Title: Temporal factors and missed doses of tuberculosis treatment: a causal associations approach to analyses of digital adherence data

Helen R. Stagg[1], James J. Lewis[2], Xiaoqiu Liu[3], Shitong Huan[4], Shiwen Jiang[3], Daniel P. Chin[4], Katherine L. Fielding[2,5]

[1] Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

[2] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

[3] National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China

[4] China Office, Bill and Melinda Gates Foundation, Beijing, China

[5] School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author: Professor Katherine Fielding, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK; School of Public Health, University of the Witwatersrand, Johannesburg, South Africa; katherine.fielding@lshtm.ac.uk; +44 20 7927 2889

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ABSTRACT

Rationale

Tuberculosis treatment lasts for six months or more. Treatment adherence is critical; regimen length, among other factors, makes this challenging. Globally, analyses mapping common types of non-adherence are lacking. For example, is there a greater challenge from early treatment cessation (discontinuation) or intermittent missed doses (suboptimal dosing implementation)? This is essential knowledge for the development of effective interventions, more ‘forgiving’ regimens, and to direct National Tuberculosis Programs.

Objective

Granularly describe how patients take their tuberculosis medication and the temporal factors associated with missed doses.

Methods

Pulmonary tuberculosis patients enrolled in the control arm of a pragmatic cluster-randomized trial in China of electronic reminders to improve treatment adherence were included. Treatment was the standard six-month course (180 days), dosed every other day (90 doses). Medication monitor boxes recorded adherence (box opening) without prompting reminders.

Patterns of adherence were visualized and described. Mixed-effects logistic regression models examined the temporal factors associated with per-dose suboptimal dosing implementation, adjusting for clustering by participant. Cox regression models examined the association between early suboptimal dosing implementation and permanent discontinuation.

Results

Across 780 patients, 16,794 of 70,200 doses were missed (23.9%), 9,487 from suboptimal dosing implementation (56.5%). By 60 days, 5.1% of participants had discontinued, 14.4% by 120 days. Most participants (95.9%) missed at least one dose. The majority of gaps were of a single dose (71.4%), although 22.6% of participants had at least one gap of two weeks' or more.

In adjusted models, the initiation-continuation phase transition (odds ratio 3.07 [95% confidence interval 2.68-3.51]) and national holidays (1.52 [1.39-1.65]) were associated with increasing odds of suboptimal dosing implementation. Early-stage suboptimal dosing implementation was associated with increased discontinuation rates.

Conclusions

Digital tools provide an unprecedented step-change in describing and addressing non-adherence. In our setting, non-adherence was common; patients displayed a complex range of patterns. Dividing non-adherence into suboptimal dosing implementation and discontinuation, both were found to increase over time. Discontinuation was associated with early suboptimal dosing implementation. These apparent causal associations between temporal factors and non-adherence present opportunities for targeted interventions.

Clinical trial registration

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INTRODUCTION

In 2017, 6.4 million incident tuberculosis (TB) cases were reported globally and an estimated 3.6 million went undiagnosed or were not notified.(1) Finding and treating these missing patients is a key target of the World Health Organization (WHO); this requires substantial international investment. It is critically important to protect this investment by providing effective treatment to every diagnosed patient.

The standard treatment for drug sensitive TB lasts for six months. Numerous studies have documented that patients struggle to adhere to the full course of therapy. An estimated 4-35% demonstrate poor adherence.(2-11) Although various definitions have been used, poor adherence is associated with a reduced likelihood of sputum conversion,(3) greater risk of an unsuccessful treatment outcome,(4, 8, 12-15) and the development of drug resistance.(16-19) Non-adherence to TB treatment is associated with various factors; those that are patient-related, derived from the healthcare provider-patient relationship, the regimen itself, and the healthcare system.(20)

In trials and observational studies, overly simplistic and non-evidence-based 80-90% adherence thresholds have traditionally been used to signify adequate adherence.(12, 21-23) Recently, however, the importance of highly accurate means of measuring adherence within clinical trials has been acknowledged by WHO as a key part of trial design.(24) Realistically, two core domains need to be considered when mapping adherence-persistence (time between first and last doses; capturing initiation and discontinuation) and dosing implementation (taking doses not as recommended e.g. skipping weekends).(25) These components constitute ‘therapeutic coverage’, the proportion of time patients are exposed to efficacious drug concentrations.(26) Detailed mapping of adherence patterns has been missing from the TB literature to date.

Knowledge of how exactly TB patients take their medications and predictors of when non-adherence is most likely to occur is critical for the directed design of interventions to improve adherence, the development of regimens that are more ‘forgiving’ of non-adherence, and to help clinicians know when to intervene with non-adherent patients. Currently, the relative burden of suboptimal dosing implementation and discontinuation is unknown globally; interventions to address these two components of non-adherence may look quite different. This is a critical knowledge gap when it comes to reducing the burden of non-adherence, which is impeding the most cost-effective implementation of the WHO guidelines on digital adherence technologies for TB treatment.(27)

Utilizing data collected from a trial of electronic reminders to improve medication adherence in China, we aimed to granularly describe how TB patients take their treatment and if temporal factors were causally associated with missed doses in order to inform control efforts. Components of this study have been previously reported through a conference abstract.(28)

METHODS

Parent study and study population for analysis

The parent study- a pragmatic cluster randomized trial of electronic reminders to improve treatment adherence among pulmonary TB patients in People’s Republic of China- from which these data has been derived has been described before (Online supplement Additional Methods).(29) Participants were enrolled into the study between 1st June 2011 and 7th March 2012. Only participants in the control arm of the trial were included in this cohort study in order to capture usual patterns of treatment adherence in the absence of an intervention (Online supplement Additional Methods).

Measuring and defining adherence to treatment

Adherence to each dose of treatment was documented by a medication monitor box (Online supplement Additional Methods). The box captured every date and time on which it was opened; box opening did not necessarily mean that drugs were taken. Medication was dosed every other day (as per the National TB Program [NTP] standard at the time), for 90 doses over a 180-day period. If the box was opened at least once within each two-day dosing window this was recorded as adherence. The standard six-month regimen for drug sensitive TB was used (two months of isoniazid, rifampicin, ethambutol, pyrazinamide, followed by four months of isoniazid and rifampicin). Medication was not dosed in combination pills.

Non-adherence data from the monitor was coded, and categorized as a dose missed due to suboptimal dosing implementation versus a dose missed due to permanent discontinuation, using accepted terminology as per Vrijens *et al*.(25) Discontinuation was defined as ceasing to adhere to treatment and not re-commencing both a) at any point during the 180-day period and b) after this period but before the end of the trial. Discontinuation is different from the programmatically defined term ‘lost to follow-up’ (previously known as ‘default’), when either a patient’s treatment is interrupted for consecutive two months or more, or a patient does not start treatment. Suboptimal dosing implementation refers to all doses missed during the 180-day period, aside from those due to discontinuation. The term ‘suboptimal’ is not intended to imply a judgement as to the appropriate level of adherence/type of adherence pattern required to achieve a positive treatment outcome, but rather reflects an implementation level below 100% of doses taken.

Temporal exposures and potential confounders

The following temporal measures were calculated from the medication monitor data: 1) day of the week, 2) treatment month, 3) whether the dose fell on a Chinese national holiday, 4) whether the patient was in the initiation or continuation phase of treatment (see Online supplement Additional Methods).

Additionally, data were available for a series of potential confounders, all of which were self-reported at entry into the study. These included age, sex, marital status, educational level, occupation, household income, type of medical insurance, registration status, and distance from home to TB clinic. The county/district in which the participant lived was grouped into whether it was broadly rural or urban.

Statistical methods

Descriptive analyses

Analyses were undertaken in Stata 15 and graphs plotted in Microsoft Excel.

Adherence to treatment was described using the following summary measures: the overall percentage of doses taken, average duration that a patient was on treatment before ceasing completely, percentage of participants achieving an 80% adherence threshold, and percentage achieving a 90% threshold. In order to account for clustering, for each measure the mean was calculated per county/district and then the geometric mean taken across the county/district values.

Adherence over time, grouped by different percentage intervals, was graphically visualized using lasagna plots, in which white indicates non-adherence.(30)

Line graphs were used to visualize non-adherence due to suboptimal dosing implementation versus permanent discontinuation from treatment for all participants in the study and by adherence levels in the initiation phase.(31) After plotting these graphs, we decided to separate suboptimal dosing implementation and discontinuation in the remaining analyses.

The length and number of gaps in treatment due to suboptimal dosing implementation were described using scatter plots.

Associations between temporal factors and suboptimal dosing implementation

We used mixed-effects logistic regression to examine the factors associated with non-adherence due to suboptimal dosing implementation, treating each dose as an observation and adjusting for clustering by individual. We focused on temporal factors, including weekends, national holidays, and the initiation-continuation phase transition (Model 1) or treatment months (Model 2). Our methodology- including details of model selection through the use of directed acyclical graphs, determination of *a priori* confounders, and assessment of potential effect modification- is detailed elsewhere (Online supplement Additional Methods). The impact of using different confounder sets on our findings was explored through Models 1A-F (Online supplement Additional Methods). Both approaches sought to address all confounding using different confounder sets to support the drawing of causal conclusions from observational data.(32)

The potential presence of an interaction between the three temporal factors weekends, national holidays, and the initiation-continuation phase transition and a) county/district or b) distance from home to TB clinic were also explored using likelihood ratio tests (LRTs) (Models 1G-H).

Associations between early suboptimal dosing implementation and time to discontinuation

Cox proportional hazards regression was used to assess whether early suboptimal dosing implementation, either in the initiation phase (Model 3) or month 1 (Model 4), was associated with time to discontinuation. Individuals who had discontinued in the initiation phase and month 1 were excluded, respectively, in order to preserve the temporality of the association. Further details on adjustment for confounding, etc., are presented in Online supplement Additional Methods. We report sensitivity analyses on the impact of confounding by county/district (Models 3F, 4F) and excluding individuals who discontinued during the last three doses of treatment (Models 3G, 4G). The potential presence of an interaction between early suboptimal dosing and a) county/district or b) distance from home to the TB clinic were also explored using LRTs.

Ethical approval

The trial was approved by the ethics committees of the Chinese Center for Disease Control and Prevention (201008) and the London School of Hygiene & Tropical Medicine (5704). All participants provided written consent prior to inclusion in the trial.

RESULTS

Characteristics of the study population

Of the 1,104 individuals randomized to the control arm of the trial, 209 (18.9%) had technical issues with the medication monitor due to power outage problems, as indicated by the box resetting the date to a baseline value (Online supplement Figure E1). A further 10.4% of patients (115) were excluded, as events such as hospitalization for more than three days removed the potential for treatment to be monitored for the entire period. Thus 780 (70.7%) patient's data were available for analysis. A comparison of the included and excluded patients revealed similarity in terms of baseline characteristics, except for county/district and distance from home to the TB clinic (Table E1).

The baseline characteristics of participants are presented in Table 1. Individuals were generally male (535, 68.6%). More than half were under the age of 50 (525, 67.3%). Farming was the largest occupation (384, 49.2%), with 516 (66.2%) individuals living in counties/districts deemed rural and 500 (64.1%) insured through rural co-operatives.

Summary measures of overall adherence

Across all 780 study participants, 70,200 doses were scheduled during the 180-day period; 16,794 of these were missed (23.9%). The geometric mean number of doses taken was

68/90 (75.6%). The geometric mean duration on treatment was 80 doses (i.e. 160 days) before discontinuation.

Overall adherence over time

Lasagna plots of adherence over time demonstrated the distribution of participants in 20% adherence intervals, with 473/780 (60.6%) in the highest category of ≥80-100% adherent (Figure 1). A clear 'staggered' pattern was observed in the lowest categories that corresponded to drop-offs in adherence with each passing month (15 doses, 30 days). Although there was a reduction in adherence over time, erratic non-adherence (suboptimal dosing implementation) was observed throughout the treatment period.

The relative importance of non-adherence due to the permanent discontinuation of treatment versus suboptimal dosing implementation is shown in Figure 2a. Of the 16,794 missed doses, 9,487 were due to suboptimal dosing implementation (56.5%) and the remainder discontinuation. The impact of discontinuation was demonstrably stronger over time. By the end of month 2 5.1% of individuals had discontinued treatment; this figure was 14.4% by the end of month 4 and continued to increase during the last two months, until it reached 36.3% at the end of the 180-day period. The latter figure reflects the fact that discontinuation captures treatment cessation without recommencement at any time point, including cessation at the last (90th) dose.

When the 121 participants with <80% adherence in the initiation phase were examined separately, they demonstrated sharp and sustained reductions in adherence due to both discontinuation and suboptimal dosing implementation (Figure 2c).

Gaps in adherence (suboptimal dosing implementation)

Suboptimal dosing implementation was demonstrated by 748/780 (95.9%) participants i.e. they displayed at least one gap in their treatment of one dose or more that was not due to discontinuation. Overall, a total of 4,677 gaps were recorded, of which 71.4% (3,337/4,677) were for one dose only. The population median of the median gap length per participant was one and the interquartile range (IQR) 1-1 (Figure 3a). When the maximum gap length per participant was examined, the median across the population was two doses (IQR 1-6; Figure 3b). Of the 780 individuals, 368 (47.2%) had at least one gap of three doses (roughly a week) or more and 176 (22.6%) of seven doses (a fortnight) or more.

Associations between suboptimal dosing implementation and temporal factors

Our analysis of suboptimal dosing implementation and temporal factors was composed of 780 patients and 62,893 dose observations (Table 1). In unadjusted analyses, a strong association was seen between the initiation-continuation phase transition and suboptimal dosing implementation. The continuation phase was associated with triple the odds of suboptimal dosing implementation (odds ratios [OR] 3.09 [95% confidence interval {CI} 2.70-3.54]). This mirrors the month-by-month findings, where suboptimal dosing implementation increased from 6.8% of doses in treatment month 1 to 19.7% in month 6. Sunday was associated with greater suboptimal dosing implementation than the other days of the week ($p<0.001$). Compared to weekdays, weekends were associated with a small increase in the odds of suboptimal dosing implementation (1.13 [1.07-1.19]). National holidays were associated with a larger increase in odds (1.62 [1.49-1.75]; 14.6% to 20.5%).

In an adjusted model controlling for age as a linear variable, sex and urban/rural setting, and with a random effect on the initiation-continuation variable ([LRT p-value <0.001), all three temporal variables were associated with greater odds of suboptimal dosing implementation (weekends: 1.14 [1.08-1.20]), national holiday: 1.52 [1.39-1.65]), initiation-continuation transition 3.07 [2.68-3.51] (Model 1). There was no evidence for interactions between the initiation-continuation transition and national holidays (LRT p-value 0.97) or weekends (LRT p-value 0.07). These findings were robust to adjustment for different combinations of confounders (Table E2; Models 1A-F).

Tests for interaction were performed between the three temporal factors and county/district or distance. For distance, the LRT p-values for the initiation-continuation phase transition, holidays and weekends were 0.52, 0.97 and 0.91, respectively. For county/district, the LRT p-values for the initiation-continuation phase transition, holidays and weekends were 0.01, <0.001, 0.79, respectively. We thus undertook stratified analyses by county/district of the relationship between suboptimal implementation and a) the initiation-continuation phase transition (Table E3, Model 1G) or b) holidays (Table E4, Model 1H). Although the magnitude of the relationship between these two temporal factors and suboptimal implementation altered by county, the direction of effect was the same in all instances, barring one instance where the CI crossed the null (Baiquan, Model 1H; 0.94 [0.75-1.18]).

Given the striking initiation-continuation phase effect found in these models, but also the more gradual pattern of reducing adherence demonstrated in Figure 1, the association between treatment month and suboptimal dosing implementation was assessed. A random effect was included on the treatment month (LRT p-value <0.001), which was treated as a categorical variable. An interaction was documented between treatment month and national holidays (LRT p-value 0.01), but the statistical evidence was less certain for an interaction between treatment month and weekends (LRT p-value 0.06).

Within a model containing the treatment month-national holiday interaction (Model 2), the association between weekends and the odds of non-adherence due to suboptimal dosing implementation changed little from Model 1 (1.14 [1.08-1.20]). From month-to-month, the likelihood of suboptimal dosing implementation approximately increased and was particularly pronounced for doses that fell on national holidays (Table 2). A dose falling on a national holiday was positively associated with suboptimal dosing implementation, with the largest increase in odds in the last month of treatment, but no clear trend month-to-month (Table 2).

Associations between time to discontinuation and early suboptimal dosing implementation

Among the individuals included in the study, 109 were found to stop treatment without recommencing within the 90-dose period, but to later recommence before the end of the trial. The latest dose taken was at 254 days. These individuals were not classified as discontinuing. Patients who discontinued during the relevant implementation period were excluded in order to preserve temporality within any associations. Thus, 740 patients contributed to an analysis of discontinuation and suboptimal dosing implementation in the initiation phase and 775 when suboptimal dosing implementation in month 1 was instead considered (Table 1).

In unadjusted analyses, increased suboptimal dosing implementation in the initiation phase and month 1 were associated within an increase in the likelihood of discontinuation (Table 1). These findings were robust in an adjusted analysis (Table 3). The impact of ≥80 to <90% versus ≥90% adherence was less certain for the initiation phase analysis (Model 3), but more suggestive of a dose-response association in the month 1 analysis (Model 4). Considering different confounder sets, these models were robust to adjustment for a fixed effect for county/district rather than urban/rural (Table E5; Models 3F and 4F). When the 52 individuals who discontinued from dose 87 onwards were excluded, our effect estimates increased for both the initiation phase and month 1 analyses (Table E5; Models 3G and 4G). Tests for interaction between early suboptimal dosing implementation and county/district revealed no evidence for an effect (LRT p-value 0.19).

DISCUSSION

Our analysis of adherence- both suboptimal dosing implementation and discontinuation- among pulmonary TB patients in China provides the first detailed description of how doses are missed over the six-month treatment period. We found that participants took 76% of their doses; 61% took 80% or more. The use of simple percentage thresholds, however, masks important variation in the patterns of missed doses over time.

Of all missed doses, 43% were due to discontinuation. A steady increase in non-adherence due to both suboptimal dosing implementation and discontinuation over time was observed. At two months, 5.1% of participants had discontinued their medication, 14.4% at four months, and 36.3% by the end of the 180-day period. During the intensive phase of treatment (the first two months), suboptimal dosing implementation accounted for the majority of non-adherence. Of the 19% of patients who were non-adherent at the end of the intensive phase, discontinuation accounted for 27% of the non-adherence and suboptimal dosing implementation the remainder. During the continuation phase (months 3 to 6), the odds of suboptimal dosing implementation were three times higher than during the intensive phase, but the percentage of patients with suboptimal dosing implementation remained stable at 17-20%. However, the percentage of those who discontinued treatment continued to accumulate, and by the fifth month, discontinuation accounted for 52% of all non-adherence.

We identified an important association between suboptimal dosing implementation early in the course of treatment and subsequent discontinuation. Suboptimal dosing implementation in the first month or overall initiation phase (months 1 and 2) was associated with higher discontinuation rates. Across participants, 96% demonstrated suboptimal dosing implementation; around three quarters of gaps were for one dose only. Nevertheless, 47% of individuals had potentially clinically important gaps of three consecutive doses or more and 23% of seven consecutive doses (a fortnight) or more. The odds of suboptimal dosing implementation were higher on national holidays (OR 1.52).

The findings of this study provide several insights into how drug-sensitive TB treatment can be improved. Firstly, NTPs should take seriously the problem of non-adherence to treatment, which is under-recognized. In this study, a high percentage of patients had gaps of a week or more in their treatment due to suboptimal dosing implementation. If these gaps are not recognized and treatment is not adjusted accordingly, then long-term, relapse-free, cure of these patients may be compromised. NTPs should place a much higher priority on improving adherence during treatment and not simply focus on ensuring completion.

Second, this study identified the importance of early adherence. Adherence worsened over the course of treatment, especially after the shift into the continuation phase. We also found an association between discontinuation and early suboptimal dosing implementation. Thus improving adherence early in the course of treatment may be important to prevent later non-adherence.

Third, this study highlights the importance of granular adherence data on individual patients. Early identification of individuals with poor adherence or who discontinue would improve the likelihood of success of adherence-promoting interventions. Identification of such individuals could result in the initiation of differentiated care, which would include more tailored adherence support for these patients. The design of such behavioral interventions should take into account data on the types of non-adherence displayed by the target population and their causes. For example, plans to support medication adherence may need to be proactively generated with patients before holiday periods, where travel to different locations may generate greater concern about stigma and result in missed doses. Adherence should also be monitored after such interventions are deployed, to check for improvement. Digital technologies to record adherence- e.g. by using pill bottle opening as a surrogate for medication intake- have been available for many years and are starting to be rolled out globally, despite operational barriers such as cost.(33) Such technologies, however, provide an opportunity to monitor TB treatment adherence for individual patients on a large scale.(33)

Fourth, these results lend support to the development of shorter treatment regimens, which may avoid the adherence drop-off later in treatment that is currently observed. Such regimens have not yet demonstrated non-inferiority (34-36) and will likely, however, increase the importance of each individual dose in ensuring cure. Retrieving patients who default from treatment is a large financial burden on NTPs; this could also be reduced with shorter regimens that result in less discontinuation. We also highlight the value of examining discontinuation of treatment, rather than programmatically defined loss to follow-up/default, in terms of capturing effective drug exposure.

Overall, studies prior to ours have provided the initial basis of a link between different adherence patterns and treatment outcomes in drug sensitive disease.(2-9, 11) For example, missing 8-16% of doses has been associated with 25 times the odds of remaining sputum positive,(3) adhering below a 90% threshold with 5.9 times the rate of an unfavorable outcome,(15) adhering below a 75% threshold with 3.2 times the odds of recurrence,(14) adhering below a 90% threshold with 3.4 times the odds of mortality,(4) and ‘irregular’ drug taking such that treatment had to be extended 2.5 times increased odds of relapse.(8) Conversely, a regimen simulating <67% adherence had no impact on recurrence.(37) Additionally, previous studies have documented a 17% additional hazard per month of acquired drug resistance if adherence is <80%,(19) or 19.7 times the odds of with half month gaps, non-engagement or <80% adherence.(16) This association is not simple; particularly poor adherence may exert little selective pressure.(17) In drug resistant disease, there is a smaller but less contradictory evidence base in terms of the implications of non-adherence: long interruptions and <80-90% adherence have been associated with poorer outcomes.(17, 19, 38, 39) What these studies lack- which potentially explains their conflicting findings- is a granular exploration of how non-adherence influences treatment outcomes using reliable sources of adherence data.(23) Our study indicates that poor adherence is complicated and heterogeneous; future studies will require granular dose-by-dose data in order to properly assess the non-adherence-outcomes relationship. Future studies should collect detailed adherence data- moving away from monthly self-reported information and chart reviews- to ascertain how they correlate to therapeutic coverage, pharmacokinetics (TB drugs with a short half-life are predicted to be less forgiving), sputum conversion rates, treatment outcomes,(40) relapse (the gold standard outcome measure), and the development of drug resistance.

This is the most detailed analysis to date of treatment adherence in TB, which makes use of exceptionally granular adherence data. It does, however, have its limitations. Whether drug intake was supported (e.g. observed by a family member) or self-administered was not documented, potentially leaving residual confounding. Opening the medication monitor box does not necessarily mean that drugs were taken, although a validation study has indicated high correlation with urine rifampicin levels.(41) Given that each dose could have been taken during a two-day period, non-differential misclassification of the temporal exposure variables may have occurred, biasing effect estimates towards the null. As fixed dose combination pills were not used, it is possible that non-adherence was underestimated per drug, as individuals may have chosen not to take all their pills per dose. The exclusion of participants for whom a whole dosing history was not available may have resulted in selection bias, as excluded participants differed from included participants in terms of the county/district in which they lived and their distance from home to their local TB clinic. On the basis of tests for interaction, it seems unlikely, however, than temporal factors (the focus of our analysis) are systematically differently associated with adherence across different levels of these variables. Data were missing on participant’s personal holidays, which could be biasing the effect size towards the null. Furthermore, part of the national holiday effect could represent individuals not transporting their monitor boxes with them when they travel, but nevertheless taking their medication. Socio-behavioral data on factors associated with non-adherence, such as stigma, were not collected, potentially resulting in residual confounding. Finally, participants may have been aware that they would be less likely to have taken their drugs at weekends and thus switched their doses from weekends to weekdays to avoid non-adherence. This is a function of the every-other-day dosing of the regimen and would result an over-emphasized effect size.

Four key factors in our study affect generalizability: this was a 1) single country dataset of 2) pulmonary TB patients 3) enrolled in a trial who 4) took their drugs every other day. Being enrolled in a trial is thought to boost adherence and the individuals who consent to participate are often more likely to be adherent; adherence data are therefore also needed from observational studies globally.(42-44) We thus recommend the need for future studies using granular adherence data from observational studies undertaken in other nations.

CONCLUSIONS

In conclusion, we demonstrate how non-adherence to TB treatment is a complex issue that needs to be taken seriously. Adherence worsens over the course of treatment, but early-stage interventions (when suboptimal dosing implementation is first detected) may prevent later discontinuation. For such interventions to be accurately targeted to the patients most in need, individual-level adherence data is required on a large scale. Shorter TB treatment regimens may reduce the impact of worsening adherence over the treatment course.

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VISUAL ABSTRACT

A visual abstract is included with this manuscript.

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FIGURE LEGENDS

Figure 1. Lasagna plot of adherence

Each patient of the 780 participants in the control arm of the original trial is a row in the graph; white indicates a dose that has not been taken. Adherence calculated as a percentage of the 90 doses taken over the 180-day period and then grouped into 20% adherence intervals. Rows are colored by adherence group. Numbers in brackets indicate the number of individuals within each 20% adherence interval.

Figure 2. Relative contribution of discontinuation and suboptimal dosing implementation to non-adherence over time

Non-adherence due to discontinuation (ceasing treatment and not re-commencing; dark grey) versus suboptimal dosing implementation (sporadic missed doses; light grey) over time in a) the 780 control arm patients from the original trial, b) the 659 patients would displayed ≥80% adherence during the initiation phase, c) the 121 patients who displayed <80% adherence in the initiation phase. Discontinuation is ceasing treatment at any stage, including only for the 90th dose. If, after the 90th dose, another was taken before the end of the trial, the patient is not recorded as having discontinued. Discontinuation is not the same as programmatically defined loss to follow-up/default. Graph style adapted from the work of Blaschke *et al.*[28]

Figure 3. Gaps in adherence

Gaps during the 90-dose medication period among the 748 participants who displayed suboptimal dosing implementation. Number of gaps per participant of any length plotted against a) the median gap length per participant, b) the maximum gap length per participant.

Table 1. Baseline characteristics. Unadjusted analyses of factors associated with non-adherence due to suboptimal dosing implementation or discontinuation

	Overall		Analysis of suboptimal dosing implementation					Analysis of discontinuation		
Exposure variables	**Participants**	**Col. %**	**Doses**	**Col. %**	**Doses missed**	**Row %**	**Unadjusted OR (95% CI)**	**Person time (doses)**	**Participants who discontinued**	**Unadjusted HR (95% CI)**
Overall	**780**	**100.0**	**62893**	**100.0**	**9487**	**15.1**	**-**	**62396**	**235**	**-**
Sex										
Female	245	31.4	19804	31.5	2683	13.5	baseline	19649	161	baseline
Male	535	68.6	43089	68.5	6804	15.8	1.20 (0.99-1.45)	42747	74	1.00 (0.76-1.32)
Age categorized (years)										
<30	230	29.5	18305	29.1	2837	15.5	baseline	18157	69	baseline
30-39	128	16.4	10099	16.1	1315	13.0	1.01 (0.95-1.08)	10021	44	0.95 (0.87-1.04)
40-49	167	21.4	13518	21.5	2077	15.4		13422	56	
50-59	136	17.4	11117	17.7	1712	15.4		11023	35	
60+	119	15.3	9854	15.7	1546	15.7		9773	31	
Occupation										
Students	32	4.1	2529	4.0	428	16.9	1.01 (0.64-1.58)	2512	13	1.34 (0.76-2.37)
Worker	74	9.5	6102	9.7	722	11.8	0.61 (0.45-0.84)	6048	17	0.69 (0.42-1.15)
Migrant Worker	74	9.5	6167	9.8	815	13.2	0.76 (0.55-1.03)	6115	17	0.68 (0.41-1.13)
Farmer	384	49.2	30763	48.9	5347	17.4	baseline	30523	122	baseline
Unemployed/ Houseworker	63	8.1	5207	8.3	624	12.0	0.60 (0.43-0.84)	5165	17	0.81 (0.49-1.35)
Other	153	19.6	12125	19.3	1551	12.8	0.68 (0.53-0.86)	12033	49	1.02 (0.73-1.42)
Educational level										
Illiterate	60	7.7	4595	7.3	858	18.7	1.38 (0.92-2.07)	4557	20	1.43 (0.79-2.59)
Lower middle school	494	63.3	39999	63.6	6254	15.6	1.03 (0.78-1.35)	39692	154	1.25 (0.82-1.93)
Upper middle school	130	16.7	10571	16.8	1216	11.5	0.73 (0.52-1.02)	10484	37	1.13 (0.68-1.89)
University or more	96	12.3	7728	12.3	1159	15.0	baseline	7663	24	baseline
Total household income in last calendar year (RMB)										
≥20,000	446	57.2	36044	57.3	4994	13.9	baseline	35754	131	baseline
<20,000	334	42.8	26849	42.7	4493	16.7	1.31 (1.10-1.57)	26642	104	1.07 (0.83-1.38)
Medical insurance										
Rural co-op	500	64.1	40583	64.5	6604	16.3	1.23 (0.96-1.57)	40261	146	0.65 (0.48-0.89)
Urban workers	92	11.8	7843	12.5	946	12.1	0.86 (0.61-1.20)	7773	18	0.40 (0.24-0.69)
No insurance	132	16.9	9855	15.7	1350	13.7	baseline	9786	53	baseline
Other	56	7.2	4612	7.3	587	12.7	0.95 (0.64-1.41)	4576	18	0.71 (0.42-1.21)
Marital status										
1st marriage	551	70.6	45024	71.6	6707	14.9	baseline	44665	161	baseline
Unmarried	184	23.6	14421	22.9	2194	15.2	1.02 (0.82-1.26)	14305	57	1.11 (0.82-1.50)
Other	45	5.8	3448	5.5	586	17.0	1.15 (0.78-1.69)	3426	17	1.43 (0.87-2.35)

Table 1. continued

	Overall		Analysis of suboptimal dosing implementation					Analysis of discontinuation		
Exposure variables	**Participants**	**Col. %**	**Doses**	**Col. %**	**Doses missed**	**Row %**	**Unadjusted OR (95% CI)**	**Person time (doses)**	**Participants who discontinued**	**Unadjusted HR (95% CI)**
County										
Baiquan	100	12.8	7629	12.1	1926	25.2	baseline	7581	46	baseline
Yilan	103	13.2	8683	13.8	1113	12.8	0.40 (0.29-0.56)	8605	15	0.26 (0.15-0.47)
Rugao	78	10.0	6366	10.1	844	13.3	0.39 (0.27-0.56)	6310	21	0.52 (0.31-0.87)
Jianhu	80	10.3	6938	11.0	1270	18.3	0.60 (0.42-0.86)	6878	13	0.29 (0.16-0.54)
Miluo	85	10.9	6961	11.1	1131	16.2	0.55 (0.39-0.78)	6905	24	0.55 (0.34-0.90)
Yueyanglou	81	10.4	5893	9.4	718	12.2	0.35 (0.24-0.50)	5856	42	1.21 (0.79-1.83)
Fengjie	70	9.0	5115	8.1	684	13.4	0.39 (0.27-0.56)	5088	40	1.34 (0.88-2.04)
Shapingba	79	10.1	6311	10.0	915	14.5	0.49 (0.34-0.70)	6258	18	0.45 (0.26-0.78)
Jiangbei	104	13.3	8997	14.3	886	9.8	0.29 (0.21-0.40)	8915	16	0.27 (0.16-0.49)
Rural/urban										
Rural	516	66.2	41692	66.3	6968	16.7	baseline	41367	159	baseline
Urban	264	33.8	21201	33.7	2519	11.9	0.67 (0.55-0.81)	21029	76	0.94 (0.71-1.23)
Residence										
Living in place of household registration	658	84.4	53187	84.6	8191	15.4	baseline	52768	198	baseline
Not living in place of household registration	122	15.6	9706	15.4	1296	13.4	0.80 (0.62-1.03)	9628	37	1.03 (0.72-1.46)
Distance from home to local TB clinic (km)										
<10	188	24.1	15984	25.4	2255	14.1	baseline	15847	37	baseline
10-19	191	24.5	15185	24.1	2199	14.5	1.05 (0.99-1.12)	15065	63	1.14 (1.04-1.24)
20-29	118	15.1	9596	15.3	1451	15.1		9524	40	-
30-39	149	19.1	11802	18.8	1782	15.1		11714	49	-
>=40	134	17.2	10326	16.4	1800	17.4		10246	46	-
Day							p<0.001			
Sunday	-	-	9009	14.3	1516	16.8	baseline	-	-	-
Monday	-	-	8997	14.3	1301	14.5	0.81 (0.74-0.89)	-	-	-
Tuesday	-	-	8939	14.2	1344	15.0	0.84 (0.77-0.92)	-	-	-
Wednesday	-	-	9004	14.3	1315	14.6	0.83 (0.76-0.91)	-	-	-
Thursday	-	-	8895	14.1	1426	16.0	0.93 (0.85-1.01)	-	-	-
Friday	-	-	9275	14.7	1251	13.5	0.74 (0.68-0.81)	-	-	-
Saturday	-	-	8774	14.0	1334	15.2	0.87 (0.80-0.95)	-	-	-

Table 1. continued

	Overall		Analysis of suboptimal dosing implementation					Analysis of discontinuation		
Exposure variables	**Participants**	**Col. %**	**Doses**	**Col. %**	**Doses missed**	**Row %**	**Unadjusted OR (95% CI)**	**Person time (doses)**	**Participants who discontinued**	**Unadjusted HR (95% CI)**
Weekend							p<0.001			
Weekday	-	-	45110	71.7	6637	14.7	baseline	-	-	-
Weekend	-	-	17783	28.3	2850	16.0	1.13 (1.07-1.19)	-	-	-
Month							p<0.001			
1	-	-	11687	18.6	789	6.8	baseline	-	-	-
2	-	-	11298	18.0	1383	12.2	2.92 (2.60-3.28)	-	-	-
3	-	-	10800	17.2	1857	17.2	5.35 (4.66-6.13)	-	-	-
4	-	-	10314	16.4	1843	17.9	5.78 (4.91-6.81)	-	-	-
5	-	-	9770	15.5	1839	18.8	6.31 (5.21-7.65)	-	-	-
6	-	-	9024	14.3	1776	19.7	6.26 (5.01-7.83)	-	-	-
National holidays							p<0.001			
No	-	-	58018	92.2	8487	14.6	baseline	-	-	-
Yes	-	-	4875	7.8	1000	20.5	1.62 (1.49-1.75)	-	-	-
Phase							p<0.001			
Initiation	-	-	22985	36.5	2172	9.4	baseline	-	-	-
Continuation	-	-	39908	63.5	7315	18.3	3.09 (2.70-3.54)	-	-	-
Initiation phase adherence*										p=0.003
≥90%	-	-	-	-	-	-	-	47419	137	baseline
80-90%	-	-	-	-	-	-	-	7373	22	1.05 (0.67-1.64)
<80%	-	-	-	-	-	-	-	6819	36	1.98 (1.37-2.86)
Month 1 adherence**										p=0.003
≥90%	-	-	-	-	-	-	-	51106	171	baseline
80-90%	-	-	-	-	-	-	-	7471	34	1.39 (0.96-2.00)
<80%	-	-	-	-	-	-	-	3757	25	2.10 (1.38-3.19)

Leftmost data columns: baseline characteristics of the 780 individuals from the control arm of the original trial. Middle data columns: unadjusted mixed-effects logistic regression for the 780 individuals included in the analysis of suboptimal dosing implementation. Each model adjusted for clustering by patient. Age and distance to TB clinic modelled as linear variables. Random effect modelled on the initiation-continuation phase and month variables within the relevant unadjusted model. Rightmost data columns: unadjusted Cox regression for the 780 individuals included in the analysis of discontinuation. *740 individuals in the initiation phase adherence model and **775 in the month 1 adherence model; these exposure variables document non-adherence due to suboptimal dosing implementation only. Age and distance to TB clinic modelled as linear variables. All columns: no data were missing for any of the variables. - - not applicable, CI- confidence interval, Col- column, HR- hazard ratio, km- kilometres, OR-odds ratio, RMB- Renminbi, TB- tuberculosis

Table 2. Adjusted odds ratios for the association between suboptimal dosing implementation and a) treatment month, stratified by national holidays or b) national holidays, stratified by treatment month

		National holidays	
		No	Yes
Treatment month, stratified by national holidays			
Treatment month	1	baseline	baseline
	2	2.87 (2.55-3.23)	3.32 (2.15-5.15)
	3	5.23 (4.55-6.01)	5.82 (3.81-8.90)
	4	5.58 (4.72-6.58)	7.34 (4.76-11.31)
	5	6.23 (5.13-7.57)	6.45 (4.11-10.12)
	6	5.90 (4.71-7.40)	10.01 (6.27-15.98)
National holidays, stratified by treatment month			
Treatment month	1	baseline	1.25 (0.85-1.84)
	2	baseline	1.45 (1.15-1.82)
	3	baseline	1.39 (1.16-1.67)
	4	baseline	1.64 (1.36-1.98)
	5	baseline	1.29 (1.06-1.58)
	6	baseline	2.12 (1.71-2.62)

Adjusted regression of the association between non-adherence due to suboptimal dosing implementation and treatment month, stratified by national holidays (top rows) or national holidays, stratified by treatment month (bottom rows); Model 2. 62,893 doses from 780 individuals from the control arm of the original trial included. The stratum-specific ORs are adjusted for weekends, age, sex and rural-urban. Random effect modelled on the month variable. Age modelled as a linear variable. Results per cell presented as OR (95% CI). CI- confidence interval, OR- odds ratio

Table 3. Adjusted Cox regression models of the association between early suboptimal dosing implementation and discontinuation

Temporal factor	Hazard ratio (95% CI)
MODEL 3	
Initiation phase adherence	p=0.004
≥90%	baseline
80-<90%	1.04 (0.66-1.63)
<80%	1.97 (1.36-2.85)
MODEL 4	
Month 1 adherence	p=0.004
≥90%	baseline
80-<90%	1.37 (0.95-1.99)
<80%	2.06 (1.35-3.15)

Model 3 examines the association between non-adherence in the initiation phase due to suboptimal dosing implementation and discontinuation, adjusting for age, sex and rural-urban. It excludes individuals who discontinued in the initiation phase, leaving 740. Model 4 examines the association between non-adherence in the month 1 due to suboptimal dosing implementation and discontinuation, adjusting for age, sex and rural-urban. It excludes individuals who discontinued during month 1, leaving 775. Age modelled as a linear variable. CI- confidence interval

ONLINE SUPPLEMENT

Temporal factors and missed doses of tuberculosis treatment: a causal associations approach to analyses of digital adherence data

Helen R. Stagg, James J. Lewis, Xiaoqiu Liu, Shitong Huan, Shiwen Jiang, Daniel P. Chin, Katherine L. Fielding

Additional Methods

Parent study and study population for analysis: additional details

Between 1st June 2011 and 7th March 2012, in the Heilongjiang, Jiangsu, Hunan, and Chongqing provinces of the People's Republic of China, 4,173 eligible pulmonary TB patients placed on the standard six-month anti-tuberculosis regimen were consented to be enrolled in a pragmatic cluster randomized trial of electronic reminders (short message service [SMS] and audio reminders from a medication monitor box) to improve treatment adherence.(1) The thirty-six clusters were rural counties or urban districts within these provinces. In all arms of the study, each month a patient's medication was placed in their medication monitor box by local health service staff. The box captured every date and time on which it was opened. These data were downloaded at the monthly clinic visits, at which new medication was dispensed.

Within the control arm of the trial, participants were managed according to the standard of care of the National TB Control Program (NTP). They received no electronic reminders to take their medications; their treatment was either self-administered, or supervised by family members or health care workers. Further restrictions to be included within the cohort analyzed in this study were: having no power outage problems with the medication monitor (resulting in box opening not being recorded), no hospital inpatient stay greater than three days, no pausing/stoppage of treatment due to side effects, and being enrolled into the trial on the same day as TB registration such that treatment had not already started and thus all doses could be captured.

Measuring and defining adherence to treatment: interpreting data from the medication monitor

Data from the medication monitor box were interpreted as follows. If the box was opened at least once within each two-day dosing window this was recorded as adherence, together with the date. If the box was not opened within this period no adherence data were recorded by the monitor. To document non-adherence at any point, we inferred the dates of missed doses and thus non-adherence when the monitor did not record being opened. Data from the first 180 days were used in the analysis; data on doses taken after this period were not used.

Temporal exposures and confounding: additional information about categorization

The following temporal measures were calculated from the medication monitor data: 1) the day of the week on which each expected dose of medication fell, 2) the treatment month of the dose (expected doses 1-15 fell in month 1, etc.), 3) whether the expected dose fell on a Chinese national holiday, and finally 4) the first 30 expected doses were assigned to the initiation phase of treatment and the last 60 doses to the continuation phase. The latter division is the norm for TB treatment; in the initiation phase four drugs are used for two months, in the continuation phase two drugs are used for four months. The Chinese national holidays considered were New Year (January), Chinese New Year (January), Tomb Sweeping Day (April), Labor Day (April/May), The Dragon Boat festival (June), mid-autumn festival (September), and National Day (October).

Levels of suboptimal dosing implementation in the initiation phase and month 1 were also calculated and categorized.

Associations between temporal factors and suboptimal dosing implementation: detailed methodology used

Adherence data were included for each patient up until the last dose taken before a permanent stoppage of treatment (discontinuation) or the 180-day end point of the regimen, whichever was sooner. Doses after the 180-day (90 dose) point were considered when assessing discontinuation, however (see Methods: Measuring and defining adherence to treatment).

Our analyses focused on the temporal factors of weekends, national holidays and, separately, either the initiation-continuation phase transition (Model 1) or treatment months (Model 2). Having drawn a directed acyclical graph (DAG), the following were deemed *a priori* confounders: age, sex and rural-urban. Assessing the effect of treatment months in place of the initiation-continuation phase transition was decided upon *ad hoc*, after examining our line graphs.

When building our main adjusted model (Model 1) the following factors were additionally considered from the DAG. On the basis of biological plausibility age, treatment month and distance to tuberculosis (TB) clinic were selected *a priori* for an assessment of goodness of fit as linear or categorical variables. Effect estimates across strata were compared and likelihood ratio tests (LRTs) undertaken. Additionally, interactions between national holidays/weekends and the initiation-continuation phase transition or treatment month were tested for using LRTs. The impact of adding a random effect for treatment month and initiation-continuation phase, such that their effect varied between individuals, was also assessed using LRTs.

Model 1 was adapted by adjusting for different sets of potential confounders in place of rural-urban in addition to the *a priori* confounders. These potential confounders could not all be simultaneously assessed due to collinearity. The confounder sets were: distance from home to local TB clinic (Model 1A), medical insurance (Model 1B), occupation (Model 1C), rural-urban and education level (Model 1D), rural-urban and total household income in the last year (Model 1E).

A sensitivity analysis was conducted to examine the impact of potential clustering by county/district, by including this variable as a fixed effect in place of rural-urban (Model 1F). It could not be included as a random effect, due to the small number of counties/districts.

Associations between early suboptimal dosing implementation and time to discontinuation: detailed methodology used

Non-adherence due to suboptimal dosing implementation was categorized into three levels: <80%, 80-89% and ≥90%. The same *a priori* confounders and rural-urban variable were adjusted for as previously, on the basis of a DAG. The validity of the proportional hazards assumption was assessed using a likelihood ratio test (LRT) for an interaction between time and the main exposure of interest.

A sensitivity analysis was also conducted for Models 3 and 4 using a fixed effect for county/district in place of rural-urban status (Models 3F and 4F). An additional analysis excluded individuals who discontinued during the last three doses (approximately a week), in order to focus on earlier time points of discontinuation (Models 3G and 4G).

Table E1. Comparison of baseline characteristics between individuals included in and excluded from the analysis cohort

p-values from X^2 tests.

	Analysis dataset				
Exposure variables	**Included**	**Col. %**	**Excluded**	**Col. %**	**p-value**
Overall	**780**	**70.7**	**324**	**29.3**	
Sex					p=0.09
Male	535	68.6	239	73.8	
Female	245	31.4	85	26.2	
Age categorised (years)					p=0.73
<30	230	29.5	103	31.8	
30-39	128	16.4	49	15.1	
40-59	303	38.8	129	39.8	
60+	119	15.3	43	13.3	
Occupation					p=0.28
Students	32	4.1	22	6.8	
Worker	74	9.5	27	8.3	
Migrant Worker	74	9.5	24	7.4	
Farmer	384	49.2	156	48.1	
Unemployed/Houseworker	63	8.1	22	6.8	
Other	153	19.6	73	22.5	
Educational level					p=0.61
Illiterate	60	7.7	21	6.5	
Lower middle school	494	63.3	199	61.4	
Upper middle school	130	16.7	64	19.8	
University or more	96	12.3	40	12.3	
Total household income in last calendar year (RMB)					p=0.92
≥20,000	320	41.0	134	41.4	
<20,000	460	59.0	190	58.6	
Medical insurance					p=0.56
Rural co-op	500	64.1	210	64.8	
Urban workers	92	11.8	42	13.0	
No insurance	132	16.9	56	17.3	
Other	56	7.2	16	4.9	
Marital status					p=0.41
1st marriage	551	70.6	219	67.6	
Unmarried	184	23.6	80	24.7	
Other	45	5.8	25	7.7	
County					p<0.001
Baiquan	100	12.8	25	7.7	
Yilan	103	13.2	20	6.2	
Rugao	78	10.0	40	12.3	
Jianhu	80	10.3	39	12.0	
Miluo	85	10.9	33	10.2	
Yueyanglou	81	10.4	38	11.7	
Fengjie	70	9.0	60	18.5	
Shapingba	79	10.1	52	16.0	
Jiangbei	104	13.3	17	5.2	
Rural/urban					p=0.79
Rural	516	66.2	217	67.0	
Urban	264	33.8	107	33.0	

Table E1. continued

	Analysis dataset				
Exposure variables	**Included**	**Col. %**	**Excluded**	**Col. %**	**p-value**
Residence					p=0.97
Living in place of household registration	658	84.4	273	84.3	
Not living in place of household registration	122	15.6	51	15.7	
Distance from home to local TB clinic (km)					p=0.003
<10	188	24.1	69	21.3	
10-29	309	39.6	117	36.1	
30-39	149	19.1	51	15.7	
>=40	134	17.2	87	26.9	

Table E2. Adjusted logistic regression of the association between temporal factors and suboptimal dosing implementation, adjusting for different confounder sets

Adjusted models of the association between the temporal factors weekend, national holidays, and treatment phase and the outcome of non-adherence due to suboptimal dosing implementation. All models derive from Model 1. Each adjusts for the other temporal factors listed in the relevant stratum of the table plus age, sex and: distance from home to local TB clinic rather than rural-urban (Model 1A), medical insurance rather than rural-urban (Model 1B), occupation rather than rural-urban (Model 1C), both rural-urban and education level (Model 1D), rural-urban and total household income in last calendar year (Model 1E), county/district rather than rural-urban (Model 1F). 62,893 doses from 780 individuals in the control arm of the original trial included. Random effect modelled on the initiation-continuation phase variable. Age and distance to TB included as linear variables, where relevant. CI- confidence interval, OR- odds ratio, TB- tuberculosis.

Temporal factor		OR (95% CI)
MODEL 1A		
Weekend		p<0.001
	Weekday	baseline
	Weekend	1.14 (1.08-1.20)
National holidays		p<0.001
	No	baseline
	Yes	1.52 (1.39-1.65)
Phase		p<0.001
	Initiation	baseline
	Continuation	3.07 (2.68-3.51)
MODEL 1B		
Weekend		p<0.001
	Weekday	baseline
	Weekend	1.14 (1.08-1.20)
National holidays		p<0.001
	No	baseline
	Yes	1.52 (1.39-1.65)
Phase		p<0.001
	Initiation	baseline
	Continuation	3.07 (2.68-3.51)
MODEL 1C		
Weekend		p<0.001
	Weekday	baseline
	Weekend	1.14 (1.08-1.20)
National holidays		p<0.001
	No	baseline
	Yes	1.52 (1.39-1.65)
Phase		p<0.001
	Initiation	baseline
	Continuation	3.08 (2.69-3.53)
MODEL 1D		
Weekend		p<0.001
	Weekday	baseline
	Weekend	1.14 (1.08-1.20)
National holidays		p<0.001
	No	baseline
	Yes	1.52 (1.39-1.65)
Phase		p<0.001
	Initiation	baseline
	Continuation	3.06 (2.67-3.50)
MODEL 1E		
Weekend		p<0.001
	Weekday	baseline
	Weekend	1.14 (1.08-1.20)
National holidays		p<0.001
	No	baseline
	Yes	1.52 (1.39-1.65)
Phase		p<0.001
	Initiation	baseline
	Continuation	3.07 (2.69-3.52)

Table E2. continued

Temporal factor		OR (95% CI)
MODEL 1F		
Weekend		p<0.001
	Weekday	baseline
	Weekend	1.14 (1.08-1.20)
National holidays		p<0.001
	No	baseline
	Yes	1.52 (1.39-1.65)
Phase		p<0.001
	Initiation	baseline
	Continuation	3.14 (2.74-3.60)

Table E3. Adjusted odds ratios for the association between suboptimal dosing implementation and the initiation-continuation phase transition, stratified by county

		Phase	
		Initiation	Continuation
County	Baiquan	baseline	5.12 (3.69-7.11)
	Yilan	baseline	2.64 (1.88-3.71)
	Rugao	baseline	2.12 (1.44-3.13)
	Jianhu	baseline	2.63 (1.83-3.78)
	Miluo	baseline	3.31 (2.28-4.78)
	Yueyanglou	baseline	2.48 (1.65-3.73)
	Fengjie	baseline	4.18 (2.71-6.44)
	Shapingba	baseline	4.05 (2.75-5.98)
	Jiangbei	baseline	2.44 (1.73-3.45)

Adjusted regression of the association between non-adherence due to suboptimal dosing implementation and the initiation-continuation phase transition (Model 1), stratified by county (Model 1G). 62,893 doses from 780 individuals from the control arm of the original trial included. The stratum-specific ORs are adjusted for weekends, holidays, age, sex and county. Random effect modelled on the initiation-continuation phase variable. Age modelled as a linear variable. Results per cell presented as OR (95% CI). CI- confidence interval, OR- odds ratio

Table E4. Adjusted odds ratios for the association between suboptimal dosing implementation and holidays, stratified by county

		Holiday	
		No	Yes
County	Baiquan	baseline	0.94 (0.75-1.18)
	Yilan	baseline	1.49 (1.18-1.88)
	Rugao	baseline	1.43 (1.08-1.89)
	Jianhu	baseline	1.39 (1.10-1.77)
	Miluo	baseline	1.77 (1.37-2.28)
	Yueyanglou	baseline	1.57 (1.17-2.11)
	Fengjie	baseline	1.41 (1.02-1.94)
	Shapingba	baseline	1.75 (1.35-2.27)
	Jiangbei	baseline	2.37 (1.89-2.96)

Adjusted regression of the association between non-adherence due to suboptimal dosing implementation and holidays (Model 1), stratified by county (Model 1H). 62,893 doses from 780 individuals from the control arm of the original trial included. The stratum-specific ORs are adjusted for weekends, initiation-continuation phase transition, age, sex and county. Random effect modelled on the initiation-continuation phase variable. Age modelled as a linear variable. Results per cell presented as OR (95% CI). CI- confidence interval, OR- odds ratio

Table E5. Adjusted Cox regression models of the association between early suboptimal dosing implementation and discontinuation- sensitivity analysis

Sensitivity analysis of the association between suboptimal dosing implementation in the initiation phase or month 1, and discontinuation. Model 3F examines the association between suboptimal dosing implementation in the initiation phase and discontinuation, adjusting for age, sex and county/district (as opposed to rural-urban in Model 3). It excludes individuals who discontinued in the initiation phase, leaving 740. Model 3G examines the association between suboptimal dosing implementation in the initiation phase and discontinuation whilst excluding individuals who discontinued after dose 86 (688 people in the model) and adjusts for the same confounders as Model 3. Model 4F examines the association between suboptimal dosing implementation in month 1 and discontinuation, adjusting for age, sex and county/district (as opposed to rural-urban in Model 4). It excludes individuals who discontinued during month 1, leaving 775. Model 4G examines the association between suboptimal dosing implementation in month 1 and discontinuation whilst excluding individuals who discontinued after dose 86 (723 people in the model) and adjusts for the same confounders as Model 4. Age modelled as a linear variable in all models. CI- confidence interval.

Temporal factor	**Hazard ratio (95% CI)**
MODEL 3F	
Initiation phase adherence	p=0.001
≥90%	baseline
80-<90%	1.17 (0.74-1.84)
<80%	2.14 (1.46-3.14)
MODEL 3G	
Initiation phase adherence	p=0.001
≥90%	baseline
80-<90%	1.28 (0.78-2.09)
<80%	2.40 (1.59-3.62)
MODEL 4F	
Month 1 adherence	p=0.002
≥90%	baseline
80-<90%	1.53 (1.05-2.22)
<80%	2.06 (1.33-3.16)
MODEL 4G	
Month 1 adherence	p=0.001
≥90%	baseline
80-<90%	1.51 (1.00-2.28)
<80%	2.39 (1.52-3.78)

REFERENCES

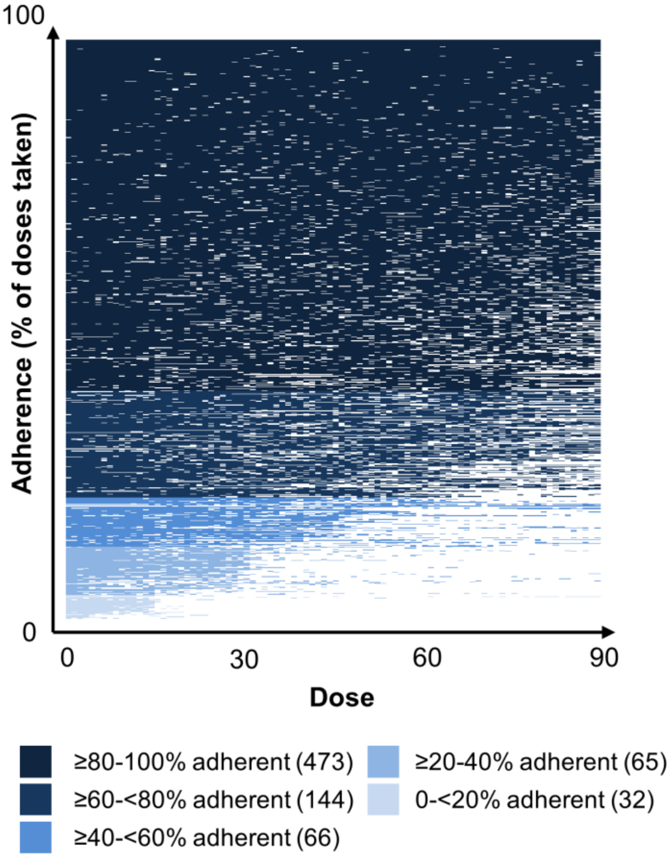
1. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. *PLoS Med* 2015;12:e1001876.

FIGURE LEGENDS

Figure E1. Flow chart of participants

Flow chart documenting participation from the original trial to this study. Side effects could lead to temporary or permanent medication stoppage; in either instance, adherence data were no longer collected.

Figure 1



100
Adherence (% of doses taken)
0
0
30
60
90
Dose
≥80-100% adherent (473)
≥60-<80% adherent (144)
≥40-<60% adherent (66)
≥20-40% adherent (65)
0-<20% adherent (32)

Figure 2

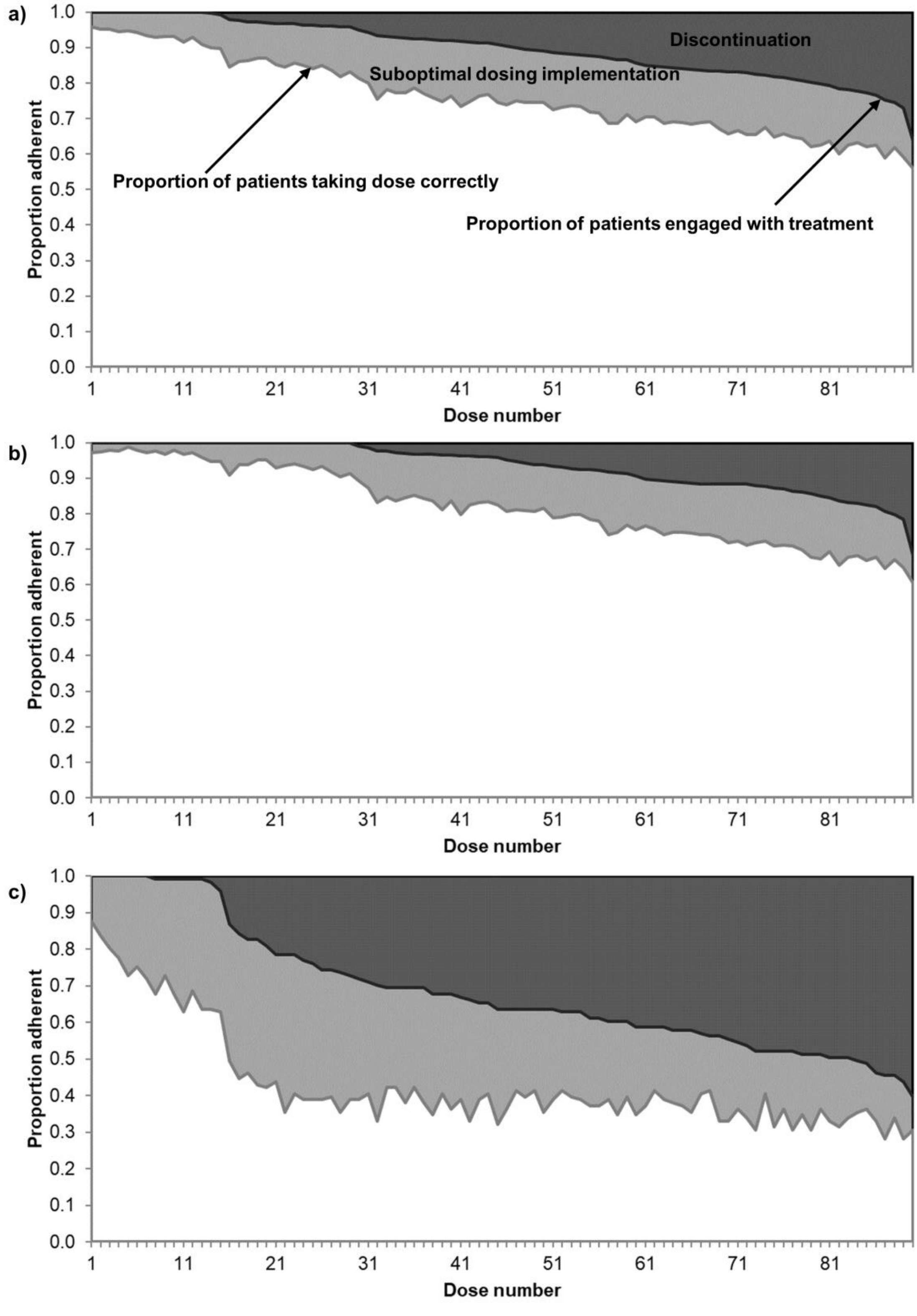
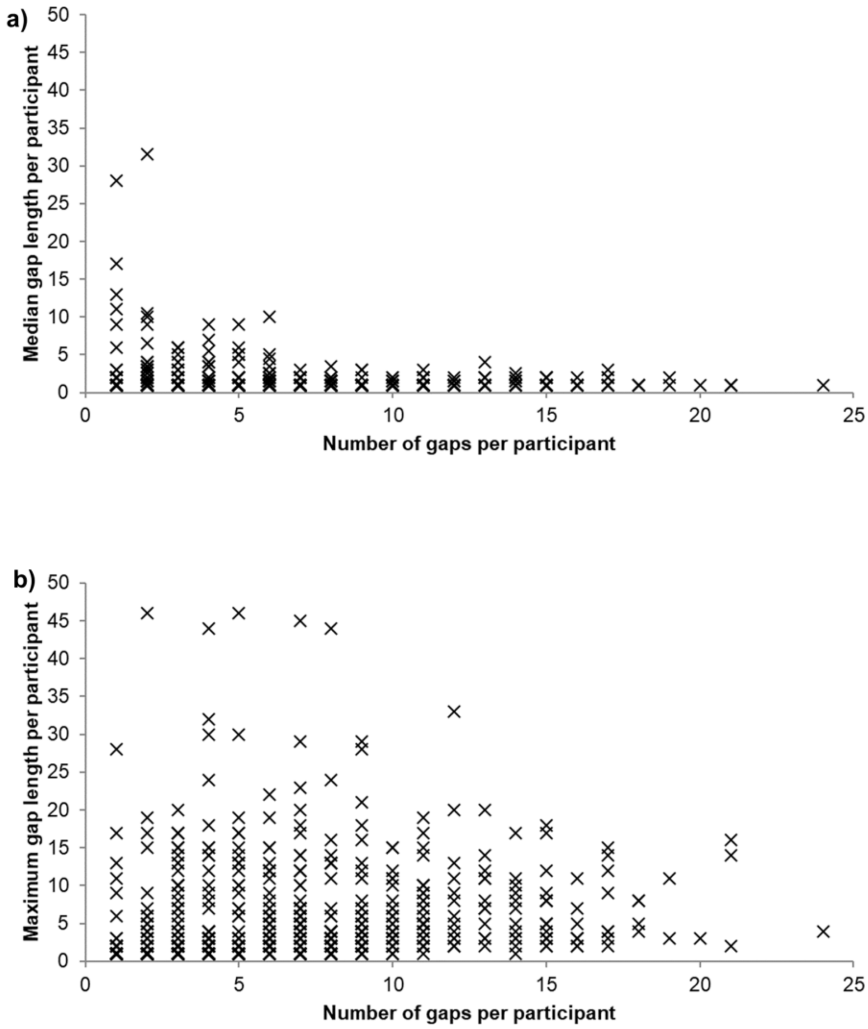
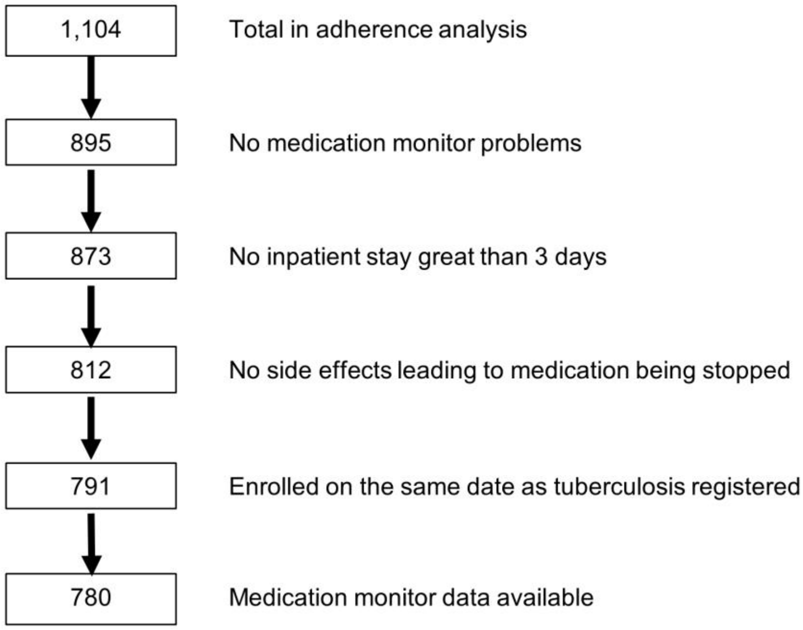

a)
Discontinuation
Suboptimal dosing implementation
Proportion of patients taking dose correctly
Proportion of patients engaged with treatment
Proportion adherent
Dose number
b)
Proportion adherent
Dose number
c)
Proportion adherent
Dose number

Figure 3



a)
Median gap length per participant
Number of gaps per participant
b)
Maximum gap length per participant
Number of gaps per participant

Figure E1


1,104
Total in adherence analysis
895
No medication monitor problems
873
No inpatient stay great than 3 days
812
No side effects leading to medication being stopped
791
Enrolled on the same date as tuberculosis registered
780
Medication monitor data available