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Improving Adherence to Antiretroviral Therapy with Triggered Real Time Text Message Reminders: the China through Technology Study (CATS)

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Abstract

Background—Real-time adherence monitoring is now possible through medication storage devices equipped with cellular technology. We assessed the effect of triggered cell phone

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Conflicts of Interest

For the remaining authors, no potential conflicts of interest were declared.

Previous presentations of data

A subset of study findings were presented to government officials and non-government personnel in China in March 2014, at the 9th International Conference on HIV Treatment and Prevention (June 8–10), and at the XX International AIDS Conference (July 20–25). However, all findings presented previously were preliminary and based on per protocol analyses. Those presented here are based on intention to treat and have not been presented previously.

reminders and counseling utilizing objective adherence data on antiretroviral (ART) adherence among Chinese HIV-infected patients.

Methods—We provided ART patients in Nanning, China, with a medication device ("Wisepill") to monitor their ART adherence electronically. After 3 months, we randomized subjects within optimal (≥95%) and suboptimal (<95%) adherence strata to intervention vs. control arms. In months 4–9, intervention subjects received individualized reminders triggered by late dose-taking (no device-opening by 30 minutes past dose time), and counseling using device-generated data. Controls received no reminders or data-informed counseling. We compared post-intervention proportions achieving optimal adherence, mean adherence, and clinical outcomes.

Results—Of 120 subjects enrolled, 116 (96.7%) completed the trial. Pre-intervention, optimal adherence was similar in intervention vs. control arms (63.5% vs. 58.9%, respectively; p=0.60). In the last intervention month, 87.3% vs. 51.8% achieved optimal adherence (risk ratio (RR) 1.7, 95% Confidence Interval (CI) 1.3–2.2); mean adherence was 96.2% vs. 89.1% (p=0.003). Among pre-intervention suboptimal adherers, 78.3% vs. 33.3% (RR 2.4, CI 1.2–4.5) achieved optimal adherence; mean adherence was 93.3% vs. 84.7% (p=0.039). Proportions were 92.5% and 62.9% among optimal adherers, respectively (RR 1.5, CI 1.1–1.9); mean adherence was 97.8% vs. 91.7% (p=0.028). Post-intervention differences in clinical outcomes were not significant.

Conclusion—Real-time reminders significantly improved ART adherence in this population. This approach appears promising for managing HIV and other chronic diseases and warrants further investigation and adaptation in other settings.

Keywords

HIV; antiretroviral therapy; adherence; intervention; China; wireless technology

INTRODUCTION

The rapid scale-up of antiretroviral therapy (ART) for HIV-positive individuals has transformed HIV from a terminal to a chronic illness, with annual deaths declining from 2.3 to 1.6 million globally between 2005 and 2012.[1] However, substantial challenges remain. Poor adherence to ART medications has been associated with treatment failure, progression of HIV to AIDS, development of resistant strains of HIV, and death.[2–8] While regimen improvements may put less demand on perfect adherence,[9–11] successful treatment requires sustained lifetime adherence, with a goal of maintaining adherence above 95%. Several reviews suggest that behavioral interventions can improve ART adherence, though the intervention effect is rarely durable.[12–16] These reviews underscore the fact that relatively few interventions have been rigorously tested, especially outside highly developed countries.

The use of mobile phone technologies has emerged as a potentially powerful strategy for ART adherence promotion.[17–22] A recent meta-analysis of evaluations of text message interventions showed that such interventions increased ART adherence; a few improved biological outcomes.[23] Of note, although four of the eight trials in the analysis were conducted in low-resource settings, none took place in Asia.

China has Asia's second-largest HIV epidemic, with an estimated 780,000 individuals infected.[1] New infections have numbered roughly 50,000 annually,[24,25] though updates suggest an increase in new cases in recent years.[26–28] Western and southern border areas have been affected disproportionately, mainly due to high rates of heroin use.[25,29–31] China's government scaled up free provision of ART beginning in 2003,[32,33] and has reported 140,000 individuals receiving ART by 2012.[25] Drug resistance is emerging as a problem, indicating widespread sub-optimal adherence,[34–36] yet few adherence interventions have been studied in China. Two exceptions include a nurse-delivered counseling intervention conducted in Beijing, which showed positive effects of counseling and reminders,[37] and our own past work in the heavily-impacted border province of Yunnan, the "Adherence for Life" (AFL) study. AFL used electronic drug monitoring (EDM) as an information and counseling tool in a predominantly heroin-using population, and found that EDM-informed counseling ("EDM feedback") significantly improved ART adherence.[38]

We hypothesized that adherence information and education are likely to be most effective when delivered in real time, and in direct response to lapses when they occur. We therefore developed and tested a real-time web-enabled adherence support intervention using wireless technology for ART adherence monitoring. This real-time adherence messaging and counseling intervention included use of a wireless medication container/communicator (Wisepill™ Technologies, South Africa) which records the date and time of each container opening and communicates the data immediately via general packet radio service to a central server.[39] Piloting showed this technology to be feasible and acceptable in China, with reliable monitoring of adherence over time.[40] To date, however, no studies have reported on its utility as an ART adherence support.[40–44] The "China Adherence through Technology Study" (CATS) assessed the effect of this *real time feedback* using triggered cell phone reminders coupled with Wisepill-generated data-enhanced counseling.

METHODS

Subjects and study design

The province of Guangxi, China, like neighboring Vietnam and other nations of Southeast Asia, has been greatly affected by the regional heroin use epidemic and associated HIV transmission. Home to numerous ethnic minorities, Guangxi has an estimated 80,000–100,000 HIV-positive individuals,[45] with new infections averaging 10,000–15,000 annually (data from late 2011).[46] This study was conducted at the Guangxi Center for Disease Control and Prevention (GX-CDC) ART clinic in Nanning, a city of seven million residents.[47] The clinic is staffed with four physicians, two nurses, and three HIV counselors and treats over 1,000 patients.

The randomized controlled trial enrolled HIV-positive adult patients on HIV treatment at the GX-CDC clinic. Most clinic patients followed a twice-daily ART regimen consisting of nevirapine or efavirenz, plus lamivudine with stavudine or lamivudine with zidovudine, though some were on a once-daily regimen of lopinavir/ritonavir plus tenofovir or abacavir. As part of usual care, all patients on ART met with adherence counselors who were available for support at the request of a clinician or patient.

Patients were eligible if they were receiving or initiating ART, aged 18 years or above, owned a mobile phone, and deemed at risk for poor adherence by clinicians or themselves. To operationalize this latter criterion, clinic staff referred to the study coordinator all patients they believed might face adherence challenges for any reason, including substance abuse, alcohol dependency, previous treatment failure, and mental health problems. Treatment-experienced patients as well as those initiating ART were eligible given time constraints and use of a randomization procedure designed to address the greatest source of potential bias (adherence level), an approach used previously with success.[38] Posters were displayed at the clinic encouraging any patient who felt at risk of poor adherence to consider participation. Subjects provided written informed consent prior to enrollment. All subjects received 150 yuan (approximately US$25) monthly as reimbursement for lost work time and travel costs associated with study participation.

Study procedures

Upon enrollment, an on-site study coordinator gave each subject an electronic adherence monitoring container for use with his/her ART medications. In consultation with the study coordinator, subjects selected one or more ART medications to be monitored within the device. Selection was based on fit and subject preference for refilling frequency. All subjects underwent baseline adherence monitoring using the device for three months and then were stratified into optimal or suboptimal adherence groups (defined as ≥95%, <95% average adherence) before starting the intervention period. Subjects were randomized within each stratum in a 1:1 ratio to intervention and control groups. Randomization was performed on site, through a block randomization procedure in which the site coordinator pulled an unmarked allocation envelope, the inside of which had a single paper stamped with either "intervention"or "control", from a larger envelope (labeled 'optimal' or 'suboptimal' as appropriate given the subject's adherence category) that originally held ten such allocation envelopes, five for each arm. When each large envelope was empty, it was replaced with another one, similarly containing ten allocation envelopes.

All subjects were seen monthly, and all received electronic adherence monitoring throughout the study. Intervention subjects received adherence counseling as clinically indicated, and an SMS mobile phone reminder sent whenever the Wisepill system failed to detect a device-opening by 30 minutes past a scheduled dose time. The text messages were personalized, with subjects selecting a reminder from a list of ten options developed jointly by clinicians and patients, including 'carry on, carry on!' and 'be healthy, have a happy family.' To prevent disclosure of HIV, text reminders did not refer to HIV, ART, or other disease-related topics. When seen monthly in clinic, subjects with prior-month adherence <95% received a behaviorally-targeted counseling session with a counselor guided by a detailed day-to-day adherence performance report with a visual display of doses taken and summary of doses taken on time, off time, and missed in the previous month. These sessions had no pre-determined length; practice sessions indicated that 15–20 minutes were sufficient for a meaningful discussion in most cases. Control subjects received usual care adherence counseling as clinically indicated at each visit, or if they self-reported suboptimal adherence (<95%). Given the nature of the intervention, it was impossible to blind subjects or clinicians to subjects' randomization arm.

Adherence counselors were trained to use supportive counseling methods. Counselors received specific training for intervention subjects: how to review the report with the subject, explore reasons for missed or off-time doses, inquire about possible challenges, and strategize about approaches to overcome them. The approach was based on the AFL counseling model, in which counseling sessions were designed to foster a personalized discussion of each subject's unique experiences characterized by lack of judgment of poor adherence.[38]

CD4-cell count and HIV plasma RNA tests were conducted at two points: (1) during or shortly before the pre-intervention interval (month 0 to month 3), and (2) post-intervention, defined as month 6–7 post-randomization (study month 9–10). CD4-cell counts were measured by FACSCalibur flow cytometry (Becton-Dickinson, CA). HIV plasma RNA tests were performed with an Organon Teknica NucliSens machine (Boxtel, Netherlands). The lower limit of the viral load assay was 50 copies per mL.

Institutional review boards at Boston University Medical Center and the Guangxi Provincial CDC in Nanning, China, approved the protocol. The study is registered on ClinicalTrials.Gov (NCT01722552).

Analytic methods

Date and time records for each device opening were used to construct detailed records of adherence over the study period. Adherence was defined as proportion of doses taken on time, in accordance with our past research (and that of others) showing that on-time adherence predicted undetectable viral load (UDVL) most significantly.[48,49] Accordingly, adherence was defined as: ([number of doses taken ±1 hour of dose time] / [total number of prescribed doses]). Doses taken outside the ±1 hour window were considered non-adherent. Other endpoints included the proportion of all scheduled doses taken, mean CD4-cell count and changes in CD4-cell count, and UDVL.

To assess efficacy of the intervention, the primary outcome was the difference between intervention and control subjects in the proportion achieving optimal (≥95%) on-time adherence post-intervention, (specifically, the last 30 days of the 6-month intervention period). In addition, we compared proportions with optimal adherence over the entire 6-month intervention period, as well as mean adherence (both in last intervention month and over the entire intervention period) between arms and within adherence groups. The secondary outcomes were post-intervention differences in CD4-cell count and UDVL, and change in CD4-cell count from baseline to month 9 between arms.

The primary analysis was by intention to treat (ITT); a secondary per protocol (PP) analysis was also conducted. The ITT analysis included data for all randomized subjects, with post-intervention adherence measured by the last 30 days of available data; adherence over the 6-month intervention period was measured using all available post-intervention data. All baseline and post-intervention CD4-cell count and HIV viral load data were used in clinical outcome analyses. We also conducted bivariate and multivariate regression analyses to assess potential bias on intervention effect of variables imbalanced at randomization.

Because the ITT and PP results were very similar, here we present the results of the ITT analysis.

To assess the impact of the triggered cell phone reminders specifically, as opposed to the combined effect of reminders and enhanced counseling, we compared the mean monthly number of 'late doses,' defined as doses not taken by 30 minutes after scheduled time, when messages were triggered for intervention subjects but not for controls, during the pre-intervention and intervention periods between arms. To explore the impact of reminders on adherence behavior, we also compared the proportion of all doses taken between 30–60 minutes past dose time. Our hypothesis was that individuals who were more than 30 minutes late for a dose would be more likely to take their dose in the next 30–60 minutes if they received a reminder.

Our sample size was designed to detect a 25 percentage-point difference in proportion achieving optimal adherence post-intervention. This difference was based conservatively on the previous AFL study, in which proportions achieving optimal adherence were 84% vs. 39% in intervention subjects vs. controls in the last intervention month. The target sample size was 120, assuming a minimum of 80% power at a two-sided alpha of $p = 0.05$, and allowing for 20% attrition. The study was not powered to detect differences in clinical outcomes. We used Cochran Mantel-Haenszel χ^2 tests for categorical variables and Student's *t* tests for continuous variables, with findings expressed as risk ratios (RR) and 95% confidence intervals (CI) for categorical variables and means and standard deviations (SD) for continuous variables. All inferences were based on a type 1 error equal to $p = 0.05$. We used SAS version 9.4 (SAS, Cary, NC).

RESULTS

Sample characteristics

Subjects were enrolled between December 2012 and April 2013. Of 166 patients eligible to participate, 120 were enrolled and 119 were randomized (63 intervention, 56 controls). Refusals to participate were due to: lack of time for monthly visits (20, 43.5%); fear of using the device around other people (18, 39.1%); belief that the device was inconvenient to carry (16, 34.8%); living far from the clinic, making clinic visits inconvenient (11, 23.9%); and lack of concern about adherence (5, 10.9%). Of the 120 enrolled, one dropped out prior to randomization; three more dropped out post-randomization, one intervention subject and two controls (Figure 1). Of these three, one subject completed 6 months of the intervention, one completed five months, and the third completed three months. A total of 116 completed the 6-month intervention period: 62 intervention subjects and 54 controls.

Randomized subjects were primarily male (63.9%); mean age was 38 years (Table 1). About one-half were married. Most (58.0%) had a middle school education; just over one-half (55.5%) were employed, with mean monthly income of approximately 3,000 yuan (US$ 500). Pre-intervention CD4-cell counts were 389 vs. 363 cells/μL in intervention and control subjects, respectively. Fewer intervention than control subjects had UDVL at baseline (74.6% vs. 98.2%, $p < 0.001$). Mean time on ART was just over 30 months, and similar in both arms, with most on twice-daily regimens (62% in intervention vs. 79% in controls, $p =$

0.049). Only ten (8.4% overall) subjects were treatment-naïve, defined as less than one month on ART; all ten were in the intervention arm. Sexual transmission was the principal infection route. Among men, 43% of intervention subjects vs 18% of controls reported infection through unprotected sex with another man (data not in table; $p = 0.020$).

Effect of real-time feedback on adherence

At randomization, the proportions with ≥95% on-time adherence during the 3 months prior to randomization were 40/63 (63.5%) and 33/56 (58.9%) in intervention vs. control subjects ($p = 0.611$) (Table 2). In month 9, six months after the start of the intervention, a higher proportion of intervention subjects had ≥95% on-time adherence (55/63 (87.3%)) than controls, among whom adherence fell slightly (29/56 (51.8%)) (RR for optimal adherence in month 9, intervention vs. control, 1.69; CI: 1.29–2.21, $p < 0.001$). Analysis of adherence during the entire intervention period found that the proportion of subjects that achieved ≥95% on-time adherence over months 4–9 was similar: 52/63 (82.5%) and 29/56 (51.8%) for intervention vs. control subjects, respectively (RR 1.59; CI: 1.21–2.10, $p < 0.001$). Secondary analyses found no significant effect of variables imbalanced at randomization on any of the adherence outcomes.

The beneficial effect of the intervention remained significant when stratified by whether subjects had optimal vs. suboptimal adherence at baseline (during the pre-randomization period). Among suboptimal adherers, optimal adherence in month 9 was 18/23 (78.3%) vs. 7/21 (33.3%), respectively (RR 2.35; CI: 1.24–4.46, $p = 0.003$). Among optimal adherers at baseline, the proportions were 37/40 (92.5%) vs. 22/35 (62.9%) (RR 1.47; CI: 1.12–1.93, $p = 0.002$), respectively (see Table 2).

Mean adherence rates also improved in intervention subjects (Table 2). Adherence was similar at randomization (month 3), 91.6% and 91.5% in intervention and control subjects, respectively ($p = 0.970$), but was higher in intervention subjects than controls in month 9: 96.2% vs. 89.1% ($p = 0.003$), respectively. Similarly, mean adherence during the entire 6-month intervention period was significantly higher in intervention vs. control arm: 96.3% vs. 88.9% ($p < 0.001$).

In the stratified analysis among those with suboptimal adherence at baseline, mean adherence in intervention vs. control subjects was 93.3% vs. 84.7% ($p = 0.039$), respectively. Among previously optimal adherers, rates were 97.8% vs. 91.7% ($p = 0.028$), respectively. Mean monthly adherence rates were higher in the intervention arm in every month, in both adherence groups (Figure 2).

Effect of real-time feedback on markers of HIV disease progression

Compared with controls, intervention subjects had similar post-intervention CD4-cell counts and rates of UDVL. At baseline, mean CD4-cell counts were 389 and 363 cells/μL, in intervention and control subjects, respectively ($p = 0.408$). These counts improved in both groups, to 445 vs. 391 cells/μL by month 9 ($p = 0.080$). The mean change in CD4-cell count between baseline and month 9 trended higher but was not significantly different in intervention subjects vs. controls, an average gain of 52 vs. 28 cells/μL ($p = 0.297$). The

proportion of intervention subjects that achieved UDVL increased significantly ($p = 0.004$) between baseline and month 9, but proportions were similar between intervention vs. control subjects at month 9, 93.6% vs. 98.2%, respectively ($p = 0.218$).

Analysis of reminder messages

During the pre-intervention period, the mean monthly number of delayed doses (not taken by 30 minutes after scheduled dose time) was 3.3 vs. 3.5 in intervention vs. control arms ($p = 0.825$). Among intervention subjects, this number declined to 2.4 during the intervention period; the number increased among controls to 4.6 ($p = 0.036$). Among those subjects who had delayed doses (N=100, both pre-intervention and intervention periods), prior to the intervention, intervention subjects took 46.6% of delayed doses within the next 30 minutes (30–60 minutes after dose time, 'on time' according to the adherence measure), compared to 56.9% among controls ($p < 0.001$) (Figure 3). During the intervention period, this proportion rose substantially in the intervention group, but dropped slightly in controls. In intervention subjects, the increase was 30 percentage points, with 76.1% of delayed doses taken on time, contrasted with a 2 percentage-point drop to 54.6% of delayed doses taken on time among control subjects ($p < 0.001$).

DISCUSSION

The use of triggered cell phone reminders and enhanced counseling based on objective adherence data from the Wisepill monitor significantly improved ART adherence in this population of HIV-infected patients. While scheduled reminders delivered to mobile phones have been shown to improve adherence,[23] this is the first study to demonstrate the impact on adherence of triggered reminders sent only when patient behavior suggests less-than-perfect adherence. This finding adds to the growing evidence regarding the potential of wireless technologies generally as an adherence tool, while highlighting the unique benefit of 'smart messages'—reminders that communicate in real time with patients based on pill-taking actions, allowing them to quickly adjust their behavior to improve adherence.

This result builds upon and confirms both our previous work and that of others indicating that effective ART adherence interventions should be individualized.[14,38] Several features of this intervention were personalized: patients selected their own reminder messages, a reminder was sent only when prompting appeared necessary given the patient's medication-taking behavior, and each counseling session was informed by the patient's individual adherence data.

As in AFL and other studies, the intervention was most helpful among the subjects whose adherence was the lowest at randomization,[13] and thus had the greatest potential for improvement. Nonetheless, we also observed a benefit in those with optimal adherence at randomization. Among these subjects, the apparent benefit was to prevent adherence from declining over time, a common occurrence in chronic disease management,[50–52] including in HIV.[53] This suggests that even patients with high adherence may benefit from real-time adherence monitoring and support.

Our findings also address the concern as to whether reminders could paradoxically train patients to take their medicines only in response to a reminder, which might leave patients vulnerable in the event of device failures or loss of cellular connectivity. Our finding that the proportion of doses taken prior to the 30-minute mark increased markedly during the intervention period mitigates this concern. This suggests that the intervention improved participants' dose-taking self-management behavior in advance of a reminder. This result should be contrasted with the experience described by Pop-Eleches et al in their work on scheduled cell phone reminders on ART adherence, in which the finding was that daily messages were no more effective than no-reminders, while weekly messages were significantly beneficial for supporting adherence.[22] At the same time, it is worth highlighting that these previous reminder interventions have all used pre-scheduled messages, in contrast to ours, which delivered reminders based on actual behavior. One might speculate that consistent daily messages become routine, and ignorable, or possibly even an irritant to subjects (i.e., SPAM). If so, then triggered reminders as in this study may be more effective, since excellent adherence leads to relief from reminders, which may have a motivating effect.

Adherence interventions based on detailed, theory-driven behavioral counseling methods can be difficult to implement and to scale up for delivery to large numbers of ART users. In contrast, the wireless monitoring and text reminder intervention is relatively simple and can be used as a tool by providers and adherence counselors already in the field. The potential for broad scalability may make it feasible to target specifically patients known to be poorly adherent or those who develop drug resistance.

The ultimate goal of any ART adherence intervention is to improve HIV viral suppression to prevent disease progression, drug resistance, and HIV transmission. This study was not designed to detect meaningful differences in HIV RNA suppression or CD4-cell count response, and while we would expect adherence changes to ultimately effect biological outcomes, we were unable to show this. Although we observed a large increase in proportion with viral suppression in the intervention arm, post-intervention proportions of UDVL were similar, due in part to the disproportionately high level of suppression among controls at baseline. The chief explanation for this combination of results is that our relatively treatment-experienced subject population turned out to be doing well in terms of adherence, CD4-cell counts, and levels of viral suppression. Given the relevance of clinical markers, we recommend that future research use larger sample sizes, and target patients particularly at risk for biological failure, such as those initiating therapy for the first time, or beginning a second regimen after an initial regimen failure.

We acknowledge several study limitations. First, subjects and clinicians were not blinded, and thus some bias may have affected counseling provided to control subjects. However, blinding was not possible in an intervention of this kind because it is impossible to conceal reminders. While clinicians and patients were unblinded, all analyses were conducted without knowledge of intervention assignment. Second, the study had a relatively short duration of follow up. Six months may be too short a time to know whether subjects may become habituated to the intervention so that it loses potency over time; changes in UDVL and CD4-cell count can be delayed by up to 2 years from sub-optimal adherence.[54,55] Third,

the study design did not permit a rigorous analysis of the individual contributions of cell phone reminders vs. enhanced counseling. That said, our analysis of the dose-taking relative to delivery of a reminder suggests that triggered reminders were highly efficacious, which by design reduced the counseling sessions required by poor adherence. Fourth, the study was not designed to measure an impact on biological endpoints. To do so, a larger cohort, ideally with low rates of UDVL at baseline will need to be enrolled and followed for a longer period of time.

Despite these limitations, this study highlights the potential of real-time feedback in the search for effective adherence promotion strategies. We conclude that 'smart reminders' that are sent to patients only when their behavior suggests a need for reminding is a promising approach in the management of HIV and other chronic diseases. We recommend further assessment and adaptation in other patient settings.

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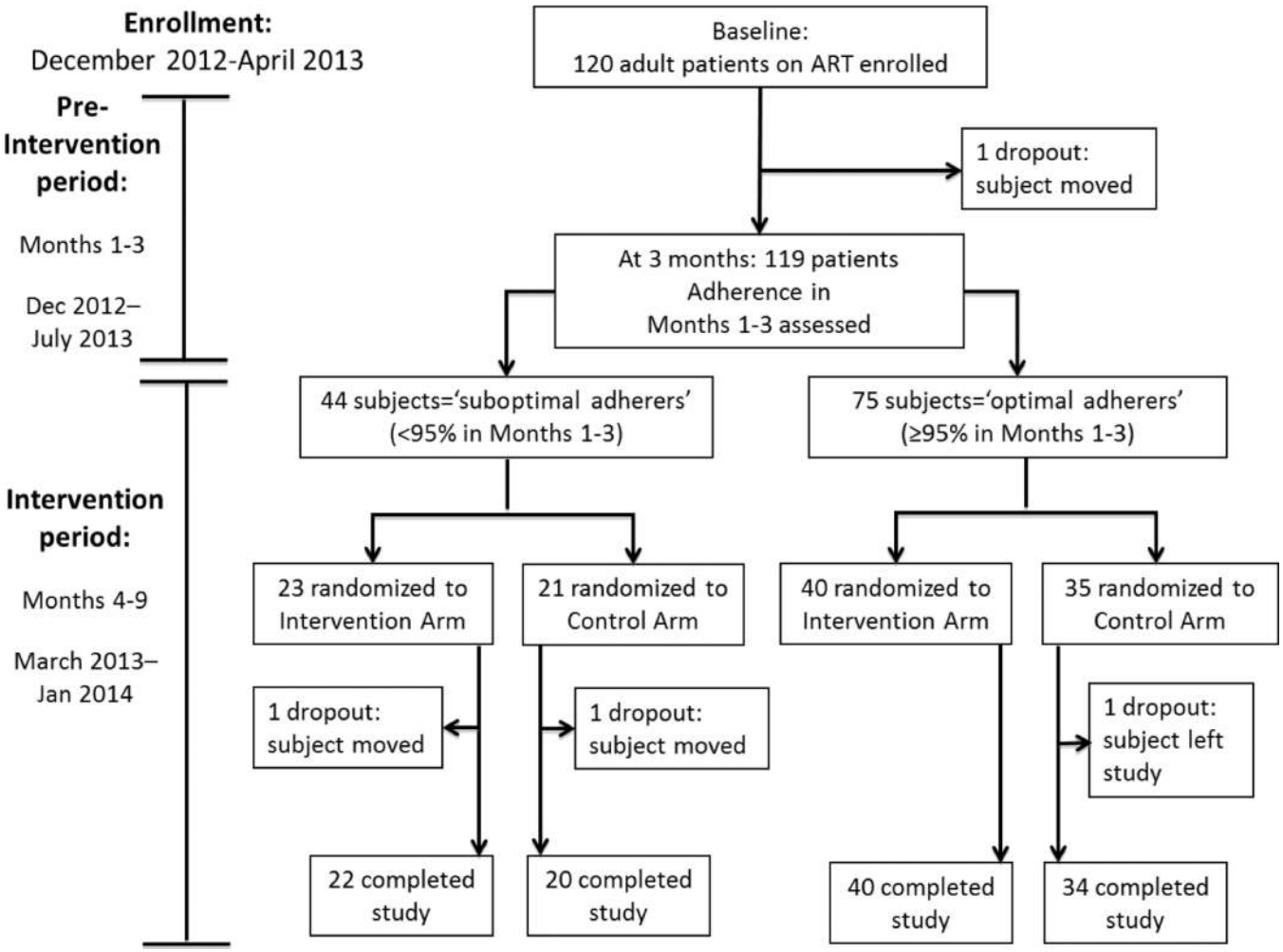

Figure 1.
Study profile

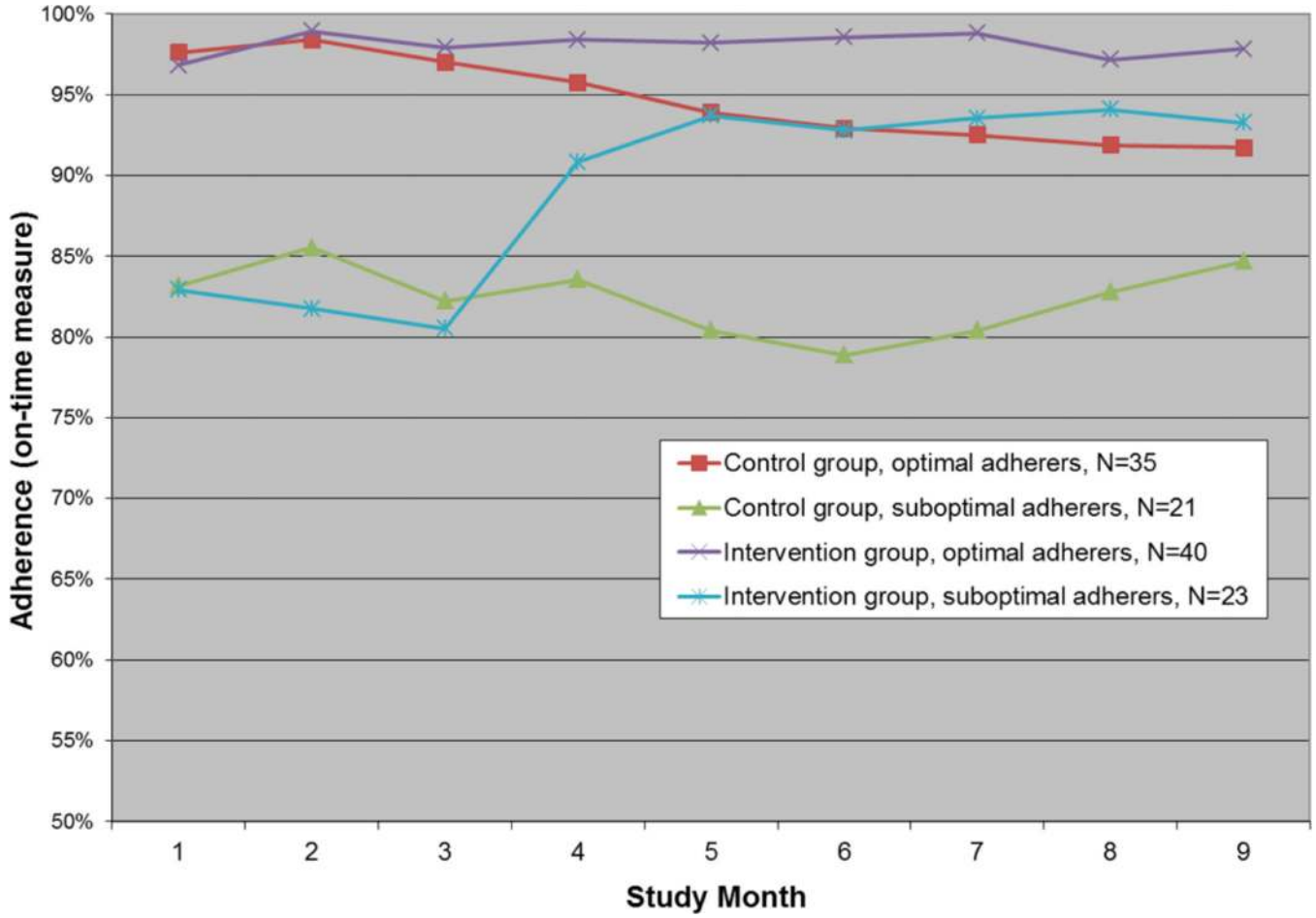

Figure 2.

Monthly mean adherence among intervention and control subjects, stratified by pre-intervention period optimal (≥95%) or suboptimal (<95%) adherence, using an on-time adherence measure

Note: Pre-intervention period refers to Months 1–3; intervention period is the subsequent 6-month period (Months 4–9) during which subjects received triggered reminders and data-informed counseling.

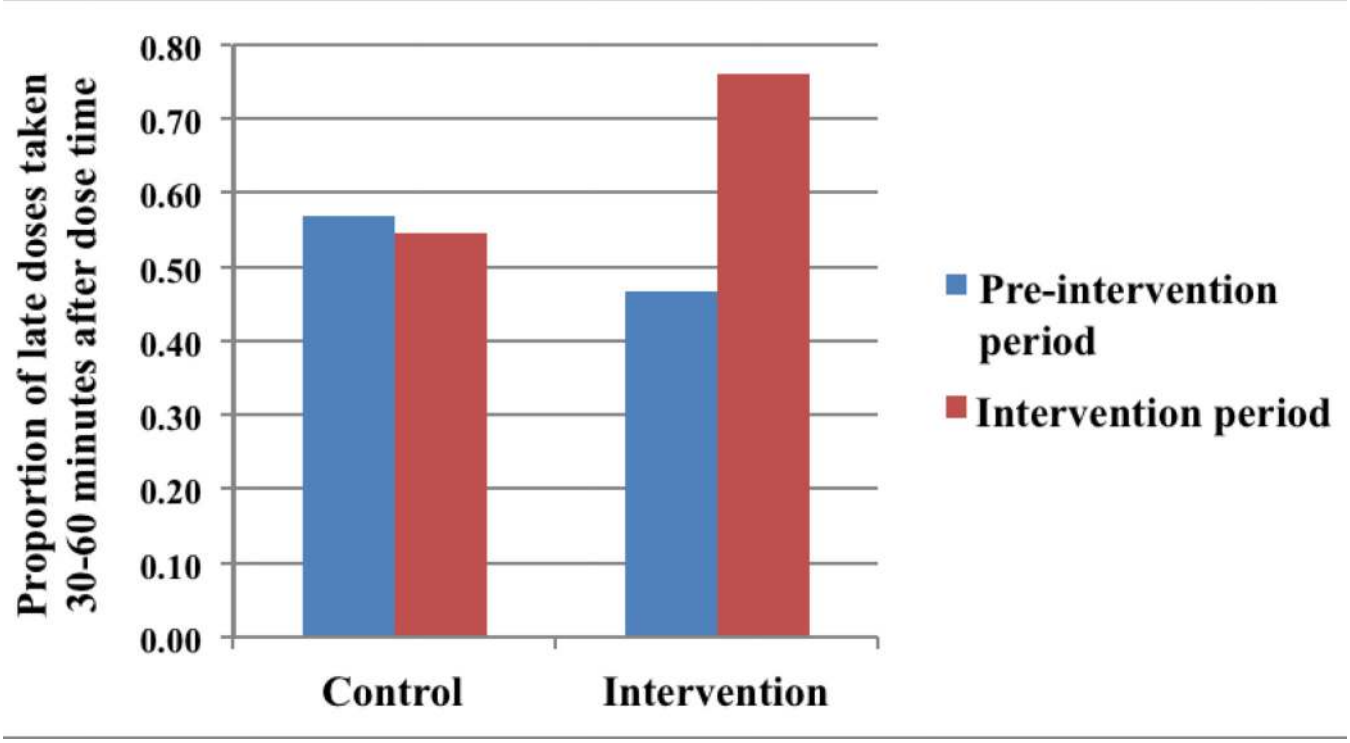

Figure 3.
Comparison of 'Late Dose Behavior' by period and randomization arms
Note: Pre-intervention period refers to Months 1–3; intervention period is the subsequent 6-month period during which subjects received triggered reminders. The figure indicates the proportion of 'late doses' (those not taken by 30 minutes after scheduled dose time) that were subsequently taken 'on time' (within the next 30 minutes).

TABLE 1

Characteristics of subjects at randomization

Characteristic	Intervention (N=63)	Control (N=56)	p-value
Age, years (SD)	36.9 (11.1)	38.4 (9.6)	0.446
Male, n (%)	42 (66.7)	34 (60.7)	0.503
Highest education level achieved, n (%)			0.697
Primary school only	14 (22.2)	13 (23.2)	
Middle/secondary school	35 (55.6)	34 (60.7)	
Beyond secondary school	14 (22.2)	9 (16.1)	
Married, n (%)	24 (38.1)	38 (67.9)	0.001
Employed, n (%)	35 (55.6)	31 (55.4)	0.983
Monthly income, yuan[§] (SD)	2553 (1982)	3388 (5996)	0.348
Time on ART, months (SD)	29.8 (32.1)	33.1 (27.7)	0.547
Twice/daily (vs. once/daily) regimen, n (%)	39 (61.9)	44 (78.6)	0.049
Used injectable street drug (ever), n (%)	7 (11.1)	8 (14.3)	0.604
Used non-injectable drug (ever), n (%)	8 (12.7)	9 (16.1)	0.601
Reported HIV transmission route, n (%)			0.055
Sex with HIV+ man	37 (58.7)	18 (32.1)	
Sex with HIV+ woman	9 (14.3)	15 (26.8)	
Shared needles	5 (7.9)	7 (12.5)	
Blood exchange	2 (3.2)	5 (8.9)	
Don't know/other	10 (15.9)	11 (19.6)	
CD4-cell count, mean cells/μL (SD)	389 (151)	363 (192)	0.408
Undetectable viral load, n/N (%)[†]	47 (74.6)	55 (98.2)	<0.001
Optimal adherence (95%), n (%)[φ]	40 (63.5)	35 (62.5)	0.911

Test statistics are Cochran-Mantel-Haenszel χ^2 tests for categorical variables and Student's *t* tests for continuous variables.

[§]The average exchange rate in March 2013, when randomization began, was US$ 1.0 = 6.2 yuan.

[†]Undetectable viral load defined as <50 copies/ml. N=118.

[φ]Defined as maintaining mean adherence ≥95% during pre-intervention period (Months 1–3), according to Wisepill.

TABLE 2

Adherence and markers of HIV progression

	Intervention (N=63)	Control (N=56)	p-value	Risk Ratio (95% CI)
Adherence outcomes[§]				
Proportion with optimal adherence, n/N (%)[ϕ]				
At Month 3	40/63 (63.5)	33/56 (58.9)	0.611	-
At Month 9	55/63 (87.3)	29/56 (51.8)	<0.001	1.69 (1.29–2.21)
Optimal at baseline (≥95%)	37/40 (92.5)	22/35 (62.9)	0.002	1.47 (1.12–1.93)
Suboptimal at baseline (<95%)	18/23 (78.3)	7/21 (33.3)	0.003	2.35 (1.24–4.46)
Throughout pre-intervention period[†]	40/63 (63.5)	35/56 (62.5)	0.911	1.02 (0.64–1.64)
Throughout intervention period[†]	52/63 (82.5)	29/56 (51.8)	<0.001	1.59 (1.21–2.10)
Mean adherence, % (SD)				
At Month 3	91.6 (15.3)	91.5 (13.7)	0.970	-
At Month 9	96.2 (6.4)	89.1 (15.9)	0.003	-
Optimal at baseline (≥95%)	97.8 (3.1)	91.7 (15.5)	0.028	-
Suboptimal at baseline (<95%)	93.3 (9.2)	84.7 (16.0)	0.039	-
Mean during pre-intervention period[†]	91.6 (11.8)	92.2 (12.5)	0.776	-
Mean during intervention period[†]	96.3 (5.8)	88.9 (14.6)	<0.001	-
Markers of HIV progression				
CD4-cell count, mean cells per μL (SD)				
At baseline	389 (151)	363 (192)	0.408	-
At Month 9	445 (166)	391 (165)	0.080	-
Change in CD4-cell count, Month 3 to Month 9				
Mean change in cells/μL (SD)	52 (116)	28 (132)	0.297	-
Proportion whose CD4 rose, n/N (%)	40/62 (64.5)	33/56 (58.9)	0.534	-
Undetectable viral load, n/N (%)[γ]				
At baseline	47 (74.6)	55 (98.2)	<0.001	-
At Month 9	58/62 (93.6)	54/55 (98.2)	0.218	-

Test statistics are Cochran-Mantel-Haenszel χ^2 tests for categorical variables and Student's *t* tests for continuous variables.

[§]Adherence outcomes all measured by Wisepill device.

[ϕ]Defined as maintaining mean adherence ≥95% during pre-intervention period.

[†]Pre-intervention period defined as Months 1–3; intervention period defined as Months 4–9.

[γ]Undetectable viral load defined as <50 copies/ml.