

Two-way mobile phone intervention compared with standard-of-care adherence support after second-line antiretroviral therapy failure: a multinational, randomised controlled trial

Robert Gross, Justin Ritz, Michael D Hughes, Robert Salata, Peter Mugenyi, Evelyn Hogg, Linda Wieclaw, Catherine Godfrey, Carole L Wallis, John W Mellors, Victor O Mudhune, Sharlaa Badal-Faesen, Beatriz Grinsztejn, Ann C Collier



Summary

Background Antiretroviral therapy (ART) non-adherence causes HIV treatment failure. Past behaviour might predict future behaviour; failing second-line ART could indicate ongoing risk for subsequent non-adherence. We aimed to find out whether a two-way mobile phone-based communication intervention would increase HIV treatment success by improving medication adherence.

Methods We did a multinational, randomised controlled trial of patients at 17 sites in nine lower-income and middle-income countries in Africa, Asia, and the Americas. Patients aged 18 years and older, with HIV infection, and on second-line protease-inhibitor-based antiretroviral regimens, were randomly assigned (1:1) to either two-way mobile phone intervention plus standard of care (MPI+SOC) adherence support or standard-of-care alone (SOC). Our study was nested within a strategy study of ART after second-line ART failure (the main study, A5288). The main study had four cohorts, which were assigned regimens according to ART history and real-time genotype. Randomisation was stratified by the main study cohort with dynamic institutional balancing. Only the clinical management committee was masked, not the participants or site personnel. Text messages were sent over 48 weeks starting once a day and tapering down to once per week; participants were to respond once to each message if taking ART without issues. Repeated non-response to three messages over a 2-week period for the first 8 weeks, and then two messages over a 2-week period for the remainder of the study, triggered problem-solving counselling by staff. For this study, the primary endpoint was plasma HIV-1 RNA 200 copies per mL or less at 48 weeks and the secondary endpoint was virological failure (two consecutive HIV-1 RNA ≥ 1000 copies per mL) at 24 or more weeks. Prespecified intention-to-treat analyses were adjusted for cohort. Follow-up continued until the last participant had reached 48 weeks, with a median follow-up time of 72 weeks. The trial is registered with ClinicalTrials.gov, number NCT01641367.

Findings Enrolment began on Feb 22, 2013, and ended on Dec 21, 2015, with the last participant completing follow-up on Feb 13, 2017. Of 545 participants in the main study, 521 (96%) were enrolled and randomly assigned to MPI+SOC (n=257) or SOC alone (n=264). 52% of patients were men and the median HIV-1 RNA 4.4 log₁₀ copies per mL (IQR 3.5 to 5.2). At week 48, HIV-1 RNA 200 copies per mL or less was reached in 169 (66%) of 257 patients in the MPI+SOC group and 164 (62%) of 264 patients in the SOC group (estimated difference 3.6% [95% CI -4.6% to 11.9%]; p=0.39). The adjusted odds ratio comparing MPI+SOC and SOC was 1.23 (0.82 to 1.84; p=0.32). Virological failure occurred in 66 (26%) patients in the MPI+SOC group and 89 (34%) patients in the SOC group during the median 72 weeks follow-up (adjusted p=0.027). Observed difference in virological failure favoured MPI+SOC in all cohorts. 23 (4%) participants died, 11 (4%) in the MPI+SOC group and 12 (5%) in the SOC group (p=0.89), with none of the deaths ascribed to ART, the MPI, or study procedures.

Interpretation Two-way MPI did not significantly improve week 48 suppression, but it did modestly affect virological failure. People failing second-line ART might not achieve benefits from phone-based triggers or enhanced adherence support (or both). More effective strategies are needed.

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Introduction

Despite the success of antiretroviral therapy (ART) in both high-income countries and lower-income and

middle-income countries (LMICs), a substantial proportion of individuals are unable to achieve sustained virological suppression.^{1,2} Although evidence suggests

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Department of Medicine (Infectious Diseases) and Department of Epidemiology, Biostatistics and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (R Gross MD MSCE); Harvard TH Chan School of Public Health, Boston, MA, USA (J Ritz MS, Prof M D Hughes PhD); Case Western Reserve University, Cleveland, OH, USA (Prof R Salata MD); Joint Clinical Research Centre, Kampala, Uganda (Prof P Mugenyi FRCPe); Social and Scientific Systems, Silver Spring, MD, USA (E Hogg BA); Frontier Science and Technology Research Foundation, Amherst, NY, USA (L Wieclaw BA); National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA (C Godfrey MD); Lancet Laboratories, and Bio Analytical Research Corporation South Africa, Johannesburg, South Africa (C L Wallis PhD); Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA (Prof J W Mellors MD); Department of Medicine, Kenya Medical Research Institute, Kisumu, Kenya (V O Mudhune MPH); Clinical HIV Research Unit, Department of Internal Medicine, University of Witwatersrand, Johannesburg, South Africa (S Badal-Faesen MBBCh); Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil (Prof B Grinsztejn MD); and University of Washington, Seattle, WA, USA (Prof A C Collier MD)

Correspondence to:
Dr Robert Gross, Perelman
School of Medicine, University of
Pennsylvania, Philadelphia,
PA 19104, USA
grossr@pennmedicine.upenn.
edu

Research in context

Evidence before this study

Before doing this study, few interventions for medication adherence had been done in lower-income and middle-income countries. Most notably, one randomised controlled trial of the *Weltel Kenya One* mobile phone-based intervention using two-way communication by short message service (SMS) found a higher proportion of patients adhered to medicine and had better virological outcomes than usual care. Additionally, other research on SMS-based communication found that once per week contact resulted in better outcomes than once a day contact. Directly observed therapy-based interventions and other modalities, such as SMS messaging without additional support, were less effective than two-way communication. Interventions that combined counselling and technology for ease of communication were the most promising but had not been tested in later-line therapy and at multiple sites.

Added value of this study

Our study found a small but not significant benefit of a mobile phone-based intervention for antiretroviral therapy adherence on the primary outcome of virological suppression at 48 weeks. A small, significant effect on the outcome of time to virological

failure was found. Interventions that use mobile technology to link participants to adherence counselling if they are encountering adherence challenges have shown positive outcomes. However, data on individuals with multiple previous regimen failures remain limited. Differences in the study populations, the active responses requested of participants, and the passive nature of triggering the intervention, might have overburdened participants. Furthermore, differences in technology challenges at different sites, the intensity of different programmes, and methods of delivery might explain why some studies do and others do not find an effect.

Implications of all the available evidence

Our study adds to knowledge that changing adherence behaviour is challenging and that technological approaches might not be as fruitful as expected in people at highest risk of non-adherence. Given our findings, it would be premature to commence large scale roll-out of two-way SMS messaging for individuals not adhering to second-line therapy. Additional research is needed to identify the optimal approach to use these tools to increase HIV treatment success.

that non-adherence is less prominent in LMICs than in high-income countries,³ non-adherence has been shown in these settings as well.⁴ Non-adherence that leads to poor virological suppression could potentially create several inter-related public health problems, including excess morbidity and mortality in the individual,⁵ development of resistant virus⁶ that is more difficult to treat and involves more expensive and complex regimens, and further HIV transmission if risk behaviours continue.⁷ Therefore, non-adherence is a crucial target for intervention.

Over the past 20 years, many adherence interventions have been tested, but only a few have been shown to be effective.⁸ Of trials done in LMIC settings, few have shown important benefits, with the notable exception of a two-way mobile phone communication system.⁹ In this intervention, participants were queried once per week via the short message service (SMS) and were invited to reply; if they were having difficulty, they were to receive additional adherence support. It was tested in a treatment-naïve population in Kenya and increased the proportion of individuals with virological suppression, which is evidence of better adherence by patients. In a study in Uganda,¹⁰ timing of the messaging was particularly important; messaging once per week, but not once a day, improved adherence. Further, a network meta-analysis¹¹ provided more evidence that SMS messaging is a promising component of adherence interventions.

Although two-way messaging has been shown to be effective in treatment-naïve individuals, treatment-experienced individuals pose a potentially greater

challenge. Although treatment failure can be due to drug stockouts,¹² drug–drug interactions,¹³ drug metabolism,^{14,15} and pre-existing viral resistance,^{16,17} populations with repeated treatment failures are likely to have a high number of individuals with repeated non-adherence.¹⁸ Therefore, we aimed to find out if an intervention consisting of a two-way messaging system, with offers of local adherence support for individuals who requested help or who were not engaged with the system, would result in better HIV treatment outcomes than standard-of-care adherence support. This trial was completed within a strategy study (main study) in which individuals from nine LMICs who had a confirmed HIV-1 RNA 1000 copies per mL or higher, on second-line ART, were assigned to one of four cohorts based on previous treatment experience and resistance testing.

Methods

Main study design and participants

The present study was nested within a main study—the AIDS Clinical Trials Group A5288 study. A5288 was an open-label, phase 4, prospective strategy study in LMICs investigating the use of new drugs and contemporary clinical decision management tools, including standard HIV genotyping, regimen selection based on the results (including possible use of new drugs), and plasma viral load monitoring.

The study population consisted of HIV-1-infected men and women in ten LMICs, aged 18 years and older, who had previously taken or who had resistance to nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors

(NNRTIs), and protease inhibitors, and who were currently accessing a second-line protease inhibitor-containing regimen, which they had been on for at least 24 weeks with no previous darunavir or etravirine exposure. For the main study, the ART history, screening genotype, and any historical genotype results were used to allocate potential participants to one of four cohorts (A, B, C, or D) and to select an associated ART regimen based on the cohort assignment. In brief, cohort A had no lopinavir resistance and susceptibility to at least one NRTI; they continued on the same protease inhibitor as in their second-line regimen, with the ability to modify NRTIs. Those assigned to cohort B had resistance to lopinavir but were susceptible to darunavir and etravirine and had no raltegravir exposure; if they were negative for hepatitis B surface antigen, they were randomly assigned to receive raltegravir and darunavir plus ritonavir with either the best available NRTIs (cohort B1) or etravirine (cohort B2). If they were positive for hepatitis B surface antigen they were assigned to cohort B3 and received raltegravir, darunavir plus ritonavir, and either emtricitabine and tenofovir disoproxil fumarate or lamivudine plus tenofovir disoproxil fumarate. Cohort C had resistance to lopinavir and etravirine but were susceptible to darunavir and had no previous raltegravir exposure; they received raltegravir and darunavir plus ritonavir with the best available NRTIs. Those ineligible for cohorts A, B, or C were assigned to cohort D and received the best available regimen that included study provided drugs and any locally provided drugs. Darunavir, etravirine, raltegravir, emtricitabine and tenofovir disoproxil fumarate, ritonavir, and rifabutin, if needed for treatment of tuberculosis, were provided by the study. A clinical management committee (study leaders) of the A5288 protocol team reviewed the site's recommendation and either agreed or suggested an alternative cohort or regimen (or both) for the site to consider. In the event of a confirmed virological failure (two consecutive HIV RNA ≥ 1000 copies per mL at 24 weeks or more on study), participants had another genotype resistance test and were assigned to a step 2 cohort after receipt of the genotype resistance report. The step 2 cohort selection and confirmation process was similar to that for the initial study regimen (step 1), except that both genotype resistance reports from screening and at step 1 virological failure were considered. Participants in cohort A in step 1 had to be allocated to one of the three other cohorts (B, C, or D) in step 2. Follow-up continued for as long as the study was open to accrual and until the last participant enrolled had reached 48 weeks on study. ART adherence was measured via self-report every 12 weeks.¹⁹

Present study design and participants

We did a randomised controlled trial comparing a two-way mobile phone-based intervention plus local site standard-of-care adherence support (MPI+SOC) with standard-of-care adherence support alone (SOC). This

trial was implemented at 17 of 19 main study sites in nine of ten participating countries (see Acknowledgments) where it was considered feasible and relevant.

The study was approved by ethics boards at all sites and all participants provided written informed consent. The study protocol is available upon request from the AIDS Clinical Trials Group.

For the study protocol see www.actgnetwork.org

Randomisation and masking

According to cohort registration in the main study (or randomisation to subcohorts B1 or B2), participants were randomly assigned 1:1 to either MPI+SOC or SOC by use of an internet web-based interface to a central computer, which provided the randomised assignment. A blocked randomisation was used stratified by cohort (and subcohort within cohort B) with dynamic institutional balancing to avoid large imbalances at any site. Site investigators and participants were not masked to intervention group, but the clinical management committee was masked.

Procedures

MPI involved a simple, automated interactive system (SMS reminder and flashback system) to identify non-adherence soon after it occurred and, in response, a site-based, culturally relevant algorithm for managing barriers to adherence was followed. SMS messages ("Everything OK?" in the local language) were sent once a day for a participant's first 8 weeks on the study, then three times per week for the next 8 weeks, and then once per week through to 48 weeks after study entry. Although previous studies showed that once per week was better than once a day messaging, we chose a more intensive strategy to start, hypothesising that more frequent contact early on would be beneficial in a population with multiple previous treatment failures. Participants chose the time of day the SMS was to be sent. The technology partner consulted with each site regarding the best way to set up and maintain the automated system (eg, where to maintain devices so power interruptions were minimised).

Unless they were experiencing a problem taking their medication, participants were expected to respond by calling a central number, which registered the call but did not complete the call, preventing charges (termed a flashback). Failure to flashback, either because the participant actively chose not to respond because they wanted to be contacted by the site or for any other reason, was tracked by the system. Site representatives had training for 2 h, in which the trigger to contact the participant was any three missed flashbacks over 2 weeks during the daily messaging period, any two missed flashbacks over 2 weeks of the three times per week messaging period, or any two missed flashbacks over 2 weeks during the once per week messaging period. These personnel were chosen by the sites and were not required to be the participant's research clinician.

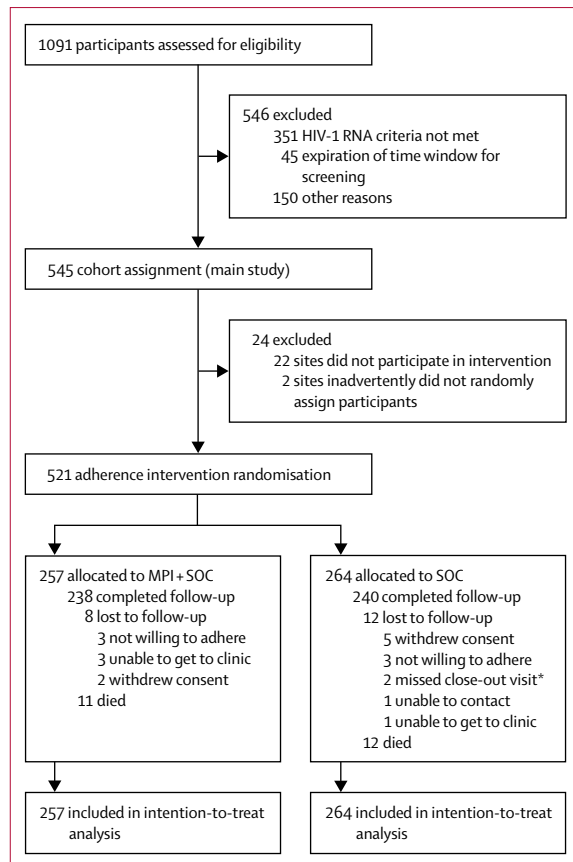


Figure 1: Trial profile
MPI=mobile phone intervention. SOC=standard of care. *Visit at 48 weeks.

Participants in both the MPI+SOC group and SOC group were provided with information about how to contact the site if they desired assistance outside of set study visits.

Outcomes

The primary outcome was HIV-1 RNA 200 copies per mL or less at week 48 in the intention-to-treat population and secondary outcomes included time to virological failure, CD4 count change, self-reported antiretroviral adherence, and adverse events. For the time to virological failure analysis (to allow the last measurement to be used as a confirmatory measurement), censoring was at the time of the penultimate HIV-1 RNA measurement; for time-to-death analysis, censoring was at last contact with the participant.

Statistical analysis

The main study's target sample size across all cohorts was 500 participants, chosen to provide good precision for estimating the virological suppression rate at week 48 (confidence interval width of approximately plus or minus 4% based on an estimated 65% of the study population achieving virological suppression), and there

were no restrictions on the number included in each cohort. The study was not specifically powered to address the randomised comparison of MPI+SOC to SOC. Reported p values were not adjusted for multiple comparisons.

In the present study, we compared outcomes between participants randomly assigned to MPI+SOC versus SOC using an intention-to-treat approach, ignoring any changes in adherence support provided and in anti-retroviral drugs being taken, and adjusting for cohort or subcohort. For analyses of the primary outcome, we included estimation of the difference in proportion of participants with an HIV-1 RNA 200 copies per mL or less at week 48 (with associated 95% CI and p value), pooling over all cohorts. For the prespecified primary analysis, comparing the primary outcome between groups, we estimated the odds ratio (OR; and associated 95% CI and p value) with adjustment for cohort and subcohort. For analyses of time to an event, we had the time origin as the day of randomisation. We used the Kaplan-Meier method to estimate the cumulative proportion with an event over time for each of the MPI+SOC and SOC groups. We used a proportional hazards model to compare the hazards of events between groups, which was further extended to compare groups adjusted for cohort or subcohort, and to assess randomised intervention by subgroup interactions.

A data and safety monitoring board was empanelled by the Division of AIDS of the National Institutes of Health. An introductory meeting was held on April 22, 2011, and reviews of interim data occurred on March 20, 2014, March 31, 2015, and April 7, 2016. No recommendations concerned major changes to the design and conduct of the study after these reviews. We did all analysis on SAS software, version 9.4. The study was registered with Clinicaltrials.gov, number NCT01641367.

Role of the funding source

Gilead, Janssen Pharmaceuticals NV, Merck, and AbbVie provided study drugs. Representatives from these companies monitored the development of the protocol and were able to provide feedback, which the research team was free to incorporate or not. The National Institutes of Health provided support through the AIDS Clinical Trials Group (ACTG), which monitored the development and implementation of the protocol, funded the study sites, and supported the salaries of the investigators. The ACTG leadership gave the authors feedback on the manuscript, which the authors were free to incorporate or not. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled from Feb 22, 2013, to Dec 21, 2015, with the last participant completing step 1 or 2 follow-up on Feb 13, 2017. A total of 545 individuals were enrolled in

the main study, of whom 521 (96%) were randomly assigned to the MPI+SOC group (n=257) or the SOC group (n=264; figure 1). Loss to follow-up was less than 4% and death occurred in fewer than 5% of patients. Five (2%) participants in the SOC group inadvertently received SMS messages, including three for 1 week and two for 3 weeks, before the errors were recognised. More men than women were enrolled and individuals from Africa made up more than half the study population (table 1); more than two thirds of the population had screening plasma HIV-1 RNA less than 5 log₁₀ copies per mL. Medium-level to high-level resistance to at least one drug in each of the three drug classes (NRTI, NNRTIs, and protease inhibitors) was present in 148 (28%) patients, two classes in 159 (31%) patients, and one class in 101 (19%) patients with no medium-level to high-level resistance in 113 (22%) patients. Resistance patterns were distributed similarly between groups (appendix).

Although the step 1 regimens varied by cohort according to the study design, the numbers receiving each specific regimen were similar between the randomised groups within each cohort (appendix). Over the four cohorts combined, participants were most commonly prescribed lopinavir plus ritonavir with emtricitabine and tenofovir disoproxil fumarate (73 [28%] in the MPI+SOC group and 73 [28%] in the SOC group), raltegravir and darunavir plus ritonavir with emtricitabine and tenofovir disoproxil fumarate (68 [26%] in the MPI+SOC group and 72 [27%] in the SOC group), atazanavir plus ritonavir with emtricitabine and tenofovir disoproxil fumarate (42 [16%] in the MPI+SOC group and 45 [17%] in the SOC group), and raltegravir, darunavir plus ritonavir, and etravirine (36 [14%] in the MPI+SOC group and 36 [14%] in the SOC group). All other regimens represented fewer than 5% of patients in either group. The median duration of follow-up for step 1 and 2 was 72 weeks and the maximum duration of follow-up for step 1 and 2 was 204 weeks.

45 (18%) participants in the MPI+SOC group and 34 (13%) participants in the SOC group permanently discontinued at least one drug in their initial study regimen. Reasons for discontinuation included death (nine [4%] patients in the MPI+SOC group vs ten [4%] in the SOC group), adverse events (nine [4%] vs four [2%]), loss to follow-up (four [2%] vs five [2%]), virological failure (12 [5%] vs nine [3%]), non-compliance with study procedures (four [2%] vs six [2%]), tuberculosis management issues (two [2%] vs 0 [0%]), drug supply issues (two [1%] vs 0 [0%]), participant decision to stop ART (two [1%] vs 0 [0%]), and the decision to enrol in another study (one [0.5%] vs 0 [0%]).

For the primary outcome measure of virological suppression (HIV-1 RNA ≤200 copies per mL) at week 48, 169 (66%) of 257 participants in the MPI+SOC group and 164 (62%) of 264 participants in the SOC group were suppressed (table 2). The absolute difference in proportion of patients who were suppressed was 3.6% (95% CI -4.6% to 11.9%; p=0.39). The OR adjusted for

	MPI+SOC group (n=257)	SOC group (n=264)
Age at entry, years	42 (35-47; [18-75])	41 (35-47; [18-71])
Sex		
Male	143 (56%)	129 (49%)
Female	114 (44%)	135 (51%)
Hepatitis B surface antigen		
Positive	15 (6%)	13 (5%)
Negative	242 (94%)	250 (95%)
Indeterminate	0	1 (0%)
Screening HIV-1 RNA category, copies per mL		
<100 000	178 (69%)	186 (70%)
≥100 000	79 (31%)	78 (30%)
HIV-1 RNA, log ₁₀ copies per mL	4.3 (3.5-5.3)	4.5 (3.5-5.1)
CD4 count, cells per mm ³	173 (78-300)	186 (67-312)
Country		
Brazil	26 (10%)	23 (9%)
Haiti	20 (8%)	25 (9%)
India	71 (28%)	57 (22%)
Kenya	26 (10%)	31 (12%)
Malawi	18 (7%)	19 (7%)
South Africa	38 (15%)	46 (17%)
Thailand	6 (2%)	12 (5%)
Uganda	41 (16%)	40 (15%)
Zimbabwe	11 (4%)	11 (4%)
Time from first ART to entry, years	8.1 (6.2-10.2)	7.8 (5.5-10.1)
Data are median (IQR), median (IQR; [range]), or n (%). ART=antiretroviral therapy. MPI=mobile phone intervention. SOC=standard of care.		

Table 1: Baseline characteristics by adherence intervention

See Online for appendix

cohort, comparing the MPI+SOC and SOC groups, was 1.23 (0.82-1.84; p=0.32). 66 (26%) participants in the MPI+SOC group and 89 (34%) participants in the SOC group had confirmed virological failure. Figure 2 shows the estimated cumulative incidence of confirmed virological failure over time and adherence intervention. With the caveat of small numbers of confirmed virological failures in most cohorts or subcohorts, except cohort A, the comparison of the MPI+SOC and SOC groups adjusted for cohort or subcohort was significant in the proportional hazards model (hazard ratio 0.70 [0.51 to 0.96]; adjusted p=0.027). The greatest difference between the MPI+SOC and the SOC groups was in cohort A, but we found no significant interaction between cohort and adherence support intervention (p=0.89). None of the Cox models violated the assumptions needed for validity of the findings.

The mean increases in CD4 count from screening to week 48 were 112 cells per mm³ in the MPI+SOC group and 107 cells per mm³ in the SOC group. The difference in mean change adjusted by cohort comparing the MPI+SOC group to the SOC group was 5 cells per mm³ (95% CI -22 to 32; p=0.73). 23 (4%) participants died, 11 in the MPI+SOC group and 12 from the SOC group

	Patients with ≤200 copies per mL at week 48	Patients with confirmed virological failure
Overall totals		
MPI + SOC	169/257 (66%)	66/257 (26%)
SOC	164/264 (62%)	89/264 (34%)
Continue second-line ART		
Cohort A: MPI + SOC	60/133 (45%)	60/133 (45%)
Cohort A: SOC	55/136 (40%)	75/136 (55%)
Best available NRTIs plus darunavir plus ritonavir plus raltegravir		
Cohort B1: MPI + SOC	32/36 (89%)	1/36 (3%)
Cohort B1: SOC	30/35 (86%)	5/35 (14%)
Darunavir plus ritonavir plus raltegravir plus etravirine		
Cohort B2: MPI + SOC	31/35 (89%)	1/35 (3%)
Cohort B2: SOC	30/35 (86%)	2/35 (6%)
Darunavir plus ritonavir plus raltegravir plus emtricitabine and tenofovir disoproxil fumarate or lamivudine plus tenofovir disoproxil fumarate		
Cohort B3: MPI + SOC	3/3 (100%)	0/3
Cohort B3: SOC	5/5 (100%)	0/5
Best available NRTIs plus darunavir plus ritonavir plus raltegravir		
Cohort C: MPI + SOC	31/34 (91%)	2/34 (6%)
Cohort C: SOC	31/35 (89%)	3/35 (9%)
Best available local and study supplied ARTs		
Cohort D: MPI + SOC	12/16 (75%)	2/16 (13%)
Cohort D: SOC	13/18 (72%)	4/18 (22%)

Data are n/N (%). MPI=mobile phone intervention. SOC=standard of care. ART=antiretroviral therapy. NRTIs=nucleoside analogue reverse transcriptase inhibitors.

Table 2: Comparison of endpoints between groups

with almost all with known causes ascribed to HIV itself or other infection, including three with confirmed tuberculosis in the SOC group. One death in each group was unrelated to HIV (trauma in the MPI+SOC group and prostate cancer in the SOC group). We found no significant difference between the two groups in cumulative incidence of death ($p=0.89$ adjusted for cohort).

Self-reported adherence was high with most participants in both groups reporting 100% adherence in the previous month at all assessments. For example, at the end of the mobile phone adherence support intervention at 48 weeks, 174 (73%) participants in the MPI+SOC group reported taking all doses in the past month compared with 173 (69%) participants in the SOC group. No significant differences were found between the groups in self-reported adherence at any of the timepoints assessed.

The SOC for adherence support at the sites was assessed at initiation of the trial and annually thereafter. They were queried regarding use of mobile phone messaging with their patients. At initiation of the trial, one site reported this use as “often”, two sites reported “sometimes”, six sites reported “rarely”, and eight sites reported “never”. This usage increased during the study

with three reporting “often”, three “sometimes”, six “rarely”, and five “never” on their last completed case report form. More than half of sites described use of the following interventions as “often” on one or both of their first and last case report forms: “one-to-one counselling after ART change” (16 [94%] of 17 on first form changing to 17 [100%] on last form), “one-to-one counselling before/at ART change” (16 [94%] to 16 [94%]), “faster service at clinic” (eight [47%] to 14 [82%]), “pill counts” (14 [82%] to 12 [71%]), “travel expense paid” (ten [59%] to 12 [71%]), “follow-up phone calls” (seven [47%] to eight [59%]), and “HIV education for family/friends” (seven [41%] to eight [47%]).

After excluding the seven individuals who opted out from the MPI without receiving any text messages, 248 (99%) of 250 participants in the MPI+SOC group who received SMS messages met the trigger for contact by the site at least once during follow-up. The trigger was generally first met very early in follow-up: the median time from randomisation was 6 days (IQR 3–51). Most participants met the trigger during every week of follow-up, indicating a high need for sites to contact participants throughout the 48 weeks of MPI. In week 1, this proportion was 56% and was then between 68% and 78% from week 2 to week 16; after week 16, when the frequency of text messages was generally once per week, the proportion reaching the trigger was reduced, generally being between 50% and 60% through to week 48.

Of the 248 participants who at some point repeatedly did not flashback and thereby met criteria for site contact, 176 (71%) reported reasons for not flashing back to the text messages during at least one contact. The most common reasons reported for 10% or more of the 248 participants were “network problem” (73 [29%]), “did not receive SMS immediately (phone off/silent/misplaced)” (61 [25%]), “insufficient airtime” (37 [15%]), “phone unusable (lost/stolen/damaged)” (32 [13%]), “no phone reception” (27 [11%]), and “international call problem” (26 [10%]).

Discussion

We tested a two-way MPI added to SOC adherence support for individuals in diverse LMICs and settings who were having treatment failure on their second-line ART. The intervention had neither statistically nor clinically significant benefit on viral suppression rates at 48 weeks and only a small but significant effect on the secondary endpoint of time to virological failure. In treatment-naive individuals in Kenya, a similar intervention with once per week contact was shown to have an effect in the small subset of individuals whom the system flagged as potentially needing help.⁹ Conversely, our trial included more intensive contact early, although we did not continue the daily contact beyond 2 months because it had been previously shown to be inferior to once per week contact when done for 1 year.¹⁰ Our finding stands in contrast to

other trials, which taken together show a small benefit of SMS-based interventions. In a meta-analysis,¹¹ SMS interventions increased adherence (OR 1.48 [95% CI 1.00–2.19]), but evidence of improvement in virological outcomes was scarce.

In well resourced areas, many adherence interventions have been tested with several showing substantial benefit,²⁰ including counselling with the use of problem solving.²¹ Successful adherence interventions are generally complex, time intensive, and tailored to the individuals' needs. Although our goal was to individualise the adherence support through problem solving, the absence of an evident benefit might have been due to insufficient training of intervening personnel, insufficient time on their part for determining adherence barriers and identifying strategies for overcoming them, or logistical difficulties with delivering and receiving the messaging and with subsequent communication.

The group in this study with the least resistance at enrolment (cohort A) had the worst virological suppression rate at 48 weeks. This finding suggests that these individuals might have used less ART in the past related to previous adherence challenges they were unable to overcome while continuing on the same or similar ARTs. Yet, the magnitude of effect of MPI in cohort A was still modest. One potential reason for the lack of effect of the intervention is that cohort A did remain on the same protease inhibitor-based regimen. If low level intolerance was responsible for previous non-adherence (eg, gastrointestinal discomfort),²² support measures were misdirected at adherence rather than tolerability.

One reason for the lack of effect in all cohorts is that individuals might have had reasons for previous failure other than non-adherence (eg, stockouts leading to suboptimal drug concentrations).¹² If so, they were not in need of adherence intervention when availed of fully active regimens. The effect of this issue would be to dampen the effect of an intervention targeted to a problem they did not have. In addition, the intervention might not have added to the multiple strategies already implemented as SOC at the sites.

Despite the promise of mobile technology for health-care interventions in LMICs, they might be more difficult to implement than previously anticipated.²³ The amount of tracking, number of calls made, and the amount of time needed per participant might have been too burdensome for sites to implement fully. The logistics of implementing technological solutions in settings where power and mobile phone infrastructure are less robust might impede the ability of an intervention to fully take advantage of these solutions.

This study had strengths. It was a large randomised trial done in LMICs in a population anticipated to be enriched for a history of non-adherence. We used an automated system that accounted for the various languages of the participants and used existing site staff without specialised

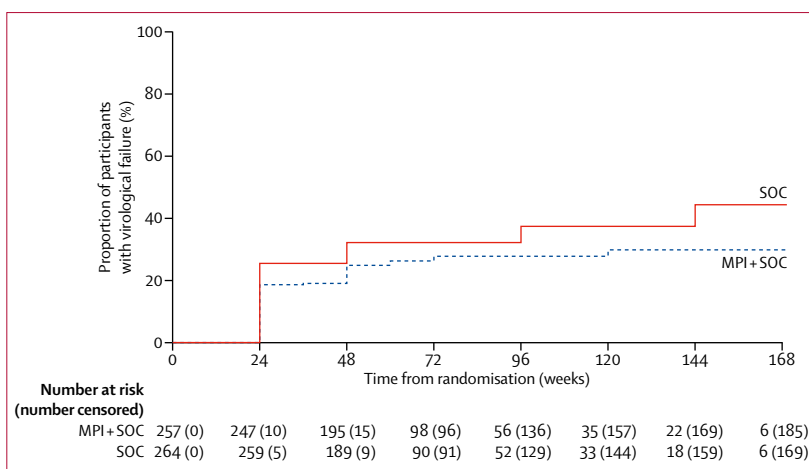


Figure 2: Cumulative incidence of the proportion of participants with confirmed virological failure by adherence intervention

MPI=mobile phone intervention. SOC=standard of care.

training in adherence support. We used local mobile phone infrastructure and widely available automated SMS technology.

Several limitations of this study are worth noting. The default assumption of non-flashback implicating non-adherence probably added to the workload burden by triggering calls for participants who simply did not reply, but did not need help. We did not track the approach taken by staff when intervening with participants. The intervention might not have been well integrated into their workflow and if they did not deliver the adherence support in a patient-centred manner, then we would expect counselling to not be effective. Moreover, we presumed that a large proportion of these individuals had previously been non-adherent but, without objective data showing previous non-adherence, we do not know if we targeted a group in need and therefore likely to benefit from the intervention if it were delivered as desired. Although adherence during the study was self-reported to be high in all cohorts, this measure is known to overestimate actual adherence,²⁴ and because cohort A had little resistance it strongly suggests they had a history of non-adherence. Yet, although overall cohort A did worse than the others with respect to virological suppression, presumably due to continued non-adherence, the intervention did not have a particular benefit in this cohort compared with the others. Also, we reported an OR instead of a relative risk since our a priori analysis plan included controlling for cohort in the analysis, which yields an OR. Yet, since the outcome was common, the relative effect of the intervention is likely to be even smaller than is reflected in the OR. Finally, the additional attention and visits from participating in this trial might have reduced the potential effect of the intervention, however, the high failure rate, particularly in cohort A, suggests that such attention probably did not abrogate non-adherence. We are unable to establish

which of these issues was the greatest obstacle to success.

In conclusion, this two-way adherence intervention did not show any clinically relevant benefit and was cumbersome and difficult to implement as intended. Yet, the high virological failure rate in those without resistance suggests that at least a subset of cohort A and possibly other cohorts remain in need of a different and perhaps more intensive adherence support intervention. Future research should focus on establishing non-adherence with objective measures, and targeting interventions that require less infrastructure and staff time, and have more salience to the barriers experienced by this population to achieve the WHO target of 90% virological suppression in all treated people living with HIV.

Contributors

RG searched the literature. RG, JR, MDH, RS, PM, EH, CG, JWM, BG, and ACC designed the study. RS, PM, CG, JWM, BG, and ACC engaged in cohort assignment for participants. LW coordinated data collection. VOM and SB-F collected data. CLW generated the resistance data for assigning cohort. JR and MDH analysed the data. All authors interpreted the results. RG wrote the first draft. JR created the figures. JR, MDH, RS, PM, EH, LW, CG, CLW, JWM, VOM, SB-F, BG, and ACC edited the manuscript for content. All authors approved the final version of the manuscript for submission.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data and a data dictionary defining each field in the set might be made available to investigators for work that was not initially proposed as part of the parent protocol. Such requests are decided on a case by case basis via application to the AIDS Clinical Trials Group (ACTG) via the link: <https://submit.actgnetwork.org/>. Completion of an ACTG Data Use Agreement might be required.

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