

# TUBERCULOSIS TREATMENT WITH MOBILE-PHONE MEDICATION REMINDERS IN NORTHERN THAILAND

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**Abstract.** Thailand's implementation of the Directly Observed Treatment, Short course (DOTS) strategy to increase tuberculosis (TB) control program efficacy has not achieved the World Health Organization (WHO) TB key targets. We defined two TB control models in the study. Patients in Model 1 were treated with a conventional DOTS strategy and in Model 2, patients were treated the same as Model method 1 but were given a phone call reminder to take their medication. Multi-drug resistant tuberculosis (MDR-TB) and non-MDR-TB patients were randomized into either Model 1 or 2. Treatment outcomes were given as cure rates, completion rates, failure rates or success rates at 18 months in the MDR-TB group and 6 months in the non-MDR-TB group. The sputum conversion rate at 1 month were evaluated for both groups. In the MDR-TB group, the sputum conversion rate was 20% (95% CI 8-45) in Model 1 and 90% (95% CI 73-98) in Model 2 ( $p<0.001$ ). In the non-MDR-TB group, the sputum conversion rate was 52% (95% CI 36-70) in Model 1 and 37% (95% CI 22-56) in Model 2 although the difference was not significant ( $p=0.221$ ). The Model 2 success rates were significantly higher (73.7%, 96.7%) in both the MDR-TB and non-MDR-TB groups ( $p<0.001$ ,  $p=0.047$ ). The MDR-TB rate in northern Thailand decreased from 4.1% during April-September 2008 to 1.8% during April-September 2009. Further study of the association between implementation of Model 2 and MDR-TB incidence reduction needs to be carried out.

**Keywords:** tuberculosis, DOTS, MDR-TB, phone call reminder

## INTRODUCTION

Tuberculosis (TB) is a health problem that has become worse due to the AIDS

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epidemic, migration of infected populations and inadequate attention by administrators (WHO SEARO, 2003). Each year there are about 5 million new patients and 2 million deaths from this disease, 95-98% are in developing countries (WHO, 2008a). The WHO has announced the TB public health problem is an emergency requiring urgent corrective action (WHO, 2007).

The WHO ranks Thailand at number 18 of the top 22 countries worldwide with a TB problem (WHO, 2007). Despite using Directly Observed Treatment, Short course (DOTS) by the National Tuberculosis Program (NTP) since 1997 (WHO, 2008b), the TB cure rate in Thailand has not achieved the WHO target and the drug-resistance rate has not decreased, especially in northern Thailand where AIDS has been spreading at a rapid rate (Weniger *et al*, 1991). Currently, 30% of TB patients are also HIV infected (Pokaew, 2009). The TB death rate is 30% (Corbett *et al*, 2003). Non-tuberculous mycobacterium (NTM) cannot be distinguished from *Mycobacterium tuberculosis* (MTB) by sputum smear for acid-fast bacilli (AFB). The rate of multidrug-resistant tuberculosis (MDR-TB) has increased, both primary drug resistance and acquired drug resistance (Yoshiyama *et al*, 2001, 2004). The rate of never treated MDR-TB patients is 4% according to the Office of Disease Prevention and Control in Chiang Mai (Kunawararak *et al*, 2010). Yoshiyama *et al* (2001, 2004) studied MDR-TB in the areas with a high prevalence AIDS in Thailand, such as Chiang Rai Province, and found the MDR-TB rate is 6.3%, showing MDR-TB is common among never treated TB patients.

DOTS is recommended by the WHO to treat MDR-TB (WHO, 2006); they recommend obtaining a culture and sensitivity from TB infected patients, having an adequate supply of medication and using DOTS in areas having a high incidence of MDR-TB. One study (WHO, 2008a) showed the TB Center Zone 10 in Chaing Mai, Thailand has used DOTS with acceptable results. The TB Center Zone 10, Office of Disease Prevention and Control 10 in Chiang Mai, Thailand can perform culture and sensitivity testing of TB iso-

lates. The Chiang Mai Provincial Health Office has used mobile phone reminders to take medications, in TB patients in San Pa Tong and Sarapi Districts with satisfactory results and improved cure rates (Visarutrat *et al*, 2009). The DOTS program using mobile phone call reminders to take medicine regularly may have a positively effect on MDR-TB control. Therefore, we aimed to study the effect of mobile phone reminders on the control of MDR-TB in northern Thailand.

## MATERIALS AND METHODS

In this study, we evaluated 2 models for TB control: DOTS only *vs* DOTS with a mobile phone reminder.

### Model 1-DOTS only

Treatment of patients in Model 1 was carried out according to WHO recommendations using DOTS (WHO, 2006b).

### Model 2-DOTS with mobile phone reminder

Treatment of patients in Model 2 was carried out the same as in Model 1 except with a daily phone call reminder to take their medication using a mobile phone.

### Study population

The study population was new sputum smear positive pulmonary TB patients (both non-MDR-TB and MDR-TB) diagnosed at a public hospital in 7 provinces of northern Thailand between April 2008 and December 2009. Once diagnosed as having TB by a doctor, the sputum was sent to the TB Center Region 10, Chiang Mai, Thailand to determine if the patient had *M. tuberculosis* using a PCR technique, with extraction using the Boom technique, amplification with the NASBA technique and detection with the molecular technique (Boom *et al*, 1990; Van Der Vliet *et al*, 1993; Tyagi *et al*, 1996) and

perform drug sensitivity testing (DST) using the methods of the National Committee for Clinical Laboratory Standards (NCCLS). Both results were reported to the treating hospital within one month.

#### **Inclusion criteria**

The inclusion criteria were patients aged >15 years diagnosed with MTB who had never been treated with a second-line TB drug, patients in whom DST and HIV testing were performed and whose liver function test results were lower than 2 times the upper limits of normal.

#### **Exclusion criteria**

Exclusion criteria were pregnant patients, MDR-TB patients resistant to three or more of six classes of second-line drugs, patients with a history of epilepsy or alcoholism, patients who could not answer questions by the researcher and patients who could not complete the treatment.

Patient in both models were treated with medication as recommended by WHO guidelines (WHO, 1997, 2006). Patients with resistance to isoniazid (H) and rifampicin (R) or HR and streptomycin (S) were treated with 6K<sub>5</sub>OPEZ/12OPEZ [kanamycin (K) ofloxacin (O), para-amino salicylic acid (P), ethambutal (E) and pyrazinamide (Z)]. Patients with resistance to HR and ethambutol (E) or HRSE were treated with 6K<sub>5</sub>OPeTz/12OPeTz [using ethionamide (Et) instead of ethambutal]. Non-MDR-TB patients were treated with 2HRZE/4HR or 2HRZS/4HR (WHO, 2006). MDR-TB patients received their medicine from a central hospital and non-MDR-TB patients received their medicine from a district hospital. Patients were seen monthly at the TB clinic at the hospital, were examined by a nurse, had a sputum examination and were given medication counseling by a pharmacist. HIV positive patients also had a home visit by a health

volunteer. A family member observed the patient taking their medicine on a daily basis in compliance with DOTS.

Model 2 patients were contacted via mobile phone by an officer of the TB Center Zone 10 to remind them to take their medication. For patients with no mobile phone, a mobile phone was provided for them to receive the reminder to take their medication, give advice about taking medication, and remind them to come in for their appointment to receive medicine and to remind them to collect a sputum specimen every month.

Ethical approval was obtained from the Department of Disease Control, Ministry of Public Health, Thailand and Chulalongkorn University Institutional Review Board and Ethics Committee.

#### **Data collection and analysis**

Data regarding MDR-TB cases was collected from the database of the TB system of the Thai MOPH-US CDC Collaboration center (TUC). Cure rates, completion rates, failure rates and success rates at 18 months for the MDR-TB group and at 6 months for the non-MDR-TB group and conversion rates at 1 month for both groups were calculated. Conversion was calculated from the onset of treatment to the date in which the sputum was negative for acid-fast bacilli (AFB) and was estimated using the Kaplan-Meier method. The difference in conversion rates was determined using the Log-Rank test. The Kaplan-Meier method was used to compare differences in conversion between the two groups (MDR-TB group, non-MDR-TB group). All values were two-sided, and a value <0.05 was considered statistically significant.

The definition for Cure Rate was the percentage of patients who completed treatment and were culture negative during

the last month of treatment and on at least one other occasion for non-MDR-TB and who had at least 5 consecutive results in the previous 12-15 months for MDR-TB. Completion Rate was defined as the percentage of MDR-TB and non-MDR-TB patients who completed treatment according to guidelines but did not meet the definition for cure or treatment failure due to a lack of bacteriological results. A Failure Rate was defined as the percentage of patients who were initially smear-positive and remained smear-positive at month 5 or later during treatment among non-MDR-TB patients. Treatment was considered to have failed if 2 or more of the 5 cultures during the final 12-15 months were positive or if any of the final three cultures were positive in MDR-TB patients. Success Rate was defined as the percentage of new smear-positive patients who were cured (negative on sputum smear examination) and the percentage who complete a course of treatment without bacteriological confirmation of cure.

Statistical analyses were performed using STATA (version 10.1.) and Epi Info (version 6.0).

## RESULTS

Three thousand nine hundred ninety-three patients had TB sputum specimens positive for AFB from April 2008 to September 2009 and NTM was found in 264 patients (6.6%) (Table 1). Of the patients with MTB (3,060), MDR-TB was found in 87 patients (2.8%).

The baseline characteristics of the patients are shown in Table 2. Of the 87 patients with MDR-TB, 38 were enrolled in the study and of the 2,980 MTB patients, 60 were enrolled in the study.

In the MDR-TB group, the sputum conversion rate at 1 month was 90%

Table 1  
Result of Mycobacteria culture in the study population.

Result of exam	Number (N =3,993)	Percent
No growth	495	12.3
Contaminated	174	4.4
NTM	264	6.6
MTB	3,060	76.6

NTM, Non-tuberculous Mycobacteria  
MTB, *Mycobacterium tuberculosis*

(95%CI, 73-98) with Model 2 (DOTS plus mobile phone) and 20% (95%CI 8-45) with Model 1 (DOTS only) (Fig 1a) ( $p<0.001$ ). In the non-MDR-TB group, the sputum conversion rate at 1 month was 37% (95%CI 22-56) with Model 2 and 52% (95%CI 36-70) with Model 1 (Fig 1b) ( $p=0.221$ ).

In the MDR-TB group treated for 18 months with Model 2 and the non-MDR-TB group treated for 6 months with Model 2, the success rates were 100%. In the MDR-TB group treated using Model 1 the success rate was 73.7% and in the non-MDR-TB group treated with Model 1 the success rate was 96.7%. The differences were significant for both the MDR-TB group ( $p=0.0001$ ) and the non-MDR-TB group ( $p=0.047$ ) between the two models (Table 3).

There was a decrease in MDR-TB patients between April 2008 and September 2009 (Fig 2).

## DISCUSSION

During the study, the incidence of MDR-TB in northern Thailand declined from 4.1% (April-September, 2008) to 1.8% (April-September, 2009).

Model 2 increased the success rate of

Table 2  
Baseline demographics and clinical characteristics of study population.

Characteristics	MDR-TB group Total 38 patients		Non-MDR-TB group Total 60 patients	
	DOTS without mobile phone Model 1 <i>n</i> (%)	DOTS with mobile phone Model 2 <i>n</i> (%)	DOTS without mobile phone Model 1 <i>n</i> (%)	DOTS with mobile phone Model 2 <i>n</i> (%)
Sex				
Male	12 (63.2)	12 (63.2)	19 (61.3)	20 (66.7)
Female	7 (36.8)	7 (36.8)	12 (38.7)	10 (33.3)
Mean age (year)	45	35.8	56.0	50.1
Type of patient				
New	6 (31.6)	7 (36.8)	30 (100)	28 (93.4)
Relapse/TAD <sup>a</sup>	13 (68.4)	12 (63.2)	0	2 (6.6)
HIV infection				
Yes	1 (5.0)	2 (10.0)	4 (13.3)	2 (6.7)
No	18 (95.0)	17 (90.0)	26 (86.7)	28 (93.3)
Diabetes mellitus				
Yes	2 (10.0)	5 (25.0)	6 (20.0)	5 (16.7)
No	17 (90.0)	14 (75.0)	24 (80.0)	25 (83.3)

<sup>a</sup>TAD = Treated after default

Table 3  
Treatment outcomes of studied population.

Treatment outcome	MDR-TB group		Non-MDR-TB group	
	DOTS without mobile phone Model 1 <i>n</i> (%)	DOTS with mobile phone Model 2 <i>n</i> (%)	DOTS without mobile phone Model 1 <i>n</i> (%)	DOTS with mobile phone Model 2 <i>n</i> (%)
Cured	6 (31.6)	19 (100)	23 (76.7)	30 (100)
Completed	8 (42.1)	0 (0)	6 (20.0)	0 (0)
Failed	5 (26.3)	0 (0)	1 (3.3)	0 (0)
Success	14 (73.7)	19 (100)	29 (96.7)	30 (100)

the sputum conversion rate at 1 month (84.1%) and may have been a factor in improving MDR-TB treatment success. The sputum conversion rate at 1 month in Model 1 was lower (57.9%).

Using a mobile phone helped improved treatment of patients with MDR-TB by reminding them to take their medicine, reminding them to submit their sputum specimen, by answering patient

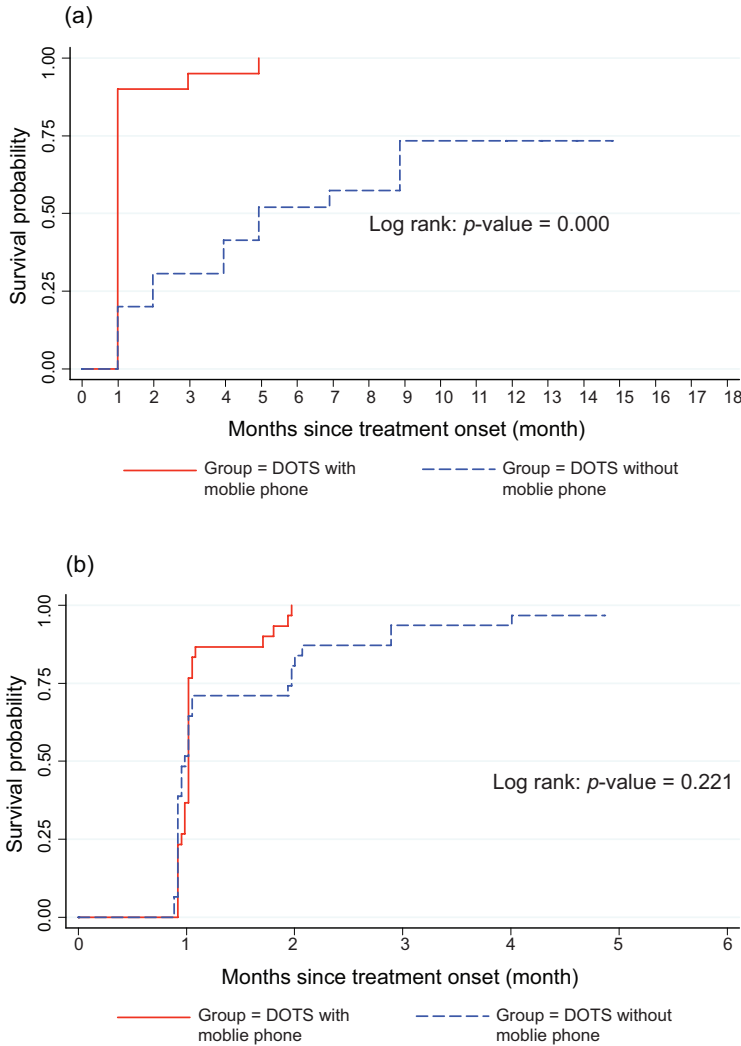


Fig 1–The Kaplan-Meier estimate for sputum conversion in the MDR-TB group by 18 months of treatment (a) and in the non-MDR-TB group by 6 months of treatment (b).

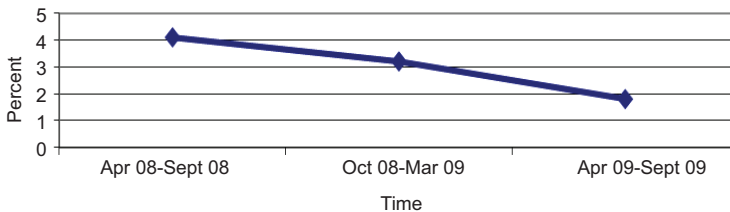


Fig 2–MDR-TB rates in northern, Thailand during April 2008-September 2009.

questions, by improving medication compliance, by improving patient understanding of the treatment of TB, by supporting patients and by maintaining confidentiality.

In one case Method 1 had a negative effect when an officer contacted a patient's teacher at school to ensure medication compliance and the teacher said he intended to have the student stop attending class. This type of problem could be avoided by following Model 2.

Our findings are similar to those of Visarutrat *et al* (2009) who found phone call reminders helped patient feel good, not alone in their treatment and not socially isolated.

In Thailand the success rate for the TB treatment program is only 72% (WHO, 2009), which is lower than the WHO target. A study in India found a treatment success rate of only 65% (Tuberculosis Research Center, 2001). WHO studies from the Philippines (Nathanson *et al*, 2006), Estonia (Tupasi *et al*, 2006) and Russia (WHO, 2005) found TB success rates using DOTS of 60-75%. The cure rate among new patients was higher than among patients who had been treated before. Model 2 resulted in better outcomes among MDR-TB patients.

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