

Effect of Digital Adherence Tools on Adherence to Antiretroviral Treatment Among Adults Living With HIV in Kilimanjaro, Tanzania: A Randomized Controlled Trial

I. Marion Sumari-de Boer, MSc, MSc, PhD,^{a,b} Kennedy M. Ngowi, MSc,^{a,c} Tolbert B. Sonda, MSc, PhD,^a Francis M. Pima, MPH,^a Lydia V. Masika, Bpharm,^d Mirjam A. G. Sprangers, MSc, PhD,^c Peter Reiss, MD, PhD,^{b,e,f} Blandina T. Mmbaga, MD, PhD,^{a,d,g} Pythia T. Nieuwkerk, MSc, PhD,^c and Rob E. Aarnoutse, PharmD, PhD^h

Background: Lifelong adherence to antiretroviral treatment remains challenging for people living with HIV (PLHIV). The aim of this study was to investigate whether any of 2 digital adherence tools could improve adherence among PLHIV in Kilimanjaro, Tanzania.

Methods: We performed a parallel 3-arm, nonblinded, randomized controlled trial with 1:1:1 allocation. We included adults aged between 18 and 65 years, living in Kilimanjaro region, and who were on antiretroviral treatment for at least 6 months. Their adherence, as judged by the study nurses, had to be suboptimal. In one arm, participants received reminder short message service (SMS) texts, followed by a question SMS. In the second arm, participants received a real-time medication monitoring (RTMM) device (Wise-pill) with SMS reminders. In the third arm, participants received standard care only. The primary outcome of mean adherence over 48 weeks was compared between arms using between-group *t* tests in a modified intention-to-treat analysis.

Results: In each arm, we randomized 83 participants: data of 82 participants in the RTMM arm, 80 in the SMS arm, and 81 in the standard care arm were analyzed. 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 97.5%, 96.6%, and 96.9% for self-report in the past month, respectively (*P* values not statistically significant).

Conclusions: Receiving reminder SMS or RTMM combined with feedback about adherence levels and discussion of strategies to overcome barriers to adherence did not improve adherence to treatment and treatment outcome in PLHIV.

Clinical Trial Number: PACTR201712002844286.

Key Words: PLHIV, adherence to treatment, digital adherence tools, clinical trials, short message service, real-time medication monitoring

(*J Acquir Immune Defic Syndr* 2021;87:1136–1144)

Received for publication December 2, 2020; accepted March 22, 2021.

From the ^aBioinformatics Unit, Kilimanjaro Clinical Research Institute, Moshi, United Republic of Tanzania; ^bAmsterdam Institute for Global Health and Development (AIGHD), Amsterdam, the Netherlands; ^cAmsterdam University Medical Centers (UMC), Location AMC, University of Amsterdam, Department of Medical Psychology, Amsterdam, the Netherlands; ^dDepartment of Pharmacy, Kilimanjaro Christian Medical Centre, Moshi, Tanzania, United Republic of Tanzania; ^eAmsterdam UMC, Location AMC, University of Amsterdam, Department of Global Health, Amsterdam, the Netherlands; ^fHIV Monitoring Foundation, Amsterdam, the Netherlands; ^gKilimanjaro Christian Medical University College, Moshi, United Republic of Tanzania; and ^hRadboudumc, Radboud Institute for Health Sciences, Department of Pharmacy, Nijmegen, the Netherlands.

Training and Mobility Grant from the European and Developing Countries Clinical Trials Partnership (TMA972).

Meetings where part of the data has been presented: ICASA2019; December 2, 2019; Kigali, Rwanda; Tanzania Health Summit 2020; November 26, 2020; Dodoma, Tanzania; National Aids Conference 2020, November 27, 2020; Moshi, Tanzania.

The authors have no conflicts of interest to disclose.

I. M. Sumari-de Boer and K. M. Ngowi have contributed equally to the work.

I. M. Sumari-de Boer was involved from the inception of writing the research proposal to the writing up of this manuscript. She coordinated the data management including database and data verification. She did the analyses and wrote this manuscript. K. M. Ngowi 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. T. Sonda was involved in the analyses of the data. F. M. Pima was involved in the data collection processes. L. Masika was overseeing the data collection in the field and was playing a major role in data verification. M. A. G. Sprangers supervised K. M. Ngowi and contributed largely to the writing up of this manuscript. P. Reiss supervised K. M. Ngowi and contributed largely to the writing up of this manuscript. B. T. Mmbaga was overseeing the progress of the study in Kilimanjaro, Tanzania, and contributed to the writing up of this manuscript. P. T. Nieuwkerk was involved from the inception of writing the research proposal to the writing up of this manuscript. She supervised K. M. Ngowi and contributed largely to this manuscript. R. E. Aarnoutse was mentoring I. M. Sumari-de Boer and was involved from the inception of writing the research proposal to the writing up of this manuscript. He contributed largely to the proposal and the manuscript. Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Kennedy M. Ngowi, MSc, Kilimanjaro Clinical Research Institute Mhealth Unit, PO Box 2236, Moshi, Tanzania (e-mail: k.ngowi@kcri.ac.tz).

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

INTRODUCTION

HIV infection remains one of the largest global health problems with 37.9 million people living with HIV (PLHIV) in 2018.¹ In Tanzania, 1.6 million people were living with HIV in 2018, with 71% of adults living with HIV being on treatment and 62% virologically suppressed.² High sustained levels of adherence (at least >85%) are needed to prevent virologic failure and the emergence of antiviral drug resistance, with newer antiretroviral regimens, especially those including dolutegravir seeming to be more forgiving for nonadherence.^{3–5}

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

Digital adherence tools (DATs) that involve the use of mobile phones and short message service (SMS) are a promising means for improving adherence to treatment and retention in care. The number of mobile phone users in Tanzania is high, being 81% in 2018, and 25 billion SMS were sent in the second quarter of 2019.¹⁴ Although several reviews have shown a positive effect of DATs on adherence and retention in care, the literature on benefit from such interventions is quite mixed and depends on factors such as the type and/or content of SMS that is used and the specific population that is studied.^{15–17} Moreover, a recent review about digital interventions aimed at enhancing medication adherence pointed out that the design of such interventions needs to be adapted to make them suitable for application in lower-income countries to prevent failure of such interventions.¹⁸ Factors 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).²⁷ 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 1 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 (see Annex IA, Supplemental Digital Content, <http://links.lww.com/QAI/B650>).

RTMM Arm

Participants in the RTMM arm received the so-called Wisepill device, an Internet-enabled medication dispenser. It can contain ART for a period of up to 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 (see Annex IB, Supplemental Digital Content, <http://links.lww.com/QAI/B650>). During the enrolment visits, participants were shown how to use the device. They were instructed about how to open it, how to take medication from it, 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,²⁹ using the stages of change model (see Annex II, Supplemental Digital Content, <http://links.lww.com/QAI/B650>).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 the 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 (see Annex IIIA, Supplemental Digital Content, <http://links.lww.com/QAI/B650>). In the standard care arm, no additional procedures were instituted aside from asking about perceived adherence (see Annex IIIB, Supplemental Digital Content, <http://links.lww.com/QAI/B650>).

Adherence Measures and Virological Response

Levels of adherence at each visit were calculated based on pharmacy refill counts and participants' self-report in the past week and past month, as displayed in Annex IV, Supplemental Digital Content, <http://links.lww.com/QAI/B650>. 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 χ^2 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 over the whole study period in the intervention arms was different from mean adherence in the control arm. Mean adherence was calculated for both self-reported adherence and pharmacy refill adherence. It was the mean of subsequent adherence measurements, as follows:

Self-reported adherence in the past week = $\{[(7 \times \text{pills to take per day}) - (\text{missed pills})] / (7 \times \text{pills to take per day})\} \times 100\%$.

Self-reported adherence in the past month = $\{[(\text{Number of days in the past month} \times \text{pills to take per day}) - (\text{missed pills})] / (\text{number of days in the past month} \times \text{pills to take per day})\} \times 100\%$.

Pharmacy refill adherence = $\{[(\text{pills given in previous visit} + \text{returned pills at previous visit}) - (\text{returned pills at current visit})] / (\text{number of days between visits} \times \text{number of pills to take per day})\} \times 100\%$.

Annex IV, Supplemental Digital Content, <http://links.lww.com/QAI/B650>, 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 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-known positive HIV test, years on current ART regimen, and virological status at study entry. For the latter, we used a cutoff value of 1000 copies/mL, which is the cutoff for distinguishing stable from unstable patients in the Tanzanian HIV treatment guidelines of 2017.²⁸ Any patient who is found to have a viral load of 1000 copies/mL or more at a single time point is considered unstable and needs enhanced adherence counseling.

Secondary Objectives: Effect on Cutoff 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 cutoff values of adherence by performing χ^2 analyses. Because 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 [viral load (VL) < 20 copies/mL at week 48] by conducting χ^2 analyses.

Additional Analyses

To better understand the underlying data, we first compared adherence rates between patients with the outcome of suppressed versus unsuppressed viral load at 48 weeks (irrespective of study arm) with Student *t* tests. Second, we analyzed the relationship between different adherence

TABLE 1. Demographic and Disease Characteristics at Enrolment (N = 249)

	Total	RTMM Arm	SMS Arm	Standard Care Arm	P
N (%), Mean (SD), Median (IQR)	249	83	83	83	
Women, n (%)	176 (71)	57 (68)	60 (72)	59 (71)	0.87
Mean age (SD)	41.2 (11.10)	42.8 (12)	39.6 (12)	41.2 (12)	0.22
Primary school (%)	152 (61)	51 (61)	50 (60)	51 (61)	0.36
Secondary school (%)	84 (34)	29 (35)	29 (35)	26 (31)	
Tertiary school (%)	11 (4)	3 (4)	2 (2)	6 (2)	
Reported suboptimal adherence (%)	169 (68)	50 (60)	57 (69)	62 (75)	0.19
Missed visits (%)	188 (76)	65 (78)	66 (80)	57 (69)	0.21
Had leftovers (%)	175 (70)	57 (69)	61 (74)	57 (69)	0.74
Median years HIV-positive (IQR)	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 (IQR)	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 (fixed dose, 2 times 1 pill), n (%)	55 (22)	17 (21)	16 (19)	22 (27)	0.28
EFV + TDF + 3TC (fixed dose, 1 pill), n (%)	97(39)	33 (40)	37 (45)	27 (33)	
EFV + TDF + FTC (fixed dose, 1 pill), n (%)	21 (8)	5 (6)	8 (10)	8 (10)	
EFV (1 pill) + AZT +3TC (2 times 1 pill)	31 (12)	11 (13)	13 (16)	7 (8)	
EFV + ABC+3TC (2 times 1 pill), n (%)					
NVP + AZT + 3TC (2 times 1 pill), n (%)	1 (0.4)	0 (0)	1 (1)	0 (0)	
ATV/r + AZT + 3TC (2 times 1 pill)	20 (8)	10 (12)	3 (4)	7 (8)	
ATV/r + TDF + FTC (2 times 1 pill)					
ATV/r + ABC + 3TC (2 times 1 pill), n (%)					
LPV/r + AZT + 3TC (1 time 3 pills), (1 time 2 pills)	24 (10)	7 (8)	5 (6)	12 (15)	
LPV/r + TDF + FTC (1 time 3 pills), (1 time 2 pills)					
LPV/r + ABC + 3TC (1 time 3 pills), (1 time 2 pills), n (%)					
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

*N = 242, for 7 participants, the results were not available.

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

assessment methods using Spearman correlation coefficients whereby a correlation less than 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.³² For all abovedescribed 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 al³³ 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,

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
Self-reported mean adherence in the past week 3	95.2 (11.8)	95.9 (10.6)	95.0 (9.5)	0.84
Self-reported mean adherence in the past month 3	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

TABLE 3. Differences in Mean Adherence Between Arms in Participants With VL <1000 Copies at Study Entry

	Control Arm, N = 62	RTMM Arm, N = 64	P	SMS Arm, N = 61	P
Self-reported adherence in the past week	93.9	95.8	0.31	97.1	0.12
Self-reported adherence in the past month	96.0	96.8	0.58	98.4	0.045
Pharmacy refill adherence	86.9	93.1	0.002	91.4	0.045

Bold values indicates for *P*-value <0.05.

TABLE 4. Differences in Reaching Adherence Cutoff Values Between Arms (Modified Intention-to-Treat Analyses, n = 243)

	Total		Control Arm		SMS Arm		RTMM Arm		P
	N	%	N	%	N	%	N	%	
Self-report									
Past week 3 100%	151	62.9	51	63	56	71	44	55	0.12
Week 3 >95%	193	80.4	66	81	65	82	62	78	0.72
SR week 3 >90%	205	85.4	70	86	69	87	66	83	0.66
SR week 3 >85%	212	88.3	72	89	70	89	70	88	0.96
SR week 3 >80%	221	92.1	73	90	74	94	74	93	0.70
Past month 3 100%	123	51.2	42	52	48	61	33	41	0.05
SR month 3 >95%	209	87.1	70	86	71	90	68	85	0.64
SR month 3 >90%	214	89.2	72	89	72	91	70	88	0.76
SR month 3 >85%	221	92.1	74	91	73	92	72	91	0.82
SR month 3 >80% ³	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

Bold and italic values indicate P-values is <0.05.

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

TABLE 5. Differences in Adherence and Virological Outcomes Between Arms (Per-Protocol Analyses, n = 225)

	Total (%)	RTMM Arm	SMS Arm	Standard Care Arm	P
	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

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 the past week (% of doses taken)	95.7	94.5	0.45
Mean self-reported adherence in the past month (% of doses taken)	95.9	92.2	0.2
Mean pharmacy refill adherence (% of doses taken)	92.1	85.6	0.008

Bold and italic values indicate P-values is <0.01.

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, Supplemental Digital Content, <http://links.lww.com/QAI/B650>; 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 ($r = 0.42$).

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 2 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 2 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.

ACKNOWLEDGMENTS

The authors thank the participants for being part of their trial and sharing their vulnerable situation with them; the field team of study nurses and pharmacists for assisting them in conducting the study and collecting the data; and, the European and Developing Countries Clinical Trials Partnership for their financial support through CDF972 to the trial.

REFERENCES

- UNAIDS. *Fact Sheet—World AIDS Day 2019 Global HIV Statistics [Internet]*; 2019. Available at: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed September 15, 2020.
- UNAIDS. *UNAIDS Factsheet United Republic of Tanzania [Internet]*; 2020. Available at: <https://www.unaids.org/en/regionscountries/countries/unitedrepublicoftanzania>. Accessed May 13, 2020.
- Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*. 2000;14:357–366.
- Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21–30.
- Mariana VM, Pascom ARP, Duarte EC. Comparative effectiveness of first-line antiretroviral therapy: results from a large real-world cohort after the implementation of dolutegravir. *AIDS*. 2019;33:1663–1668.
- Colvin CJ, Konopka S, Chalker JC, et al. A systematic review of health system barriers and enablers for Antiretroviral Therapy (ART) for HIV-infected pregnant and postpartum women. *PLoS One*. 2014;9:e108150.
- Langebeek N, Gisolf EH, Reiss P, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. *BMC Med*. 2014;12:1–14.
- Ammon N, Mason S, Corkery JM. Factors impacting antiretroviral therapy adherence among human immunodeficiency virus-positive adolescents in Sub-Saharan Africa: a systematic review. *Public Health*. 2018;157:20–31.
- Hodgson I, Plummer ML, Konopka SN, et al. A systematic review of individual and contextual factors affecting ART initiation, adherence, and retention for HIV-infected pregnant and postpartum women. *PLoS One*. 2014;9:e111421.
- Rao D, Feldman BJ, Fredericksen RJ, et al. A Structural equation model of HIV-related stigma, depressive symptoms, and medication adherence. *AIDS Behav*. 2012;16:711–716.
- Van Den Boogaard J, Msoka E, Homfray M, et al. An exploration of patient perceptions of adherence to tuberculosis treatment in Tanzania. *Qual Health Res*. 2012;22:835–845.
- Lyimo RA, de Bruin M, van den Boogaard J, et al. Determinants of antiretroviral therapy adherence in northern Tanzania: a comprehensive picture from the patient perspective. *BMC Public Health*. 2012;12:716.
- Coetzee B, Kagee A, Vermeulen N. Structural barriers to adherence to antiretroviral therapy in a resource-constrained setting: the perspectives of health care providers. *AIDS Care*. 2011;23:146–151.
- Tanzania Communications Regulatory Authority. *Quarterly Communications Statistics Report*; 2019. Available at: <https://tcra.go.tz/statistic/2019%20Quarterly%20Statistics%20Reports/december>. Accessed September 23, 2020.
- Gurman TA, Rubin SE, Roess AA. Effectiveness of mHealth behavior change communication interventions in developing countries: a systematic review of the literature. *J Health Commun*. 2012;17(suppl 1):82–104.
- Kanters S, Park JJH, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV*. 2017;4:e31–4.
- Mayer JEFFP. Meta-analyses on the effect of text message reminders for HIV-related compliance. *AIDS Care*. 2017;29:409–417.
- Lee SB, Valerius J. mHealth interventions to promote anti-retroviral adherence in HIV: narrative review. *JMIR Mhealth Uhealth*. 2020;8:e14739.
- Demena BA, Artavia-Mora L, Ouedraogo D, et al. A systematic review of mobile phone interventions (SMS/IVR/calls) to improve adherence and retention to antiretroviral treatment in low-and middle-income countries. *AIDS Patient Care STDS*. 2020;34:59–71.
- Lester RT. Ask, don't tell—mobile phones to improve HIV care. *N Engl J Med*. 2013;369:1867–1868.
- Van Heuckelum M, Van Den Ende CHM, Houterman AEJ, et al. The effect of electronic monitoring feedback on medication adherence and clinical outcomes: a systematic review. *PLoS One*. 2017;12:1–18.
- Sabin LL, Bachman DeSilva M, Gill CJ, et al. Improving adherence to antiretroviral therapy with triggered real-time text message reminders: the China adherence through technology study. *J Acquir Immune Defic Syndr*. 2015;69:551–559.
- Haberer JE, Musiimenta A, Atukunda EC, et al. Short message service (SMS) reminders and real-time adherence monitoring improve antiretroviral therapy adherence in rural Uganda. *AIDS*. 2016;30:1295–1299.
- Kennedy M, Maro E, Pythia T, et al. Technical feasibility of sending SMS to remind taking medication among pregnant and breastfeeding women living with HIV in Kilimanjaro, Tanzania. *BMJ Glob Health*. 2019;4(suppl 3):A1–A68.
- Ngowi KN, Maro E, Aarnoutse RE, Mmbaga BT, Sprangers MA G, Reiss P, Nieuwerkerk PT, Sumari-de Boer IM. Feasibility of SMS to remind pregnant and breastfeeding women living with HIV to take antiretroviral treatment in Kilimanjaro region, Tanzania: a pilot study. *Afr Med J*. 2020;4:140–148.9.
- Sumari-de Boer IM, van den Boogaard J, Ngowi KM, et al. Feasibility of real time medication monitoring among HIV infected and TB patients in a resource-limited setting. *AIDS Behav*. 2016;20:1097–1107.
- Vrijens B, De Geest S, Hughes DA, et al, ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73:691–705.
- Ministry of Health, community development, gender, elderly and children. 6th ed. National Guideline for the Management of HIV and AIDS 2017, 2017;(October):384. Available at: www.nacp.go.tz. Accessed August 12, 2020.
- Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Heal Promot*. 1997;12:38–48.
- Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf*. 2009;42:377–381.
- Gupta S. Intention-to-treat concept: a review. *Perspect Clin Res*. 2011;2:109.
- Dawson-Saunders BTR. Interpreting correlation coefficients. In: *Basic & Clinical Biostatistics*. 2nd ed. East Norwalk, CT: Appleton & Lange; 1994:53–54.
- Lyimo R, van den Boogaard J, Msoka E, et al. Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and acceptability of the Medication Even Monitoring System. *BMC Public Health*. 2001;11:92.
- Orrell C, Cohen K, Mauff K, et al. A randomized controlled trial of real-time electronic adherence monitoring with text message dosing reminders in people starting first-line antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2015;70:495–502.
- Kassaye SG, Ong'Ech J, Sirengo M, et al. Cluster-randomized controlled study of SMS text messages for prevention of mother-to-child transmission of HIV in rural Kenya. *AIDS Res Treat*. 2016;2016:1289328.
- Mwapasa V, Joseph J, Tchereni T, et al. Impact of mother–infant pair clinics and short-text messaging service (SMS) reminders on retention of HIV-infected women and HIV-exposed infants in eMTCT care in Malawi: a cluster randomized trial. *J Acquir Immune Defic Syndr*. 2017;75:123–131.
- Braunholtz D, Edwards SJLR. Are randomized clinical trials good for us (in the short term)? Evidence for a “trial effect.” *J Clin Epidemiol*. 2001;54:217–224.
- Haberer JE, Kiwanuka J, Nansera D, et al. Challenges in using mobile phones for collection of antiretroviral therapy adherence data in a resource-limited setting. *AIDS Behav*. 2010;14:1294–1301.