The Use of Cell Phone Reminder Calls for Assisting HIV-Infected Adolescents and Young Adults to Adhere to Highly Active Antiretroviral Therapy: A Pilot Study

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ABSTRACT

Long-term medication regimen adherence is challenging in all populations, but in the HIV-infected adolescent population the frequency of poverty, homelessness, substance abuse, and mental illness make highly active antiretroviral therapy (HAART) adherence even more challenging. In 2003, we developed a pilot program for HIV-infected adolescents and young adults between the ages of 16 and 24 who were either going to begin a HAART regimen for the first time or begin a new HAART regimen. Participants received a free cell phone with a local service plan for approximately 6 months. Participants received phone call reminders for 12 weeks. Call frequency was tapered at 4-week intervals. Patients were assessed at 4-week intervals to determine the perceived intrusiveness or helpfulness of receiving calls, and missed medication doses. Eight consecutive patients were recruited for the study, and five were able to complete it through the 24 weeks. Most participants found the calls to be helpful and the level of intrusion into their daily lives acceptable. Using cell phone reminders to assist patients does not require an extensive amount of daily staff time. Tapering calls rapidly over 3 months, followed by discontinuation of calls provided inadequate support for subjects, especially those with significant psychosocial issues such as substance abuse. Use of cell phone reminders to assist adolescents adhere with HIV medications was practical and acceptable to pilot study participants. Viral suppression waned for all but two patients after termination of cell phone reminders and suggests that a 12-week intervention was not adequate for most subjects. Larger prospective studies of cell phone observation of therapy will be needed to determine if this intervention can improve long-term adherence and health outcomes.

INTRODUCTION

THE INTRODUCTION OF highly active antiretroviral therapy (HAART) has extended the life span of HIV-positive patients and has brought about many changes in how these people view their disease. However, it has been demonstrated that patients on HAART must take at least 95% of their medication doses consistently to lower their viral load count to less than 50 and to avoid developing drug resistance,\textsuperscript{1-3} causing medication regimen adherence to be extremely difficult. Adherence to medication has been defined as having in place
“the necessary conditions to achieve therapeutic success.”\textsuperscript{1} These conditions for success have been grouped into four categories: regimen characteristics, patient specific factors, provider–patient relationship, and overall health care systems.\textsuperscript{2} Common barriers to HAART adherence have been described as complex dosing, debilitating side effects, depression, unstable housing, and limited social support.\textsuperscript{3} With the development and increased use of twice-daily, or once-daily dosing for HAART therapy, the barrier of complex dosing schedules has been reduced. Long-term medication regimen adherence is challenging in all populations, but in the HIV infected adolescent population developmental factors (i.e., invulnerability, experimentation, etc.) coupled with the frequency of poverty, lack of social support, homelessness, substance abuse and mental illness,\textsuperscript{4} make HAART adherence even more difficult for HIV-infected youth. In a study of adherence factors conducted by Murphy et al.,\textsuperscript{5} the most commonly cited reason for nonadherence in HIV infected adolescents was “simply forgetting.” Factor analysis indicated that medication related side effects and complications in day-to-day routines were most relevant.\textsuperscript{5} The study concluded that adherence was tied closely with daily routines. Long-term follow-up in HIV-infected adolescents who reached undetectable viral loads found that by 1 year, 50% had virologic failure.\textsuperscript{6}

There have been very few studies evaluating interventions to improve adherence to HAART. A review of adherence interventions by Cote et al.\textsuperscript{7} found very few interventions and only three major trials that reported significant adherence improvement in both adults and adolescents. The review by Cote and Godin\textsuperscript{7} concludes that adherence interventions are in their infancy, and that more innovative interventions need to be developed to achieve greater adherence from patients on the HAART regimen.

A review of randomly controlled trials attempting to enhance antiretroviral adherence published by Simoni et al.\textsuperscript{8} found a small number but a wide variety of intervention attempts that had a range of success rates. The authors conclude that future adherence interventions should combine strategies, focusing on patient characteristics, patient–provider relationships, variables related to the illness and treatment, and contextual factors. They also suggest that different patient populations will most likely respond to different types of interventions, such as individualized counseling, reminder aids, and cue-dosing.\textsuperscript{8}

Recently, researchers have explored the use of directly observed therapy (DOT) to improve adherence to HIV medication regimens. Historically, DOT has been an extremely effective approach to the management of patients with tuberculosis\textsuperscript{9} and based on this success, similar approaches to the treatment of patients with HIV on the HAART regimen have been studied. A small number of pilot studies using modified directly observed therapy (MDOT) for treatment of HIV have shown possibility for increasing adherence to HIV medication regimens.\textsuperscript{10} These pilot studies involve the direct observation of patients taking one dose of a multiple daily dose regimen for HIV treatment.\textsuperscript{9} In an article discussing the possible benefits and burdens of directly observed antiretroviral therapy (DAART), Lucas et al.\textsuperscript{11} points out that providing DOT for patients with HIV has some major differences from providing DOT to those patients being treated for tuberculosis. The three major differences between these two treatment groups are (1) patients with HIV are facing a lifelong treatment schedule, (2) dosing requirements are still daily for those with HIV, and (3) HIV has a short generation time with error-prone replication and rapid emergence of resistance. However, the paper also holds hope for DAART, with the emergence of daily dosing and utilizing DAART as one component in a comprehensive treatment approach.

The following study, while not specifically utilizing DOT, encompasses several of the elements of DOT that we postulate are contributing to its success, and contribute to the success of adherence in general, including the establishment of good patient–provider relationships and the establishment of lifestyle routines related to medication self-administration. Adolescents with other chronic diseases, such as diabetes, are often enrolled in classes to improve their organizational skills, as well as to help develop and solidify daily schedules around
medication administration.\textsuperscript{5} By using a modern form of communication (i.e., cell phones), we hoped to put into place some of the necessary conditions required for medication adherence by helping to develop and solidify daily routines with the use of cell phone reminder calls. This pilot study represents the first steps in the development of a clinical trial evaluating the use of cell phone reminders to improve HAART adherence in HIV-infected adolescents by evaluating the practicality and acceptability of a telephone call reminder intervention utilizing cell phones.

**METHODS**

In 2003, eight consecutive patients, between the ages of 16 and 24, known to this facility and team were recruited for this pilot study targeting HIV-positive youth. At the time of recruitment, participants were either going to begin HAART for the first time or were going to start a new HAART regimen for HIV treatment. This pilot study received approval by our institution’s Review Board. Parental consent was waived and written patient consent was obtained before any research activities were performed. Participants were given a preparticipation assessment to determine their experience with HAART adherence and to obtain demographic information (Table 1). HAART regimens that were used in the study, allowed for a once per day or twice per day dosing schedule included either efavirenz, didanosine, lamivudine alone, or an alternative combination of tenofovir, lamivudine, atazanovir, and ritonavir. Study participants received a free cell phone with 250 free local anytime minutes and free nights and weekend calls. Participants received $10 for completing each questionnaire. Participants received phone calls from an adolescent medicine research team for 12 weeks. For the first 4 weeks, calls occurred on a daily basis. During weeks 5 through 8, calls were only made Monday through Friday. Weeks 9 through 12 calls occurred on Sunday, Tuesday, and Thursday. Subjects were allowed to choose their call times, within the limits of medication requirements. On each of the determine call days, patients were contacted for each medication dose (once or twice per day). For the first 12 weeks while patients were receiving calls, patients were assessed at 4-week intervals to determine the perceived intrusiveness or helpfulness of receiving calls, and missed medication doses (Table 2). They were assessed again with the same queries at the end of the study (24 weeks), 12 weeks after calls were terminated. Laboratory tests drawn at the same intervals included: complete blood cell count, copies of HIV RNA determined by polymerase chain reaction (PCR; viral load), CD4 cells, aspartate amino transferase, and amino alanine transferase. Participants had outgoing calls discontinued for the remainder of the month if they went over their monthly allotment of cell phone minutes. Participants were terminated from the cell phone reminder and 4-week surveys if they missed 3 calls. Survey data at week 24 and laboratory data at all study visits was obtained for all subjects.

**RESULTS**

The subjects in this pilot study ranged in age from 16 to 24 years; 7 were male and 1 was fe-

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\begin{tabular}{llllllllllll}
\hline
Gender & Age & Ethnicity & Age infected & Mode of transmission & Prior HAART & Dosing & Substance abuse \\
\hline
A & Female & 24 & Latino & 24 & FSM & None & QD & Yes \\
B & Male & 20 & Caucasian & 17 & MSM & None & BID & Yes \\
C & Male & 21 & AA & Neonatal & Blood transfusion & Yes & QD & No \\
D & Male & 21 & AA & 19 & MSM & Yes & QD & Yes \\
E & Male & 20 & Latino & Birth & Maternal transmission & Yes & BID & No \\
F & Male & 23 & Latino & 18 & IVDU & Yes & QD & Yes \\
G & Male & 20 & Latino & 20 & MSM & None & QD & No \\
H & Male & 16 & Mixed & Birth & Maternal transmission & Yes & BID & No \\
\hline
\end{tabular}
\caption{Demographics of Participants}
\end{table}

FSM, female having sex with a male; MSM, male having sex with male; IVDU, injection; QD, once per day dosing schedule; BID, twice per day dosing schedule.
male. Of the subjects, 2 were infected at birth, 1 as a neonate from a transfusion, 1 from injection drug use, 3 from a male to male sexual contact, and 1 from heterosexual contact. Three of the subjects were naive to HAART and 5 were not. The demographics including age, sex, and gender are described in Table 1. Four of the patients struggled with substance abuse throughout the study. Five of the 8 patients recruited for this pilot study completed the 12 weeks of cell phone reminders. Three subjects, (B, C, and F) were unable to complete the study and were dropped as a result of missing three calls each. Study subject B developed neurosyphilis, was hospitalized, and while in the hospital, experienced methamphetamine drug withdrawal. This led him to leave the hospital against medical advice, relapse, and subsequently miss the reminder calls. Subject C missed more than 5 calls in the first month and was terminated from the study. Subject F was hospitalized because of drug fever and was discontinued from medications, relapsed onto drugs, lost cell phone.

Table 2 details the data regarding missed phone calls, missed medication doses (reported), and viral load of the subjects. Of the subjects who were dropped from the study, most missed calls were a result of unexpected hospitalizations or incarceration. In the first 4 weeks of the study when calls were daily, very few phone calls or medications were reported missed by any of the subjects. In the second 4 weeks of the study, when the calls were tapered to weekdays only, few calls were missed and few medication doses were missed. Overall, the subjects that did not experience institutionalization, or major chaotic life changes did very well receiving phone calls, and also did well with adherence to medication doses. Significant decrease in viral load tracked positively with adherence to call reminders, with the exception of subject D, who admitted later in the study that he was not taking any medication, despite answering all of the phone calls.

While initially the telephone call reminders were generally reported to be “annoying, but

| Table 2. Missed Telephone Calls, Missed Medication Doses and Viral Load |
|--------------------------|-------------------|---------------|----------------|---------------|---------------|
|                          | A                | B             | C              | D             | E             |
| Missed calls             |                  |               |                |               |               |
| Post 4 weeks             | 0                | 0             | 3<sub>d</sub>  | 1             | 1             |
| Post 8 weeks             | 0                | 2             | 2              | 1             | 1<sub>e</sub> |
| Post 12 weeks            | 3<sup>a</sup>    | <sup>c</sup>  | 3              | 1             | 2             |
| Missed medication        |                  |               |                |               |               |
| Post 4 weeks             | 0                | 0             | 1              | 0             | 0             |
| Post 8 weeks             | 0                | 2             | 1              | 0             | 1             |
| Post 12 weeks            | 14               | 1             | 3              | 1             | 1             |
| Viral load               |                  |               |                |               |               |
| Baseline                 | 25,000           | 8901          | 5915           | >100,000      | 342,536       |
| Post 4 weeks             | 137              | 60            | 12,890         | 70,787        | 8054          |
| Post 8 weeks             | 153              | 175           | 15,569         | 68,662        | 429           |
| Post 12 weeks            | <50              | 1338          | <50            | >100,000      | 50            |
| 24 weeks                 | 14,000           | 14,000        | <50            | 100,000<sub>b</sub> | 242         |

<sup>a</sup>Subject A was incarcerated, telephone confiscated while in jail, and was not able to complete last 2 weeks of study.
<sup>b</sup>Subject D admitted after the study concluded that he was not taking any HAART medications.
<sup>c</sup>Subject B was hospitalized for neurosyphilis; after discharge, he lost the telephone recharger and was unable to receive calls and was terminated from the study at the beginning of the third phase.
<sup>d</sup>Subject C missed more than 5 calls in the first month and was terminated from the study.
<sup>e</sup>Subject F was hospitalized because of drug fever and was discontinued from medications, relapsed onto drugs, lost cell phone.
by the 12-week follow-up, subjects reported the calls being “less annoying,” and still helpful. Some felt it was invasive to get calls in the middle of the evening, and would have preferred receiving calls at other times. Others became very attached to the calls, looking forward to them and using the calls to ask various kinds of questions such as, “When is my next appointment?,” “Do I need a psychiatry appointment?,” “I can’t sleep what can I do?,” and “My partner is having a problem what should I do?” No patient reported that the calls were too long. Only one patient reported throughout the study that he would have preferred not to receive future calls.

The time required by the provider to make the cell phone reminder calls was very minimal, diminishing throughout the study period. The average time for each call in the first 4, 8, and 12 weeks of the study was 2.4, 1.8, and 1.3 minutes, respectively. On a weekly average, it only took approximately 20 minutes to check cell phone utilization to ensure subjects had not exceeded their 250 allotted anytime minutes. However, it took about another hour and a half per week to contact participants to inform them about going over their allocated minutes and explain repeatedly why the outgoing calls needed to be suspended. Seven of the eight subjects went over their allotted minutes at least 1 month of the study. Four subjects went over the allotted minutes every month, two subjects went over allotted minutes in 2 months, and one went over for 1 month.

**DISCUSSION**

This study examined the feasibility and logistical challenges of providing cell phone reminder calls to patients receiving HAART for HIV treatment in order to increase adherence to medication regimens. Most subjects found the phone calls helpful with the level of intrusion into their lives acceptable. The cost of the phones each month was $50 per subject, which includes the cost of overage fees (0.35 cents per minute) and 411 calls. Although a shared minutes plan may be more cost effective, overage of minutes is still a distinct possibility. Utilizing plans with unlimited minutes, adding family lines for only a few extra dollars, and not allowing extra features may be a few effective strategies to keep costs down when designing a larger scale intervention using cell phones.

Using cell phone reminders to assist patients with adhering to HAART did not require an extensive amount of staff time. The time required for the actual phone calls to the subjects was not overwhelming, but checking the usage of minutes, informing subjects they were over their minutes and canceling outgoing calls on the phones was time consuming. Having cell phone plans with limited minutes increased staff time needed to facilitate the study and created a potential adversarial relationship with participants.

There are a few limitations of this pilot study that need to be discussed. The first is that cell phone reminders do not address every barrier to medication adherence. Social Action Theory provides a model for understanding health behaviors. The three broad factors that determine health behavior (e.g., medication adherence) include individual self-regulatory processes (e.g., attitudes, developmental stage, personality type), internal affective states (e.g., mental health disorders such as depression, substance abuse disorder) and environmental/external factors (e.g., medication factors, housing status, social support). Cell phone reminders can assist youth who have internal self-regulatory systems that may direct them to focus on things other than medication (may account for issues such as forgetting medication, leaving home without medication, impulsive lifestyles, etc.). They may also help those with disruptive external factors such as patients with housing difficulties, frequent medication dosing, poor social support, etc. Major chaotic events were deterrents to success in the study, and may reflect deterrents to adherence for any patients being treated for any chronic illness. Cell phone reminders do not deal directly with mental health issues such as depression (demonstrated to be associated with nonadherence) or substance abuse. Future studies should explore whether access to cell phones provides health care team members easier contact with patients and whether that might increase utilization of services for these internal affective states.
A second limitation inherent to any pilot study is the small sample size. The generalizations that we make for this study might not be relevant in all populations of youth. Our study had one Hispanic female and we know that African American females make up a large portion of the HIV-infected youth population. It is possible that this group may not have the same acceptance to cell phone reminders. Social response bias may also have affected our survey data evaluating the acceptability of calls although the rates of answering call reminders argues against this.

The main feature of this study design that caused problems was the rigidity within the protocol concerning study termination criteria. Tapering calls rapidly over 3 months regardless of patient’s adherence or life events provided inadequate support to maintain adherence at 24 weeks. This is evidenced by only two of the eight subjects having undetectable viral loads at 24 weeks. In addition, terminating reminder calls after three missed calls did not allow the flexibility necessary for youth whose personal issues that impacted adherence waxed and waned throughout the study period. Three of the subjects that lost adherence and viral suppression struggled with substance abuse and became nonadherent with the cell phone calls after major life events (two hospitalizations and one with incarceration). These patients might have become adherent again if the protocol did not drop them from the study after missing three calls. Research with adults has demonstrated that changes over time based on fluctuating ambivalence, changing beliefs and attitudes and major life events affects adherence. Clearly, these fluctuations also occur in the adolescent population. Future interventions will require more flexibility to match the fluctuating needs of youth with HIV.

Most of the study subjects, and most of our patients with HIV, live in chaotic environments, making it difficult to impose firm rules about participation without giving them more than one chance to miss calls. In future studies, it might be more helpful if termination criteria were more flexible and had allowances for missed calls, missed appointments, and a lack of a virologic control. Frequency and duration of calls could either be tapered or increased depending on acceptable levels of viral load and adherence. Temporary phone service restrictions for missing call reminders could be incorporated on a monthly basis. With the beginning of a new month, removing the restrictions would most likely facilitate long-term adherence and would allow for an opportunity for positive reinforcement. The review by Cote and Godin suggests that short-term interventions may or may not be effective, generally resulting in transient or “a tendency” toward improvement in adherence to HAART. In a future cell phone study, perhaps a longer intervention period would result in increased effectiveness of the intervention, and offer a greater opportunity to tailor cell phone calls to each patient’s needs. Eventually, cell phone reminders could be incorporated into multifaceted adherence interventions. Recent adherence reviews have suggested that this approach may be required for long-term adherence to HAART.

Larger and longer prospective studies of cell phone utility will be needed to further determine patient’s acceptance of phone calls, efficacy of the phone calls and strategies for tapering phone calls.

REFERENCES


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