

This mixed-methods study provided insights into participants' experiences in relation to the acceptability of the DAT interventions used in a trial aimed to improve ART medication adherence. In our exploration of each of the constructs of the TFA, we found that the interventions were generally acceptable as patients felt highly motivated to adhere to ART medication and were satisfied with the intervention. However, patients also reported

challenges with respect to the content and number of SMS, carrying of the devices and network availability. Future studies on DATs and their implementation should address these barriers.

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AUTHOR CONTRIBUTION

K.N. was involved as study coordinator and developed the study protocol. He was responsible for designing and writing the whole manuscript including compiling of inputs from the listed authors and responding to the queries. Also, he supervised qualitative data collection, analysis and interpretation.

F.M. was involved in data collection and interviewing study participants. Also, he was engaged in translation and transcription of qualitative data.

R.E.A. was involved in development of the study protocol and critically reviewed the final version of this manuscript.

B.T.M. provided managerial support to the study and reviewed the paper before submission.

P.R. critically Reviewed several versions of this manuscript before submission and supervised KN.

P.N. was involved in development of the study protocol. She critically reviewed all the earlier versions of the manuscript during writing and provided technical inputs on translating the analysis data. Also, she provided directives on statistical methods to be applied during data analysis.

M.S. provided technical expertise and was involved in interpretation of the theoretical framework with related constructs. Also, she critically reviewed several versions of the manuscript before submission. Furthermore, she supervised KN.

M.S.B. developed the study protocol and supervised the study procedures as principal investigator. Also, she was involved in organizing the manuscript methodology and data and involved in daily supervision. She critically reviewed the initial and final drafts of the manuscript.

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APPENDIX

Table 2: Exit interview questions with narrative explanations from participants.

TFA Constructs	Feedbacks	N(%)	Missing(N)
Affective Attitude	**General experience using RTMM device** Not good at all Good Very good	 1(1) 43(58) 30(40)	1
	General experience with receiving SMS Not good at all Not good Good Very good	 1 (1) 1 (1) 91 (64) 47 (33)	3
	SMS delivered on time Yes No	 107(75) 32 (22)	4
	Display Medication intakes in graph Not good Good Very Good	 6(4) 93(65) 43(30)	1
	Happy with the intervention Yes No	 140(98) 1(1)	2
	Opinion about SMS Reminder Not good at all good Very good	 1(1) 39(27) 28(20)	0
	Experienced any Network problems Yes No	 51(36) 92(64)	
	Explanations of network problems • There is network problem at my working place but not at home. • There was network problem in a place where I was staying before I shifted to new place. • There was a period I went to stay in village I got network problem for four months.		
	Explanations of Did not like content (n=4) • The words 'you are reminded to take medication' was not good to me. • It breaks the confidentiality. • The word 'take medication' is not good. It breaches confidentiality. • The SMS which says 'medication' is not good if someone else sees it.		
	Is it okay to receive SMS only three times per week? Yes No	 34(50) 34(50)	
	If no, why? Because other day I can forget to take my drug. We are taking medication every day why don't you remind every day?		**1**
Perceived Effectiveness	**Intervention improves adherence** Yes	 142(99)	1
	Preferred to Receive more than one SMS per day Yes No	 60(42) 80(56)	3

Perceived Burden	**Experience Problems with SMS** Yes No	 6 (4) 134(94)	3
	Explain the problems • There were days I forgot my phone, my friend saw SMS and started to ask me a lot of questions which I did not like. • There were some people who saw the SMS and started to ask me questions and to follow me.		
	Experienced any stigma (not related with intervention) Yes No	 33(23) 109(76)	1
	Difficult to use the Device Yes No	 **2(2)** **72(96)**	**1**
	Concern about Daily monitoring Yes No	 **6(8)** **68(91)**	1
	Challenge to Refill medication Yes No	 **1(2)** **73(97)**	**1**
	Worry to Lose device Yes No	 **7(9)** **67(89)**	**1**
	Appropriate receive SMS Yes No	 130(91) 9(6)	4
	Difficulties with receiving SMS Yes No	 9 (6) 131 (92)	3
	Explanations of bad experience (n=2) • The SMS as they come in, sometimes I'm not with my phone, so if someone else sees that you are reminded to take medications - this may lead to lack of confidentiality – disclosure. • I'm living in a rural area with a lot of problems with network, so sometimes SMS is delayed to come on time. Once I woke up and saw the SMS in the morning.		
	Burden Keeping device at home Yes No	 **4(5)** **70(93)**	1
	Explain not good at all (n=1)(Opinion about content) I was uncomfortable when I got such SMS		
	SMS delivered on time Yes No	 107(75) 32 (22)	
	Explanations of SMS not arriving on time • The SMS were late most of the times about 30 minutes later • Sometimes she finds the SMS in the morning • Sometimes the SMS is delayed up to one day		

Ethicality	**Opinion about content** Not good at all Not good Good Very good	 4 (3) 7 (5) 78 (55) 50 (35)	4
	Appropriate receive SMS Yes No	 130(91) 9(6)	4
	If not good at all/not good, content could be The word Medicine should be removed from the content and say that "don't forgot to keep ball in the net" • The content should be "Don't forgot to use our product instead of medication" • The word Medicine should be removed and keep the word like BUNDLE • "Don't forget to use your voucher" or remember your responsibilities"		
self-efficacy.	**Non recorded in regarding to self-efficacy**		
Intervention coherence	**Difficulty charging** Yes No	 9(12) 64(85)	
	Able to reply SMS Yes No	 62(91) 5(9)	1
	Explanation for not being able to reply • My phone was broken • My phone has gotten problem in written SMS • There was no network		
	Take medication on the days not receiving SMS Yes No	 67(99) 1(1)	
	Difficult to Refill medication Yes No	 **1(2)** **73(97)**	**1**
	Understand Display Medication intakes in graph **Yes** **No**	 6(4) 136(95)	1
Opportunity Costs	**Concern about Daily monitoring** Yes No	 **6(8)** **68(91)**	1
	N=1 I have problem especially inside of my house when someone calls me, I must go outside of my house		

Table 3: Demographic and adherence characteristics of participants of in-depth interview

ID number	Arm	Sex	Age	Years since positive HIV test	Years on current ARV	Regimen	Adherence pill counts	Adherence SR week	Adherence SR month	Adherence SMS/RTMM	Problems	VL V7
1	SMS	F	19	Unknown	10	EFV+AZT+3TC	62%	74.3	75.4	53%	Answered 58%	6679
2	RTMM	M	21	Unknown	13	NVP+AZT+3TC	99%	95.2	98.9	97%	No SMS sent	<20
3	RTMM	F	53	15.1	3.3	EFV+TNF+FTC	99%	97.6	99.5	97%	No problems	30
4	SMS	F	50	12.8	6.8	EFV+TNF+FTC	98%	100	100	100%	No problems	<20
5	RTMM	F	20	11.9	0.9	ATV/r+AZT+3TC	94%	81	81.2	88%	No problems	<20
6	SMS	M	34	8.8	8.7	EFV+AZT+3TC	90%	85.7	96.8	100%	Missed two visits	33
7	SMS	M	48	23.4	6.2	EFV+ABC+3TC	84%	100	100	66%	Answered 66%	82
8	RTMM	F	49	11.1	10.2	NVP+AZT+3TC	92%	95.2	97.6	98%	No problems	<20
9	SMS	F	47	12.3	11.1	EFV+AZT+3TC	95%	100	100	100%	No problems	<20
10	RTMM	M	57	4.4	4.3	EFV+TNF+3TC	98%	100	100	99%	No problems	<20
11	SMS	F	23	1.8	1.8	EFV+TNF+3TC	94%	100	99.4	100%	No problems	<20
12	RTMM	F	45	13.2	5.7	EFV+TNF+FTC	96%	83.3	83.3	74%	No problems	142
13	SMS	F	40	11.5	3.6	EFV+TNF+3TC	95%	100	100	100%	No problems	<20
14	RTMM	M	33	4.6	4.6	EFV+AZT+3TC	97%	85.7	96.7	59%	No problems	12447
15	SMS	M	38	7.8	7.5	NVP+AZT+3TC	82%	100	100	100%	No problems	8632
16	SMS	F	45	0.8	0.8	EFV+TNF+3TC	83%	100	100	100%	No problems	74449
17	RTMM	F	39	2.2	1.9	EFV+TNF+3TC	100%	100	100	97%	No problems	<20
18	SMS	F	40	0.6	0.6	EFV+TNF+3TC	100%	100	100	100%	No problems	57
19	RTMM	M	54	7	6.6	EFV+TNF+3TC	100%	97.6	99.4	69%	No problems	<20

Table 4: Themes and Quotes

Themes	Subthemes	Illustrative Quotes
Affective Attitude	• Happy with intervention • Experience with the device (size and appearance) • Satisfied with graph report • Disappointed to end the study • Wish to keep the device after end of study • Wish to continue to receive SMS after study • Experience with SMS content	• The effects of not taking medications as directed by the doctors are that, the viral loads will be high and the communicable diseases will follow you, you may die and leave your family in pain and even the nation will miss workforce. • They are supposed to be finished by the end of the month. To be seen that I followed well the dose taking I am supposed to finished by the end of the month. • For me to be enrolled in the project, it was something that made me feel very happy and I would say it was a good opportunity to me…especially when I was given the device which helped me to store my medications, which I could open at any place and take my medications without any stress; • What I would request is for the project to put…or continue with the system of reminding people, even after the project has ended, messages could remain on the phone so that people could still be reminded. • If you don't take medications on time, this causes the virus to multiply, but if you take medications as directed, it makes the virus not able to multiply it means they become less in the blood. • I wished they [read SMS] were coming every day because they motivated me to remember taking medications. • Yes, I would sometime take the dose but most of time chances of skipping are there. • I found the device was very useful to me because I could be taking it anywhere I went. It was easy to store my medicines in there, more than keeping into a container whereby when you open it, you draw everybody's attention.

		• If I travel, I put it into my bag also. I used to store it in a can container, but if I travel that container makes noises, so different from device. I do refill my medicines in the device nobody knows what I am carrying. • I was keeping the device in my pocket, and sometimes I could hold it in my hands and nobody could ask me because it almost resembles my phone handset" • I found the device was very useful to me because I could be taking it anywhere I went. It was easy to store my medicines in there, more than keeping into a container whereby when you open it, you draw everybody's attention. If I travel, I put it into my bag also. I used to store it in a can container, but if I travel that container makes noises, so different from device. I do refill my medicines in the device nobody knows what I am carrying
Perceived effectiveness	• Better treatment outcome • Change of behaviour • Achieved expectation • Effect on adherence	• I was given the device, it was very helpful which gave me a motivation to remember that I had not taken my medication. • Before, it was very difficult for me to take my medications in the place with many people, but with the device, I could just open it, take my medications without anybody noticing what I have just done. • In my side I see it for inspiring because I know vividly, my medicines are in the certain container and when it reaches the time I shall open it and take my medications. • The project helped me to remember the time for medication, as I was very careless in not in remember taking the medication. • But after the project, immediately go to take my medication. The messages rescued me as I have already opened a red card by nurses at the clinic, but after the project, Later I was removed from the red card and opened another file • Is my sister, I explained to her about the project, that I think I am very much happy with this research project as I think it helped me a lot. She asked me not to think of a bus fare I am getting from the project, I should think of my health, because she has realized my health has improved a lot since I was enrolled on the project. • The messages rescued me as I have already opened a red card by nurses at the clinic [meaning having bad treatment outcomes], but after the project, I was removed from the red card and opened another file.

Perceived Burden	• Too many SMS • Too long feedback session • Carrying device • Being daily monitored • Cost • Intervention Stigma	• I used to take a little rest before the time, if I would wake up before 10.00 when the message comes, and take my medications, only to find I have over slept!! That is how it came where the report shows that I skipped my medications. • if somebody saw the message it could cause some problem, but I could defend that I am using the medicine could be for TB or Blood Pressure, and if he even saw it, once he wouldn't know it was a continuous message or know that it was coming from a certain institution using that kind of system. • The message had a problem where it was reading MEDICINE (DAWA) This word should be changed or look for another word to be used so that the message can be understood. This is because my phone gets handled with several people. • Yes, if the word medication could be removed it should be replaced with another way let's say the message could be saying DO YOU REMEMBER? And I could reply saying 'yes' I remember. • I try to hide it, my mother forced me to give it [the phone] to her to read, saying she must see the message, I told her it is the message regarding the medications, then she was asking me what kind of medications. • if the word medicine could be removed it should be replaced with another word. Let's say the message could be saying DO YOU REMEMBER? And I could reply saying 'yes I remember'. Its shape was good, but for a person who did not know what was it, it was easy for him to take it just to see what was that, or could be mistaken with the phone and somebody could disappear with it. • Nobody can ask me why are you taking medications, because in our country we have freedom on everything except where we are breaking the laws. The only difficult times come when taking the medications from the device, there will draw people's attention. • Yes, it is big, and if I travelled, I used to put it into my bag because to put it in my pockets, its size is bigger than the touch phone. So, to carry this device in my pockets plus the phone, really looks a big load in my trouser pockets. That is why many times I carried it in my bag. • The interview with nurses at the clinic was too long until I get tired. May be the interview should be made shorter in future studies. Also, that nurse's tablet was somehow giving trouble to operate.
	HIV Stigma	• Sometime you find yourself in a family not all family members know you are sick • Another challenge is that when you are seen taking medicines very Often what will you say?

		• In my house no medicine containers, completely, you cannot come at any time and find them because I have friends, when they come they may go after my clothes or this or do and that: Some of friends may come for proof after hearing that certain person is sick, so they may just come for proof. Therefore, I am not giving people such chance. • Yes, I leave hem at the pharmacy, even the surplus, I put them in what they call the pain killer containers. Medicines are also kept in my shop. • No! I did miss clinic only for three reasons: First the people around me, secondly, I am just living here at the KCMC, the third, people are just sitting like you but there is legion • Mt. Meru Hospitals, people treat you nicely, just because they do not know you. So, when you come back to this place, you just come fresh, because nobody has evidence of what is going on with you. But here at the KCMC I do meet people • I felt uncomfortable and found myself leaving the place, very unhappy, why because you find somebody serving inside here, sick like me, yet he goes out and tell people, that girl!! There is nothing there, she is sick!!! • In the past we used to take our medications from the place the doctors have seen us. So, we would request that after seen the doctors, if we could get our medications at the upstairs. • Before device, what contributed most was that, when people realize your situation, they don't want even to touch something that you are holding, they just form a stigma situation on you. • It happened that I went to visit him and he offered me a soft drink, after I finished I gave back the empty bottle to his child to put it back to the crate but to my surprise, he asked his child not to touch the bottle, he took it and dropped it into the pit latrine. Straight from there he stigmatized me. • I did not like Mawenzi, because, at Mawenzi if you go there late, you find a security guard at the gate, who takes your card he opens and read it, and then calls you harshly to go inside. Therefore, I went to ask the doctor to give me a permission to change to the KCMC • They did not see the SMS but were hearing the message delivery tone which came at 08.30 and 09.00 am and then asked me why so often messages every day on the same time. I told them they were the lottery messages, then they never asked me again.
		• Yes, device made them to believe that I was taking my medication • Obviously, my sister has never mentioned to me the word medicine in her life: You just hear the

Ethicality	• Fit with lifestyle (religion, belief, rights, culture) • Social Support	word (pipi) sweets that is it. So, when you hear Pipi you just remember yourself time to take medication • They all know about my situation and were very happy that I got that device to help me because they knew there was no more time for forgetting time for medication or dropping the tablets under my bed, that is what made them very happy about device. • I share my phone with my husband, so when the message comes in, he just tells me the KCMC doctors have asked you to take your medications • They all know about my situation and were very happy that I got that device to help me because they knew there was no more time for forgetting time for medication or dropping the tablets under my bed, that is what made them very happy about device. • For my daughter to be aware of my situation, receiving SMS was a great opportunity for me not feeling like a punishment of my misbehaving to have HIV. So, my daughter knows well that if I will leave the study I die.
Self-efficacy	Influenced behaviour changes	• Before the project I was drinking alcohol extensively. So, when I came home at night it was difficult for me to take medications at that time while my wife adhered to the medications. I had to pretend in front of her I took medication while I didn't. Now since I know I'm being monitored, I have stopped drinking alcohol and decided to stick on my medications as usual.
Intervention Coherence	Understanding how to charge device charging Understand how to refill the device Understanding to reply the SMS Understanding about the tablet use	• She was asking me the progress of my health and the medication. And she was opening her big telephone and read the progress of how I replied the messages. She showed me the messages that I did not reply and those I had replied • I think they were testing me, when there was no message that I should keep myself alert that this is the time for medication, even if there are no messages. • Yes, messages were just coming at random hours, I also have said this to sister. • "Did you take your medications on time" when it came, I knew it was the time for my medications. Sometimes it was writing "Do you take your medications as per the doctor's description?" After that I knew it was almost my time for medication, so even how busy I was, I prepared myself for taking medication. • The nurse used to explain to me about the project, she was taking her tablet and read to me that you have been able to answer certain messages and you were not able to answer such and such messages. I realized that I was replying messages before I was even sent the message.

		• I told him that this is the thing which I was given to me as a test for me to take medications. If I miss a medication dose, I should be failing the text as well. Therefore, my child was very keen in reminding me to take my medications and knowing that if mother misses the done she has felt the test • She was asking me the progress of my health and the medication. And she was opening her big telephone and read the progress of how I replied the messages. She showed me the messages that I did not reply and those I had replied. • She was telling me that my report is good and that I should continue with that good report. She did not show me a graph. • I do fill 20 in the front and 20 at the back, meaning when I have taken almost all and one is remaining, the next day I open and refill it. I have never left it to be completely empty • I used to put my medications on its two sides and was able to hold me for several days. • I have been using device, and it has two parts: because I was given two types of medications, so I used device to store those two types into its two parts, one side used to store those strong medications and another side I used to store those to calm down. Each time I opened it I used to take medications from both sides. • Three times even up to four times. I was receiving messages telling me for example in the morning you are told, remember to take your medication. Please follow doctor's instructions. At night you are also told!! remember to take your medication.
Opportunity Cost	Incurred extra cost for the sake of the study	• The reason I moved from village to town was because my device was not communicating and the report was showing I was not opening the device while I did. • I stayed with device for six months before it was off the charge, and because at home we did not have electricity, I took it to the young man who was educated, I told him not to open it but just put it on the charge and he charged me 2000/- shilling.

Chapter Seven

Predicting viral load suppression by self-reported adherence, pharmacy refill counts and Real Time Medication Monitoring among people living with HIV in Tanzania.

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Submitted

ABSTRACT

Introduction: Monitoring of adherence to antiretroviral treatment (ART) is of utmost importance to prevent treatment failure. Several measures to monitor adherence have been applied in low-resource settings and they all have pros and cons. Our objective was to examine whether any of the following adherence measures is a better predictor of participants' viral load suppression: (1) self-report, (2) pharmacy refill count, (3) Real Time Medication Monitoring (RTMM), (4) a combination of self-report and pharmacy refill count or (5) all three adherence assessment methods combined.

Methodology: This was a post-hoc analysis of data from our 48-week REMIND-HIV randomized controlled trial in which adherence to ART was measured using self-report, pharmacy refill counts and RTMM among ART-experienced adults living with HIV subjectively judged to be nonadherent to ART. For each adherence measure, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for predicting virological failure defined as a viral load (VL) of >20 copies/mL. To determine at which percentage of adherence the prediction was strongest, we evaluated adherence cut-offs of 80%, 85%, 90%, 95% and 100% using receiver operating characteristic (ROC) curves. VL data were obtained after 48 weeks of follow-up in the trial.

Results: A total of 233 people living with HIV (PLHIV) were included in this analysis. When comparing the ability of self-reported adherence with pharmacy refill count and RTMM adherence to predict viral load >20 copies/ml, self-reported adherence had the lowest sensitivity, ranging from 6% to 17%, but the highest specificity, ranging from 100% to 86%, depending on cut-off values from 80% to 100%. Area under the ROC curves (AUC) were 0.54 for RTMM, 0.56 for pharmacy refill count and 0.52 for self-report, indicating low discriminatory capacity for each of the adherence measures. When we combined the self-report and pharmacy refill count measures, sensitivity increased, ranging from 28% to 57% but specificity decreased, ranging from 83% to 53%. When all three measures were combined, we observed the highest value of sensitivity, ranging from 46% to 92%, and PPV, ranging from 32% to 36%, at high cut-offs ranging from 80% to 100%. Upon combination of three adherence measures, the AUC increased to 0.59.

Conclusion: Our results show that adherence assessed exclusively by self-report, pharmacy refill count or RTMM were insufficiently sensitive to predict virologic failure. Sensitivity markedly improved by combining all three measures, but the practical feasibility of such an approach would need to be studied.

INTRODUCTION

In 2019, an estimated 24 million people were living with HIV (PLHIV) in Sub-Saharan Africa, of whom approximately 73% were adults 15-49 years of age, approximately 75% of whom were on antiretroviral treatment (ART).[1] Maintaining high rates of adherence to ART is vital to maintain viral suppression and reduce morbidity, disease progression and mortality among PLHIV in a sustained manner.[2–5] The level of adherence to ART required to prevent virological failure and the emergence of antiretroviral drug resistance was previously considered to be at least 95%.[6] However, more recent studies suggest that current regimens are more forgiving of missing doses, with levels of 80% adherence potentially being sufficient.[3] Maintaining consistently high adherence levels over long time periods has been challenging for PLHIV. This is due, among others, to medication fatigue and dissatisfaction with HIV consultations provided at the clinic.[7,8] Commonly used adherence assessment methods applied by clinicians in low-resource settings are self-reported adherence, pill counts and pharmacy refill counts.[9,10] These methods are often used in standard clinical practice to support meaningful discussion about adherence between PLHIV and health care providers.[10] However, due to recall and social desirability bias, self-report methods tend to overestimate PLHIV's actual adherence levels, whereas pill counts and pharmacy refill counts can easily be manipulated and may be too cumbersome to perform in routine clinical practice.[11]

Several alternative adherence monitoring tools have been recommended to overcome these drawbacks including digital adherence tools (DAT) [12], which make use of mobile phone communication. With the widespread use of mobile technology in Sub-Sahara African countries, adherence strategies deployed by mobile phones have the chance to reach a large user audience.[13] An example of such a strategy is the Wisepill® device for real-time medication monitoring (RTMM). RTMM records the date and time of each opening of a medication box and is thus less susceptible to overestimating medication adherence than self-report and pill counts.[14] However, RTMM has its own technical challenges due to the fact that it relies on a battery in the device and on network availability in order to send a signal about an opening of the box to a server as a reflection of actual medication intake.[2,15] As a result, inconsistent capturing of actual doses missed was reported in several studies investigating the use of RTMM.[16–19] Moreover, RTMM may underestimate actual adherence levels if participants do not ingest the pills directly from the device, but for example put retrieved pills in their pockets, so-called pocket dosing.[20]

Previous studies have investigated which of the adherence assessment methods self-report, pharmacy refill count, or RTMM, may be the best predictor of virological suppression.[21–24] However, to our knowledge, there is limited evidence of the ability of those adherence methods to predict viral suppression when combined in a low income setting. Therefore, as part of our REMIND-HIV trial [25], the objective of this study was to examine whether any of the following adherence measures is a better predictor of PLHIVs' viral suppression: (1) self-report, (2) pharmacy refill counts, (3) RTMM, (4) a combination of self-report and pharmacy refill count or (5) all three adherence assessment methods combined.

METHODS

We conducted a post-hoc analysis of part of the data from the randomized controlled REMIND-HIV trial, in which PLHIV had been randomly allocated to (1) RTMM, (2) Short Message Service (SMS) reminder texts or (3) standard of care and followed for 48 weeks. Details of the trial have been described elsewhere.[25] 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. The trial was registered at the Pan African Clinical Trials Registry under PACTR201712002844286.

Study population

Participants were recruited from two sites, which were Kilimanjaro Christian Medical Centre (KCMC) and Majengo Health Centre, both located in Moshi, Tanzania. PLHIV were approached by study nurses during a common clinic visit. Informed consent was obtained from all participants followed by screening for eligibility. The inclusion requirements were: (1) 18–65 years of age, (2) receiving antiretroviral treatment for at least six months, (3) subjectively judged by a nurse counsellor to be poorly adherent to medication, based on missed clinic visits, returning excess leftover medication, and/or having continuously high viral loads, (4) able to read and write and (5) able and willing to provide consent to study participation. We excluded participants if they (1) were admitted to the hospital and/or (2) participated in similar studies investigating digital adherence tools.

Study Procedures

After obtaining informed consent from participants, study nurses interviewed participants and completed a screening form, containing inclusion and exclusion criteria, demographics, medical history, HIV history and times of usual ART intake. A secured web-based electronic

data capture software system (REDcap) was used to collect and manage data. RedCap supports data validation, has an auditing trail and allows for data verification.[26] After completion of screening, the data manager performed randomization in REDcap using block randomization, stratified by gender and study site. Participants were randomized in one of three arms, RTMM, SMS or control arm, at a 1:1:1 ratio.[25] Participants were expected to attend the clinic every two months, according to standard care.[27] At each clinic visit, adherence was recorded through self-report, pharmacy refill count and, in the RTMM arm, additionally through RTMM. Participants were followed for 48 weeks. Viral load was measured at baseline and at the last week 48 study visit. For the present study, adherence and viral load data obtained at the week 48 study visit are used. Adherence measures considered the period since the last study visit preceding week 48. We did not include adherence data from the full study follow-up due to incompleteness of the data during earlier visits, though we considered leftover medication from the before-last visit.

Adherence Measures

Self-Reported adherence

Self-reported (SR) adherence was measured using a questionnaire that was administered during a face-to-face interview by study nurses at each study visit. The questionnaire included two adherence questions: (1) 'How many pills do you take per day?' and (2) 'How many pills did you miss in the past week?' We calculated adherence as follows:

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

Pharmacy refill counts (PR)

A case report form was administered face to face to record pharmacy refill data at each study visit. The study pharmacist recorded the number of pills dispensed during the previous visit by asking 'How many pills were given to you at the previous visit?' while checking the medical file for the same information. In addition, the left-over pills returned during the previous and current visit were counted. For the participants who did not return pills, we asked to recall the number of pills that were left at home. In case leftover pills were unknown, our assumption was that all pills had been taken as prescribed in during the previous visit. Adherence was calculated as follows:

Pharmacy-refill adherence: (((pills dispensed at 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%. Assuming that levels higher than 100% were representing 100%, we truncated maximum adherence at 100%.

RTMM adherence

Participants in the RTMM arm were given a Wisepill® RTMM device to monitor their medication intake in real time. When the device is opened, information including the time stamp is wirelessly sent using General Packet Radio Services (GPRS) to a secured web-based central database. Each opening was recorded, which was taken as a sign that the participant ingested the dose. If the box was not opened on time (agreed time between participant and healthcare provider), the participant received a short message service (SMS) text on his/her mobile phone which acted as a reminder to take medication.

Adherence levels were calculated at the 48-week follow-up visit of the study.

Adherence= (Number of openings over a given period/number of expected openings (based on prescription of number of dosing moments per day)) *100%.

Virological failure

HIV viral load data were obtained at 48 weeks of follow-up. The Tanzanian HIV guidelines direct health care workers to act once someone has 1000 copies/mL i.e. to provide enhanced adherence counselling or switch treatment.[27,28] However, laboratory equipment can determine viral load as low as 20 copies/ml. Therefore, plasma HIV RNA < 20 copies/ml was defined as virologically suppressed, while plasma HIV RNA <1000 copies/ml was categorized as stable and plasma HIV RNA >1000 copies/mL was categorized as unstable. As the trend in analyses of both cut-off values were the same, to answer our objective, we only considered a viral load level >20copies/mL as representative of virological failure.

Analysis

Statistical analyses were conducted with Stata v.15. In the analyses, we included all participants who had a viral load measurement at week 48. The analyses that included RTMM-based adherence were only based on participants who were in the RTMM arm as RTMM was not used in the other arms.

To evaluate the ability of the various adherence measures to predict a detectable viral load, we conducted analyses using a cut-off of >20 copies/mL. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different adherence cut-off values for each adherence assessment method separately. We classified participants as having poor adherence or good adherence using adherence cut-off values of 80%, 85%, 90%, 95% and 100% whereby the percentage stands for the percentage of doses taken. We used these to determine at which cut-off the prediction of a viral load $\geq$ 20 copies/mL was strongest.

For each of the adherence measures, its sensitivity was defined as the percentage of participants with a viral load ≥20 copies/ml who were identified by the methods as being poorly adherent at a certain adherence cut-off. Its specificity was defined as the percentage of participants with viral load < 20 copies/mL who were identified as being adherent at a certain adherence cut-off. The positive predictive value (PPV) was defined as the percentage of non-adherent participants with a detectable viral load, and the negative predictive value (NPV) as the percentage of adherent participants with an undetectable viral load.

The adherence measures were also combined to determine how two or three of them might impact sensitivity, specificity, PPV and NPV. To create composite adherence measures, participants were identified as non-adherent if they were below the adherence cut off in any of the combined measures under consideration. For example, when self-report and pharmacy refill counts were combined at a certain same cut-off and adherence was below 95% in either self-report or pharmacy refill count, the combined variable also was considered being below 95%.

For each of the adherence measures, sensitivity and (1-specificity) at the various adherence cut-off values were plotted in receiver operating characteristic (ROC) curves based on all the adherence data to determine the accuracy of an adherence measure to predict viral load. An Area under the ROC curve (AUC) value of 0.5 indicates that a test has no discriminatory capacity and an AUC of 1.0 indicates perfect discriminatory capacity. For screening purposes an AUC of 0.7 or higher is usually considered sufficient.[29]

Besides the ROC curves analysis, logistic regression was used to identify which adherence measure predicted detectable a viral load $\geq$ 20 copies/mL while adjusting for demographic and

clinical characteristics, including sex and type of ART regimen, whether someone was on a first line regimen, being on treatment at study entry, and entry VL. Analysis of baseline data of the parent trial had shown that TLE (the combination of tenofovir, lamivudine, efavirenz) was a significant predictor of viral load<20copies/ml at study entry and therefore type of ARV regimen was categorized as TLE or another regimen. Two-sided p-values of <0.05 were considered statistically significant in all analyses.

RESULTS

A total of 249 participants were enrolled and randomized and 233 (93.6%) completed the 48 weeks of the study with an available HIV viral load result at week 48. Of those, 72 participants (30.9%) had a viral load ≥ 20 copies/ml and 29 (12.4% of the 233) had a viral load ≥ 1000 copies/ml at week 48. The majority (70.4%) was female. The mean age was 41.2 years. The 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. Most participants (76%) were using a first-line regimen which included efavirenz, nevirapine or dolutegravir and for eight participants the regimen was not recorded at week 48 (**Table 1**).

Predictive value of individual adherence measures

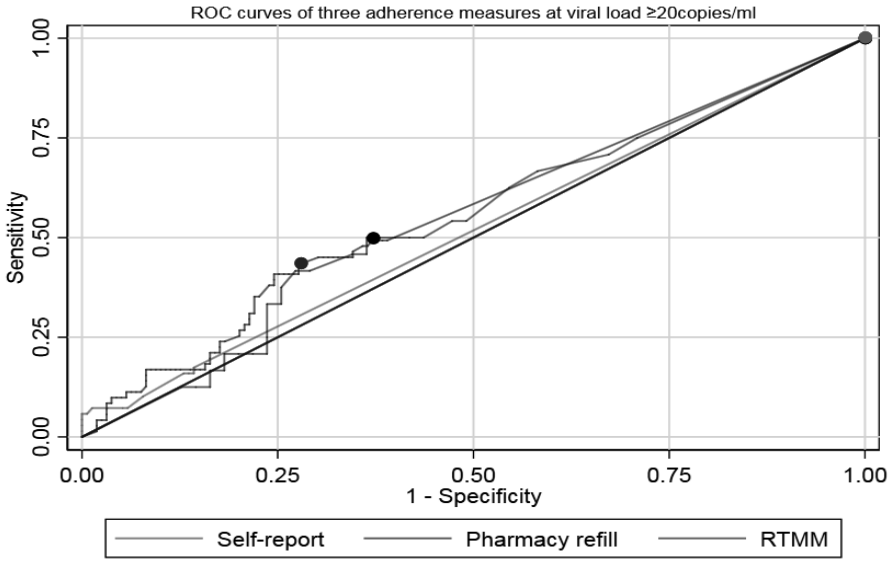
In terms of the ability to predict a detectable viral load of ≥ 20 copies/ml, table 1 shows that the *sensitivity* was lowest for self-reported adherence, higher for adherence by pharmacy refill counts and highest for adherence by RTMM at all adherence cut-off levels. Conversely, *specificity* was highest for self-reported adherence, lower for adherence by pharmacy refill counts and lowest for adherence by RTMM. The PPV ranged from 100% to 35% for self-reported adherence depending on the cut off value, while it was below 42% for adherence by pharmacy refill counts and RTMM. The NPV was consistently high (above 70%) for each of the measures at all cut-offs (see **Appendix 1. T1).**

Table 1: Demographic and treatment characteristics of participants (N=233).

Variable	N	**Mean, Median**	**SD/IQR/%**
Female Male	164 69		70.4% 29.6%
Mean age		41.2	11.9
Median years on current ART		4.4	2.1-8.0
NVP+AZT+3TC	36		15%
EFV+TDF+3TC	74		32%
EFV+TDF+FTC	13		6%
EFV + AZT+3TC EFV + ATV EFV + ABC+3TC	18		8%
ATV/r+AZT+3TC ATV/r+TDF+FTC ATV/r+ABC+3TC	29		12%
LPV/r+AZT+3TC LPV/r+TDF+FTC LPV/r+ABC+3TC	18		8%
DTG+3TC+TDF DTG+AZT+3TC DTG+ABC+3TC	37		16%
Missing	8		3%
Viral load ≥ 20	72		30.9%
Viral load ≥ 1000	29		12.4%
First line regimen	178		76%
Second line regimen	47		20%

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; LPV, lopinavir; NPV, nevirapine; r, ritonavir; TDF, tenofovir disoproxil fumarate. DTG, dolutegravir

Overall, the AUCs of sensitivity versus 1-specificity of the individual adherence measures was lower than 0.7. Pharmacy refill and RTMM had AUC values of 0.56 and 0.54 respectively, while self-report had an AUC value of 0.52. The optimal adherence cut-off points, closest to the upper left part of the figure were 89% for RMM, 96.2% for pharmacy refill and 100% for self-report *(see dots in figure 1).*



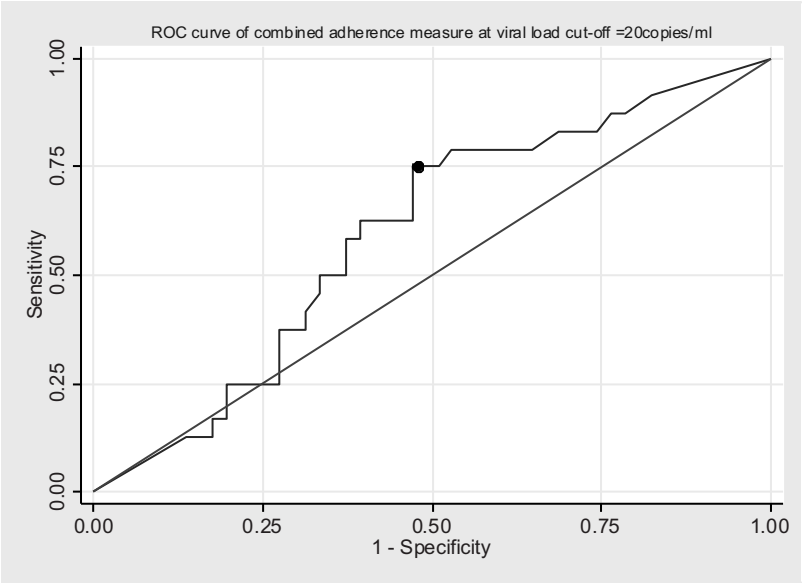
	Self-report	Pharmacy refill	RTMM
AUC	0.52	0.56	0.54
Optimal adherence cut-off point	100	96.2	89.0

Figure 1: Receiver Operating Characteristic (ROC) curves for each assessment method (VL≥20copies/ml) based on continuous adherence data.

Of the three measures, only self-reported adherence was significantly predicting viral load >20 copies/ml at cut-offs of 85%, 90% and 95% in logistic regression analyses after adjustment for age, sex, study site, type of ART regimen. A regimen consisting of efavirenz, tenofovir and lamivudine, i.e., TLE, was a significant predictor of virological failure (p<0.03). However, confidence intervals were wide, indicating low precision **(see Appendix 1. Table 2).**

Predictive value of combinations of adherence measures

When we combined self-reported adherence and adherence by pharmacy refill count, there were no major difference in sensitivity and specificity compared to the individual measures (See **Appendix Table 3).** However, when all the three measures were combined, we observed a higher value of sensitivity and NPV at high cut-offs ranging from 95% to 100% **(see Appendix Table 4: Combined measures at VL≥20).** The AUC for the combined measures slightly increased (0.60) as compared to the AUC values recorded among single-adherence measures (0.56, **see figure 2).** The optimal adherence cut-off point for the combined measures, closest to the upper left part of the figure, was 92% *(see dots in figure 2)*



	Combined measures of self-report, pharmacy refill and RTMM
AUC	0.60
Optimal adherence cut-off point	92

Figure 2: Receiver Operating Characteristic (ROC) curves for combined assessment method (VL≥0copies/ml) based continuous adherence data.

In logistical regression models, the combined adherence measures did not significantly predict adherence at any adherence cut-off level **(See Appendix Table 5).** Furthermore, regardless of the cut-off used, being on a TLE regimen was the only independent predictor of a viral load <20 copies/ml ($p<0.03$).

DISCUSSION

This paper describes the accuracy by which three adherence measures, individually or in combination can predict virological failure, at different adherence cut-off levels. Overall, we found that adherence assessed exclusively by self-report, pharmacy refill count or RTMM were insufficiently sensitive to predict virological failure. Sensitivity markedly improved by combining all three measures, but the practical feasibility of such an approach would need to be studied.

We found that self-reported adherence had the lowest sensitivity, but the highest specificity to predict virological failure as compared to adherence assessed by pharmacy refill count and

RTMM. This implies that virological failure occurred in many participants despite a high level of self-reported adherence. This finding is in line with previous studies, which have shown that participants tend to overrate their adherence level. This likely reflects recall and/or social desirability bias and fear of being judged negatively by health care workers.[22, 28] Our finding that self-report had the highest specificity is in line with previous studies showing that reports of poor adherence can be trusted. Other advantages of self-reports are that they are relatively cheap and easy to implement in clinical practice.[30–34]

All adherence measures investigated in the present study had areas under the ROC curves that were below 0.70, the minimal value for screening purposes, indicating insufficient ability to distinguish between patients with and without virological failure. Still, we observed that adherence by pharmacy refill counts and RTMM had showed a more promising performance compared with self-reported adherence. Similar findings of pharmacy refill adherence and RTMM having higher AUC values than self-report methods were observed in studies conducted in Tanzania and Botswana.[31,35,36] Other studies also found that an electronic monitoring device had a higher sensitivity in predicting virological failure compared to self-report for participants with >80% adherence.[10,37]

Therefore, in the context of routine clinical practice, where RTMM is not yet available, or is quite expensive, our findings demonstrate that pharmacy refill counts could provide a better prediction of virological failure given its higher sensitivity compared to self-reported adherence. In addition, RTMM could be cost-effective in a context of differentiated service delivery, i.e. if prioritized for use in poorly adherent participants. This could be particularly relevant in settings were viral load monitoring is not available.[38]

When we combined the three measures, we observed the measures performed better compared to individual measures as the highest sensitivity and PPV were recorded at a higher range of cut-offs (95-100%) for viral load of >20 copies/mL. The ROC curve of combined adherence measures indicated a slightly higher AUC value compared to single-adherence measures.

Our results imply that where possible, existing adherence methods need to be combined to obtain a more comprehensive assessment of adherence as each adherence assessment method may capture a different aspect of medication taking behaviour and will give a better prediction of virological failure.[37,39] Our findings also imply that self-reports of poor adherence should be taken seriously, and that patients reporting poor adherence might benefit from adherence counselling and intervention.

This study has some limitations. First, each adherence measure has its own specific limitations that may have affected the results. For RTMM, we assumed that all the openings of the device

indicated intake of the medication by participants. We are aware that medication may not have been taken, but rather shared, or dumped.[40] Moreover, the Wisepill® device occasionally lost connectivity with the server and failed to record intake data on time, as participants had forgotten to charge the device. Second, the sample size was small, particularly concerning the number of participants using the RTMM device (one-third of the total trial population) which has likely limited our ability to predict virological failure. Hence, our results should be considered exploratory. Third, the study was conducted in only two clinics from the urban Kilimanjaro region, limiting the generalizability of the study outcomes, e.g. to rural populations of PLHIV.

The strength of this paper is that, to our knowledge this is the first study that compared the performance of three adherence measures in the context of a randomized clinical trial. Also, our findings included both manually recorded data (self-report, pharmacy refill) during clinic visits and electronically (automated real time data from the Wisepill box). This allowed us to compare and identify potential discrepancies between the data sources as described previously.[41]

CONCLUSION

Our results show that adherence assessed by either self-report, pharmacy refill count or RTMM on its own did not perform well in predicting virologic failure. This could potentially be improved by combining all three measures, but the practical feasibility of such an approach would need to be studied. Given the fact that we had a small sample size, particularly considering the number of participants using the RTMM device, we would encourage researchers to investigate the same in bigger studies in order to be able to have adequate power for conclusions. In a context where RTMM is not available, our data show that pharmacy refill adherence could provide a better prediction of virological failure than self-report, but that reports of poor adherence should be taken seriously.

AUTHOR CONTRIBUTIONS

K.N. was involved as study coordinator and developed the study protocol. He was responsible for designing and writing the whole manuscript including compiling of inputs

from the listed authors and responding the queries. Also, he was involved in data collection, analysis and interpretation and identifying relevant literature.

L.M. was involved in the study as statistician and was engaged in all the data analyses as well as interpretation of the analyses outcomes.

M.S.B. developed the study protocol and oversaw the study procedures as principal investigator. Also, she was involved in organizing the manuscript methodology. She critically reviewed the initial and final drafts of the manuscript.

R.E.A. was involved in development of the study protocol, provided support during the entire study and critically reviewed the manuscript before submission. He provided critical inputs and suggestions on data analysis.

L.M. worked as study pharmacist and was involved on the follow-up process of enrolled participants and interviewing them. Also, she participated in data collection and interpretation of the data.

M.S. was the main supervisor of KN and provided technical expertise and Critically reviewed several versions of the manuscript before submission.

F.P. was involved as assistant study coordinator of the study and assisted the team on the follow-up of the enrolled participants.

B.T.M. provided managerial support to the study team and reviewed the final version of manuscript before submission.

P.R. critically reviewed several versions of the manuscript before submission and supervised KN.

P.N. was involved in development of the study protocol. She reviewed all the earlier versions of the manuscript during writing and provided technical inputs interpreting the analysis results. Also, she provided directives on statistical methods to be applied during data analysis.

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APPENDIX

Table 1: Sensitivity, specificity, PPV and NPV of self-report, pharmacy refill and RTMM at viral load >20 copies/ml

Cut-off %						
Adherence measure	Viral load					
	≥20	<20	Sensitivity	Specificity	PPV	NPV
Self-report						
<80%	4	0	5.8	100	100	70.3
≥80%	65	154				
Pharmacy refill						
<80%	14	26	19.7	83.6	35.0	70.0
≥80%	57	133				
RTMM						
<80%	10	16	41.7	70.9	38.5	73.6
≥80%	14	39				
Cut-off 85%						
	Viral load					
Self-report	≥20	<20	Sensitivity	Specificity	PPV	NPV
<85%	4	1	5.8	99.3	80.0	70.2
≥85%	65	153				
Pharmacy refill						
<85%	17	29	23.9	81.8	37.0	70.6
≥85%	54	130				
RTMM						
<85%	11	19	45.8	65.4	36.7	73.5
≥85%	13	36				
Cut-off 90%						
	Viral load					
Self-report	≥20	<20	Sensitivity	Specificity	PPV	NPV
<90%	4	1	5.8	99.3	80.0	70.2
≥90%	65	153				
Pharmacy refill						
<90%	21	34	29.6	78.6	38.2	71.4
≥90%	50	125				
RTMM						
<90%	12	22	50.0	60.0	35.3	73.3
≥90%	12	33				
Cut-off 95%						
	Viral load					
Self-report	≥20	<20	Sensitivity	Specificity	PPV	NPV
<95%	5	8	7.2	94.8	38.5	69.5
≥95%	64	146				
Pharmacy refill						
<95%	29	40	40.8	74.8	42.0	73.9
≥95%	42	119				

RTMM						
<95%	13	26	54.2	52.7	33.3	72.5
≥95%	11	29				
Cut-off 100%						
	Viral load					
Self-report	≥20	<20	Sensitivity	Specificity	PPV	NPV
<100%	12	22	17.4	85.7	35.3	69.8
100%	57	132				
Pharmacy refill						
<100%	35	62	49.3	61.0	36.1	72.9
100%	36	97				
RTMM						
<100%	18	39	75.0	29.1	31.6	72.7
100%	6	16				

*PPV-Positive Predict Value; NPV-Negative Predict Value; RTMM-Real Time Medication Monitoring

Table 2: Logistic regression models showing adherence measures at different adherence cut-offs predicting detectable viral load at cut-off of >20 copies/ml

Adherence	**Viral load**	
≥80%	**≥20**	
	AOR (95%CI)	**P**
Self-report	-	-
Pharmacy refill	0.8 (0.4 – 1.8)	0.679
RTMM	0.6 (0.2 – 1.7)	0.322
≥85%	**≥20**	
	AOR (95%CI)	**P**
Self-report	0.1 (0.01– 1.0)	0.053
Pharmacy refill	0.8 (0.4 – 1.5)	0.454
RTMM	0.7 (0.2 – 2.0)	0.508
≥90%	**≥20**	
	AOR (95%CI)	**P**
Self-report	0.1 (0.01– 1.0)	0.053
Pharmacy refill	0.7 (0.4 – 1.4)	0.365
RTMM	0.7 (0.2 – 1.9)	0.465
≥95%	**≥20**	
	AOR (95%CI)	**P**
Self-report	0.6 (0.2 – 2.1)	0.477
Pharmacy refill	0.5 (0.3 – 1.0)	0.051
RTMM	0.7 (0.2 – 1.9)	0.492
100%	**≥20**	
	AOR (95%CI)	**P**
Self-report	0.7 (0.3 – 1.5)	0.356
Pharmacy refill	0.7 (0.4 – 1.2)	0.190
RTMM	0.8 (0.2 – 2.6)	0.727

*AOR=Odds ratios adjusted for gender and ART regimen
*AUC=Area Under the Curve
*RTMM=Real Time Medication Monitoring

Table 3: Sensitivity, Specificity, NPV and PPV for combined self-reported and pharmacy refill adherence

Cut-offs	Viral load		Sensitivity	Specificity	PPV	NPV
	≥20	<20				
<80%	14	26	20.3	83.2	35.0	70.1
≥80%	55	129				
<85%	17	29	24.6	81.3	37.0	70.8
≥85%	52	126				
<90%	21	34	30.0	78.1	38.2	71.2
≥90%	49	121				
<95%	30	45	42.9	71.0	40.0	73.3
≥95%	40	110				
<100%	40	74	57.1	52.6	35.1	73.2
100%	30	82				

*PPV-Positive Predict Value; NPV-Negative Predict Value; RTMM-Real Time Medication Monitoring

Table 4: Sensitivity, Specificity, NPV and PPV for combined self-report, pharmacy refill and RTMM adherence measure

Cut-offs	Viral load		Sensitivity	Specificity	PPV	NPV
	≥20	<20				
<80%	11	20	45.8	63.0	35.5	72.3
≥80%	13	34				
<85%	14	22	58.3	59.3	38.9	76.2
≥85%	10	32				
<90%	15	26	62.5	52.7	36.6	76.3
≥90%	9	29				
<95%	19	33	79.2	40.0	36.5	81.5
≥95%	5	22				
<100%	22	46	91.7	16.4	32.3	81.8
100%	2	9				

*PPV-Positive Predict Value; NPV-Negative Predict Value; RTMM-Real Time Medication Monitoring

NB: N is small due to RTMM being part of this analyses and a small percentage of participants used RTMM

Table 5: Logistic regression models showing combined adherence measures at different adherence cut-offs predicting detectable viral load at cut-off of >20 copies/ml

Cut-off	**Viral load**	
	≥20	
	AOR (95%CI)	**P**
≥80%	0.78(0.28-2.18)	0.64
	≥20	
	AOR (95%CI)	**P**
≥85%	0.60(0.215 – 1.72)	0.345
	≥20	
≥90%	**AOR (95%CI)**	**P**
	0.65 (0.23 – 1.82)	0.410
	≥20	
	AOR (95%CI)	**P**
≥95%	0.43 (0.134 – 1.37)	0.158
	≥20	
	AOR (95%CI)	**P**
100%	0.55 (0.098 – 3.07)	0.496

*AOR=adjusted odds ratio
*AUC=area under the curve

Chapter Eight

General discussion

The REMIND Study

The primary aim of this thesis is to describe the findings of the REMIND-HIV trial in which we investigated the effectiveness, feasibility and acceptability of two different Digital Adherence Tools (DATs), i.e. (1) "short messaging service (SMS) texts" and (2) "Real time medication Monitoring (RTMM)". For SMS, we developed a scheme whereby we sent a reminder on three random days a week followed by another SMS asking whether participants took their medication. For the pillboxes, we made use of the so-called Wisepill box that sends a reminder when the box is not opened on an agreed time. The results indicated that these particular DAT interventions did not support our hypothesis that their use would increase the mean level of adherence to HIV treatment. However, the results did show that there was potential impact with a higher proportion of participants reaching high levels of adherence, i.e. 85-90%. Together with the high acceptability of the interventions, participants reported a number of positive experiences, including the feeling that 'someone' was taking care of them, better engagement in care, increased social support, improved HIV knowledge, specifically on the importance of adherence, and a higher motivation to remain in care. Secondary aims of this thesis were to address the potential barriers and challenges experienced by participants with regard to the DAT strategies which were used, and to investigate to what extent the adherence measures including pharmacy refill counts, self-reported adherence and real time medication monitoring (RTMM) predicted virological suppression.

Digital Adherence Tools

Participants' experience with using Digital Adherence Tools (DATs) is described in **chapters four and Six.** Respondents indicated that these tools made them feel like someone cared about their health. Also, the ability of DATs to remind them in real time to not forget taking a dose of medication, was mentioned as positive. An extra advantage as described in **chapter six,** was that digital pillboxes enabled clinicians to take rapid action including extensive adherence-counselling to prevent treatment failure. Previous studies have described DATs for a number of medical treatments, including those for HIV and tuberculosis and for use of pre-exposure antiretroviral prophylaxis. Within the context of HIV care, DATs aim to: (1) improve the monitoring of ART treatment, (2) record accurate medication histories, (3) individualize adherence feedback and (4) enhance the patient's self-motivation towards medication adherence.[1–6] Accordingly, the World Health Organization (WHO) encourages developing countries to implement DAT for HIV care as it is considered a potential tool in achieving the global goals on reducing HIV in the world.[7]

Difficulties using the DAT

Despite the fact that DATs were accepted and used by most participants, a few of them did not incorporate the interventions in their daily routine as they continued to rely on traditional reminders, such as a (wall)clock, alarm, news hour, or family members, as revealed in qualitative interviews, described in **chapter four**. Such findings have also been described in other studies examining the use of DATs, where patients acknowledged the use of additional means to facilitate adherence.[8–13] One study recommended that the target population should be engaged in the development of the intervention.[14] Another issue concerned how the DAT was perceived by participants and healthcare care workers. We found that some participants had difficulties in understanding the adherence graphs generated from the interventions, how to charge the RTMM devices and how to reply to the SMS reminders. We also noticed that replacing the routine clinical means of supporting adherence with DATs caused challenges especially for healthcare care workers who had limited knowledge of DATs. We believe this may have minimized the ability for the healthcare care workers to maximize the benefit of DAT to improve adherence.

The risk of unwanted disclosure in using the DATs

Cultural, religious and family norms in developing countries have been described to play a major role in the effectiveness of interventions.[15,16] Similar evidence has been described in **chapter two** addressing an SMS intervention for pregnant women who were living with HIV. Whereas the intervention was found to be technically feasible, women identified concerns about the SMS contents. Women who did not disclose their HIV status to others, recommended using neutral SMS contents such as "Don't forget to take your sweets!" or "Hi, how do you feel today".[17] Similar findings have been described in **chapter four,** where we also found that participants mentioned that SMS contents should be neutral to avoid unwanted disclosure of their HIV status to friends and family members. **In chapter four**, few participants who had not disclosed their HIV status to family members, indicated that the pillbox had intruded their privacy due to its "colour" and "size". Similar negative effects were reported in South Africa where patients found the appearance of the box to be too conspicuous for family members with whom the participants lived.[18] In conclusion, these findings underscore the need to tailor SMS messages to the client's preference and, more generally, engage them in designing interventions to promote adherence. DATs should avoid limiting the patients' privacy and be designed in concordance with their cultural background.[19]

Health care system-related factors that may impede the implementation of DAT

The DATs used in our study were associated with limited technical problems related to poor mobile network connectivity and delayed and failed SMS transmission. The major barriers to DAT delivery originated from the health care system itself. Particularly, some limitations of routine clinic care impeded the efficient delivery of DATs, including clinic staff rotation, poor patient monitoring, and delays in obtaining viral load results. Moreover, some nurses had difficulty in understanding how the interventions worked, were not entirely motivated to use the intervention, or had negative perceptions regarding the utilization of DAT. Consequently, more effort is needed with increased emphasis on training to appropriately equip nurses with the required knowledge and skills to use DATs.

Facilitators for implementing DATs

The main facilitators were derived from the views and feedback provided by participants enrolled in the intervention arms during the in-depth interviews. Several facilitators were mentioned with the most important being the fact that being monitored in real time had motivated participants to adhere more to medication as they felt cared for by someone. Other facilitators were that the use of SMS reminders had motivated participants to take responsibility of their ART treatment. Moreover, the ease of taking medication, packing pills in a container and carrying the device were described to be essential to maintain the medication time during traveling. Furthermore, the graphs generated by the interventions also supported participants to change their non-adherence behaviour as the graphs made them aware about the trend of their medication intake.

Adherences Assessment Measures

Self-reported adherence and pharmacy refill counts using questionnaires are commonly used because of their simplicity and low cost. However, several barriers are associated with these measures including social desirability for self-reported adherence, not being able to distinguish between dumping or sharing of pills from pill intake for pharmacy refill counts and recall bias for both these measures.[20–26] In **chapter four**, six participants using DATs were found to have a high level of adherence according to self-report. However, the reports generated by the DAT intervention indicated a low level of adherence. These contradictory findings or discrepancies make it unclear whether the patients took the medication or not. Another participant, described in **chapter five,** died of cryptococcal meningitis despite high levels of adherence recorded according to self-report, pill-counts and Real Time Medication Monitoring (RTMM) (> 99%). It appeared that she was not taking the medication as her relatives returned

eight months' worth of dispensed medication to the clinic after she had died, clearly indicating she had not actually taken the medication.

In **chapter seven**, we compared the prediction of virological outcomes by three adherence measures which were (1) self-report, (2) pharmacy refill counts and (3) RTTM. We found that self-reported adherence had lowest sensitivity but higher specificity in predicting virological failure, compared to pharmacy refill adherence and RTMM adherence. When we combined the three measures, we observed the highest value of sensitivity and positive predictive value. Evidence from other studies suggests that direct measures to detect drug levels in blood/urine/hair could provide more accurate adherence information.[27,28] However, these measures are more expensive and are rarely included in standard care within resource-limited settings. In addition, the disadvantage of particularly the urine method is that it detects only recently ingested medication but cannot detect whether medication intake had been stopped before the most recent intake.[29]

Again, our results support the general recommendation that using multiple low-cost strategies to assess accurate adherence is warranted for ART monitoring.

Limitations of the Studies

The studies conducted have several limitations. A possible explanation for the limited effect we found of our intervention could be the Hawthorne effect. This effect implies that being part of a study may positively influence the study outcome, in this case adherence, even in the control group.[38] Although we did not see an improvement in adherence over time in the control group, the average adherence level in the control arm might be higher compared to patients receiving standard care outside the context of a study. Careful discussion with the study staff indeed 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 routine practice.

Another limitation, observed in both REMIND trial sites, was that the nurses were not sufficiently comfortable with using digital tools, despite thorough training on using the electronic means. For example, they were still implementing a paper-based case report form for data collection while we had provided them with electronic case report forms and devices to enter the data. Therefore, we speculate that their understanding of and comfort to use the DATs may have been suboptimal.

The REMIND-trial was conducted among patients who were all recruited in Kilimanjaro, Tanzania, a region with the highest literacy rate and largest availability of basic infrastructure

(i.e. electricity, mobile network) in Tanzania. We therefore do not know how generalizable the results are to the community of PLHIV elsewhere in the country. Similar findings described in a systematic review of mobile health studies in Kenya showed that studies conducted in cities are more likely to produce positive results due to higher accessibility to mobile networks and educated personnel in clinics.[6]

Participants in the intervention arm received standard messages as reminders on three random days a week, and we did not personalize the SMS content or the frequency according to participants' preference as recommended by other studies.[2,14,30] This may have limited the DATs' effectiveness as not all participants may have felt comfortable with the SMS. Furthermore, the selection of patients for the trial was based on subjective judgement by nurse counsellors without screening for drug resistance and measuring viral load. This may have caused bias in the selection of study participants. The fact that some enrolled participants were already virologically suppressed or fully adherent to the treatment, despite records showing or nurses reporting missed clinic visits or missed pills, could also have contributed to a limited effect of the interventions.

Strengths

The first strength is that we conducted a randomized clinical trial comparing two different DATs with standard care alone. Second, our study was conducted in a real world setting whereby several implementation bottlenecks emerged. This has helped to better understand the reasons why the interventions did not work as intended. Furthermore, it gave insight of what could be done in the future to move toward scaling-up. Another strength is the implementation of different adherence measures. This allowed us to examine different aspects of adherence, as for example, self-report invites more social desirability compared to pharmacy refill counts and RTMM. In addition, we used a mixed-methods design; by using both quantitative and qualitative approaches, we were not only able to assess the effect of the intervention, but also to gain insight into the context of our findings.

Recommendations for future DAT-studies

Despite the fact that our participants did not show significant effects of ART adherence we learned that DATs have the potential to improve ART adherence to attain the UNAIDS 90-90-90 goal.[31] Currently, growing evidence in resource limited settings indicates that DATs might have underperformed because of poor infrastructure, understaffing, high costs of interventions and technology illiteracy. However, we believe that the integration of DATs in routine care will open up opportunities in improving treatment outcomes in areas that are hard

to reach because of poor infrastructure. Several issues learned from this study need to be considered to ensure that DATs are sustainable, feasible and acceptable as recommended by Curran et al.[32] The following three lessons merit particular consideration:

Stakeholder engagement. Development of DATs requires involvement of all relevant stakeholders, including patients, health care providers (i.e., nurses and doctors), supporting staff in the hospitals and policymakers to ensure engaging those who will be at the frontline in working with DATs. This will reduce the potential risk of DATs performing poorly when rolled out in practice. Researchers should carefully introduce the concept of DATs to stakeholders, conduct key informant interviews including in-depth interviews and focus group discussions with topic guides. Especially, end-users should be highly involved. This will help to conceptualize all stakeholders' requirements when designing DATs.

Alignment with health care priorities. The complexity of clinic environments especially in resource limited settings may affect the performance of a new intervention. Therefore, before DATs are rolled out in the health facilities, full understanding of health care priorities is essential.

Training. Among the issues we learned is the technology-illiteracy of health care workers in using the DATs. First of all, for researchers, understanding the factors affecting knowledge uptake by health care workers is crucial. Evidence learned from this research has shown that, to overcome this barrier, well-coordinated extensive health care worker training is required to address the questions: (1) what are the benefits of DATs on treatment outcome and (2) what are the reasons for implementing DATs? With respect to the more technical aspects, health care workers should be trained in (1) how to operate the DAT software, (2) how to use the software manual and maintenance procedures of DAT and (3) how to troubleshoot technical issues including the network/signal.

Future work and scalability of DATs in Africa

Planning for the scaling up of DATs is vital for reaching the sustainable development goals.[33] We acknowledge that our study could not meet the expected outcomes, but still believe the interventions were innovative and highly acceptable, hence having the potential to be improved and scaled-up. The bottlenecks described in this thesis can help to customize interventions based on individual requirements in order to enhance the success of scale-up. Building capacity of the research team to increase their technical and systems capacity is essential to implement future DATs using innovative technologies. Based on our experience of working together with Wisepill RT2000 from South Africa[34] which has extensive experience with the technical

aspects of DATs in resource-limited settings, we aim to pursue this partnership in order to develop better innovative solutions for Tanzania.

Furthermore, through several research networks within Africa, we will share the findings of the study and for the purpose of overcoming bottlenecks start writing proposals for implementation and scale-up. In addition, working with international institutions across Europe, we will open doors for gaining further expert input toward the scale-up of the interventions.

Finally, the recognitions we have received for publishing scientific reports as well as conference proceedings have increased our opportunity to leverage funding opportunities in the implementation of future DATs.

CONCLUSIONS

In our investigation of DATs, this thesis produced important findings on the effectiveness and implementation of DATs in influencing adherence to ART treatment. Given the great penetration of mobile technology in Tanzania, digital health technology provides a unique opportunity to improve adherence to ART treatment. The WHO strongly supports the implementation of DATs in view of their potential to enhance the delivery of quality HIV care, particularly for communities that are hard-to-reach. Furthermore, our studies indicate that RTMM and SMS reminders have the potential to raise awareness about the importance of ART adherence and improve patient-nurse communication during clinic visits. The particular DATs used in our study did not significantly improve adherence among our study participants. Based on our findings we recommend for future studies to incorporate patients' and health care providers' preferences from the start in designing DATs. This means that they should be involved in discussing and designing the intervention before its deployment. This is vital for pre-testing the intervention and understanding the needs for individually tailored message content, the timing and frequency of SMS, in order to fit patients' values and health care system requirements. This would hopefully improve the acceptability and enhance the odds that the interventions would be used effectively.

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Chapter Nine

General Summary

SUMMARY

This thesis describes detailed information about the implementation of digital adherence tools (DATs) to support adherence to anti-retroviral treatment (ART) and to improve HIV treatment outcomes among people living with HIV (PLHIV).

Chapter one describes the state of the art of using DATs among PLHIV to improve adherence to ART and provides a critical overview of the studies on adherence to ART. In this chapter, we discuss reviews, recommendations and the rationale for using several measures to monitor and improve adherence. Additionally, factors affecting adherence to ART, which are related to patient perspectives as well as health care settings, are described. Finally, this chapter provides an outline of this thesis.

In **chapter two,** we described a pilot study about the acceptability and feasibility of sending SMS reminders to pregnant and breastfeeding women living with HIV (WLHIV) to take their antiretroviral medication. Women were recruited from May to December 2017 attending ante-natal or postnatal care at Kilimanjaro Christian Medical Center (KCMC) in Moshi, Tanzania.. Eligible women received a reminder-SMS 30 minutes before usual time of intake. One hour later, we sent an SMS with the question if they took medication to which they could reply with 'Yes' or 'No'. Messages were sent three times a week on randomly chosen days to prevent reliance on daily messages. We followed participants for six months and in each clinic visit, the study doctor conducted exit-interviews about their experience with receiving SMS by using a short semi-structured questionnaire. To determine whether sending SMS-reminders was feasible, we calculated the percentage of the number of SMS delivered, failed to be delivered, and replied to. Furthermore, to understand how patients engaged with the SMS system, we analyzed the exit-interviews. We found that the majority of participants had positive experiences with receiving SMS and were pleased with the SMS content. However, few participants had concerns about the SMS content that could lead to unwanted disclosure and stigma. Additionally, almost all SMS (99%) were sent and actually delivered to patients' phones. We concluded that the SMS system was technically feasible. However, concerns raised by respondents about message contents should be addressed by future researchers.

In Chapter three we describe the findings of the REMIND-trial in which we investigated the effect of two DATs, (1) real time medication monitoring (RTMM) and (2) SMS, on adherence to treatment among PLHIV. The eligibility criteria were adults living with HIV from two HIV

treatment centers in Tanzania who were judged by nurse counselors to have low levels of adherence. Participants were randomly assigned in a 1:1:1 ratio to receive (1) SMS text message reminders, (2) an RTMM device with SMS reminders, or (3) no additional intervention to standard HIV care. We found that both DATs did not improve the mean adherence level in comparison to standard care as measured with self-report adherence and pharmacy refill. However, in a secondary analysis both DATs were found to enhance adherence for participants who had a viral load below 1000 copies/ml. These results do not fully support our hypothesis and in-depth discussions with nurse counselors revealed limited knowledge to understand how the intervention work "intervention coherence". Therefore, we recommend that future studies should investigate other factors that may hamper the acceptability of DATs. Those factors may include inadequate knowledge of nurse counselors about digital tools, potential unwanted disclosure and stigma for carrying/keeping the devices or receiving SMS content, and limited network connection.
Given the richness of the data, we looked more closely into the trial data.

In **chapter four** we elaborate on the findings about user experience and discrepancies in adherence rates, established by different adherence assessment methods. In the REMIND-trial, during bimonthly study visits, we recorded self-reported adherence, number of potentially ingested and leftover pills and adherence recorded by SMS text messaging or RTMM. As a result, we identified discrepancies between the different sources of adherence while halfway the trial enrolment. We only described discrepancies of those participants who had completed 5 follow-up visits and whose self-reported adherence was consistently more than 95%, while other adherence assessment methods indicated less than 75% adherence. To gain insight into the reasons of these discrepancies, the participants were invited for a short, face-to-face in-depth interview. Of the first 26 participants who had completed five follow-up visits, six reported a mean adherence level of 98% while the SMS or RTMM recorded a mean of 46%. Five of the six respondents indicated that their adherence to ART was high as they took medication as usual but were not responding to the message or did not open/use the device. One was afraid to open the device in front of people due to involuntary disclosure of HIV status. Alternative reminders, such as radio, television (news hour) and alarm clock were still being used by participants as reminder cues. Only one participant experienced poor network coverage. We concluded that psychosocial barriers should be addressed prior to the introduction of new digital adherence tools.

In Chapter five we report about a participant who died of cryptococcal meningitis shortly after completing the REMIND-trial, despite high levels of adherence based on self-report, pill-counts and RTMM. At study entry, she was on a first-line antiretroviral regimen of efavirenz, lamivudine and tenofovir and used the RTMM-device to monitor her medication intake during the remind-trial. This respondent completed all REMIND study visits and in each study visit, self-reported adherence, pharmacy refill adherence and adherence measured through RTMM were recorded to be above 95%. These results indicate that she had opened the device every day making the study team and nurse counselors to believe that she took all her medication adequately. However, her health status was continuously deteriorating with a viral load that continued to be high (> 200,000 copies/ml). Later, she became weak and fatigued. She was being diagnosed to have cryptococcal meningitis and had to be admitted to hospital for close monitoring and was switched to another regimen. Sadly, after several months she died. After she died, her relatives unsolicited brought back a stock of medication covering around eight months of treatment. This report underscores that opening the RTMM device does not necessarily imply that patients take their medication. Therefore, consideration of multiple adherence measures (e.g., including viral load) is needed to provide enough evidence or to notice patient's non-adherence.

In **Chapter six,** we describe the findings of a post-intervention evaluation, which we conducted as part of the REMIND-trial to examine the acceptability of the two DATs, RTMM and SMS, in improving adherence among PLHIV. We conducted a cross sectional mixed-methods study in which we collected data of participants who completed all 48 weeks of the REMIND-trial. These participants were invited for a face to face exit-interview to explore their experiences with using either RTMM or SMS. In addition, 20 randomly selected participants were invited for in-depth interviews to provide more contextual information of the quantitative data. The specific aim of this study was to gain insight into the acceptability of the interventions including the successes, potential challenges, barriers and behaviour change. We used Sekhon's theoretical framework of acceptability (TFA) to guide the analysis process which comprises of seven constructs i.e. affective attitude, perceived burden, perceived effectiveness, ethicality, self-efficacy, intervention coherence and opportunity costs.
A total of 143 (86%) respondents were reached and interviewed (68 in the SMS arm and 75 in the RTMM arm). Most (98%) participants indicated to be satisfied with the interventions. Their general experience with RTMM was that it was easy to manage, including opening the device, refilling the pills, and recharging the box. In the SMS arm, 94% of participants reported no

difficulties in responding to the SMS-reminders. Few reported to be concerned about the SMS-content, experienced network problems and feedback session was too time-consuming.. In general, both DATs were found to be acceptable among PLHIV in this ART adherence trial as indicated by a high positive affective attitude, low perceived burden, high perceived effectiveness and the DATs being considered ethically supportive.

In Chapter seven, we investigated which of the following adherence assessment methods: self-report, pharmacy refill counts or adherence measured through real-time medication monitoring (RTMM) or combinations of these methods is a better predictor of virological failure. This was a post-hoc analysis of all participants who had successfully finished the REMIND-study, i.e., attended the last scheduled visit at 48 weeks follow-up. A viral load cut off of >20 copies/mL was used to investigate the prediction of adherence measures at cut-offs of 80%, 85%, 90%, 95% and 100% doses taken. For each measure and combined measures, we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the different adherence cut-off values. In addition, receiver operating characteristic (ROC) curves were plotted to determine the accuracy of the adherence measures to predict viral load. Overall, we found that adherence assessed exclusively by self-report, pharmacy refill count or RTMM was insufficiently sensitive to predict virological failure. However, when combining the measures, sensitivity markedly improved but the practical feasibility of such an approach would need to be studied. We also found that self-reported adherence had the lowest sensitivity, but the highest specificity to predict virological failure as compared to adherence assessed by pharmacy refill count and RTMM, suggesting that reports of poor adherence should be taken seriously. Based on these results, we recommend that using more than two adherence measures improves the accuracy of predicting virological failure.

Chapter eight is a reflection on and discussion of the results of this thesis. We first discuss the key findings of the REMIND-Trial, case studies and mixed-method study. We then describe the limitations and strengths of these studies. We finally present the lessons we have learned regarding future implementation of DATs, including the scaling up and sustainability of future DATs.

SAMENVATTING

Dit proefschrift geeft gedetailleerde informatie over de implementatie van digitale hulpmiddelen (digital adherence tools; DATs) om therapietrouw aan antiretrovirale therapie (ART) te bevorderen en hiv behandelingsuitkomsten van mensen die met hiv leven, te verbeteren.

Hoofdstuk één beschrijft de huidige stand van zaken van het gebruik van DATs bij mensen die leven met hiv om therapietrouw te verbeteren en geeft een kritisch overzicht van het onderzoek naar therapietrouw aan ART. In dit hoofdstuk bediscussiëren we review artikelen, aanbevelingen en redenen voor het gebruik van verschillende manieren om therapietrouw te volgen ('monitoren') en te verbeteren. Bovendien beschrijven we factoren die therapietrouw aan ART beïnvloeden welke verband houden met patiënt perspectieven en de gezondheidszorg. Als laatste geeft dit hoofdstuk een overzicht van de hoofstukken van dit proefschrift.

In **hoofdstuk twee** beschrijven we een pilot studie waarin we de aanvaardbaarheid (acceptability) en geschiktheid (feasibility) onderzochten van het sturen van sms berichten aan zwangere vrouwen en vrouwen die borstvoeding gaven en die met hiv leefden in Kilimanjaro (Tanzania). De berichten waren bedoeld om hen te herinneren hun medicatie in te nemen. We wierven vrouwen die vanaf mei tot december 2017 de prenatale en postnatale polikliniek van het Kilimanjaro Christian Medical Center (KCMC) in Moshi, Tanzania bezochten. Vrouwen die in aanmerking kwamen om mee te doen, ontvingen een herinnerings-sms 30 minuten voor hun gewoonlijke inname tijd van de medicatie. Een uur na de gewoonlijke inname tijd stuurden we een sms met de vraag of ze hun medicatie ingenomen hadden. Ze konden dan antwoorden met 'Ja' of 'Nee'. Sms berichten werden elke week op drie aselect gekozen dagen verstuurd om te voorkomen dat vrouwen gingen vertrouwen op dagelijkse herinneringen. We volgden de deelnemers zes maanden en in elk bezoek aan de kliniek hield de studiedokter een exitinterview over de ervaring met het ontvangen van de sms berichten. We gebruikten daarvoor een korte semigestructureerde vragenlijst. Om na te gaan of herinneringsberichten via sms geschikt waren, berekenden we het percentage afgeleverde sms berichten, niet afgeleverde sms berichten en beantwoorde sms berichten. Bovendien analyseerden we exitinterviews om te begrijpen hoe patiënten met de sms berichten omgingen. De resultaten lieten zien dat het overgrote deel van deelnemers een positieve ervaring had met het ontvangen van de herinneringsberichten via sms en dat ze tevreden waren met de inhoud van de sms berichten.

Echter, een aantal deelnemers had zorgen over de inhoud ervan aangezien die kon leiden tot ongevraagde onthulling van de hiv status en stigmatisering. Daarnaast werden bijna alle sms berichten (99%) verzonden en afgeleverd in de telefoon van de patiënten. We concludeerden dat het sms-systeem technisch geschikt was. Echter, de zorg van sommige respondenten over de inhoud van de berichten moet door toekomstige onderzoekers worden aangepakt .

In **hoofdstuk drie** beschrijven we de bevindingen van de REMIND-trial waarin we het effect van twee DATs onderzochten, nl. (1) real time medication monitoring (RTMM) en (2) sms berichten, op therapietrouw bij mensen die leven met hiv. De inclusie criteria voor deelname waren volwassen zijn, leven met hiv, in twee hiv behandelingscentra in Tanzania behandeld worden en volgens hiv consulenten een beperkte therapietrouw hebben. Deelnemers werden willekeurig toegewezen in een 1:1:1 ratio aan een van drie condities waarin (1) sms herinneringsberichten werden ontvangen, (2) een RTMM apparaatje moest worden gebruikt in combinatie met sms berichten of (3) men kreeg geen aanvullende interventie op de standaard hiv zorg. De resultaten lieten zien dat beide DATs de therapietrouw, gemeten via zelfrapportage en apotheekafhaalgegevens, niet verbeterden ten opzichte van standaardzorg. Echter, in een secundaire analyse vonden we dat therapietrouw hoger was voor deelnemers met een “plasma viral load” lager dan 1000 kopieën/ml bloed die één van beide DATs toegewezen kregen. Gezien het feit dat deze resultaten niet volledig onze hypothese ondersteunen en het feit dat gesprekken met onze hiv consulenten lieten zien dat de interventie niet altijd goed werd geïmplementeerd, zou toekomstig onderzoek vooral gericht moeten zijn op het bestuderen van de factoren die de aanvaardbaarheid van DATs kunnen vergroten. Daarbij kan gedacht worden aan de beperkte kennis van hiv consulenten over DATs, de indringende inhoud en het aantal sms berichten, stigmatisering door het bij je dragen van een apparaatje en beperkt mobiel netwerk.
Gegeven de rijkdom van de data, hebben we deze in meer detail onderzocht.

In **hoofdstuk vier** gaan we in op de gebruikservaring van de DATs en de verschillen in therapietrouw percentages tussen de verschillende meetmethoden. In de REMIND-trial, onderzochten we tijdens tweemaandelijkse bezoeken aan de kliniek, zelf-gerapporteerde therapietrouw, aantal ingenomen en overgebleven pillen (apotheekafhaalgegevens) en therapietrouw gemeten via sms berichten of RTMM. Halverwege het onderzoek constateerden we verschillen in de uitkomsten van de verschillende therapietrouw meetmethoden. We selecteerden de deelnemers die vijf follow-up bezoeken hadden gehad en die telkens 95%

therapietrouw rapporteerden, terwijl een van de andere methoden minder dan 75% therapietrouw liet zien. Om inzicht te krijgen in de redenen voor deze verschillen, werden de deelnemers uitgenodigd voor een kort face-to-face diepte-interview. Van de eerste 26 deelnemers die vijf follow-up visites hadden gehad, rapporteerden zes van hen een gemiddelde therapietrouw van 98% terwijl rapportages op basis van sms of RTMM een gemiddelde van 46% liet zien. Vijf van de zes respondenten gaf aan dat hun therapietrouw aan ART hoog was want ze namen hun medicatie gewoon in maar reageerden niet op sms of openden het apparaatje niet. Eén respondent was bang het apparaatje te openen in het bijzijn van anderen vanwege onvrijwillige onthulling van de hiv status. De deelnemers gebruikten nog steeds alternatieve manieren om hen te helpen herinneren medicatie in te nemen, zoals radio, televisie (nieuwsuur) en de alarmklok. Maar één deelnemer had een slecht netwerk. We concluderen dat psychosociale barrières aangepakt moeten worden wanneer nieuwe digitale middelen worden geïntroduceerd.

In **hoofdstuk vijf** rapporteren we over een deelnemer die overleed aan cryptococcen meningitis net nadat ze haar deelname aan het REMIND-onderzoek had afgerond. Ze overleed ondanks hoge niveaus van therapietrouw op basis van zelfrapportage, de getelde pillen en RTMM. Bij haar start aan de studie gebruikte ze een eerstelijns ART regime van efavirenz, lamivudine en tenofovir en het RTMM-apparaatje om haar medicatie inname te volgen. Deze respondent kwam bij elk studiebezoek opdagen en in elk bezoek was haar therapietrouw gemeten via zelfrapportage, apotheekafhaalgegevens en RTMM meer dan 95%. Deze resultaten impliceren dat ze elke dag het apparaatje had geopend waardoor zowel het onderzoeksteam als de consulenten geloofden dat ze al haar medicatie innam. Echter haar gezondheid bleef achteruitgaan en de plasma viral load bleef hoog (>200,000 kopieën/ml bloed). Later werd ze zwak en vermoeid. Ze werd gediagnosticeerd met cryptococcen meningitis, moest opgenomen worden in het ziekenhuis en kreeg een ander ART regime. Helaas overleed ze na enkele maanden. Nadat ze was overleden, kwamen haar familieleden naar de kliniek en brachten ongevraagd een voorraad ART mee wat ongeveer acht maanden therapie behelsde. Deze casus laat zien dat het openen van het RTMM apparaatje niet per sé impliceert dat patiënten hun medicatie innemen. Daarom zijn meerdere therapietrouw maten nodig (bv. ook viral load) om voldoende bewijs te hebben of om lage therapietrouw van patiënten te kunnen opmerken.

In **hoofdstuk zes** beschrijven we de bevindingen van een post-interventie evaluatie die we hebben uitgevoerd als onderdeel van de REMIND-trial. Daarin onderzochten wij de aanvaardbaarheid (acceptability) van de twee DATs, RTMM en sms, om therapietrouw te verhogen. We voerden een cross-sectionele mixed-methods studie uit waarin we data verzamelden van deelnemers die de 48 weken durende studie hadden voltooid. De deelnemers werden uitgenodigd voor een face-to-face exitinterview om hun ervaring met het gebruik van RTMM en sms te inventariseren. Ook hebben we 20 willekeurige deelnemers uitgenodigd voor een diepte-interview om meer contextuele informatie te verkrijgen rond de kwantitatieve data. Het specifieke doel van deze studie was de acceptatie van de interventie te onderzoeken inclusief de successen, potentiële uitdagingen, barrières en gedragsveranderingen. We gebruikten het Sekhon theoretisch raamwerk voor acceptability (aanvaardbaarheid). Dit bestaat uit zeven constructen en wel affectieve houding, ervaren last, ervaren effectiviteit, ethiek, self-efficacy, begrip over werking van interventies en alternatieve kosten die nodig zijn voor deelname aan de interventie. In totaal konden we 143 (85%) respondenten bereiken en interviewen (68 in de sms arm en 75 in de RTMM arm). De meeste deelnemers (98%) gaven aan tevreden te zijn met de interventies. Hun algemene ervaring met RTMM was dat het makkelijk in gebruik was, inclusief het openen van het apparaatje, het vullen met pillen en het opladen. In de sms arm gaf 94% van de deelnemers aan geen moeilijkheden te hebben ervaren met het beantwoorden van sms berichten. Een aantal gaf aan niet tevreden te zijn vanwege zorgen rond de inhoud van de sms, ervaren netwerk problemen en het tijdrovende proces tijdens de feedback over ART therapietrouw tijdens kliniek bezoek. Over het algemeen werden beide DATs acceptabel bevonden door deelnemers aan dit onderzoek, gegeven een hoge waargenomen affectieve houding, weinig ervaren last, hoge waargenomen effectiviteit en de hoge mate waarmee de interventie past in het leven van de participant.

In **hoofdstuk zeven** onderzochten we welke van drie therapietrouw meetmethoden, zelfrapportage, apotheekafhaalgegevens en RTMM of een combinatie van deze methoden, de beste maat was voor het voorspellen van de plasma viral load. Alleen deelnemers die de REMIND-studie hadden afgerond, dat wil zeggen die ook de laatste studie visite op week 48 hadden voltooid, werden geïncludeerd in de analyses. Een plasma viral load afkapwaarde van >20 kopieën/ml bloed werd gebruikt om therapietrouw te voorspellen bij afkapwaarden van 80%, 85%, 90%, 95% en 100% van ingenomen medicatie. We berekenden de sensitiviteit, specificiteit, positief voorspellende waarde (positive predictive value or PPV) en negatief voorspellende waarde (negative predictive value or NPV) voor de verschillende afkaapwaarden

van therapietrouw. Daarnaast berekenden we receiver operating characteristic (ROC) curves om de nauwkeurigheid ('accuracy') van de voorspelling te beoordelen. We vonden dat wanneer therapietrouw enkel werd beoordeeld op basis van zelfrapportage, apotheekafhaalgegevens of RTMM, de voorspelling van virologisch falen onvoldoende sensitief was. Echter, als we alle methoden combineerden, nam de sensitiviteit toe. De praktische toepasbaarheid van deze benadering moet verder onderzocht worden. We vonden ook dat zelfrapportage de laagste sensitiviteit had, maar de hoogste specificiteit in vergelijking met apotheekafhaalgegevens en RTMM, wat suggereert dat rapportage van slechte therapietrouw serieus genomen moet worden. Op basis van deze resultaten, raden we het gebruik van meerdere maten voor therapietrouw aan omdat de combinatie ervan de nauwkeurigheid van de voorspelling van plasma viral load verbetert.

Hoofdstuk acht is een reflectie op en discussie van de resultaten van dit proefschrift. We bediscussiëren eerst de belangrijkste bevindingen van de REMIND-trial, de gepresenteerde cases en het mixed-methode onderzoek. Daarna beschrijven we de zwakke en sterke punten van deze studies. Als laatste presenteren we de lessen die we hebben geleerd voor de toekomstige implementatie van DATs, inclusief hun opschaling en duurzaamheid.

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Lastly, to my dear wife and my paranymph who were at my side, *Martina Mariki* and my dear children Ian, Jayden and Jayleen, I would like to thank you for always being there for me. Without your great understanding and encouragement, it would have been impossible for me to complete my study, particularly when I was thousands of miles away in Europe for PhD activities. The support and motivation you gave me during the PhD period were an essential factor for this PhD achievement.

Thanks, Asante Sana

A quote from Julius Kambarage Nyerere (president of Tanzania from 1964 to 1985)
"If a door is shut, attempts should be made to open it; if it is ajar, it should be pushed until it is wide open. In neither case should the door be blown up at the expense of those inside."

PhD PORTFOLIO

Name PhD student: Kennedy Michael Ngowi

PhD period: 2017 to 2021

Names of PhD supervisor(s) & co-supervisor(s):

Supervisors Prof. dr. M.A.G. Sprangers
Prof. dr. Peter Reiss

Co-Supervisors Dr. Pythia Nieuwkerk,
Dr. Marion Sumari – De Boer

1. PhD training

	Year	ECTS
General courses		
- Good Clinical Practice (Online)-DUKE University	2018,2021	0.6
- Policy Briefing (Kilimanjaro Clinical Research Institute and National Institute of Medical Research (NIMRI)-Tanzania)	2017,2021	1.2
- Communicating science to specific target-audiences (National Institute of Medical Research-Tanzania)	2021,2016, 2017	0.6
- Qualitative Data Management & Qualitative social science methods (Online training)-UK	2017, 2021	0.7
- Analysis with NVivo (Concept & Approaches) (Kenya and Kilimanjaro Clinical Research Institute)	2017,2021	1.7
- Introduction to mHealth (webinar and physical) UK and NIMRI - Tanzania	2017	0.5
- Financial & Project Management Training (EDCTP) - The Hague	2017	0.3
Specific courses		
- Scientific Writing in English	2018	1.5
- Project management	2018	0.6
- Randomized Controlled Trials	2019	0.6
- Systematic Review	2019	0.7
- Observational Epidemiology	2019	0.6
- AMC World of Science	2019	0.7

Seminars, workshops and master classes		
- Strategic Plan Development workshop-Tanzania	2017-2019	0.6
- Manuscript writing workshop-Tanzania	2019, 2021	1.7
- COVID-19 Clinical Research Coalition -UK (Online)	2020, 2021	0.5
- Workshop on the use of digital platforms for the early translation of research evidences-Tanzania	2021	1.5
- PhD Skills lab: present like a boss AMC -NL (Online)	2021	0.4

Presentations - Ninth EDCTP Forum-2018, Lisbon Portugal: Poster presentation *"Technical feasibility of sending SMS to remind taking medication among pregnant and breastfeeding women living with HIV in Kilimanjaro, Tanzania"*	2018	0.5
- 7th East African Health and Scientific Conference-2019, Dar es Salaam, Tanzania: Poster presentation *"SMS to remind pregnant and breastfeeding women living with HIV to take antiretroviral treatment in Kilimanjaro region, Tanzania: a pilot feasibility-study"*	2018	0.5
- ICASA 2019-Kigali, Rwanda (Oral Presentation) *"Real Time Medication Monitoring improves virological outcome among People Living with HIV on Antiretroviral Treatment in Moshi, Tanzania*"	2019	0.5
- Tanzania Health Summit 2020 , Dodoma Tanzania(Oral presentation) "Interactive Voice Response Calling For Increasing Knowledge And Access To Family Planning Methods Among Maasai: Participatory Action Research",		
- The International AIDS Society(IAS 2021) (Oral presentation) Berlin, Germany "*I Wish To Continue Receiving The Reminder SMS": A Mixed Methods Study On The Acceptability Of Digital Adherence Tools Among Adults On Antiretroviral Treatment"*	2021	0.5
- THE EUROPEAN & DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP (EDCTP) 2021, Maputo, Mozambique (Oral Presentation*)* *" Sensitivity and Specificity in Predicting viral load suppression by Self-reported adherence, Pharmacy Refills and Real Time Medication Monitoring among PLHIV living in Tanzania"*	2021	0.5
- NATIONAL HIV SYMPOSIUM 2021 (Oral Presentation) Mbeya, Tanzania "*Predicting viral load suppression by self-reported adherence, Pharmacy Refill counts and Real Time Medication Monitoring among people living with HIV in Tanzania."*	2021 2021	0.5 0.5

(Inter)national conferences		
- AIDS 2018 conference- Amsterdam, Netherlands	2018	1.2
- Ninth EDCTP Forum - 2018, Lisbon Portugal	2018	1.5
- International Conference on Family Planning-2018, Kigali Rwanda	2018	1.5
- 7th East African Health and Scientific Conference-2019, Dar es Salaam, Tanzania :Poster presentation	2019	1.7
- ICASA 2019, Kigali Rwanda	2019	1.8
- Tanzania Health Summit 2020, Dodoma, Tanzania	2020	1.5
- National HIV/AIDS conference 2020, Moshi, Tanzania	2021	0.5
- IAS 2021- the International AIDS Society (Virtual) Berlin, German	2021	1.1
- Tenth EDCTP Forum 2021, Maputo, Mozambique	2021	1.2
- NATIONAL HIV SYMPOSIUM 2021, Mbeya, Tanzania	2021	1.4

2. Teaching

	Year	ECTS
Lecturing		
- Development of standard operating procedures (KCMC University)	2021	0.5
- Qualitative Research Training (Kilimanjaro Clinical Research Institute)	2021	0.7
Tutoring, Mentoring		
- Master Students (Scientific writing and Project Management)-(KCRI)	2021	1.5
- Research Management -Junior Researchers (KCRI)	2017-2022	4.0
- Staff at study sites (Research Management and Good clinical practice)-Tanzania	2017-2022	4.0
Supervising		
- Master Students (The Nelson Mandela African Institution of Science and Technology (NM-AIST))	2021-2022	1.5

3. Parameters of Esteem

	Year
Grants	
HIV Research Trust: Joep Lange Institute scholarship	2017
Awards and Prizes	
- Best Abstract Award-International Conference on AIDS and Sexually Transmitted Infections in Africa (ICASA 2019)	2019
- IAS 2021 Scholarship	2021
- Tenth EDCTP Forum Scholarship	2021

4. Publications

	Year
Peer reviewed	
- Feasibility of SMS to remind pregnant and breastfeeding women living with HIV to take antiretroviral treatment in Kilimanjaro region, Tanzania: a pilot study *EAST AFRICAN HEALTH RESEARCH JOURNAL* DOI: https://doi.org/10.24248/eahrj.v4i2.637	2020
- Effect of digital adherence tools on adherence to antiretroviral treatment among adults living with HIV in Kilimanjaro, Tanzania: a randomized controlled trial *JAIDS Journal of Acquired Immune Deficiency Syndromes* DOI: 10.1097/QAI.0000000000002695	2021
- Technical and psychosocial challenges of mHealth usage for antiretroviral therapy (ART) adherence among people living with HIV in a resource limited setting: Case series. *JMIR Formative Research* DOI: https://doi.org/10.2196/14649	2020
- Returning of antiretroviral medication dispensed over a period of 8 months suggests non-adherence despite full adherence according to real time medication monitoring. *AIDS Research and Therapy* DOI https://doi.org/10.1186/s12981-020-00313-z	2020
- "I wish to continue receiving the reminder short messaging service": A mixed methods study on the acceptability of digital adherence	

tools among adults living with HIV on antiretroviral treatment in Tanzania. *Patient Preference and Adherence* DOI https://doi.org/10.2147/PPA.S290079 Predicting viral load suppression by self- reported adherence, pharmacy refill counts and Real Time Medication Monitoring among people living with HIV in Tanzania *AIDS Research and Therapy* Submitted	2021 2022
Other (Publications are not part of dissertation) - Feasibility of Using Short Message Service and In-Depth Interviews to Collect Data on Contraceptive Use Among Young, Unmarried, Sexually Active Men in Moshi, Tanzania, and Addis Ababa, Ethiopia: Mixed Methods Study With a Longitudinal Follow-Up *JMIR Formative Research* DOI doi:10.2196/12657 - "The phone number is telling us good things which we didn't know before." Use of Interactive Voice Response Calling for Improving knowledge and uptake of family planning methods among Maasai in Tanzania - *PLOS DIGITAL HEALTH* Submitted	2019 2022