

ADAPTING TO NEW INTERNATIONAL TB TREATMENT STANDARDS WITH MEDICATION MONITORS AND DOT GIVEN SELECTIVELY

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Tropical Medicine and International Health Volume 12, No. 11, pp 1302-1308, November 2007.

The definitive version is available in the journal or at www.blackwell-synergy.com

Summary:

In contrast to previous recommendations New International Standards no longer require directly observed therapy (DOT) for all TB patients, but state practitioners must be capable of assessing adherence and addressing poor adherence when it occurs. This removes much of the burden that DOT imposes on both patients and treatment delivery systems. However, the new recommendations may lead to treatment failures and drug resistance because consistent accurate assessment of adherence is at best problematic. Electronic medication monitors, devices that determine when medication is removed from a container may significantly help overcome this problem even in poor developing countries, if they were mass-produced to reduce cost. Both health facilities and community workers could dispense drugs for self-administered treatment (SAT) in medication monitors and retrieve the adherence record with inexpensive built-in displays. These devices could keep the adherence record from the beginning of therapy for managing patients who move. Pharmacists using medication monitors could provide surveillance of SAT prescribed by private physicians with less adherent patients referred to health departments. Health departments could oversee Family Member DOT with these devices. Less adherent patients could be managed with focused counseling, DOT when necessary, and extensions in treatment duration. Removal of the DOT burden would encourage patients to seek free high quality supervised public care and help expand effective TB treatment services. If the resources saved by giving less DOT were focused on poorly adherent patients and defaulters, medication monitor based programs could create less acquired drug resistance than overwhelmed treatment programs that attempt but fail to give uninterrupted DOT to all patients.

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I. INTRODUCTION

In response to the problems encountered by many health systems in providing directly observed therapy (DOT) for TB, New International Standards no longer insist on DOT for all patients but state "Practitioner must not only prescribe an appropriate regimen, but also be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs". (Tuberculosis Coalition for Technical Assistance 2006) Furthermore, the world health organization (WHO) now recommends that all patients have a treatment supporter acceptable to the patient who is trained and supervised by health services. (WHO 2006) The supporter may or may not give DOT. Unfortunately, these recommendations fail to overcome a dilemma that has plagued TB control efforts for half a century, namely the lack of a practical and accurate means of determining who is adherent. This paper describes a neglected and emerging technology that needs to be tried and evaluated as a means to overcome this quandary, improve the effectiveness of the treatment supporter, and achieve more successful treatment outcomes.

II. THE SUCCESS AND PROBLEMS WITH DOT

In 1994 WHO launched a five-component program called the DOTS strategy (WHO 1994) that included DOT for all patients at least in the initial phase of treatment, to overcome serious deficiencies in earlier programs based largely on self-administered treatment (SAT). (Raviglione and Pio 2002) The 1994 WHO recommendation has been accompanied with improved successful treatment rates that averaged 86% in 2004. (WHO 2007).¹ Success rates were based on relatively lax criteria: 1) patients with a negative sputum smear at the end of therapy (cures), plus 2) patients who complete 6 months of treatment but no end of treatment sputum smears were obtained.

An excellent review of the multiple problems encountered by patients and health care delivery systems in implementing DOTS is available (Lienhardt and Ogden 2004) The review refers to the diversity of patients' attitudes towards the disease, the extreme variability of access to care, the costs incurred by the patients, the aggravation of stigma, the non use of direct observation for some patients in DOTS programs, the deselection of patients deemed least likely to comply, and the use of additional interventions that may not be sustainable because they require external funding. Consequently, they questioned the appropriateness of DOT as a universal paradigm for TB control. Another group documented false reporting given by compassionate caregivers. (Pungrassami et al. 2002) They found that SAT was given when DOT was allegedly given: 11% of time for clinic DOT, 23% for community worker DOT, and 35% for family DOT.

¹ However, full implementation of DOTS is very difficult, and programs without sufficient resources often fail to reach this modest goal. For instance, a carefully evaluated DOTS program in Tamil Nadu State, India only achieved 75% success at the end of treatment with 12% relapses by 18 months. (Thomas et al. 2005)

III. RELIABLE PATIENTS - A POTENTIAL RESOURCE FOR REDUCING THE ADHERENCE PROBLEM

A Cochrane database review found DOT to be no better than SAT in 10 trials. (Volmink and Garner 2006) Neither this review, nor other randomized controlled trials has studied the development of drug resistance in DOT vs. SAT regimens. (Rusen et al. 2007) Because multiple visits per week to a health facility requires significant patient motivation one might speculate that many if not most of the successful DOT patients could have been successfully treated with SAT. Another study showed DOT to be less cost effective than SAT. (Khan et al. 2002) In two resource limited programs 60% to 65% of patients were successfully treated with SAT. (Zwarenstein et al. 1998; Walley et al. 2001) These adherent patients represent a large potential resource for expanding TB treatment services, if they could be reliably identified.

IV. DETERMINING THE ADHERENCE OF PATIENTS

A) Predictions or Judgments of Adherence

It is well documented that provider estimates, patient self-report, measures of appointments kept, pill counts, and assays for the presence of drugs are relatively insensitive measures of adherence. (Sumartojo, 1993) While one study showed a positive correlation between predictions of adherence and actual adherence to outpatient therapy, the nurses and physicians who made the predictions had treated the patients in hospitals for months prior to outpatient therapy. (Moulding 1979A) Furthermore, they were not able to predict all poorly adherent patients. Multiple studies have shown that no one or no combination of factors can consistently determine or predict which patients are or will be adherent. (Miller et al. 2002)

B) Assessing Adherence with Medication Monitors

Non-electronic devices, which record when medication is removed from a container, (medication monitors) were proposed in 1962 (Moulding1962), and subsequently modified (Moulding et al. 1967; Moulding 1979B). Since then electronic medication monitors have been developed. Three 'trace sheet monitors' that record when each pill is removed by breaking lines of conductive ink over cavities in blister cards have been marketed. ([Cypak Inc. 2007](#); [Certus International Inc. 2007](#); [Information Mediary Inc. 2007](#)) Three cap removal monitors that indicate when a cap is removed from a medication container are available. ([Aardex Ltd. 2007](#); [Information Mediary Inc. 2007](#); [Simpill Inc. 2007](#)) While these latter devices do not record how many pills are taken out when the cap is removed, devices based on this concept, like the cover opening monitor shown on this website (Moulding and Ellis 2007) may prove to be the most practical means of assessing adherence, since it is the least expensive to manufacture and easy to refill. (See: [Cover and Cap Opening Monitors](#), scroll to figures one and two.) Multiple alternative monitor designs, which determine when each dose is removed, have been placed on an this website, to allow investigators and funding sources to chose the optimal device for their needs and encourage inventors to develop improvements. (Moulding and Ellis 2007)

Although none of these medication monitors prove ingestion of the doses removed, they provide far greater supervision of SAT than any other measure of adherence. (Moulding 1979A) The frequency of 'on schedule' medication removal without ingestion needs to be determined and weighed against the limitations of giving DOT to all patients.

C) Built in Displays to Retrieve the Adherence Record and Assist the Patient

To make medication monitors useful in all settings, a variety of built in displays to retrieve the adherence record without computers or personal digital assistants (PDAs) could be used. The least expensive is a single multi-color light emitting diode (LED), which costs <\$ 0.15. (See: Cover and Cap Opening Monitors, scroll up to the written material entitled 'Use of the Display by the Caregiver'.) The LED could present the percentage of medication taken since the last time the device was refilled with a green flash for >90% adherence, yellow for 75-90% and red for <75%. Additional red flashes could be displayed for greater degrees of poor adherence. Furthermore, the LED could display the adherence record for each month since the start of therapy, valuable data that could be used to plan additional therapy if the chart were lost or the patient moved to another health facility.

The LED could also answer a common questions asked by many patients, "Did I or did I not take medication today?" With the push of a button the LED would flash green if the patient should take medication and a red if he should not.

V. EXPERIENCE WITH SELF ADMINISTERED TREATMENT GIVEN IN MEDICATION MONITORS (MONITORED SAT)

Among 122 patients in the United States taking mainly isoniazid (INH) and para amino salicylic acid (PAS) as self administered treatment from non-electronic medication monitors, (monitored SAT) for 18 to 24 months, 82.3% took 70% or more of their prescribed medication and 60.7% took more than 90% of their medication. (Moulding et al. 1970) Homeless and alcoholic patients were not included in the study. Among 106 patients in Haiti taking a combined preparation of INH and thiacetazone from non-electronic medication monitors for one year who received counseling based on the monitor record (focused counseling) 79.5% took >80% of their medication. Focused counseling reduced defaulting by 45%. (Moulding and Caymittes 2002) These data demonstrate that there are reliable patients who can be treated with SAT and less reliable patients who require additional measures to ensure adherence.

A study of adherence to latent tuberculosis treatment with 104 patients in Canada using electronic medication monitors found that therapy completion was closely associated with the percent of doses taken in the first month of treatment. ($P < .0001$). (Menzies et al. 2005) The study also found that patients who took medication nearer the same point in time each day were more likely to complete treatment. This was determined by the variability of the interval between doses (in hours). ($P = .003$) The accuracy of prediction improved when both indicators were considered together. ($P < .0001$) Since these latent TB patients were not sick, these findings may or may not be applicable to patients with active TB who are usually motivated to take treatment

initially when they are ill. However, the monitor study in Haiti with patients who were sick with TB showed that patients with > 90% adherence in the first 11 weeks were approximately three times more likely to have good adherence during one year of treatment ($p < 0.01$), and six times less likely to default ($p < 0.01$). (Moulding and Caymittes 2002). While these studies suggest that an early monitor record helps predict later adherence and defaulting, additional confirmatory studies are clearly needed.

VI. PROPOSED SUPERVISION OF TREATMENT BASED ON MONITORED SAT AND DOT GIVEN SELECTIVELY

Monitored SAT appears to be a promising tool to help caregivers and treatment supporters identify those patients who can be successfully treated with SAT. The resources saved not giving DOT to reliable patients could be directed to the less reliable patients using appropriate supportive and remedial measures such as

- 1) Focused counseling of the patient and family,
- 2) DOT when necessary (selective DOT),
- 3) Enlisting a new supporter if the original supporter is ineffective,
- 4) Retrieval of defaulters, and
- 5) Extending the duration of therapy to compensate for poor adherence when it occurs.

The early monitor record which appears to identify patients at increased risk of defaulting would alert caregivers and supporters to make sure they knew the address(s) of potential defaulters, increase the counseling of these patients and their families, and make prompt home visits whenever they miss a refill appointment. Furthermore, monitored SAT should reduce the motivation for defaulting by minimizing the number of time consuming and potentially stigmatizing visits to clinics or community workers for DOT.

WHO recommends extending the duration of treatment when poor adherence occurs. (WHO 2006; WHO 2003A) A poor record of picking up medication refills is the usual indication of poor adherence when SAT is given. The monitor record should provide much more detailed adherence data for judging how much additional therapy is needed and for convincing patients, their families, and if necessary community leaders that therapy must be taken for a longer time.

For additional compensatory therapy to be effective, drug resistance must not have developed during the period of interrupted treatment. The use of fixed dose combinations (FDCs) of anti TB drugs, which prevents monotherapy, removes one cause of drug resistance. A WHO publication that quoted indirect evidence from South Africa and Brazil (Blomberg et al. 2001) plus subsequent data from Los Angeles (Moulding et al. 2004) suggest that drug resistance occurs infrequently, despite interrupted treatment, when FDCs containing INH and RMP are given. WHO treatment guidelines recommend FDCs. (WHO 2006; WHO 2003A) While the issue needs further study, especially for HIV positive patients, extending the duration of therapy when poor adherence occurs should result in treatment success in most cases as long as FDCs are used.

VII. USE OF MONITORED SAT TO IMPROVE TREATMENT OUTCOMES AND EXPAND SERVICES IN VARIOUS SETTINGS

A) At Clinics and Health Facilities

Clinics can be overwhelmed by having to provide DOT multiple times each week for all TB patients. DOT often becomes impossible for patients who live too far away or whose work commitments conflict with clinic hours. Providing monitored SAT for reliable patients together with supportive and remedial measures for the less reliable patients would reduce the clinic workload and help solve these problems.

B) By Private Physicians and Pharmacies.

The private sector, which rarely uses DOT, treats a large proportion of the world's TB patients. (Uplekar et al. 2001) Unsupervised pharmacies often provide TB medication. (Lonnroth et al. 2000) Apparently, the burden imposed by DOT plus increased fear of stigma motivates many patients to pay for TB treatment despite the availability of free superior public care.

WHO stresses public private partnerships to address this problem. One of the most successful was in Delhi, India, which achieved 81% success among 168 sputum positive patients. (Lonnroth et al. 2004) However, it took 18 months of active dialog with the community physicians before the program was launched and only a fraction of the physicians participated.

Public private partnerships could probably be more effective, if private patients received their drugs in medication monitors from trained and subsidized pharmacies who reported the adherence record to the private physicians and public health officials. Since physicians could keep their reliable patients without having to provide DOT, they should be more willing to cooperate.

C) By Community Members or Community Workers

WHO recommends an increased community contribution and the use of community workers. (WHO 2003B) Community based lay health workers giving DOT achieved 74% success compared with 57% with clinic based DOT, and 59% with SAT. (Zwarenstein et al. 2000) Unfortunately, attrition of volunteer workers who eventually want to be paid (Kironde and Klaasen 2002) and maintenance of effective supervision (Connolly et al. 1999) can be significant problems. If community workers provided monitored SAT, retrieved the adherence record with the built in LED display, spent minimal time with adherent patients, and focused their attention on the less adherent patients, fewer workers would be needed, modest stipends could probably be given, attrition reduced, and supervision of the workers simplified.

D) By Family Members

The vast majority of patients live in families. Therefore, having a family member give DOT is attractive but controversial. It has been called a slippery slope to sloppy DOTS because of concern that the medication will not be consistently observed. (Frieden and Sbarbaro 2002) However, family member DOT is very attractive because it imposes less of a burden on the patients and the health care system. A cluster randomized controlled trial found family member DOT to be as effective as community member DOT in rural areas in Nepal. (Newell et al. 2006) When patients in Senegal were given a choice, 59.4% had their treatment supervised by a family member, 31.5% by a nurse, and 9.1% by a community health worker. (Thiam et al. 2007) Furthermore, 88% of patients supervised by a family member were cured vs. 77% for all other treatment supervisors. (Thiam et al. 2007) Therefore, despite the controversy it appears that family member DOT with well-trained supporters improves adherence, even though each dose may not be observed. If further supervision were added by providing the drugs in medication monitors, together with adequate supportive and remedial measures when poor adherence was found, even better results would probably be achieved. In fact monitor supervised family member DOT could become the most successful means of delivering DOT.

E) For Patients who Change Their Address

Records are often lost when patients move, despite well-described procedures for preventing this. (Meijnan et al. 2002) For these patients, medication monitors that keep the adherence record from the beginning of treatment and critical clinical data like the sputum status would greatly help subsequent caregivers plan appropriate therapy.

VIII. CAN MEDICATION MONITORS HELP PREVENT DRUG RESISTANT DISEASE

Recently, serious concern has been expressed about an alarming increase in multi drug resistant (MDR) and extreme drug resistant (XDR) TB. WHO officials quite properly point out that this problem is a reflection of the weakness of TB management, which should include strict supervision of treatment to minimize the emergence of drug resistance. (Raviglione and Smith 2007). Does this concern and does this statement imply we should return to the old policy of DOT for all patients?

DOT is often given 2 or 3 times a week (intermittent regimens) at least in the continuation phase of therapy for patients being treated for the first time. A review of intermittent regimens for TB found that they had somewhat higher relapse rates than treatment given daily. (Saltini 2006) In HIV positive patients rifampin resistance developed in 1.7 to 3.7% of patients who received intermittent DOT (Li et al. 2005; Nettles et al. 2004). The emergence of MDR-TB has been noted in a community based DOT program. (Davies et al. 1997) One study showed that acquired INH drug resistance occurred in 20% of the patients who relapsed after DOT. (Thomas et al. 2005) WHO reports that 14% of patients did not achieve treatment success in 2004 (WHO

2007). While not documented, drug resistance probably occurred in some of these patients. Furthermore, the difficulty many patients have in complying with DOT motivates some of them to get poor quality treatment from pharmacies or private physicians, which increases the opportunity for drug resistance to emerge. This type of information suggests that a policy of strict DOT for all patients has significant limitations.

However, the new standards (Tuberculosis Coalition for Technical Assistance 2006) which recommend assessing adherence and addressing poor adherence when it occurs may be equally ineffective or less effective in preventing drug resistance, because current means of assessing adherence are frequently inaccurate. If medication monitors were used to determine adherence to daily regimens, the effectiveness of the new standards could probably be greatly improved. If adequate supportive and remedial measures were taken when poor adherence is found, less drug resistance could emerge than now occurs in communities that attempt but fail to give uninterrupted DOT to all patients.

On the other hand until there is significant positive experience with monitored SAT, daily DOT should be given to patients that are known to have drug resistant disease prior to starting treatment, because if treatment fails there is often no other effective treatment regimen.

IX) USE OF MEDICATION MONITORS WHEN MANAGING HIV/AIDS and HIV/AIDS/TB

Treatment of HIV/AIDS with anti-retroviral drugs poses even greater adherence problems, since the patient must take anti-retroviral therapy for life. However, if inexpensive medication monitors and focused counseling improved treatment results by as little as 10%, a case could be made that medication monitors should be used, since anti-retroviral drugs are relatively expensive and decreases in the viral load have been shown with improved adherence. (Paterson et al. 2000)

X) EXPENSE AND PRACTICALITY OF USING MEDICATION MONITORS

While doctors, nurses, pharmacologists, bacteriologists, drug companies, and clinical trial experts have all contributed partial solutions to the adherence problem, it remains a major obstacle to effective TB control. Therefore, is it not time to enlist the expertise of an additional discipline, engineers, who could use modern inexpensive electronic technology to help solve this persistent serious problem?

In developed countries the cost of medication monitors should not inhibit their usage. For developing countries, the expense may at first glance appear unrealistically excessive. However, manufacturing costs in large volume production in low wage countries are estimated to vary between <\$5.00 and <\$10.00 per device. (Personal Communication Dr. Daniel Hillis –Applied Minds Inc. 2006) The ultimate cost per patient treated should be lower, since the equipment could be reused for numerous patients until it is lost or broken. To place these costs in

perspective, WHO estimates that in high burden countries median costs for first line drugs are \$26.00, and total costs for each new patient is \$259.00 (WHO 2007) If using medication monitors leads to more efficient use of program resources, greater acceptance of treatment by patients, and better treatment results, the additional cost for medication monitors could be readily justified.

XI. EVALUATION

The central question needing evaluation is "Can monitored SAT, focused counseling, selective DOT, and extensions in the duration of therapy achieve better overall results with less acquired drug resistance than a policy of DOT for all patients?" Initially, operational pilot studies will be needed to determine 1) the proportion of adherent patients who need only minimal attention, 2) the effectiveness of focused counseling carried out by caregivers and treatment supporters in improving adherence among poor compliers when directed to patients and families, 3) how many patients require selective DOT, 4) how many patients default and 5) the effectiveness of extending the duration of therapy when poor adherence occurs. Based on these pilot studies temporary guidelines for the proper mix of monitored SAT and DOT can be developed, followed by well-planned randomized controlled trials to develop optimal treatment strategies in multiple different settings.

XII. IN SUM

Universal DOT imposes significant burdens on both health departments and patients. At least sixty to sixty-five percent of patients are sufficiently reliable that they can be successfully treated with SAT. If further developed and reduced in cost by mass production, electronic medication monitors, could identify these reliable patients in most cases. Management of less reliable patients would require focused counseling, selective DOT, retrieval of defaulters, and extensions in the duration of treatment. Such a medication monitor based program could lead to more satisfied patients, better use of limited resources, and better treatment outcomes.

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Acknowledgement. The author wishes to acknowledge the significant contribution of Dr. Don Ellis at Spiderwort Design <spiderwort@pcisys.net> for advising on technical matters and collaborating in the development of medication monitor designs.