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A neglected research approach to prevent acquired drug resistance when treating new tuberculosis patients

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SUMMARY

The occurrence of significant drug resistance in many countries, coupled with known problems in delivering directly observed therapy (DOT), calls for a re-examination of tuberculosis (TB) treatment delivery strategies. Electronic medication monitors, devices that determine when medication is removed from containers, and videophone-based strategies are being introduced to determine if they can effectively differentiate 1) patients who are adequately adherent to self-administered treatment (SAT), 2) less reliable patients who could be successfully treated with SAT if given more intensive counseling and 3) patients who require DOT. The adherence record could be used in deciding on longer compensatory treatment when poor adherence occurs. The time saved not giving DOT to all patients could be used to retrieve defaulters. Together these components constitute a monitor-based strategy. The program could be extended to supervise the adherence of private patients to medication provided by trained and subsidized pharmacies with the physicians or, when necessary, health departments managing poorly adherent patients. When patients move, the device could transfer essential data to the new care giver. To obtain optimal results, the requirements for the best possible devices and procedures for dealing with poor adherence need to be carefully evaluated.

KEY WORDS: medication monitors; directly observed therapy; self-administered therapy; drug resistance

IT IS ESTIMATED that approximately 490 000 new multidrug-resistant tuberculosis (MDR-TB) cases emerged in the world in 2006.[1] The global proportion of drug resistance among all cases was 4.8%.[1] Treating these MDR-TB patients will take a massive effort, including directly observed therapy (DOT) for all MDR-TB patients (universal DOT).

However, the prevention of acquired drug resistance in patients being treated for the first time is equally, if not more, important. The World Health Organization (WHO) has strongly recommended universal DOT in the past.[2] However, in November 2010, the WHO website stated, 'Supervised treatment *may* have to include DOT' (note the word 'may').[3] These evolving positions indicate that the optimal means of managing poor adherence remains a significant unresolved issue.

MEANS OF DETERMINING ADHERENCE

The modified position of the WHO requires a means to determine who needs DOT. Staff judgments of adherence are often wrong: studies using early non-electronic medication monitors documented that predictions of adherence by nurses and physicians who had treated the patient in the hospital for months were only partially accurate.[4] The adherence of patients seen for brief periods of time in clinics is probably even less accurate. Multiple studies have shown that no one factor or combination of factors can consistently determine or predict which patients are or will be adherent.[5] If acquired drug resistance in patients being treated for the first time is to be prevented, or at least minimized, research to develop and evaluate a cost-effective means for determining which patients are adherent is clearly needed.

Non-electronic medication monitors were proposed in 1962,[6] prototyped in 1967,[7] studied among 122 patients in the United States in 1970,[8] modified for use in developing countries in 1979,[9] and studied among 123 patients in Haiti in the 1980s and 1990s.[10] Multiple engineering groups subsequently developed portable battery-powered electronic medication monitors,* and multiple additional designs have been

*AARDEX Group, Sion, Switzerland, http:www.aardexgroup.com; Cypak Inc., Stockholm, Sweden, http://www.cypak.com; Information Mediary Corporation, Ottawa, ON, Canada, http://www.informationmediary.com; Innovators in Health, Boston, MA, USA, http://www.innovatorsinhealth.org/solutions/pillbox.shtml; Shanghai Guifan Digital Technology Co Ltd., Shanghai, China, http://www.sditchina.com/contact-us/outsourcing-opportunities.htm; Simpill Inc., London, UK, http://www.simpill.com; Wisepill Inc., Cape Town, South Africa, http://www.wisepill.com

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proposed.[11] Several companies or groups are working on devices that prove or come close to proving that the medication is ingested,* and the use of videophones to observe medication ingestion (videophone DOT) has been explored.[12,13]

The international non-profit organization PATH carried out a worldwide mail survey of adherence policies and practices in TB programs.[14] Forty respondents answered some of the questions. While DOT was a requirement for at least part of the treatment in all programs, this policy was not always implemented. Among 25 respondents who answered the question, 8% officially allowed patients to take medication home throughout treatment, 44% allowed patients to take medication home in the continuation phase, and 2% had no policy on this issue. The report went on to state that, while many countries do not have policies that support self-administration, in actual practice it is prevalent. The authors concluded that medication monitoring technology could be an effective tool for supporting adherence in some TB programs.

Real-time adherence monitors have been used in TB trials in South Africa and in human immunodeficiency virus (HIV) trials in Uganda (L Marshall and D Bangsberg, personal communications). A TB monitor study is being planned in China (A Berman, personal communication), and more monitor trials can be anticipated. With the plethora of devices available and the probability that additional devices will be developed, the components needed in an optimal yet reasonably priced device should be carefully examined.

TWO TYPES OF MEDICATION MONITORS

Medication monitors that fall into the reasonable cost range for use in developing countries can largely be separated into two groups.

Cover or cap-opening monitors

These devices determine when the cover or cap of a container is opened, but do not detect how much, if any, medication is removed when the device is opened. If the patient opens the device to see how many pills remain (curiosity openings) or a child plays with it by opening the cover, an inaccurate record of pill removal is created. If the device includes a light-emitting diode (LED) or beeper to remind the patient to take his/her medication, these helpful features are inactivated with each spurious cover opening. If the record shows that the cover has not been opened for a period of time, the patient can claim he/she removed excess doses prior to that period that were ingested while away on a trip, when in fact no medication was ingested. If the patient makes such a claim, the care giver would not know how forcefully to deal with the probable but not definite occurrence of non-adherence. On the other hand, cover opening monitors are the least complicated and least expensive, with an estimated cost of US$10 each in production quantities (D Ellis, personal communication).

Dose-removal monitors

Dose-removal monitors overcome many of the limitations of cover-opening monitors by determining when each dose of medication is removed, but they will be somewhat more costly, at around US$13.40 each, in production quantities (D Ellis, personal communication). As the device can be reused, the cost per patient would be less. This expense needs to be weighed against the cost of delivering universal DOT and the much greater costs of retreating failure MDR-TB patients.

MECHANICAL REQUIREMENTS FOR OPTIMAL MEDICATION MONITORS

1 The device should be designed for daily treatment: the widely used intermittent (2 times weekly and 3 times weekly) TB treatment regimens were introduced to make DOT less of a burden for patients, clinics and care givers. While results in controlled trials showed them to be effective,[15] evidence has subsequently emerged that intermittent regimens provide less than optimal long-term results in service programs.[16] While a meta-analysis of randomized controlled trials found little difference between daily and intermittent regimens,[17] reports from routine DOT service programs, in which patients often fail to report for prescribed doses, reveal more relapses among patients taking intermittent treatment.[16,18] Furthermore, two studies show that intermittent regimens lead to more drug resistance if the patient is HIV-positive.[19,20]

In addition, patients are more likely to remember to take medication once a day than two or three days per week. Daily regimens would therefore avoid adding the scheduled interruptions of intermittent therapy to the interruptions caused by the patients.

2 The device should be designed for fixed-dose combinations (FDCs) of drugs:
   i to have fewer different items in the supply lines from the factory to the clinics to reduce logistics problems and stock-outs of individual drugs in the clinics;[21]
   ii to reduce the risk of drug resistance by avoiding stock-outs and preventing the patient from taking some, but not all, of the prescribed drugs;
   iii to have fewer prescribing errors compared with prescribing individual drugs;[22]
   iv to reduce the size of the device.

* Etect, Gainesville, FL, USA, http://www.etectbio.com/; Proteus Technology, Redwood City, CA, USA, http://www.proteusbiomed.com/technology/

3 The device must provide protection against ambient moisture, at least for regimens containing ethambutol, which is very hygroscopic.
   i The optimal way to achieve moisture protection is to use the packaged FDCs distributed by the WHO's Global Drug Facility.*
   ii Packaging at the clinic level is possible, if electrically powered sealing equipment is available, but factory packaging is much more likely to be applicable in most programs.
   iii Adequate moisture protection may be achieved with desiccants in a monitor with a moisture resistant cover and a buzzer to motivate the patient to close the cover.[11]
4 The device must allow dosage adjustments for patients of different weights without multiple doses of the same drug or drug combination in the supply lines.
5 The device should be as small as possible to make it portable while capable of dispensing at least a 2-week supply of drugs in the initial phase of therapy and a 4-week supply in the continuation phase.
6 The device should contain a means for patients to see how much medication remains to alert them to return on time for refills. Alternatively, but less effectively, an LED could be used for this purpose.
7 The device should minimize the likelihood that children or adults will play with it and remove medication at the wrong time or open a cover-opening monitor without removing medication.
8 The record provided by the device should distinguish days when medication was not removed and not ingested from periods when medication was not removed but may have been ingested from an excess supply removed several days earlier.
9 Without using a lock that requires a key, which the care giver could lose, the device should be difficult for an uninformed person to open to take out the battery, but easy for an informed care giver to open for refilling medication and replacing the battery when needed.

The device that comes closest to achieving these objectives is the stack monitor, shown in Figure 1.[11]

MEANS OF OBTAINING AND INTERPRETING THE ADHERENCE RECORD

The adherence record could be downloaded into computers and hand-held electronic devices, or viewed with displays built into the monitor.

An LED dot matrix display, which costs US$1.75, incorporated in a stack monitor (Figure 1), could provide an easily viewed, detailed adherence record.[11] It could provide the record from the start of therapy with a series of displays provided sequentially. On each display a green dot would appear for those days

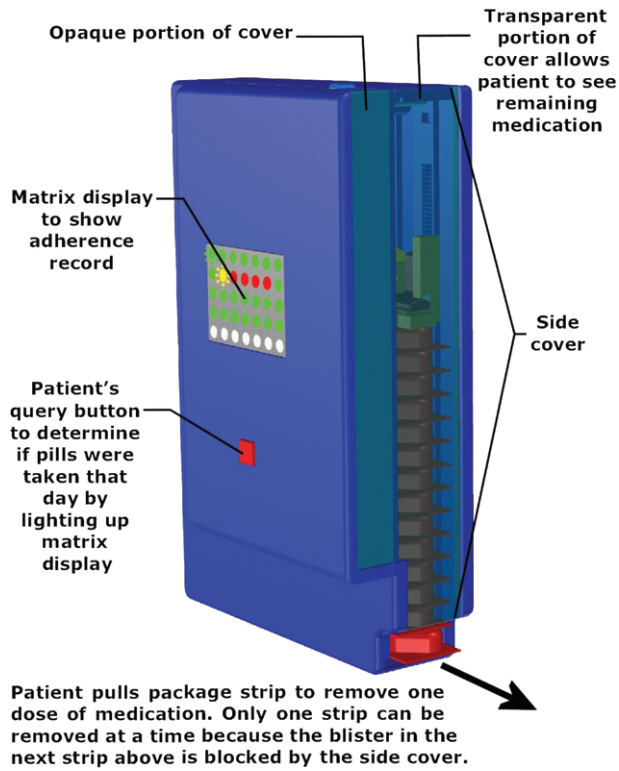

Figure 1 Stack type monitor containing Global Drug Facility packages. For details of the device, go to http://www.medicationmonitors.net/page15.html; for details of the dot matrix display, see http://www.medicationmonitors.net/page21.html, scroll to Section VII, B and C.

when a dose was removed, a red dot for those days when a dose was not removed, and multiple yellow flashes on those days when more than one dose was removed.

In the second row of this dot matrix display, the four red dots that follow the yellow dot may represent days when the patient failed to ingest medication. However, on those four days the patient may have ingested excess doses that were removed on the second day of the week for which the display showed four yellow flashes. In addition, critical clinical information such as sputum and HIV status can also be displayed with the same dot matrix display.[11] These data would be particularly helpful when the patient moved or when the chart was lost.

Alternatively, a US$0.12 red/green/yellow single LED can summarize the adherence record for each refill interval since the start of therapy, as shown in Figure 2.[11] It can also show the detailed adherence record, but to do so the care giver would have to go through the tedious process of examining the adherence for each day separately.

Mobile phone technology has been used to send the adherence record from medication monitors to the care giver.† This is attractive because it permits the

* Global Drug Facility, http://www.stoptb.org/gdf/

†Simpill Inc., London, UK, http://www.simpill.com; Wisepill Inc., Cape Town, South Africa, http://www.wisepill.com

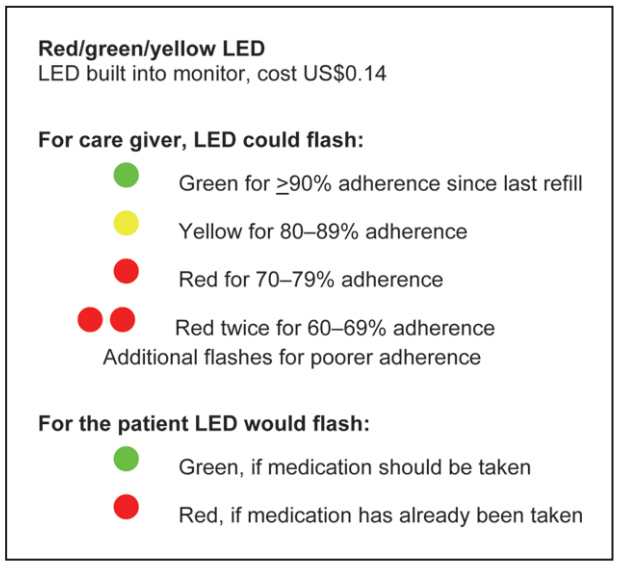

Figure 2 Single red/green/yellow LED to provide summary of adherence record. For additional details, go to http://www.medicationmonitors.net/page21.html, Section VII, D and E.

care giver to promptly make a phone call to the non-adherent patient at the first sign of poor adherence. Unfortunately, using mobile phone technology is much more expensive than using displays built into the monitors or using computers in those clinics with computers. Furthermore, mobile phone services are not available in many locations. If, in the future, wider coverage and less expensive equipment become available, mobile phones could become the preferable means to retrieve the adherence record.

MEANS OF REMINDING AND INSTRUCTING THE PATIENT TO TAKE MEDICATION

If mobile phones are not feasible the patient can be instructed and reminded to take medication with an LED display or beeper or a combination of an LED and beeper.[11]

Videophones attached to land-lines have been used by clinic personnel to observe patients at home ingesting TB medication.[12] This procedure has been tried in Kenya using mobile videophones.[13] This is most likely too expensive for widespread use in developing countries at this time.

PREVIOUS EXPERIENCE WITH MEDICATION MONITORS FOR TREATING TB

Studies using non-electronic medication monitors have documented both good and poor adherence when patients were given medication at routine clinic visits. In Denver, Colorado, USA, 61% of 122 patients took ⩾90% of SAT in the latter months of treatment,[8] while in Port au Prince, Haiti, 58.5% of 123 patients took ⩾90%.[10] Homeless and alcoholic patients were excluded in Denver and defaulters were excluded in Haiti. From these studies, one can roughly estimate that approximately 50% of patients given SAT will take 90% or more of their medication and would not need resource-intensive DOT.

In Haiti, the adherence record in the first 3 months of therapy tended to predict adherence in the last 9 months of a 12-month course of isoniazid and thiacetazone.[10] Two medication monitor studies of treatment for latent TB infection in Montreal, Canada, showed that good adherence early in therapy and taking medication near the same point in time each day predicted better treatment completion.[23,24] If replicated with additional studies, the early adherence record should be helpful in planning the support and supervision that each patient needs.

An obvious problem with all but the most expensive medication monitors is that patients may remove medications on time and not ingest them. Some patients receiving DOT are known to deceive care givers by placing the pills in their mouths and subsequently expectorating them when not being observed. One may therefore anticipate that some patients will remove drugs from monitors as scheduled without ingesting them. While this problem may prove to be significant, one can argue that it will occur infrequently because it requires a daily repetitive act. The extent of this practice needs investigation by comparing monitor records with tests for the drug in urine or blood collected at surprise visits. The results of such a study will then have to be weighed against the frequency with which patients refuse to cooperate or fail to report regularly for DOT.

POTENTIAL APPLICATIONS OF ELECTRONIC MEDICATION MONITORS

Details of monitor-based strategy

Patients with a monitor record that shows medication removal every day, or nearly every day, could be seen at monthly intervals with routine education and encouragement. Less adherent patients could be seen more frequently for focused counseling of patients and their families. If this fails, DOT should be used. In addition, the adherence record would be used to plan additional treatment to compensate for medication not taken. The staff time saved by reducing DOT use could be used to return defaulters to therapy.

It may be difficult, although not impossible, to require a poorly adherent patient to take DOT after taking SAT. In Denver, among 34 patients who took less than 90% of their medication, 25 had improved adherence with additional counseling and 9 were given DOT.[8] To minimize the need to change back from SAT to DOT, it may be reasonable to start all patients on DOT, to give SAT in medication monitors only to patients who come in regularly, and to advise all patients given SAT in medication monitors (monitored SAT) that they may be required to take DOT again if they have poor adherence records. If videophone

DOT becomes less expensive, it may prove to be a viable way to deal with difficult patients.

Community worker use of monitor-based strategy

The WHO has strongly and properly advocated employing community workers to provide convenient treatment close to patients' homes.[25] The display built into the monitor, which shows the adherence record, would simplify the task of giving monitored SAT by community workers.

Monitor-based strategy for family member DOT

Family member DOT consists of a trained family member observing the patient ingesting each dose of medication. This method is attractive because it utilizes minimal staff time and imposes little or no burden on the patient. However, it has been severely criticized as a 'feel good' but ineffective way of giving DOT, as the family member is not an independent observer and is less likely to observe ingestion of the medication.[26] However, at least one study shows it modestly improves adherence.[27] Medication monitors could further improve family member DOT by providing supervision. This will probably be the most effective way of using medication monitors, as the home visitor will usually have multiple family members to work with should poor adherence occur.

In a family member DOT program, the clinic or community worker would:

- provide the drugs in medication monitors to be taken daily;
- choose a leading family member to observe medication ingestion;
- carefully instruct the patient, the chosen observer, and all family members about the importance of uninterrupted treatment;
- check the adherence record using the display mounted in the monitor when the patient visits the care giver or the care giver visits the home;
- initially see all patients once a week;
- subsequently see patients with good records less frequently: every 2 weeks and later every 4 weeks;
- continue to see patients with poor records frequently, with increased counseling of patients and their families;
- assume the task of giving the DOT if these measures fail;
- use the adherence record for deciding on how long to continue therapy.

Patients who do not live with families could be managed in a similar manner, with a close associate chosen as a guardian to observe medication ingestion.[28]

Monitor-based strategy for private sector treatment

The private sector, where DOT is rarely used, treats a large proportion of the world's TB patients,[29] but such treatment is often inadequate.[29] Unsupervised pharmacies sometimes provide TB treatment without a physician's prescription.[30] Forty-eight per cent of initial defaulters from public programs in Viet Nam chose private providers for their treatment,[31] and private physician care in India is very common despite a well-developed public TB treatment program that uses DOT extensively.[29] In a survey of private patients in India, 68% stated that DOT was unacceptable, 91.5% preferred buying the drugs themselves to visiting a public treatment center, and 45% were not prepared to be observed while swallowing their TB drugs, seeing it as an intrusion of privacy.[32]

Public-private partnerships have been set up to address this problem, but this requires a great deal of effort from the public sector to gain private physician cooperation, with variable degrees of success.[33] If public programs provided monitored SAT instead of DOT for most patients, this should encourage more patients to seek free, high-quality supervised public care.

For those patients who still prefer private care, physicians could give monitored SAT, with trained, subsidized pharmacies filling the monitors with free medications. This should increase the cooperation between physicians and pharmacies and provide a reasonable degree of patient supervision. The pharmacies would report the adherence record to the physicians and public health officials, who could decide collectively on interventions when poor adherence was observed.

Monitor-based strategy for patients who move

Providing uninterrupted treatment for patients who move, especially for rural patients who reside temporarily in cities and migratory agricultural workers, can be very difficult. Medication monitors that include the means to keep the adherence record from the start of therapy, together with basic clinical information, such as sputum and HIV status, could help in managing these patients.[11] All patients would be instructed to present their medication monitors to the care giver in their new location should they move. The new care giver could retrieve the necessary data by using the display in the monitor with a little training, without having additional technology such as computers or hand-held devices.

Medication-based strategy to reduce the defaulter problem

Patients who default or fail to complete treatment represent a major problem that increases the risk of treatment failure. Finding and returning such patients to treatment can take excessive resources. Medication monitors could help solve this problem. First, avoidance of multiple visits for DOT will make it easier for patients to continue treatment and reduce the motivation to default. Second, not giving DOT to reliable patients would free up staff time to retrieve defaulters. Third, the evidence that early monitor

records appear to predict patients who are more likely to default could be used to direct additional counseling to potential defaulters and their families.[10,23,24] Fifth, if a defaulting patient moves to a new location, the data in the monitor would help in planning further treatment.[11]

COMPARISON WITH UNIVERSAL DOT

For patients being treated for MDR or extensively drug-resistant TB, DOT should be given, if at all possible, because if the treatment fails there is rarely any other effective therapy.

There are experts who strongly oppose both SAT and family DOT for patients being treated for the first time.[26] In many developing countries, there are large numbers of unemployed potential community workers who could give DOT at or near the patients home, if trained and paid to do so. In addition to providing treatment, paying these workers would provide badly needed employment.

However, treatment observers are not always reliable. In Thailand, community workers were found to give SAT 23% of the time when they reported DOT.[34] When patients learned they had to take DOT, many chose to pay for alternative inferior treatment from private physicians and pharmacies.[31] Furthermore, data from service programs, indicating that daily treatment is more effective than treatment given two and three times per week,[16,18–20] shed doubt on the effectiveness of the widely used intermittent DOT programs.

Probably the strongest argument against universal DOT are the reports that DOT is not given regularly in many programs,[14] despite strong DOT advocacy by the WHO and the International Union Against Tuberculosis and Lung Disease since around 1995. Given this reality, a monitor-based strategy should become a high priority for multidisciplinary research that includes engineers, clinicians, nurses and administrators.

EVALUATION

The effectiveness of a medication monitor-based strategy will ultimately require cluster-randomized control trials (CRCTs) in various settings. Before doing so, the number of patients who remove drugs on schedule from medication monitors but fail to ingest them will need to be determined. The next step will be to study the individual components of a monitor-based strategy: 1) How many patients are sufficiently adherent that they require no more than monthly refill visits? 2) How many less-adherent patients can achieve adequate adherence after more frequent contact with the care giver for repetitive counseling? 3) How many poorly adherent patients require strict DOT? 4) How much effort is needed to implement strict DOT? 5) How much additional therapy is needed to compensate for different degrees of non-adherence?

Assuming this preliminary work shows promising results, CRCTs will be needed to confirm the value of the program. Such trials could include, but are not limited to, 1) monitor-based family DOT compared to family DOT without monitoring, 2) a monitor-based strategy compared to universal DOT for patients who live alone, and 3) a monitored-based strategy compared to ordinary SAT given to private physicians' patients or to migratory agricultural workers. Ideally, the results of all studies would be based on the number of patients who achieve culture negativity at the end of treatment and at specified follow-up periods, together with the number of defaulters lost to follow-up and the cost per patient cured. The effectiveness of medication monitors in managing patients with an apparently stable address who subsequently move will most likely be based on less rigid criteria derived from program experience, as patients' moves are sporadic and unpredictable.

CONCLUSION

Because of widespread poor adherence to self-administered TB therapy, supervision with DOT has had strong international advocacy for over 10 years. However, the use of DOT has not been fully implemented due to patient resistance and lack of program resources. This lack of full implementation has contributed to significant drug resistance in many parts of the world. Clearly, a new means of supervising adherence is needed. A monitor-based strategy is one such means that has considerable promise but needs careful evaluation.

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RÉSUMÉ

L'apparition d'une résistance significative aux médicaments dans un grand nombre de pays couplée avec les problèmes connus d'administration du traitement directement observé (DOT) appelle à un réexamen des stratégies d'administration du traitement de la tuberculose (TB). On a introduit des moniteurs électroniques de médications, instruments qui enregistrent le moment où le médicament est retiré de sa boîte ainsi que des stratégies basées sur la vidéophonie pour déterminer dans quelle mesure elles peuvent différencier de manière efficiente 1) les patients qui adhérent correctement au traitement auto-administré (SAT) ; 2) les patients moins fiables qui pourraient être traités avec succès par le SAT, si on leur donnait des conseils plus intensifs ; et 3) les patients qui exigent le DOT. Les dossiers d'adhésion pourraient être utilisés pour décider un allongement compensatoire du traitement en cas d'adhésion médiocre. On pourrait utiliser le temps épargné en ne pas administrant le DOT à tous les patients pour rechercher les abandons. Ces composantes représentent ensemble une stratégie basée sur la surveillance. Le programme pourrait être étendu à la supervision de l'adhésion des patients privés aux médicaments fournis par des pharmacies formées et subsidiées avec les médecins ou, en cas de nécessité, par les départements de la santé prenant en charge les patients à adhésion médiocre. En cas de déménagement des patients, l'outil pourrait transmettre les données essentielles au nouveau pourvoyeur de soins. Si l'on veut arriver à des résultats optimaux, il est nécessaire d'évaluer avec soin les exigences qu'impose l'obtention des procédures les meilleures possibles en vue de maîtriser les cas de médiocre adhésion thérapeutique après leur détection.

RESUMEN

La aparición de farmacorresistencia en muchos países, aunada a los problemas conocidos de suministro del tratamiento directamente observado (DOT), exige una nueva evaluación de las estrategias de administración del tratamiento antituberculoso. Se han introducido monitores electrónicos de medicamentos que captan el retiro de los medicamentos de los envases y estrategias de videotelefónicas con el fin de estudiar si estos dispositivos permitirían diferenciar en forma eficaz a: 1) los pacientes que cumplen adecuadamente con el tratamiento autoadministrado; 2) los pacientes menos fiables que se podrían tratar con una estrategia autoadministrada (SAT) si reciben una orientación más intensiva; y 3) a los pacientes que necesitan un tratamiento directamente observado. El registro del cumplimiento podría contribuir a la decisión de prolongar el tratamiento con el fin de compensar las fallas en la observancia. El tiempo ahorrado al no aplicar el DOT a todos los pacientes se podría invertir en la recuperación de los pacientes que abandonan el tratamiento. Estos componentes combinados constituyen una estrategia de monitorización. El programa se podría extender a la supervisión del cumplimiento terapéutico de los pacientes en la práctica privada que reciben sus medicamentos en farmacias subvencionadas con personal entrenado, con un mecanismo de seguimiento de los pacientes que no cumplen, parte de personal médico o cuando fuese necesario de los departamentos de salud. En caso de mudanza, los dispositivos podrían transferir los datos esenciales al nuevo profesional encargado. Con el fin de lograr resultados óptimos es preciso evaluar con atención las condiciones necesarias para introducir estos dispositivos y los procedimientos más eficaces de manejo de la observancia terapéutica deficiente.