

## RESEARCH NOTE

# A STEP-WISE APPROACH TO FIND A VALID AND FEASIBLE METHOD TO DETECT NON-ADHERENCE TO TUBERCULOSIS DRUGS

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**Abstract.** A step-wise approach to identify valid and feasible methods to detect non-adherence to tuberculosis drugs was evaluated in a prospective study among pulmonary tuberculosis patients in an outpatient clinic in Indonesia. First, adherence was measured by self-reporting with the standardized Morisky questionnaire, physician assessment, pill-count, visit attendance, diary and an electronic medication event monitoring system (MEMS). Next, validity of single methods was assessed against MEMS as gold standard. Feasibility of methods was then judged by physicians in the field. Finally, when valid and feasible methods were combined, it appeared that self-reporting by a questionnaire plus physician assessment could identify all non-adherent patients. It is recommended to use a systematic approach to develop a valid and locally feasible combination of methods to detect non-adherence to TB drugs.

### INTRODUCTION

Non-adherence to tuberculosis (TB) treatment is a major problem for cure of TB. It may lead to treatment failure, relapse, acquired drug resistance and continuing transmission of TB (Fox, 1983; Sumartojo, 1993; Pablos-Mendez *et al*, 1997). The WHO has recommended DOT (Directly Observed Therapy) and this has been shown to increase patient adherence, decrease drug resistance and transmission of TB in the community (Weis *et al*, 1994). However, daily witnessed drug intake is not always feasible in a high volume setting, such as our outpatient clinic in Indone-

sia, a country with the third highest TB case-load worldwide (WHO, 2006). Patients in our clinic are involved in clinical trials with TB drugs and this requires good adherence. Therefore, valid and feasible method(s) to detect non-adherence are needed both for the clinical and research setting.

Numerous direct and indirect methods for measuring patient adherence are now available (Farmer, 1999). All these methods have specific advantages and disadvantages, for which reason a combination of methods is recommended for monitoring adherence (Farmer, 1999). In regard to the validity of these methods, many consider electronic monitoring using MEMS (Medication Event Monitoring System) as the reference or gold standard (Urquhart, 1992; Cramer, 1995; Farmer, 1999). MEMS is a standard-sized medication

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container fitted with a special cap containing a microprocessor, which records each time the cap is opened as a presumptive time of drug intake (Cramer, 1995). Apart from being valid, a method for measuring adherence should also be feasible in the setting where it is to be used. Our study aimed to evaluate a step-wise approach to identify a combination of valid and feasible methods to detect non-adherence to TB treatment.

## MATERIALS AND METHODS

We conducted a prospective study on consecutively selected pulmonary TB patients in the first two months of TB treatment, who were aged > 15 years old and were treated at an out-patient urban pulmonary clinic (BP4) in Bandung, Indonesia, visited by more than 12,000 patients per year. All patients received TB drugs and pyridoxine according to the Indonesian National TB Program. Exclusion criteria were inability to read or write or attend the clinic every 2 weeks as appointed.

Our step-wise approach to identify valid and feasible methods to detect non-adherence started by measuring adherence with several methods. As a second step, the validity of each method was assessed among those patients who used MEMS by calculating the sensitivity, specificity, positive and negative predictive values (Ransohoff and Feinstein, 1978) for the detection of non-adherence, with MEMS as gold standard. Thirdly, the feasibility of each single method was assessed based on experience gained with monitoring all patients in the study. Finally, an optimal combination of two methods was defined based on previously assessed validity and feasibility of each of the single methods.

Available methods used in this study were self-assessment using a questionnaire, physician assessment, pill count, visit attendance, diary and MEMS. Due to the expense of MEMS, a subset of patients (the first 30 pa-

tients) received these devices. All patients were monitored for four weeks and adherence was assessed at two and four weeks.

For self-assessment, patients filled-in the standardized Morisky questionnaire, consisting of four questions related to the intake of medication (Morisky *et al*, 1986). For physician assessment, a physician with experience in counseling and treating TB patients estimated each patient's adherence based on a short discussion about drug intake. A pill-count was performed by comparing the number of returned empty drug blisters to the number of blisters that was handed out at the previous visit. According to the visit attendance method, adherence was 100% if the patient attended the clinic according to the appointments, 0% if they did not. A diary was used by the patients to record any drug intake and time of intake. Finally, for 30 patients we put 28 pyridoxine tablets of the TB program into a MEMS bottle and asked patients to take these tablets from this device.

The extent of adherence was expressed as a percentage, except for the Morisky questionnaire, which defines adherence as high, medium or low. As we wanted to be sure that we would detect all non-adherence, adherence values below 100%, or medium/low according to Morisky scale, were considered as non-adherence.

## RESULTS

Seventy-nine patients were included; 30 were given MEMS bottles. The median age of the patients was 32 years (range: 16 - 84 years) and 49% were male. Most of them (80%) had an income of two US dollars or less per day combined with a low educational level (50% had only completed primary school). Three quarters (76%) of the patients were in the first month of TB treatment, and had more than four symptoms of pulmonary TB (81%). There were no differences in



baseline characteristics between patients who were given MEMS caps and those who were not.

According to the various individual methods, 43% (self-reporting with the Morisky questionnaire), 50% (physician assessment), 47% (pill-count), 26% (visit attendance), 23% (diary) and 43% (MEMS, applied in 30/79 patients) of patients were non-adherent to some extent. As assessed by the first three methods, there were no differences in the percents of non-adherent patients between those who used MEMS and those who did not.

All methods apart from visit attendance were considered to have an acceptable sensitivity and negative predictive value to detect non-adherence, when compared with MEMS as the gold standard (Table 1).

The physician assessment and pill-count methods of assessing compliance were simple and easy to carry out. The diary method imposed too much a burden on the patients, be-

cause they had to write down their drug intake every day. MEMS is the gold standard, but is too expensive in our setting.

During the final stage of our stepwise approach, we focused on three methods with higher sensitivity to detect non-adherence that were also feasible: self-reporting with the standardized Morisky questionnaire, physician assessment and pill-count. All non-adherent patients were identified by combining physician assessment and self-reporting (100% sensitivity, Table 1). The pill-count did not have any added value for detecting non-adherence.

## DISCUSSION

In this study we applied a systematic, step-wise approach with MEMS as the gold standard to identify a combination of valid and locally feasible methods to detect non-adherence to TB treatment. We aimed to find a combination of methods, since each method has its own disadvantages. A combination of

Table 1  
Validity of methods for detecting non-adherence compared with MEMS as the gold standard ( $n=30$ ).

Methods	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Morisky questionnaire	69	76	69	76
Physician assessment	85	71	69	86
Pill-count	60	87	75	76
Visit attendance	38	82	63	64
Diary	61	100	100	77
<b>Combination methods</b>				
Morisky questionnaire + Physician assessment	100	59	65	100
Morisky questionnaire + Pill-count	77	53	56	75
Physician assessment + Pill-count	85	59	61	83

Sensitivity: proportion of non-adherent cases detected

Specificity: proportion of adherent cases detected

Positive predictive value: proportion of truly non-adherent cases among those which were detected as non-adherent

Negative predictive value: percentage of truly adherent cases among those which were detected as adherent

methods may provide a better result in detecting non-adherence.

The similar approach of comparing some methods with MEMS as a reference standard has been applied in similar studies focusing on adherence to other drugs (Knobel *et al*, 2002; Vriesendorp *et al*, 2007; Zeller *et al*, 2008). Only a few studies have evaluated MEMS in the prophylaxis of tuberculosis so far (Fallab-Stubi *et al*, 1998; Menzies *et al*, 2005).

In our study, combining physician assessment and patient self-reporting using the standardized Morisky questionnaire gave the highest sensitivity in detecting non-adherence. These methods allow an efficient focus on patients with adherence problems. In these patients, a tailored approach may be carried out to try and enhance adherence. This might include additional counseling or full or modified DOT for these particular patients.

This study was limited by a small sample size and was conducted in a single clinic, so care should be taken to extrapolate the results to other settings. In addition, the period of follow-up was relatively short. Further studies with larger sample sizes conducted in multiple centers are warranted to evaluate our stepwise approach and the effectiveness of combinations of methods in detecting non-adherence to TB drugs.

In summary, DOT is not always possible in every setting. We have presented and recommend a step-wise approach to select a combination of valid and locally feasible methods to detect non-adherence to TB drugs.

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