

## Real-Time Electronic Drug Monitoring for HIV-Positive Adolescents: Promising Acceptability and Feasibility in China

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### Abstract

**Objective:** Little research to date has focused on measuring adherence among and tailoring adherence interventions to HIV-positive youth. To explore the potential of emerging mHealth technologies as adherence tools for youth, we assessed the acceptability and feasibility of a real-time web-linked electronic drug monitoring (EDM) device to support antiretroviral (ART) adherence among HIV-positive adolescents in China.

**Methods:** Twenty patients ages 10-15 years who were on ART at the Guangxi Center for Disease Control ART clinic in Nanning, China used a wireless EDM device for medication for one month. We monitored adherence in real time, and explored the device's acceptability among patients using a mixed-methods approach.

**Results:** Using EDM data, median adherence was 93.9% (IQR 10.2) of prescribed doses taken and 90.2% (IQR 13.3) using the on-time measure. Only 20% (4/20) of patients met the strictest generally-accepted criterion for optimal adherence ( $\geq 95\%$  using on-time measure) over the observation period. Self-reported median adherence for the month was 100% proportion taken. Although they expressed concerns about inconvenience and the device's size and appearance in open-ended questions, all adolescent participants reported a positive overall experience with the device in closed-ended questions.

**Conclusion:** Wireless EDM technology represents an acceptable and rigorous method of measuring ART adherence, and a potentially useful adherence support, for HIV-positive adolescents at a critical time in their lives, as well as for adolescents who take medications for other chronic health conditions. Future studies should focus on identifying ways of strengthening caregiver-adolescent relationships and developing tailored, age-appropriate intervention packages to support adherence.

**Keywords:** Adolescent; Wireless technology; Antiretroviral therapy; Adherence; China; HIV/AIDS

### Introduction

The benefits of antiretroviral therapy (ART) have been well documented [1-5], but achieving and sustaining high adherence to ART remain vital to treatment success in children and adults [6-8]. Systematic reviews of adherence in children and adolescents in low and middle income countries have found generally suboptimal adherence levels [9,10]. In China, where more than 3500 children and adolescents are currently on ART, early reports on the country's pediatric ART treatment rollout are encouraging [8,11]. Still, concerns are rising regarding adherence in the adolescent age group [12].

Given the complexity and interrelatedness of individual, caregiver, clinical, and societal and cultural influences at play [13], sustaining high adherence to ART in adolescents presents unique challenges. As older children begin to assume responsibility for their own medication, the wide array of emotional and physical changes of adolescence, juxtaposed against powerful social and cultural factors, may present obstacles to a child's ability to adhere to treatment regimens, although they may also offer potential opportunities for adherence support. How best to monitor and support adherence among adolescents represents a critical area for research.

Measuring adherence objectively is a particular challenge in adolescents due to the complex transition of health-care responsibilities, including medication administration, from caregivers to children as children age. Adherence measures have primarily taken the form of self-report or other proxy indicators such as pill count and pharmacy refill

[9,14-17], typically shown to be poor measures of actual adherence in adults [18-20]. We identified four studies that have used electronic drug monitoring (EDM), considered a more objective adherence measure, in pediatric patients [21-24]; in only one did adolescents themselves use an EDM device [24].

Evidence-based interventions to support adolescent ART adherence are also sparse [25,26]. Recently, technology-based interventions have been tested in small samples of HIV-positive adolescents in the U.S. with promising initial findings, including cell phone reminders [14-16] and a web-based training program [17]. However, each study used self-reported rather than objectively measured adherence. Two small pilot studies [27,28] investigated the feasibility of motivational interviewing to support adherence, one in combination with financial incentives [28]. Although these initial forays are encouraging, more studies of interventions using rigorous adherence measures are urgently needed [25,29].

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Based on recent success using a wireless adherence device and EDM-feedback among adults in China [30-32] and given the need for adherence interventions for youth on ART, we conducted a study among HIV-positive Chinese adolescents to measure feasibility and acceptability of wireless EDM monitoring and feedback in this patient group.

## Materials and Methods

### Study site and population

The study was led by Boston University's Center for Global Health and Development, with enrollment at the Guangxi Center for Disease Control and Prevention ART clinic in Nanning, China, which in 2014 was treating 370 children. With assistance from clinicians, we recruited twenty adolescent ART patients aged 10 to 15 years. Patients were on three-drug NRTI-based regimens, taken twice daily. All patients and caregivers recommended by clinicians agreed to participate.

### Socio-demographic and wireless EDM experience data

Baseline and follow-up questionnaires were administered in Mandarin Chinese by trained interviewers. The caregiver completed the baseline questionnaire, which included questions on his/her demographics and the adolescent patient's age, gender, and school level. The follow-up instrument directed to the adolescent included closed- and open-ended questions covering acceptability and usability of the EDM device, in addition to self-reported adherence.

### Wisepill medication dispenser and adherence monitoring device

The wireless EDM device has been described in detail elsewhere [30,32,33]. The device creates a date and time stamp each time it is opened and transfers this information to a central server via general packet radio service (GPRS). Data are then available to authorized personnel via a secure, internet-based interface. Patients were instructed to keep one of their three ART medications in the device.

### Adherence data and measures

We monitored participants' use of the device for one month, without providing them with adherence information generated by the device. Data on device openings were transmitted continuously. Investigators calculated mean adherence for the month using two measures: proportion taken and proportion taken on-time according to the formula: (# doses taken +/- one hour of dose time)/(# prescribed doses). We also calculated self-reported proportion taken from the visual analog scale (VAS) from the follow-up questionnaire, and compared this with the EDM-generated data.

### Clinical data

Participants' most recent (past six weeks) CD4 and viral load test results were collected from medical charts.

### Data analysis

For quantitative data, we calculated descriptive statistics (medians and interquartile ranges (IQR) for continuous variables, frequencies and percents for categorical variables) using SAS 9.4 (The SAS Institute, Cary, NC). Qualitative data from open-ended questions were analyzed using a thematic approach.

The study was approved by the Institutional Review Boards at Boston University Medical Center, the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and

Prevention in Beijing, and the Guangxi Provincial Center for Disease Control in Nanning. Caregivers of adolescent participants provided written informed consent prior to enrollment; adolescents provided written informed assent.

## Results

### Participants

Table 1 provides a profile of the adolescent participants and their caregivers. Among adolescents, the median age was 12.5 years (IQR 3.0 years), and the majority (13/20, 65%) were male. The median duration of ART treatment was 2.8 years (IQR 6.1 years), and adolescents had a median CD4-cell count of 669 cells/ $\mu$ l (IQR 367 cells/ $\mu$ l). All had undetectable viral load (UDVL, <50 copies/ml). One participant dropped out before the follow-up visit because his/her caregiver was too busy. This participant's baseline information and EDM adherence data are included in results since he/she used the device for 28 days.

Among caregivers, the median age was 38.5 years (IQR 5.5 years),

Characteristic, Adolescent	N (%) or Median (IQR)
Gender (female)	7 (35.0)
Age (years)	12.5 (3.0)
Grade	
grade 3 primary	4 (20.0)
grade 4 primary	2 (10.0)
grade 5 primary	4 (20.0)
grade 6 primary	1 (5.0)
grade 1 middle	6 (30.0)
grade 3 middle	3 (15.0)
CD4 count (cells/ $\mu$ l)	669 (367)
Undetectable viral load (UDVL; N=19)	19 (100)
Time on ART (years)	2.8 (6.1)
Characteristic, Caregiver	
Gender (female)	14 (70.0)
Age (years)	38.5 (5.5)
Relationship to child	
Mother	13 (65.0)
Father	3 (15.0)
Grandparent	2 (10.0)
Aunt	2 (10.0)
Married	16 (80.0)
Language	
Mandarin	2 (10.0)
Other	18 (90.0)
Ethnic background	
Han Chinese	13 (65.0)
Other	7 (35.0)
Education level	
Incomplete primary	4 (20.0)
Middle school	8 (40.0)
Secondary school or higher	8 (40.0)
Monthly income category	
Under 200 yuan	4 (20.0)
201-1000 yuan	2 (10.0)
1001-5000 yuan	14 (70.0)

**Table 1:** Demographic, socioeconomic and psychosocial characteristics of participants and caregivers (N=20 pairs).

the majority were female (14/20, 70%), and sixteen (80%) were married. Most caregivers were the child's mother (13/20, 65%); the remainder were fathers (3/20, 15%), grandparents (2/20, 10%), or aunts (2/20, 10%). Most (18/20, 90%) reported a local dialect (not Mandarin Chinese) as their first language. Sixty percent (12/20) had completed middle school or lower.

### Adherence levels

Adolescent patients used the wireless EDM device for a median 36.0 days (IQR 7.5 days). Using EDM data, median adherence was 93.9% (IQR 10.2%) of prescribed doses taken and 90.2% (IQR 13.3%) using the on-time measure (Table 2). Only 20% (4/20) of patients met the strictest generally-accepted criterion for optimal adherence ( $\geq 95\%$  using on-time measure) over the observation period. Self-reported median adherence for the month was 100% proportion taken.

### Acceptability of EDM device

Of the 19 adolescent participants who completed the follow-up questionnaire, all reported a "positive" or "very positive" overall experience with the EDM device, and all reported feeling "very positive" or "somewhat positive" about being monitored (Table 3). Sixteen (84.2%) found the device very easy to use; the remaining three (15.8%) found it "somewhat easy" to use. However, the majority (12/19, 63.1%) said that it was "somewhat inconvenient" or "very inconvenient." All participants reported willingness to participate in a larger intervention study.

Qualitative responses, summarized below, reveal more complex nuances of adolescents' experiences with the EDM device.

### Ease and convenience of use

When asked what they thought about using the device, participants had a wide variety of responses, and a large majority expressed both positive and negative impressions, i.e., enthusiasm about the technology and concept, but frustration with the particular configuration of the device. Positive statements included: "It's convenient and light," "It's easy to take and easy to get my dose" and "It enables me to be independent." One caregiver added, "It helps the child to form the habit of taking their medicine."

Many adolescents had more negative comments, such as:

Measure	N (%) or Median (IQR)
Ever forget to take medicine	2 (10.5)
Ever stop because feel worse	2 (10.5)
Times missed last week (never)	19 (100.0)
Wrong time last week	
Never	17 (89.4)
1-2 times	1 (5.3)
3-5 times	1 (5.3)
Days did not take any ART, last three months (number)	0 (0.0)
Days off time, last three months (number)	0 (0.0)
Visual adherence scale (VAS) self report	
90%	1 (5.3)
95%	2 (10.5)
100%	16 (84.2)
Adherence from EDM device (N=20)	
Proportion of doses taken (%)	93.9 (10.2)
On-time measure (%)	90.2 (13.3)

Table 2: Adherence (N=19).

Measure	N (%)
Days used (median (IQR))	36.0 (7.5)
Always used EDM	2 (10.5)
Only opened when time to take a dose	7 (36.8)
Ever took extra doses out for later	1 (5.3)
Sometimes forgot to close container	1 (5.3)
Ever stored meds in a different container	2 (10.5)
Only took out one dose each time	18 (94.7)
Ever opened EDM but didn't remove pills	11 (57.9)
Never left container open	18 (94.7)
Ease of use	
very easy	16 (84.2)
somewhat easy	3 (15.8)
Convenience	
very convenient	4 (21.1)
somewhat convenient	2 (10.5)
somewhat inconvenient	10 (52.6)
very inconvenient	2 (10.5)
How did you feel about monitoring ?	
very positive	8 (42.1)
somewhat positive	11 (57.9)
Willingness to participate in future study	
very willing	7 (36.8)
somewhat willing	12 (63.2)
Overall experience with EDM device	
very positive	7 (36.8)
somewhat positive	12 (63.2)

Table 3: Electronic drug monitoring (EDM) device experience (N=19).

"I don't really like it. It's inconvenient to take it out with me when I go out for fun" (Boy, age 14)

"I don't like it. I want to throw up when I see the pill bottle. It's too big, and it's inconvenient to carry around" (Girl, age 10)

One child expressed no need for the device, since he was already accustomed to taking his medicine regularly:

"I have been on medication for ten years, so it's already a habit" (Boy, age 13)

Many participants complained about the size and appearance of the device. Yet some also expressed a desire for greater capacity (several said both). When asked "what makes the container difficult to use", typical responses were:

"Low capacity" (Boy, age 15)

"It's too big and inconvenient to take it out" (Girl, age 14)

"There are only a few inner compartments, so it's not enough to put all three medicines in it. It's inconvenient to store three medicines separately; the capacity is too small" (Boy, age 11)

"Too big, and it's not pretty. It's inconvenient to carry around. The light makes people uncomfortable. It's inconvenient to take it out and difficult to open" (Girl, age 10)

"Too big, but the capacity is too small, and not convenient to carry around" (Boy, age 12)

Only two participants reported difficulties in actually using the device. One reported not being able to find the opening when he/she was asleep, and the other expressed concern about privacy, hinting at fears of revealing HIV status.

“When I take the pill bottle out with me, it is rather troublesome to use it to take my medicine when there are other people around. I have to find a less conspicuous place to take my medicine” (Boy, age 13)

### Device management and storage strategies

Many adolescents reported collaborating with their caregivers on medication management. Two illustrative statements were:

“In the morning, my grandma gives me my medicine when the alarm goes off. In the evening, I check the time and take my medicine myself” (Girl, age 12)

“My parents remind me a few minutes in advance. Sometimes, I check the time myself. I usually play computer games all night and go to bed after I take my medicine at 6 in the morning” (Girl, age 13)

Additionally, most participants seemed to tailor use of the device to fit their own needs, and stored all three medications in the device, enough for 4 or 5 days, rather than only one, as instructed by researchers. As one explained:

“I put 5 days’ medicine in it at once. I just randomly put all three types of medicine in these two compartments. The sizes of my pills are different, so I can distinguish them. I only open the pill bottle when I take my medicine. I open and refill it when it runs out of pills” (Girl, age 13)

### Feelings about being monitored

The majority (11/19) of the adolescents spoke positively about having their adherence monitored. As three participants explained:

“I like using this pill bottle. Monitoring my medication is helpful to my adherence” (Boy, age 15)

“I like it. I pay more attention to my medication when someone is watching me” (Boy, age 13)

“I like it. The light on the pill bottle is on every time when I open it. It’s funky and interesting. It monitors my medication. Pretty good” (Girl, age 13)

However, a few (4/19) were less positive about being monitored:

“I feel so-so about this pill bottle. I don’t like other people supervising my medication” (Boy, age 10)

“I don’t really like it. I don’t like the feeling that someone is watching my medication. I feel uncomfortable” (Girl, age 11)

### Recommendations for improvement of device

Three participants recommended a larger device that could hold all of the medicines; one requested a smaller container that would hold a single day’s medications. Nearly 70% (13/19) suggested (unprompted) that a reminder function be added to the container.

### Discussion

We found that use of a wireless EDM device to monitor adherence was feasible and acceptable in a cohort of adolescent ART patients in China. Participants reported few difficulties in using the EDM device, and all reported a positive or very positive experience with it in closed-ended questions. At the same time, open-ended questions elicited reports of inconvenience and dislike of the device’s size and appearance, similar to our findings with adults [31].

For pediatric patients, the point at which they begin to assume

responsibility for taking their own medication represents a critical stage in the process of establishing good habits, which may promote good lifelong adherence. It is possible that using the EDM device could act as either a facilitator of or a barrier to a sense of independence and taking control of one’s medication-taking behavior. On the one hand, some participants liked being watched, while others did not, indicating varied opinions regarding privacy and a desire for external support. This is in contrast to our experience with adult patients in China, the vast majority (114/119, 96%) of whom reported a positive monitoring experience, and in qualitative interviews, generally said that they liked knowing that someone cares and is watching them (unpublished findings). More research is required to help us understand the full complexity of adolescents’ views of adherence-promoting tools, as well as culturally-specific norms that may be at play. Specifically, we need to examine more rigorously what it is about the device itself, as opposed to particular individual characteristics and certain developmental stages, that may be conducive to incorporating technological devices into the lives of individuals as they go through the process of becoming independent and assume responsibility for their own medication-taking.

The co-management of medication-taking that we noted in the sample is a very real component of adherence in practice, and the caregiver’s role in helping to manage this transition to health-promoting habits is crucial. In China, young ART patients usually take responsibility for their medications when they go to middle school. Disclosure often occurs at this age (12 years) as well. In accompanying interviews, caregivers spoke about the challenge of helping youth of this age manage school, extra classes, and taking medication, in addition to difficulties with stigma and disclosure (unpublished findings). The nature of the child’s relationship and communication with his/her caregiver may also have important implications for adolescents’ adherence. Future studies should probe the nature of adolescent/caregiver relationships, with a focus on identifying ways of supporting these relationships.

The large majority of participants who requested that a reminder mechanism be included in the device suggest that the real-time triggered reminder intervention approach that we found effective in improving adherence in the adult CATS cohort may be a reasonable option for use with adolescents as well. Yet simply transferring the CATS intervention to an adolescent population without adapting it to the unique developmental and cognitive situation of adolescents would be imprudent. Development of an effective intervention package for adolescents will require a better understanding of how youth view their disease, their constraints, and medication-taking preferences, as well as the degree to which their status has been disclosed to them and they are acting independently of their caregivers.

The spectrum of opinions among the study cohort regarding size, capacity, and convenience of the device suggests that developing individualized approaches to adherence support will be essential for an adolescent patient population. An effective, acceptable intervention package for adolescents might look quite different from one designed for adults. Youth might like a different color or size of the device or carrying case, for example, or a different appearance or delivery mode of the adherence performance report. Given the comments from those participants who disliked being monitored, it is possible that some adolescents might opt for no counseling at all—and even do better psychologically without additional interactions with clinic staff. An intervention might be used short-term to establish and reinforce skills, then discontinued once sustainability of impact (the “good habit”)

is established. Those interventions that have been piloted recently (motivational interviewing, financial incentives, cell phone reminders) represent options that might be linked with wireless technology for monitoring and/or intervention. Making the device fun to use through incorporation of simple games, snazzy messages, or trivia quizzes may well increase the attraction of EDM devices. Finally, the field of wireless technology is expanding rapidly and may be of particular interest to adolescents. It is important to remain open to other emerging technologies that might be adapted as adherence supports, some of which might have enhanced appeal for youth.

We acknowledge the study's small sample size as a limitation. Since these 20 participants were being treated at a specialized clinic that cares for most pediatric HIV patients in the province, they may not be representative of all adolescent ART patients in China. In addition, because the cohort was effectively selected by clinicians who may have disproportionately chosen cooperative patients with supportive caregivers, the cohort could be biased toward those who might have a tendency toward greater acceptance of the device. On the other hand, it should also be noted that while participants commented on the negatives of the device, they had as yet no experience of the benefits that it could deliver to them. Participants' opinions might change substantially if the device were employed as an intervention and provided feedback to them, rather than just serving as a passive adherence monitor, suggesting that the opinions expressed by this sample might be overly negative. We are currently planning a larger intervention study with adolescents, using an EDM device as part of the intervention; this study will be powered to detect differences between intervention and control patients, and will include only adolescent patients who have documented adherence challenges.

## Conclusion

Wireless EDM technology represents an acceptable and rigorous method of measuring ART adherence, as well as a potentially useful adherence support, for adolescents at a critical time in their lives, when they can ideally establish good practices to support the ability to take vital ART medication long-term. Monitoring adherence using an EDM device, perhaps paired with triggered reminders, appears to be a promising tool for helping youth develops such good habits. Further research with adolescents is required first to develop appropriate interventions, and then to assess their efficacy. Finally, although we specifically studied the experience of Chinese adolescents, the tool is quite possibly appropriate for use by adolescents in other socio-cultural settings in Asia and elsewhere. What will appeal to adolescents, and be effective, will undoubtedly be influenced by socio-cultural and environmental factors, however. What may work for an adolescent in a large family in a semi-rural setting in sub-Saharan Africa may be quite different than what will appeal to a teenager in Hanoi or Beijing. Tailoring an intervention package for youth in different contexts will warrant careful planning and design.

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