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Viewpoint: **Adapting to new international tuberculosis treatment standards with medication monitors and DOT given selectively**

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Summary New international standards no longer require directly observed therapy for all tuberculosis (TB) patients, but state that practitioners must be capable of assessing adherence and addressing poor adherence. Mass-produced electronic medication monitors, which record removal of medication from a container, could help overcome the problem of assessing treatment adherence accurately even in poor countries. Both health facilities and community workers could dispense drugs for self-administered treatment 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 self-administered treatment prescribed by private physicians with less adherent patients referred to the health departments. Less adherent patients could be managed with focused counselling, directly observed therapy when necessary, and extensions in treatment duration. Removal of the directly observed therapy burden would encourage patients to seek free high-quality supervised pubic care and help expand effective TB treatment services. If resources saved by giving less directly observed therapy were focused on poorly adherent patients, medication monitor-based programmes could create less acquired drug resistance than overwhelmed treatment programmes that attempt but fail to give uninterrupted directly observed therapy to all patients.

keywords tuberculosis, DOT, self-administered treatment, medication monitors

Introduction

In response to the problems encountered by many health systems in providing directly observed therapy (DOT) for tuberculosis (TB), new international standards no longer insist on DOT for all patients but state that 'Practitioners 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 WHO (2006) now recommends that all patients have a treatment supporter acceptable to the patient who is trained and supervised by the health services. 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.

Success and problems of directly observed therapy

In 1994, WHO launched the DOTS strategy, a five-component programme that included DOT for all patients at least in the initial phase of treatment (WHO 1994), to overcome serious deficiencies in earlier programmes based largely on self-administered treatment (SAT) (Raviglione & Pio 2002). The 1994 WHO recommendation has improved successful treatment rates to an average of 86% in 2004 (WHO 2007). Success rates were based on relatively lax criteria: patients with a negative sputum smear at the end of the therapy (cures), plus patients who completed 6 months of treatment without the evidence of end-of-treatment sputum smears. Even so, full implementation of DOTS is very difficult, and programmes without sufficient resources often fail to reach this modest goal. For instance, a carefully evaluated DOTS programme in Tamil Nadu, India only achieved 75% success at the end of the treatment with 12% relapses within 18 months (Thomas *et al.* 2005).

In their review of the multiple problems encountered by patients and health care delivery systems in implementing DOTS, Lienhardt and Ogden (2004) mentioned the

following: diversity of patients' attitudes towards the disease; extreme variability of access to care; costs incurred by the patients; aggravation of stigma; non-use of direct observation for some patients in DOTS programmes; exclusion 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 universal appropriateness of DOT for TB control. Pungrassami *et al.* (2002) documented false reporting by compassionate caregivers: alleged DOT was in fact SAT 11% of the time for clinic DOT, 23% for community worker DOT, and 35% for family DOT.

A Cochrane database review (Volmink & Garner 2006) found DOT to be no better than SAT in 10 trials. Neither this review, nor other randomized controlled trials studied the development of drug resistance in DOT *vs*. SAT regimens (Rusen *et al.* 2007). Because multiple visits per week to a health facility require significant patient motivation, one might speculate that many if not most of the successful DOT patients could have been successfully treated with SAT. Khan *et al.* (2002) showed DOT to be less cost-effective than SAT. In two resource-limited programmes, 60–65% of the patients were successfully treated with SAT (Zwarenstein *et al.* 1998; Walley *et al.* 2001).

Determining the adherence of patients

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, health staff were not able to predict all poorly adherent patients. Multiple studies have shown that no one factor or combination of factors can consistently determine or predict which patients are or will be adherent (Miller *et al.* 2002).

Non-electronic devices, which record when medication is removed from a container (medication monitors), were proposed in 1962 (Moulding 1962), and subsequently modified (Moulding *et al.* 1967; Moulding 1979b). Since then, electronic medication monitors such as 'trace sheet monitors' that record when each pill is removed by breaking lines of conductive ink over cavities in blister cards (Certus International Inc 2007; Cypak Inc. 2007; Information Mediary Inc. 2007) and cap removal monitors that indicate when a cap is removed from a medication container (Aardex Ltd. 2007; Information Mediary Inc. 2007; Simpill Inc. 2007) have been developed. While cap removal monitors do not record how many pills are taken out, devices based on this concept, such as the cover opening monitor shown in Figure 1, may prove to be the most practical means of assessing adherence, as they are the least expensive to manufacture and easy to refill. Other monitor designs, which determine when each dose is removed have been placed on an online repository, to allow investigators and funding sources to choose the optimal device for their needs and encourage inventors to develop improvements (Moulding & Ellis 2007).

Although none of these medication monitors proves ingestion of the doses removed, they provide far greater supervision of SAT than any other measure of adherence

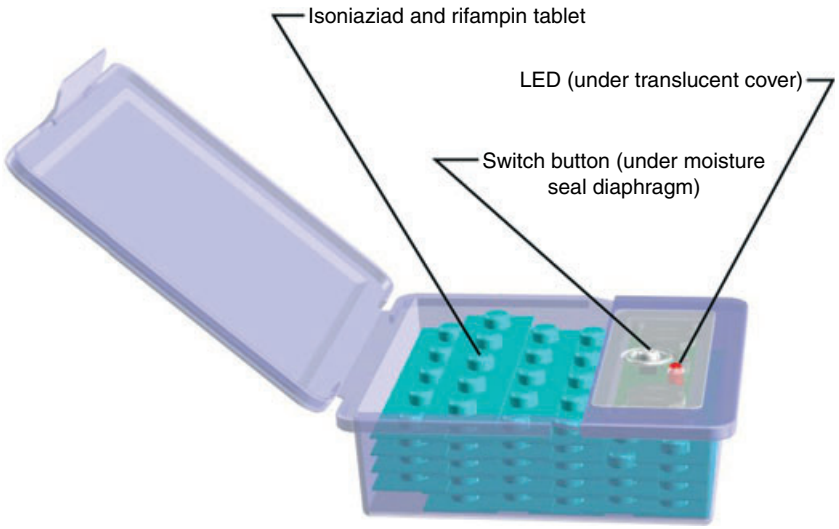

Figure 1 Cover Opening Monitor for WHO's Packaged Medication.

(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.

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 (PDA) could be used. The least expensive is a single multi-colour light-emitting diode (LED), which costs less than US$ 0.15 (Moulding & Ellis 2007). 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 question: '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 red if he should not (Moulding & Ellis 2007).

Monitored self-administered treatment

Among 122 patients in the United States taking mainly isoniazid and para-amino salicylic acid as SAT from non-electronic medication monitors (monitored SAT) for 18–24 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 isoniazid and thiacetazone from non-electronic medication monitors for 1 year who received counselling based on the monitor record (focused counselling), 79.5% took ≥80% of their medication. Focused counselling reduced defaulting by 45% (Moulding & Caymittes 2002). These data demonstrate that reliable patients can be treated with SAT and less reliable patients require additional measures to ensure adherence.

A study of adherence to latent TB treatment with 104 patients in Canada using electronic medication monitors found that therapy completion was closely associated ($P < 0.0001$) with the percentage of doses taken in the first month of treatment (Menzies *et al.* 2005). In addition, patients who took medication nearer the same point in time each day were more likely to complete treatment, as determined by the variability of the interval between the doses ($P = 0.003$). The accuracy of prediction improved when both indicators were considered ($P < 0.0001$). Because these latent TB patients were not sick, the 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, in the monitor study in Haiti with sick TB patients, those with ≥90% adherence in the first 11 weeks were approximately three times more likely to show good adherence for 1 year ($P < 0.01$), and six times less likely to default ($P < 0.01$) (Moulding & Caymittes 2002). While these studies suggest that an early monitor record helps predict later adherence and defaulting, additional confirmatory studies are needed.

Supervision of treatment based on monitored self-administered treatment and selective directly observed therapy

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 by not giving DOT to reliable patients could be directed to the less reliable patients using appropriate supportive and remedial measures, e.g. focused counselling of the patient and family; DOT when necessary (selective DOT); enlisting a new supporter if the original supporter is ineffective; retrieval of defaulters; and 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 counselling 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 (2003a, 2006) recommends extending the duration of treatment when adherence is poor. 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 of anti-TB drugs 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) suggests that drug resistance is rare, despite interrupted treatment, when fixed dose combinations containing isoniazid and rifampin are given. WHO treatment guidelines (2003a, 2006) recommend fixed dose combinations. While the issue needs further study, especially for human immunodeficiency virus (HIV)-positive patients, longer therapy should result in treatment success for most poorly adherent patients as long as fixed dose combinations are used.

Monitored self-administered treatment in various settings

Clinics can be overwhelmed by having to provide DOT several 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 help solve these problems.

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 and increased fear of stigma motivate many patients to pay for TB treatment despite the availability of free superior public care.

Public–private partnerships have been tried 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 dialogue with the community physicians before the programme 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. As physicians could keep their reliable patients without having to provide DOT, they should be more willing to cooperate.

WHO recommends greater community involvement and the use of community workers (WHO 2003b). Community-based lay health workers giving DOT achieved 74% success compared with 57% achieved by clinic-based DOT, and 59% with SAT (Zwarenstein *et al.* 2000). Unfortunately, attrition of volunteer workers who eventually want to be paid (Kironde & 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.

The use of family members as supporters to give DOT has been called a slippery slope to sloppy DOTS because of concern that the medication will not be consistently taken (Frieden & 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. Exactly 88% of those supervised by a family member were cured *vs.* 77% of those supervised by others (Thiam *et al.* 2007). Therefore, despite the controversy it appears that family member DOT with well-trained supporters improves adherence, although each dose may not be observed. If further supervision was 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.

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

Can medication monitors help prevent drug-resistant disease?

Recently, serious concern has been expressed about an alarming increase in multidrug-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 & Smith 2007). Does this statement imply we should return to the old policy of DOT for all patients?

DOT is often given twice or thrice a week (intermittent regimens), at least in the continuation phase of therapy for patients being treated for the first time. Intermittent regimens for TB have higher relapse rates than daily regimens (Saltini 2006). In HIV-positive patients, rifampin

resistance developed in 1.7–3.7% of the patients who received intermittent DOT (Nettles *et al.* 2004; Li *et al.* 2005). MDR-TB emerged in a community-based DOT programme (Davies *et al.* 1999); and isoniazid resistance developed in 20% of the patients who relapsed after intermittent DOT (Thomas *et al.* 2005). Drug resistance probably developed in some of the 14% of DOTS recipients who were not successfully treated in 1994 (WHO 2007). The difficulty many patients have in complying with DOT may lead them to receive poor quality treatment from pharmacies or private physicians, which increases the risk of emerging drug resistance. Thus, 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 adherence is poor, drug resistance could be less than occurs in communities that attempt but fail to give uninterrupted DOT to all patients. However, until there is sufficient documented positive experience with monitored SAT, daily DOT should be given to patients who have drug-resistant disease before they start treatment, because if treatment fails there is often no other effective treatment regimen.

Use of medication monitors when managing HIV/AIDS and HIV/AIDS/TB

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

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 for 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 in low wage countries are estimated to vary between ≤$5.00 and ≤$10.00 per device (Dr Daniel Hillis – Applied Minds Inc. 2006, personal communication). The ultimate cost per patient treated should be lower, as 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 the total cost for each new patient is $259.00 (WHO 2007). If using medication monitors leads to more efficient use of programme resources, greater acceptance of treatment by patients, and better treatment results, the additional cost for medication monitors could be readily justified.

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 the following: (i) the proportion of adherent patients who need only minimal attention; (ii) the effectiveness of focused counselling by caregivers and treatment supporters in improving adherence among poor compliers when directed to patients and families; (iii) how many patients require selective DOT? (iv) how many patients default? and (v) 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 randomized controlled trials to design optimal treatment strategies in different settings.

Conclusion

Universal DOT imposes significant burdens on both health departments and patients. At least 60–65% of the patients are reliable enough to be successfully treated with SAT. If further developed and made cheaper by mass production, electronic medication monitors could identify these reliable patients in most cases. Management of less reliable patients would require focused counselling, selective DOT, retrieval of defaulters, and longer treatment. Such a medication monitor-based programme could lead to more satisfied

patients, better use of limited resources, and better treatment outcomes.

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