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Toward improved adherence: a text message intervention in an human immunodeficiency virus pediatric clinic in Guatemala City

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Abstract

As access to human immunodeficiency virus treatment expands in Low to Middle Income Countries, it becomes critical to develop and test strategies to improve adherence and ensure efficacy. Text messaging improves adherence to antiretroviral treatment antiretroviral treatment in some patient populations, but data surrounding the use of these tools is sparse in pediatric and adolescent patients in low to middle income countries. We evaluated if a text message intervention can improve antiretroviral treatment adherence while accounting for cell phone access, patterns of use, and willingness to receive text messages.

We carried out a cross sectional study to understand willingness of receiving text message reminders, followed by a randomized controlled trial to assess effectiveness of text message intervention.

Enrolled participants were randomized to receive standard care with regular clinic visits, or standard care plus short message service reminders. Adherence was measured 3 times during the study period using a 4-day Recall Questionnaire. Outcome was measured based on differences in the average adherence between the intervention and control group at each time point (baseline, 3 months, 6 months).

Most respondents were willing to receive text message adherence reminders (81.1%, n = 53). Respondent literacy, travel time to clinic, cell phone access, and patterns of use were significantly associated with willingness. In the randomized trial the intervention group (n = 50) experienced a small but significant mean improvement in adherence over the six-month period (4%, $P < .01$) whereas the control group (n = 50) did not (mean improvement: 0.8%, $P = .64$).

Text message interventions effectively support antiretroviral adherence in pediatric patients living with human immunodeficiency virus. Studies designed to assess the impact of text messaging interventions must examine local context for cellular phone infrastructure and use and must account for potential loss to follow up when patients miss appointments and study assessments.

Abbreviations: ART = antiretroviral treatment, HIV = human immunodeficiency virus, PLHIV = People Living with HIV, SMS = short message service.

Keywords: Adherence, human immunodeficiency virus, pediatric, text-message

1. Introduction

In 2018, approximately 47,000 people in Guatemala were living with human immunodeficiency virus (HIV) of which 2000 were children between 0 to 14 years old.[1] The highest prevalence of HIV is found in at-risk populations such as men who have sex with men, transgender persons, male and female sex workers, clients of sex workers and their partners, ethnic groups such as the Garifuna, and populations that move between geographic locations over time.[2] The region has historically received support from the United States President's Emergency Plan for

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AIDS Relief mainly to increase access to antiretrovirals. More recently, regional President's Emergency Plan for AIDS Relief and UNAIDS programs have joined to define the 90-90-90 goals aiming to identify 90% of all HIV cases by 2020, providing 90% of all diagnosed People Living with HIV (PLHIV) with antiretroviral treatment so that 90% of all PLHIV on treatment are virally suppressed by 2020.[3,4] As a result of this support, antiretroviral treatment (ART) use has continually increased. In 2016 only 36% of the eligible population had received ART in Guatemala, by 2017 ART coverage expanded to 40%, and in 2018 ART coverage was reported to be 69%.[1,5] Access to and use of antiretrovirals is expected to continually grow.

As access to treatment expands, developing and testing strategies to improve ART adherence is critical to managing HIV in Guatemala. Patients frequently report non-optimal adherence with subsequent disease progression, morbidity, and mortality.[6] Given growing access to mobile phone technologies, PLHIV in Guatemala may benefit from short message service (SMS) text messaging reminders as a potential intervention to support ART adherence. Studies conducted in Africa have provided high quality evidence that SMS reminders are a cost-effective intervention used to improve adherence in HIV patients living in low to middle income countries.[7,8] Weekly text message reminders to adult patients have improved adherence rates and viral loads after 52 weeks.[9–11] Despite the success of SMS in adults, evidence supporting use of SMS reminders in pediatric and adolescent HIV populations varies. One factor influencing this variability is challenges in design and implementation of specific SMS reminder programs for different child developmental stages. Additionally, country-specific culture around cell phone use can be challenging to generalize from study to study which may greatly influence ultimate success of the intervention.

HIV care in Guatemala is centralized in 3 major clinics in the capital city of Guatemala providing service to the entire country. Poor adherence among HIV adult patients is attributed to forgetfulness, leaving medications at home, and being too busy with other activities.[12] Achieving adequate adherence is complex particularly in pediatric patients living in Low to Middle Income countries where poor socio-economic status influence how patients obtain and use medications.[13] Patients residing in rural areas must travel to the capital city to obtain medications, with the additional costs in travel and lodging acting as further potential barriers to adherence.

In 2013, we conducted a study in 1 of the 3 major clinics in Guatemala City, Guatemala (the Pediatric Infectious Disease Clinic at the Roosevelt Hospital) to measure adherence in 134 patients ranging from birth to 24 years old. We found that 80% of patients had self-reported inadequate adherence.[14] Eighty percent of patients relied on strategies to remind themselves to take medication, using watch alarms in most cases (75%). In order to address findings in poor adherence, we conducted a pre-post intervention pilot study in 2014 to assess the utility of SMS text-message to both remind and motivate patient adherence. Among 38 patients who received text messages over the period of a year, the median adherence improved from 89.3% to 94.4% demonstrating the promise of SMS reminders as an effective tool to achieve adequate adherence in this population.[14,15] In the current study, we present a more rigorous evaluation to assess the utility of SMS text messages to improve ART adherence in pediatric HIV positive patients in Guatemala. The primary objectives were to explore willingness to receive text messages for improving ART adherence, and to conduct a randomized trial to evaluate the effectiveness and associated impact of SMS reminders on adherence.

2. Methods

The study was carried out at the Pediatric Infectious Disease Clinic at the Roosevelt Hospital Guatemala City, Guatemala, a Public Ministry of Health supported clinic. This clinic provides care for both HIV positive patients and persons who have other infectious diseases. Patients are classified as pediatric from the time that they are newborns up until 18 years of age. A proportion of patients continue to receive care in the clinic until they are 24 years old and have established care in the adult HIV clinic. All HIV pediatric patients receiving care at this clinic obtained HIV through vertical infection. Patients obtain ART medications from pharmacies within the clinics, provided by National AIDS Program of the Guatemalan Government as well as international Non-Governmental Organizations including the Global Fund to Fight AIDS, Malaria & Tuberculosis (Global Fund).

2.1. Cell phone patterns of use and willingness to receive text messages

A cross-sectional survey was developed to assess willingness receive SMS text message reminders to support ART adherence and to understand the factors which might be related to this willingness. The questionnaire was based on 4 categories demonstrated in other studies to affect willingness to receive text message reminders:

(1) Socio-demographic factors;
(2) Access to service;
(3) Psychosocial support;
(4) Behavioral factors; and
(5) Cell phone patterns of use.[16]

Specific information on variables collected is provided in the supplement, Table S1, http://links.lww.com/MD/F741.

Pediatric patients were invited to participate in the study if they were HIV positive and willing to give full disclosure regarding HIV status, accompanied by a consenting adult, recipients of ART for at least 6 months, and were Spanish speaking. All who fit inclusion criteria during the study period were invited to participate. The questionnaire was verbally administered to patients between the ages of 6 to 12 years and their caregivers. Patients between the ages of 13 to 24 years old were administered the questionnaire alone after informed assent and informed consent of their caregiver. Study personnel at the clinic administered the questionnaire from February to March 2017.

Descriptive statistics were used to characterize independent and dependent variables. The primary outcome, willingness to receive cell phone text messages, was assessed for relationships to each categorical response. Fisher exact and Student *t* tests were used to determine factors associated with willingness to receive cell phone text messages. *P*-values less than .05 were considered significant.

2.2. Effectiveness of a text message intervention on ART adherence

From January to September 2017, a randomized trial was conducted to evaluate the effectiveness of text message

interventions on ART adherence. Prior to participant recruitment, a chart review was conducted to screen the patient population for eligibility and to determine potential sample size. The following inclusion criteria were used to identify eligibility: documentation of HIV positive status, age zero to 24 years old, at least 6 months on ART, and possession of a cell phone capable of receiving SMS messages. A total of 298 patients belonged to the clinic at the time of the chart review of which 186 met inclusion criteria.

We calculated the sample size based on the comparison of 2 independent proportions. We assumed that 80% of the patients in the control group versus 98% in the test group would experience an improvement in adherence, with an expected response rate of 60%. A sample size of 146 (assuming equal group sizes of 73) would achieve a power of 80% and a level of significance of 5%.[14,17,18] (R, R Development Core Team, 2013). Patients identified in the chart review were pre-allocated to the intervention or control arm using computerized block random assignment (block size of 6 stratified by sex, age text message recipient (participant/guardian).[18]

Participants were recruited during routine appointments beginning in January 2017 until March 2017 on a rolling basis until the target sample size was met. Patients were taken through screening and were recruited for study participation if accompanied by a consenting parent-guardian, literate in Spanish (able to read and write), and if they possessed a telephone capable of receiving SMS text messages. Patients were excluded if they were currently experiencing virologic failure (over 400 copies/mL). Although patients experiencing virologic failure are often targeted for SMS adherence interventions, we opted to exclude this group because they are often assigned to intensive clinical follow up, resulting in additional patient-focused care which may have introduced bias in adherence outcomes. Patients were also excluded if they lived in orphanages because they were presumed to receive care and medications based on well-established schedules aimed at treating larger groups of children infected with HIV.

Upon enrollment, allocation records were reviewed, and patients were assigned to either the control or intervention arm. Participants in the control group received standard care with regular clinic visits and adherence measures (see below). The intervention group received standard care plus SMS reminders. Phone numbers of participants in the intervention arm were added to a contact list, and an SMS was sent to them 3 times per week (Monday, Wednesday and Friday) for 6 months. Frontline SMS[18] was used to send SMS messages to the entire intervention group at the same time of the day.[19] Messages were designed to improve each of the areas measured in the adherence questionnaire: taking medications consistently, taking medications at the same time every day, following instructions on how to take medications (i.e. with/without food). If the enrolled intervention-patients were between 6 and 12 years old, the message and the questionnaire was directed to the caregiver. For enrolled intervention -patients from 13 to 17 years old, text messages were sent to either the caregiver or the patient, according to participant preference. Patients between 18 and 24 years old were sent text messages directly. The cost of each text message was documented and the pharmacists time associated to the intervention program was documented.

The outcome variable, a continuous numerical adherence score, was measured 3 times during the study period using a 4-day Recall Questionnaire[20,21] developed for adherence measurement in patients with chronic diseases. The questionnaire aimed to evaluate adherence with daily ART administration, how often patients followed dosing schedule (taken at the same time every day), and how often medication-related instructions were followed. The questionnaire was administered upon enrollment, 3 months, and at six months after study initiation in both the intervention and control arms. Adherence ratios were calculated for each of the 4-day recalls as: [1 – number of doses missed/number of doses prescribed]. Likert scales were used to score how often patients followed dosing schedule (0 = never, 4 = always); how often medication instructions were followed (0 = never, 4 = always); and last skipped dose (0 = never, 5 = within past 2 days). Adherence ratios were calculated taking into account 4-day recall adherence, self-reported adherence to dose schedule, and skipped doses. Each response was weighted for recall bias, thus calculating overall adherence. Interpretation of adherence scores were as follows: "non-adherent" if lower than 95%, "adequately adherent" if between 95% and 98%, and "highly adherent" 99% or above based on guidelines from 2016.[21] The equation used to calculate adherence, can be found in the supplemental file, http://links.lww.com/MD/F742 and is based on findings from previous studies, equation S1, http://links.lww.com/MD/F741.[20] Student *t*-test was used to determine any differences in the average adherence value (continuous numeric variable) between the intervention and control group at each time point (baseline, 3 months, 6 months). P-values less than 0.05 were considered significant. A dichotomous measure of "improved adherence" was constructed by categorizing any patient who was "adequately adherent" at 1 month, and moved to the "highly adherent" category at the 6 month point. Odds ratios were calculated to determine the odds of improving adherence by comparing the "improved adherence" dichotomous variable between the intervention versus control group. Participants with missing data were omitted from the final analysis.

This study and all study documents including consent forms were approved by the Human Research Protection Program Institutional Review Board (IRB) at UCSF (approval # 16-21197, ref 181473), and at the Roosevelt Hospital Independent Ethics committee in Guatemala (CODEIHR No. 07 02032017).

3. Results

3.1. Willingness to receive SMS adherence reminders

Fifty-seven patients were approached for recruitment in the cross-sectional survey, of which 53 met inclusion criteria and consented. Participants were evenly distributed between the age ranges of 6 to 12 years old (49.1%), and 13 to 24 years old (50.9%). The majority of participants were able to read (77.4%) and write (75.5%). Many participants already used alarms reminders for medication adherence (47.2%). Most respondents were able to send and receive SMS (86.8%) but half reported infrequent use of text messaging (50.9%). Most participants reported a willingness to receive text message adherence reminders (81.1%). Significant associations between individual characteristics and willingness to receive adherence reminder texts were found, specifically for literacy (ability to read and write independently at the highest level), travel time less than 3 hours to the clinic, owning their own cell phone, reliable cell phone service/signal, possessing a cellphone with a fully charged battery, ability to receive texts, prior use of cell phone alarms, and privacy/autonomy of cell phone text messages (all $P < .05$, Table 1).

Table 1

Participant characteristics and percentage willing to receive text messages.

Respondent Characteristics	Willingness to receive text message	
	No n=10	Yes n=43
Sociodemographic factors		
Participant literacy (reading)*		
Unable	30%	10%
A little	30%	2%
More or less	0	2%
Yes	40%	86%
Participant literacy (writing)*		
Unable	30%	9%
A little	30%	5%
More or less	0	2%
Yes	40%	84%
Travel time to clinic*		
Mean≤3.00 h	0	100%
Mean≥5.85 h	100%	0
Environmental factors		
Cell phone owner*		
No	40%	0
Yes	60%	100%
Cellphone signal reaches place of living*		
Never	10%	0
Sometimes	30%	12%
Usually	10%	16%
Always	10%	72%
No response	40%	0
How often is cell phone batter fully charged*		
Never	40%	0
Sometimes	40%	0
Usually	0	2%
Always	20%	98%
Cell phone patterns of use		
Participant is capable of sending or receiving text messages*		
No	30%	0
Yes	30%	100%
No response	40%	0
How often participant uses alarms as an adherence reminder*		
Usually	20%	81%
Sometimes	20%	9%
Rarely	0%	5%
Never	20%	5%
Probability of others reading participant's text messages*		
Extremely	10%	5%
Very	0	7%
Moderately	0	5%
Slightly	0	7%
Not at All	30%	77%
NA	20%	0%

* $P < .05$ significant.

3.2. Randomized Trial: Effectiveness of SMS Text Messaging

Of 144 patients approached, 143 agreed to participate in the text message intervention trial. Seventy-one participants (50.3%) were assigned to the control group, and 72 participants to the intervention group (49.7%). There were no statistical differences in age or sex between intervention and control groups. One hundred participants completed the 6-month study (69.9%) divided evenly between the control and intervention groups. Participants who dropped out were excluded from final analysis. Low retention rates were due to several factors including: missing appointments or arriving late to the clinic (n=22), transfer to another clinic (n=17), or change of phone number (n=4).

A total of 72 unique SMS text messages in 3 categories were successfully sent over the study period (Table 2). The supplemental files 2 and 3, http://links.lww.com/MD/F743 include the text messages and with a date stamp in Spanish and English. From study initiation to the final adherence measure, the text message intervention group demonstrated improved adherence by 4% ($P < .01$). The control group experienced a non-significant adherence improvement of 0.85 percentage points

Table 2

General theme and quantity SMS messages sent to participants*.

Type of SMS Message	SMS Sent to each participant
Taking medications consistently	32
Taking medications at the same time every day	19
Following instructions on how to take medications	21

SMS = short message service.
* See supplemental files 2 and 3, http://links.lww.com/MD/F743 for specific content.

($P = .64$). This result was consistent when adherence results were stratified by age group. In the intervention group, 6 to 12 yo baseline adherence compared to 6-month adherence improved by 3.4% ($p < 0.01$), 13 to 18 yo by 6% ($P < .01$), and in participants older than 18 yo by 6% ($P < .05$). Control groups across these age ranges had non-significant changes in adherence from baseline to 6 months, ranging from -2% to 1% and were non-significant (Table 3).

When results were pooled, the intervention group had a 4 fold higher odds of improved adherence from baseline to 6 months ($P < .05$, CI 1.47; 11.56). Upon stratification of age groups, 6 to 12 yo demonstrated 2-fold higher odds of improving adherence during the study period ($P = .25$, CI 0.60; 7.0) while 13–18 yo 10-fold higher odds of improving adherence ($P = .05$, CI 1.02 to 102.76). Odds ratios were null for participants greater than 18 yo; intervention patients in this category (n = 2) all demonstrated improvement (1) and there were no control patients(n = 3) that demonstrated improvement (0).

3.3. Cost of text message intervention

The study intervention required 1 pharmacist working part time during 6 months in order to set up, carry out and measure the impact. Text messages cost $3.12 USD per cellphone number to send.

4. Discussion

In our study, the majority of participants were willing to receive text message reminders. Additionally, patients who received text message reminders demonstrated an improvement in adherence compared to the control group, a finding that has been reported in a similar study carried out in youth and young adults and suggest the feasibility and potential effectiveness of SMS interventions in this HIV infected population.[11] The simplicity of our intervention distinguishes it from more complex designs. One Argentinean study (n = 25) intervened in pediatric patient adherence using a cell phone app in combination with social messaging including WhatsApp and Facebook yielding 70% improvement in patient viral loads. This study was associated with high costs and logistical issues limiting the overall generalizability of findings.[22] Interventions accompanied by incentives and positive reinforcement in Ugandan Youth Living with HIV have been shown to encourage patient motivation and adherence between clinic visits yet drive up the complexity and cost of SMS platforms rendering these programs inaccessible or impractical for many clinics to implement.[23] Similar additional studies conclude that effective SMS interventions would likely increase efficiency of ART programs by improving HIV treatment outcomes at relatively low costs while improving patient communication with health care workers.[24] In our Guatemalan clinic, initial costs to set up the intervention may be justifiable given potential long-term sustainability if the effectiveness of text messages can be improved. Identifying the optimal population and refining text intervention accordingly may help to achieve this outcome. Our intervention represents a modest, reasonably effective approach to supporting adherence in a large pediatric patient population.

We found that patients, older than twelve years, had the most notable improvement in adherence as a result of the SMS messaging intervention. There may be several reasons for a potentially larger effect in adolescents. First, some patients in this age group were actively directly in the study, receiving text messages directly, which may have impacted their adherence behavior more effectively. One study in the US reported similar findings in adolescents where the use of personalized messages improved 4-day recall over a period of 6 months.[25] In other studies involving adolescents, SMS reminders improved retention in early HIV care but not adherence[26,27] offering alternative benefits of SMS communication in this technologically savvy patient demographic. In some countries, children under 15 yo use the internet as frequently as adults over 25 yo. Further, youngsters from 15 yo to 24 yo are demonstrably the most "connected" age group in the world.[28] Thus, SMS interventions have the potential to effectively reach adolescents LHIV in low to middle income countries to improve outcomes in HIV. We provide evidence supporting the use of SMS to improve adherence, but larger trials must be carried out to confirm these findings.

We encountered challenges in retaining contact with participants and found that several patients owned 2 or more cellphone SIM cards. Changing cell phone numbers, or possession of more than 1 number (SIM card) have been reported in other text message intervention studies in this age group and lead to underrepresentation in text message intervention outcomes.[22,29] In addition to multiple phone numbers, multiple users of a single cell phone threaten patient privacy.[16] Both cellphone ownership and the extent of text message privacy were significantly related to willingness to receive text message reminders in our study.

Table 3

Adherence results.

	Control			Intervention		
Age group (yr)	n	% Change in mean adherence*	*P* value	n	% Change in mean adherence*	*P* value
6–12	37	1.8	.23	33	3.4	.01†
13–18	10	−2.2	.18	15	5.5	<.00†
>18	3	−1.0	.38	2	5.5	.04

† Statistically significant, $P < .05$.
Statistically significant improvement in mean adherence found in intervention group when comparing adherence at study initiation to adherence at 6-month follow-up.
* Percentage change from baseline to 6 months per 4-day recall adherence measure.

These are characteristics that merit in-depth exploration before initiating programs using text message adherence reminders, yet they are uncommonly assessed in SMS intervention trials and.[30] Further, text message intervention trials should ensure the clinic's ability to follow the constant flux in cell phone possession to achieve clinical impact and sustainability.

In our randomized trial, SMS messaging improved ART adherence yet there were some limitations. First, the dropout rate prevented the study from achieving adequate power to determine the pre-specified differences between groups. As experienced in many clinics, patients often have difficulty adhering not only to their medication, but also to clinic appointments, resulting in a missed opportunity for assessment. Also, we observed an improvement in adherence in both groups after 3 months of the intervention which may be due to the Hawthorne effect or to other demographic variables that were not collected in this study (ethnicity, socio-economic status, travel time to clinic). Our intervention was a 1-way text messaging intervention, but given patient challenges attending clinic, a 2-way text messaging intervention may have been favorable in order to keep the patient in closer contact with their care providers. Additionally, patients with high viral load (VL) were not included in this study due to inherent bias of receiving more personalized clinical care and may be a population that would benefit most from this type of intervention. And finally, due under funding in the HIV ministry of health clinics in Guatemala, the adherence measurement relied on self-report instead of viral load counts, which is a more reliable endpoint for adherence interventions. Future studies should consider including VL counts as local funding and clinic infrastructure permits.

Text message interventions hold promise to support antiretroviral adherence in pediatric patients living with HIV. Studies designed to assess the impact of text messaging interventions must examine local context for cellular phone infrastructure as well as use and must account for potential loss to follow up when patients miss appointments and study assessments. Additionally, socio-demographic factors, environmental factors and factors related to patterns of cellphone can be assessed to identify groups of patients where willingness to receive text messaging would support potential costs of implementing an intervention.

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