A Randomized Controlled Trial of Real-Time Electronic Adherence Monitoring With Text Message Dosing Reminders in People Starting First-Line Antiretroviral Therapy

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Background: There are conflicting findings about whether mobile phone text message reminders impact on antiretroviral adherence. We hypothesized that text reminders sent when dosing was late would improve adherence and HIV viral suppression.

Methods: Antiretroviral therapy (ART)-naive participants, from a South African outpatient ART clinic, were randomized to standard of care (SoC, 3 pretreatment education sessions), or intervention (SoC and automated text reminders if dosing >30 minutes late). Dosing time was recorded by real-time electronic adherence monitoring devices, given to participants at ART start. CD4 cell count and HIV RNA were determined at baseline, 16 and 48 weeks. Primary outcome was cumulative adherence execution by electronic adherence monitoring device. HIV-1 viral suppression (<40 copies/mL) at week 48 and count of treatment interruptions (TIs) >72 hours were secondary outcomes. Analysis was by intention to treat (missing = failure). Registration was with the Pan-African Clinical Trials Registry: PACTR201311000641402.

Results: A total of 230 participants were randomly assigned to control (n = 115) or intervention (n = 115) arms. Median adherence was 82.1% (interquartile range, 56.6%–94.6%) in the intervention arm, compared with 80.4% (interquartile range, 52.8%–93.8%) for SoC [adjusted odds ratio for adherence 1.08; 95% confidence interval (CI): 0.77 to 1.52]. Suppressed HIV RNA (<40 copies/mL) occurred in 80 (69.6%) of control and 75 (65.2%) of intervention (adjusted odds ratio for virological failure in intervention arm 0.77; 95% CI: 0.42 to 1.40). In the intervention arm, the count of TIs of >72 hours was reduced (adjusted incident rate ratio, 0.84; 95% CI: 0.75 to 0.94).

Conclusions: Text message reminders linked to late doses detected by real-time adherence monitoring reduced the number of prolonged TIs, but did not significantly improve adherence or viral suppression.

Key Words: real-time adherence monitoring, antiretroviral therapy, mobile phone use, text message, virological failure

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INTRODUCTION

Increasing numbers of HIV-positive individuals are receiving antiretroviral therapy (ART) in resource-limited countries such as South Africa.[1] Although early concerns about poor adherence to ART among HIV-positive individuals have proved untrue in sub-Saharan Africa,[2,3] treatment expansion to earlier stage disease, however, is creating new adherence challenges, including treatment interruptions (TIs) and treatment failure.[4–7] Reliably measuring and improving adherence to first-line therapy is a key component of the 2013 World Health Organization (WHO) consolidated guidelines.[8]

Electronic adherence monitoring, linked to text message adherence interventions, potentially offers a scalable and accurate adherence monitoring strategy and personalized adherence intervention.[8,9] As in many low- to middle-income country settings, South Africa has a well-developed mobile phone network and a high proportion (87%) of the South African population has a mobile phone.[10,11]

Mobile phone text message reminders have had variable success at improving adherence. Of 9 recent randomized controlled trial studies, using text messaging or automated voice messages as an intervention, 6 have shown some improvement in adherence.[12–17] Two of these also noted improvement in a biological outcome, either HIV RNA or

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CD4 cell count.[13,16] The other 3 randomized controlled trial studies showed no improvement, either in adherence as measured by self-report or tablet return, or in biological outcome.[18–20] Many of these studies were of short duration of 6 months or less.[14–19] Most used messaging in a cyclical manner, usually once or twice weekly, so as not to induce message fatigue. Only 1 study to date has linked mobile phone text message reminders to real-time detection of missed doses.[17]

We conducted a randomized controlled trial to determine whether text messages triggered by missed doses would improve overall daily adherence execution in ART-naive South African adults commencing ART. We also examined the impact of the reminder messages on the frequency of TIs and HIV-1 RNA suppression.

METHODS

Participants and Setting

The Hannan Crusaid Treatment Centre (HCTC) in Gugulethu, Cape Town, is a large public sector urban ART outpatient clinic, which provides free ART to 7500 HIV-positive individuals. From 2012 to 2014, multidisciplinary clinic staff included 3 medical officers, 3 nurse practitioners, 7 clinic-based counselors, and 18 community care workers as described elsewhere.[21] During the period of this study, ART-naive individuals could access ART with clinically advanced disease or a CD4 count of <350 cells per microliter according to the South African National ART Guidelines.[22,23]

Standard of Care

Treatment Preparedness

All ART-naive individuals attending the site received 3 group treatment preparedness sessions before or within the first month of commencing ART. These sessions were delivered by HIV-positive peer counselors. The information included details about HIV (eg, what are HIV and a CD4 cell; the importance of the HIV RNA), the ART to be prescribed (including possible side effects, the important of daily adherence, and the consequences of poor adherence), and advice on healthy living with HIV. All individuals were given a plastic 7-day pill-box on the day they commenced ART.

Antiretroviral Therapy

First-line ART in South Africa at the time of the study included tenofovir, lamivudine, and efavirenz, given as 3 separate tablets once a day. Toward the end of the study period in October 2013, a fixed-dose combination became available, but priority was given to naive patients entering care and few of the study participants were switched to the fixed-dose combination during the study. Zidovudine, stavudine, nevirapine, and lopinavir in combination with ritonavir were available as alternative agents.

Clinical Visits and Laboratory Sampling

Individuals attended the clinic twice before commencing ART and then on day 1 of treatment; after which they attended every 4 weeks to collect ART and be reviewed by a clinician until week 16. Subsequently, they attended every 8 weeks to collect ART with clinical review every 16 weeks. A CD4 count was completed before starting treatment and at week 48, and an HIV-1 RNA was drawn at weeks 16 and 48 (and both annually thereafter).[22]

Adherence Monitoring

Tablet returns were counted at every visit where ART was dispensed in all participants. Peer counselors counted the returns and calculated the percentage of tablets taken from the last dispensing to the current dispending date. This was recorded in the clinical notes before the individual seeing the clinician. All participants with tablet count adherence less than 90%, or viral RNA >40 copies per milliliter, received additional adherence counseling, which included an individualized education session with a peer counselor and monthly dispensing with clinician review until adherence improved.

Missed Clinic Visits

A tracking list was generated for all missed visits at the end of each month. Individuals were added to this list if they were more than 4 weeks late for an appointment, that is, no clinic visit, blood draw, or ART dispensing had occurred in the last 8 weeks for those in the first 16 weeks of therapy, or within the last 12 weeks for those after 16 weeks on ART. All those on the community tracking list were called by a community care worker and, if they could not be contacted by phone, visited at home. This process was repeated every week for up to 3 attempts. If tracking was unsuccessful, the individual was classified as lost to follow-up.

Study Design

The study was a randomized controlled trial in ART-naive individuals attending the HCTC, investigating the impact of a real-time electronic adherence monitoring device (EAMD), called Wisepill, on adherence to ART over 48 weeks. All participants received the EAMD on study entry, in exchange for the plastic pillbox given by the clinic on ART commencement, and were randomized to either (1) standard of care (described above, with Wisepill device in lieu of the pillbox) or (2) reminder text messages linked to nonopening of the device.

Inclusion and Exclusion Criteria

Participants were recruited from ART-naive adults and adolescents (≥15 years) commencing treatment at the HCTC. Possession of their own mobile phone was required for inclusion into the study. Written informed consent or, in the case of participants younger than 18 years, assent, was given by each participant. Entry into the study was offered consecutively to all eligible participants presenting to the clinic.

Study Visits and Sampling

All participants received care at the HCTC as per the standard of care detailed above.[4,24] Participants were seen by study staff, in addition to their clinic visit, at their first visit to

the clinic (screening visit), their first day of ART (day 1, baseline visit), and at weeks 16, 32, and 48 on treatment. Study staff included a study coordinator and 3 research assistants, who collected the study data and completed the questionnaires with each participant, but who offered no clinical care or adherence support. Study visits were timed to coincide with booked clinic visits to minimize inconvenience to the participant. Participants were reimbursed for local travel (R20 or ~US$2) at each study visit and in addition, for the 3 on-treatment study visits (weeks 16, 32, and 48), were given a gift of a T-shirt, bag, or mug valued at R80 (~US$8) to compensate them for their time.

Demographic and psychosocial details, including age, gender, weight, height, anxiety, and depression scores using the 14-question Hospital Anxiety and Depression Score (HADS), alcohol abuse as assessed by the 4-question CAGE score [Have you ever felt you should Cut down on your drinking; have people Annoyed you by criticizing your drinking; have you ever felt bad or Guilty about your drinking; and, have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye opener)?],[25] and details of any friends or family to whom they had disclosed their HIV status were collected at the screening visit.[26,27] Nondisclosure was defined as not having revealed his/her HIV status to anyone outside of the clinic.

Blood was drawn by the study coordinator or the clinic nurse for CD4 cell count (FACS Count, Beckton Dickinson, NJ) and HIV-1 RNA (HIV-1 RNA 3.0 assay; Bayer Healthcare, Leverkusen, Germany), at screening, weeks 16 and 48. Baseline HIV RNA and CD4 cell count at week 16 were the only samples drawn in addition to those routinely completed by the clinic. Prescribed ART and WHO clinical stage were recorded at the baseline visit. Participant's eligibility for the study was confirmed and randomization occurred thereafter.

Self-reported 3-day recall of adherence, questions on EAMD acceptability, disclosure status, and the CAGE questionnaire were asked by the study counselors at weeks 16 and 48. The 14-question HADS was completed again at week 48. Weight was measured and current ART confirmed at all visits. At all visits, mobile phone numbers were confirmed and note was made of participants on tuberculosis treatment or who were pregnant.

Throughout the study, clinic adherence monitoring and tracing after a missed visit continued as per standard of care. The EAMD was returned and exchanged for a standard pill box at the end of study visit, 4 weeks after the week 48 visit. Participants were reimbursed R150 (~US$15) at this visit.

Randomization

Participants were randomized 1:1 to control and intervention arms. Allocation to study arm was concealed in sealed individual opaque envelopes, which were numbered from 1 to 230 and opened consecutively after a participant met study entry criteria. The random number sequence and envelopes were generated off-site. The envelopes were opened by the study nurse, blinded to the allocation, on-site. Staff (both study and clinic) and participants were not masked to arm allocation after randomization.

Adherence Monitoring

The Wisepill device is a locally produced electronic device, the size of a mobile phone which can store up to a week of medication in a 7 compartment pill box.[28] This EAMD has been used in other resource-limited settings to measure adherence. In these studies, the device was shown to be reliable, and adherence by EAMD to be significantly associated with viral suppression.[29,30] All participants received a Wisepill device and were given additional internal pill boxes with instruction on refilling and replacing these weekly. On opening, a signal was sent in real time through the wireless telecommunications network to a secure central computer in Somerset West, Cape Town.

Each EAMD gave a daily "heartbeat" signaling that it was still on-line and checking the battery voltage. Charged batteries lasted for about 3 months. Each participant was given a wall charger to use at home and the option of bringing their device to the clinic for recharging. If the "heartbeat" showed a low voltage, a message was sent to the participant reminding them to charge the device: "Sicela utshaje ibhokisi yakho yeepilisi okanje uyizise ekliniki sikutshajele. Please charge your Wisepill box or bring to the clinic so we can charge it for you." In addition, a weekly low-battery report was sent to the study coordinator, who called these participants and reminded to charge their EAMD.

Intervention

All participant's preferred daily dosing time was recorded in the Wisepill system. Intervention participants received a text message if the device was not opened within 30 minutes of the scheduled dosing time. This window was chosen by the participants as they did not want to be woken by a later message (due to evening dosing of efavirenz regimens). The first 5 participants randomized were asked to construct a simple message that would remind them to take their tablets, but not disclose their HIV status to others at home or in the community. These message options were then made available for the rest of the cohort, in either English or Xhosa. Once each participant in the intervention arm had chosen a message, they received the same message throughout the study when their dosing was late. Messages included "Have you forgotten something?" (Awulibelanga nto?), "Just take it!" (Yithathe!), "Wake up" (Vuka!), It's 8 o'clock! (Ngu 8 o'clock!), or their study number (eg, XX9999). In addition, for the intervention participants, a report of on-time, late, and missed doses over the previous 4 months was placed in their clinical folder for the ART clinician to review every 16 weeks during the study.

Outcomes and Statistical Analysis

Participants were classified by the following retention in care outcomes before calculating the primary adherence and virologic outcomes:

- Completed study: these participants were in care at the clinic at the time of the end of study visit.
- Transfer out: some participants requested a transfer to another ART clinic. Transfer out date was recorded as the

last date the participant attended the HCTC. These participants were censored at transfer out date.
- Death: deaths were ascertained from clinical notes or from discussion with the family. Date of death is usually clear, but if not, date of last contact with the clinic was used. These participants were censored at date of death.
- Loss to follow-up (LTFU): participants were considered LTFU if they had not attended the clinic, had blood drawn, or collected medication for more than 12 weeks. In addition, they could not be traced, as per standard of care for missed visits and were not known to have transferred out or to have died. The date of LTFU was taken as the last date they attended the clinic. For per protocol analyses, these participants were censored at their LTFU date. For intention-to-treat analyses, these participants were censored at their calculated week 48 date, that is, the date of randomization plus 336 days. EAMD opening data recorded after last date in clinic and before calculated week 48 date were included in the analysis.

The primary outcome was adherence execution as measured by the EAMD. Adherence execution was calculated by the number of days the container was opened over the number of days in the period in care (for those who completed the study, transferred out or who died); and for the period from randomization to calculated week 48 for those LTFU. Multiple openings on 1 day were truncated at 100%. Days without battery charge were censored.

The adherence data were modeled both as categorical and continuous variables. A fractional logit model (continuous data assessed using a generalized linear model with a logit link) was used for the continuous data and a logistic regression model using a logit transformation was used for the categorical data. The cutoff for the categorical adherence data was informed by the median of the continuous data. We used an intention-to-treat approach for this primary outcome.

Retention in care, virological suppression, and number of >72 hours TIs were secondary outcomes. Those who completed the study or who were transferred to care elsewhere were considered retained in care. Those who died or were lost to follow-up were considered lost to care. The impact of the intervention on retention in care was modeled using a multinomial logistic regression model.

The impact of the intervention on virological outcomes (both to <40 and <400 copies/mL) was modeled using linear mixed-effect models. The impact of the intervention on the number of TIs was modeled using Poisson regression. TIs were defined as interruptions of 72 hours or longer, that is, 3 or more missed doses, as it has previously been shown that sustained missing of doses has more impact on virological outcome than single missed doses, with each day beyond 2 missed days increasing the risk of virological breakthrough.[31]

Data were analyzed using Stata 13.0 (Stata Corporation, College Station, TX). Descriptive statistics were used to summaries the baseline characteristics of the participant group. The χ^2 test was used to compare proportions and the 2-sample *t* test to compare continuous variables. Variables were preselected for inclusion in the multivariate analyses.

Ethical Approval

The University of Cape Town Faculty of Health Science Research Ethics Committee gave approval to conduct this study. Each participant provided written informed consent or assent. The trial was registered in the Pan African Clinical Trials Registry, number PACTR201311000641402.

RESULTS

Between July 2012 and April 2013, 319 participants were screened and 230 were randomized. Eighty-nine people were not randomized because of the reasons given in Figure 1. Baseline characteristics were similar between those who randomized and those who were not, as well as similar by randomization arm (Table 1). The mean age of the enrolled cohort was 34.5 (±9.1) years, with 150 (65.2%) women. Median CD4 count at start was 225.5 [interquartile range (IQR), 133–287] cells per cubic millimeter. All participants had detectable HIV RNA at baseline. There was no significant difference in either HADS scores or the CAGE score at baseline by randomization arm.

Most participants were started on efavirenz-based regimens (n = 228, 99.1%) and 2 on nevirapine-based regimens. All ART included lamivudine. The majority (n = 225, 97.8%) were started on tenofovir as the second nucleoside reverse transcriptase inhibitor. Depression (n = 74, 32.1%), anxiety (n = 89, 38.7%), and alcoholism (n = 35, 15.2%) were highly prevalent. Most participants had disclosed their status to at least one other person (n = 219, 95.2%).

The 230 participants were in care for a median of 380 days (IQR, 359–414 days). Only one person withdrew consent during the study. The majority (n = 186, 80.9%) remained in care at the site and most also completed the study visits, as noted in Figure 1; or were transferred to care at another site (n = 16, 6.9%). Nineteen participants (8.3%) were lost to follow-up and 8 (3.5%) died.

Primary Outcome—Adherence

At week 48, there was no difference in median adherence by self-report or tablet return by arm. By tablet return, the median adherence was 100% in both arms (IQR, 95%–110% in the intervention arm and 94%–100% in the control arm). By self-report, median adherence was 100% in both arms (IQR, 100%–100% in both arms).

Median adherence by EAMD was 82.1% (IQR, 56.6%–94.6%) in the intervention arm and 80.4% (IQR, 52.8%–93.8%) in the control arm. This difference was not significant either when modeled as a continuous variable (Table 2) or as a categorical variable in a logistic regression model, using adherence >80% as the cutoff value (model not shown). Age was the only variable significantly associated with adherence execution (Table 2). The number of pills taken, relative to the number of pills not taken, increased by 27% for each 10-year increase in age: odds ratio (OR), 1.27 [95% confidence interval (CI): 1.05 to 1.52]. Gender, nondisclosure, anxiety and depression scores, and baseline CD4 cell count did not impact on adherence execution in this model.

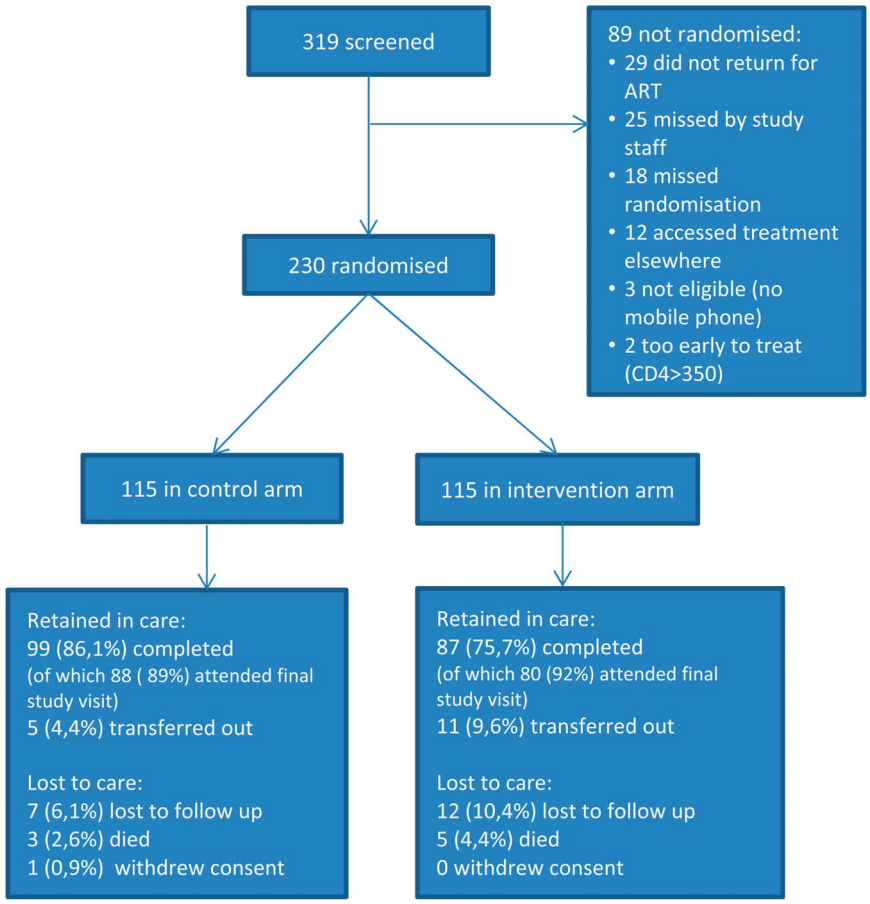

FIGURE 1. Flow diagram describing the outcome of the 319 individuals screened and the 230 individuals randomized to the study.

EAMD data revealed that there were 82,311 participant-dosing days recorded; 40,188 were in the intervention arm and 42,123 in the control arm. Of these, 8362 (10.1%) were dead-battery days. Dead-battery days were evenly distributed by arm.

In the intervention arm, 19,142 text messages were sent to 114 individuals, equating to 47.6% of doses not being taken within 30 minutes of the specified dosing time. The most popular message was "Have you forgotten something?" in English, chosen by 31 (26.9%) participants; followed by "Vuka" chosen by 27 (23.5%). There was no difference in adherence execution by message. After the message, on 5340 occasions (13.2%), the EAMD was opened, in a median time of 22 minutes (IQR, 6–47 minutes). There was no evidence of reminder fatigue by weeks on study. In the control arm, 23,255 (55.2%) of doses were taken on time, and on 4069 occasions (9.7%) dosing was taken later that day, without reminder.

Figure 2 shows the median time (in minutes) from the dosing time specified by each participant to the actual time of dosing. The density on the *y* axis reflects the probability or frequency of the dose being taken at each time point. More people in the control arm took their tablet on time while a subset of those in the intervention arm (solid line) waited for the text message at 30-minute postspecified dosing time before dosing.

Secondary Outcomes—HIV RNA

At week 16, 198 of 230 (86%) participants had an HIV RNA available. Of note, 143 (72%) achieved an HIV RNA of <40 copies per milliliter: 73 of 97 (75.3%) in the intervention arm and 70 of 101 (69.3%) in the control arm. At week 48, of the 182 participants remaining in care, 155 (85.2%) had an HIV RNA of <40 copies per milliliter: 75 of 86 (87.2%) in the intervention arm and 80 of 96 (83.3%) in the control arm. There were 32 missing values at week 16 and 48 missing values at week 48. Using intention-to-treat analysis, where the missing values equaled failure, a mixed-effects model showed no difference in the odds of virological failure (>40 copies/mL) in the intervention arm (OR, 0.77; CI: 0.41 to 1.4; $P = 0.393$). Only a baseline HIV RNA of >5 log copies per milliliter significantly increased the chance of virological failure (OR, 2.03; 95% CI: 1.1 to 3.9; $P = 0.034$). The model is shown in Table 3. There was similarly no difference in virological outcome by arm using per protocol analysis where missing values were kept as missing values.

Secondary Outcomes—TIs

The median duration of TIs was 8 (IQR, 5–15) days, with no difference by study arm. However, using a Poisson regression model for the estimation of incidence rate ratios (IRRs), the count of TIs of >72 hours in the intervention arm

TABLE 1. Baseline Demographic, Clinical, Treatment, and Psychosocial Characteristics of Participants

	Control	Intervention	*P*
N	115	115	
Female sex: n (%)	77 (67.0)	73 (63.5)	0.678
Age (yrs): mean (SD)	34.3 (9.0)	34.6 (9.2)	0.779
Height (cm): mean (SD)	164.0 (8.6)	164.1 (8.6)	0.932
Weight (kg): median (IQR)	68.4 (60.1–79.6)	67.0 (56.1–80.0)	0.320
WHO stage: n (%)			0.946
1	42 (36.5)	42 (36.5)	
2	24 (20.9)	23 (20.0)	
3	36 (31.3)	39 (33.9)	
4	13 (11.3)	11 (9.6)	
CD4 count: median (IQR)	229 (136–292)	225 (121–283)	0.543
Log HIV RNA (copies/mL): median (IQR)	4.8 (4.4–5.4)	5.0 (4.5–5.4)	0.324
Range of HIV RNA at baseline (minimum–maximum copies/mL)	109–1,481,459	1021–2,381,184	
NNRTI at start: n (%)			0.498
Efavirenz	115 (100.0)	113 (98.3)	
Nevirapine	0 (0.0)	2 (1.7)	
NRTI at start*: n (%)			0.361
Tenofovir	114 (99.1)	111 (96.5)	
Zidovudine	1 (0.9)	3 (2.6)	
Stavudine	0 (0.0)	1 (0.9)	
HADS depression score of 8 or above (borderline or case)†	43 (37.4)	31 (27.0)	0.09
HADS anxiety score of 8 or above (borderline or case)†	51 (44.3)	38 (33.0)	0.08
Nondisclosure	5 (4.4)	6 (5.2)	0.757
CAGE ≥2	20 (17.4)	15 (13.0)	0.359

*All were taking lamivudine or emtricitabine in addition.
†HADS.
NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

was significantly less than in the control. This was seen in both univariate analysis, where there was an 18% reduction in the count of these TIs in the intervention arm (IRR, 0.82; 95% CI: 0.74 to 0.92), and in multivariate analysis (adjusted Incidence Rate Ratio [aIRR], 0.84; 95% CI: 0.75 to 0.94; $P = 0.003$), as shown in Table 4, compared with control. Additional factors associated with TIs were age, which was protective. A 14% reduction in frequency of TIs was noted for each 10-year increase in age (aIRR, 0.86; 95% CI: 0.80 to 0.92). There was a 36% increase in the frequency of TIs for those with an HADS depression score >8 (aIRR, 1.36; 95% CI: 1.21 to 1.53) and a 30% increased frequency of TIs in men compared with women (aIRR, 1.3; 95% CI: 1.15 to 1.47).

Secondary Outcomes—Retention in Care

The characteristics of those who died, were lost to follow-up and transferred out, as in Figure 1, were compared with those who had completed the study using a multinomial logistic regression model (model not shown). There was no difference between those who died were lost to follow-up or transferred out and the completed group by intervention arm.

TABLE 2. GLM of Cumulative Adherence by EAMD Over Time on Study (Data From 230 Participants Included in the Model)

Adherence	Odds Ratio	Standard Error	*P*	95% Confidence Interval
Intervention arm	1.08	0.19	0.642	0.77 to 1.52
Age*	1.02	0.01	0.014	1.00 to 1.04
Anxiety score >8	1.05	0.19	0.797	0.74 to 1.49
Depression score >8	0.74	0.14	0.100	0.51 to 1.06
CD4	1.00	0.00	0.699	1.00 to 1.01
Male sex	0.96	0.17	0.802	0.68 to 1.34
Nondisclosure	0.72	0.30	0.368	0.32 to 1.63
Screen CAGE ≥2	1.05	0.45	0.819	0.67 to 1.67

*The number of pills taken, relative to the number of pills not taken, increases by 27% for each 10-year increase in age: OR, 1.27 (95% CI: 1.05 to 1.52).

DISCUSSION

Our randomized controlled trial found that the use of a novel, wireless, EAMD, which generated a text message reminder for device openings >30 minutes late, significantly reduced the frequency of TIs longer than 72 hours, but had no effect on overall adherence execution, retention in care, or HIV RNA suppression among ART-naive individuals attending a South African community clinic. Time from message to dose ingestion did not fatigue over the study, suggesting durability of the intervention effect. However, participants in the intervention arm were more likely to take their dose outside of the 30 minutes dosing window, suggesting that they relied on the intervention to remind them to dose.

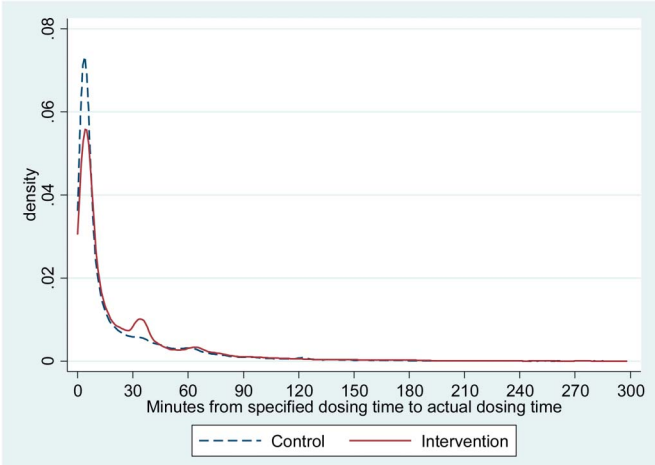

FIGURE 2. Graph showing the median time (in minutes) from the dosing time specified by each participant to the actual time of dosing. The area under the curve equals to one, and the density (*y* axis) shows the probability of patients taking their dose at that time point. More people in the control arm (dotted line) dose on time. In the intervention arm (solid line), the effect of individuals waiting for the text message at 30 minutes after their specified dosing time can be seen.

TABLE 3. Linear Mixed-Effect Model for Virological Failure (VL >40 Copies/mL at Weeks 16 and 48)

HIV RNA >40 Copies/mL	OR	Standard Error	*P*	95% Confidence Interval
Intervention arm	0.77	0.23	0.393	0.42 to 1.40
BMI	0.96	0.03	0.195	0.91 to 1.02
B-l VL >5 log copies/mL	2.03	0.68	0.034	1.05 to 3.91
Age	0.97	0.02	0.143	0.94 to 1.01
Male sex	0.91	0.33	0.800	0.45 to 1.86
CD4 count	0.99	0.00	0.187	0.99 to 1.00
Week 48	0.67	0.17	0.109	0.41 to 1.09

Missing results equaled failure.

The intervention significantly reduced the frequency of TIs of over 72 hours, which was a prespecified end point. This is an important finding as TIs >72 hours have been shown to be a significant cause of virologic failure and acquisition of drug resistance independent of average overall adherence among participants receiving nonnucleoside reverse transcriptase inhibitor treatment.[31–33] The intervention altered the pattern of adherence behavior, changing the frequency of longer TIs, despite similar median adherence. Text message reminders made it more likely that participants on the intervention arm would dose at least every 72 hours, whereas those in the control arm had longer gaps in dosing.

The median duration of TIs was 8 days, with an IQR of 5–15 days. People on nonnucleoside reverse transcriptase inhibitor–based regimens, like the participants in our study, have a 50% chance of viral rebound after a 14-day interruption, although this risk of failure decreases with the duration of viral suppression before the interruption occurs.[31,34,35] It is likely that the TIs in our study were either too short or occurred after sufficient viral suppression to generate a difference in viral suppression at week 48.[31]

Age, gender, and depression were significantly linked with an increased frequency of TIs. Specific populations, namely younger people, men, and those with symptoms of depression, might benefit from focused adherence interventions. Younger people were also more likely to have poor adherence execution, and to be lost to care. Further exploration of simple adherence interventions such as the one used in this study would be warranted in these young people.

TABLE 4. Poisson Regression Model for Count of TIs (ITT, 230 Participants Used in the Model)

Count of TI >72 h	IRR	Standard Error	*P*	95% Confidence Interval
Intervention arm	0.84	0.049	0.003	0.75 to 0.94
Age*	0.99	0.003	0.000	0.98 to 0.99
Baseline CD4	0.99	0.000	0.616	0.99 to 1.00
Male sex	1.30	0.079	0.000	1.15 to 1.47
Anxiety score >8	0.96	0.058	0.466	0.85 to 1.08
Depression score >8	1.36	0.083	0.000	1.21 to 1.53
Screen CAGE ≥2	1.08	0.087	0.331	0.92 to 1.26
Nondisclosure	1.19	0.163	0.194	0.91 to 1.56

*The relative count of TI for each 10-year increase in age decreased by 14%: aIRR, 1.86 (95% CI: 0.80 to 0.92).

Transfers to care at other clinics (6.9%) and losses to care (8.2%) were similar to what has previously been reported at this site.[36,37] Eight people (3.5%) died; a smaller proportion than noted in the same earlier studies, likely reflecting earlier entry to care with the expansion of the South African ART program and raise in baseline CD4 cell count inclusion criteria (from 200 to 350 cells/mm^3) in August 2011.[22] The intervention in this study did not impact on these losses. Those who were lost to care were younger than those who remained in care and were more likely not to have disclosed their HIV status to anyone else.

Our study has several strengths including objective monitoring of adherence, 12-month follow-up, and use of HIV-1 RNA as an outcome. One potential limitation of the study is that adherence in this cohort is already excellent.[21] All participants received a higher level of adherence support at our clinic than is routine in most settings, including thorough treatment preparedness, regular clinic pill counts, and extra support through education and home visits, should adherence flag. All of these interventions are known to improve adherence.[38,39] A further potential limitation is that we sent our text messages to the participant's own mobile phones and, despite regular confirmation of telephone numbers, other than the increased numbers of people dosing at the time the message was sent (Fig. 2), we do not have data to confirm that all messages were actually received.

In summary, our study found that electronic monitoring with text reminders for late doses reduced the frequency of TIs without a difference in overall adherence or HIV RNA suppression in the context of high levels of adherence support. Although systematic reviews and meta-analyses have concluded that text messaging is a potential option to support adherence to ART,[9,40–45] future studies are needed to determine best timing of the reminders and whether the level of adherence support supplied by electronic monitoring can replace intensive counseling linked with home visits in this population.

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