Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study

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Objective To assess adherence to community-based directly observed treatment (DOT) among Tanzanian tuberculosis patients using the Medication Event Monitoring System (MEMS) and to validate alternative adherence measures for resource-limited settings using MEMS as a gold standard.

Methods This was a longitudinal pilot study of 50 patients recruited consecutively from one rural hospital, one urban hospital and two urban health centres. Treatment adherence was monitored with MEMS and the validity of the following adherence measures was assessed: isoniazid urine test, morisky scale, brief medication questionnaire, adapted AIDS Clinical Trials Group (ACTG) adherence questionnaire, pill counts and medication refill visits.

Findings The mean adherence rate in the study population was 96.3% (standard deviation, SD: 7.7). Adherence was less than 100% in 70% of the patients, less than 95% in 21% of them, and less than 80% in 2%. The ACTG adherence questionnaire and urine colour test had the highest sensitivities but lowest specificities. The Morisky scale and refill visits had the highest specificities but lowest sensitivities. Pill counts and refill visits combined, used in routine practice, yielded moderate sensitivity and specificity, but sensitivity improved when the ACTG adherence questionnaire was added.

Conclusion Patients on community-based DOT showed good adherence in this study. The combination of pill counts, refill visits and the ACTG adherence questionnaire could be used to monitor adherence in settings where MEMS is not affordable. The findings with regard to adherence and to the validity of simple adherence measures should be confirmed in larger populations with wider variability in adherence rates.
from their community (usually a relative or spouse) who is instructed on how to provide daily DOT at home. Patients on community-based DOT are supposed to collect their medication once a week in the first two months of treatment and once every two weeks in the remaining four months. They should return medication blisters for pill counts and their clinic attendance is registered.

**Study design and procedures**

This was a longitudinal pilot study in which treatment adherence among 50 patients on community-based DOT was monitored by MEMS throughout treatment. MEMS was used as a gold standard to validate several other adherence measures (single and in combinations) in this patient group. The adherence measures were selected for their applicability in the Tanzanian setting and included an isoniazid (INH) urine test, a urine colour test for rifampicin, the Brief Medication Questionnaire (BMQ), the Morisky scale, an adapted version of the Medication Questionnaire (BMQ), the Isoniazid urine test, a brief medication questionnaire. We scored any answer other than “never” to the questions in sections C and D or less than “somewhat satisfied” to the questions in section B as positive. A positive score was regarded as indicative of non-adherence.

**Refill visits and pill counts**

The patients’ clinic attendance for medication refills was registered and remaining tablets were counted at every refill visit. Patients who delayed at least once for a medication refill visit and those who had an incorrect number of tablets remaining at least once were classified as non-adherent.

**Data analysis**

MEMS data were analysed by using Powerview software (AARDEX Ltd, Sion, Switzerland). Periods of “pocket dosing” (i.e. taking out medication for later use) that were identified by the MEMS use questionnaire were excluded from the analysis as non-monitored periods. Statistical analysis was performed in SPSS version 16.0 (SPSS Inc., Chicago, United States of America). Means are presented with standard deviation (SD) and medians with interquartile range (IQR). Means were compared by using the Student t-test. The sensitivity, specificity, positive and negative predictive values and accuracy of single and combined adherence measures were calculated by using MEMS as the gold standard. For combined measures, non-adherent patients were those who were classified as non-adherent by at least one of the single measures in the combination.
Ethical approval

The study was approved by the institutional review board of the Kilimanjaro Christian Medical Centre (Moshi, United Republic of Tanzania) and the National Institute for Medical Research (Dar es Salaam, United Republic of Tanzania).

Results

Patient characteristics and treatment outcomes

We enrolled 31 male and 19 female patients. Their characteristics are summarized in Table 1. Six of the 22 patients who were co-infected with HIV used antiretroviral medication and 14 were on co-trimoxazole prophylaxis. Although all patients were on community-based DOT, seven had no formal treatment supporter.

Thirty-seven patients successfully completed treatment. Six patients died; all were HIV-positive. Three patients defaulted and four patients dropped out of the study (three were transferred to another region and one developed jaundice and his treatment had to be interrupted).

Treatment adherence according to MEMS

No MEMS data were available for three patients (one defaulter and two who died) because the medication bottle was not returned. For the other 47 patients, a total of 6871 treatment days were monitored by MEMS. On 194 monitored days the MEMS bottle was not opened; the median per patient was 2 days (IQR: 0–5). The mean adherence rate was 96.3% (SD: 7.7) and did not differ significantly between patients with and without a treatment supporter: 96.2% (SD: 8.2) and 97.1% (SD: 3.1), respectively ($P=0.79$).

Adherence was less than 100% in 70% of all patients; less than 95% in 21% of them, and less than 80% in 2% (Table 2). Among the patients who completed the six-month treatment course, adherence was less than 100% in 73%, less than 95% in 19% and less than 80% in none, respectively.

Monthly adherence rates were fairly constant. In the group of patients who completed treatment, the median monthly adherence rate was 100% and the mean monthly adherence rate varied between 95.4% (SD: 7.3) in month 6 and 98.5% (SD: 2.7) in month 3.

Validation of adherence measures

For the validation of the alternative adherence measures only patients who completed the six-month treatment course ($n=37$) were included. As shown in Fig. 1, the proportions of non-adherent patients identified by the different measures varied widely. Table 3 shows the sensitivity, specificity, positive and negative predictive value and accuracy of the adherence measures in terms of their ability to differentiate between adherent and non-adherent patients. The ACTG adherence questionnaire and urine colour test had the highest sensitivities but lowest specificities. The Morisky scale and refill visits had the highest specificities but lowest sensitivities. The sensitivities of most measures improved when the cut-off value to differentiate be-
Table 2. Median monitored treatment days and adherence rates, and proportions of patients who were less than 100%, 95% and 80% adherent, as assessed by the Medication Event Monitoring System (MEMS), United Republic of Tanzania, 2010

<table>
<thead>
<tr>
<th>Patients*</th>
<th>Monitored days</th>
<th>Adherence rate (%)</th>
<th>&lt;100% adherent</th>
<th>&lt;95% adherent</th>
<th>&lt;80% adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (47)</td>
<td>Median (IQR)*</td>
<td>168 (138–172)</td>
<td>98.4 (95.7–100)</td>
<td>33 (70)</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Completed treatment (37)</td>
<td>169 (168–180.5)</td>
<td>98.4 (95.7–100)</td>
<td>27 (73)</td>
<td>7 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Defaulters (2)</td>
<td>40.0/113c</td>
<td>50.0/100d</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Deaths (4)</td>
<td>63 (29.5–104)</td>
<td>98.4 (95.6–99.6)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Study drop outs (4)</td>
<td>33 (21–73)</td>
<td>98.3 (88.4–100)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
* Only values given are medians and IQRs except for the values of the two defaulters.
+ Number of monitored days for defaulter 1 and defaulter 2, respectively.
- Adherence rates of defaulter 1 and defaulter 2, respectively.

Patients’ experience with MEMS use

The questionnaire about the use of MEMS, which was filled out by the 37 patients who completed treatment, revealed that only one patient had correctly understood the purpose of MEMS despite verbal and written information at the onset of the study. Twenty-five patients (68%) stated that the white, bulky appearance of the MEMS bottle reminded them to take the medication. However, the other patients said that the use of MEMS had not influenced their adherence behaviour. Mean adherence rates did not differ between these two groups: 97.5% (SD: 3.0) and 97.3% (SD: 3.2), respectively ($P=0.86$).

Eight patients occasionally opened the MEMS bottle to take out medication for later use (resulting in a total of 42 non-monitored treatment days). This usually occurred when patients did not want to take the bottle along on travel occasions.

Discussion

This is the first study in which MEMS was used to assess treatment adherence rates in patients on community-based DOT over the full six-month tuberculosis treatment course. We observed high adherence rates in our pilot study of 50 Tanzanian patients. Almost 80% of the patients were more than 95% adherent and only one patient was less than 80% adherent. These findings do not confirm the concern that patients on community-based DOT are prone to become non-adherent, even though the study did reveal that some patients (i.e. those without a formal treatment supporter) turn community-based DOT into unsupervised treatment.

The participants’ demographic characteristics, such as the ratio of males to females and their treatment outcomes, were comparable to those of the general tuberculosis patient population in the Kilimanjaro region. This suggests that we studied a regionally representative patient sample. However, the adherence rates of our patients could have been biased by their participation in the study. Although we tried to deviate as little as possible from routine practice, the repeated adherence questionnaires and urine tests certainly made participants aware of our interest in their adherence behaviour. Two thirds of the patients felt that their adherence behaviour had been influenced by the use of MEMS, but their average adherence rate did not differ from those observed among patients who stated that MEMS had not influenced their behaviour. Findings from other studies suggest that when MEMS is used over long periods, its "interventional
The main objective of our study was to use MEMS as a reference standard to calculate the validity of several adherence measures whose use is feasible in patients on community-based DOT in resource-limited settings. The high adherence rates in the study population forced us to apply high adherence rate cut-off values to calculate the validity and reliability of the adherence measures. This resulted in wide gaps between the sensitivities and specificities of the measures. Combinations of measures were found to be more accurate than single measures in identifying as many true non-adherent patients as possible (reflected in high sensitivities and negative predictive values). The sensitivity and negative predictive value of the routinely used combination of pill counts and clinic attendance for medication refills improved substantially by adding a simple and cheap measure such as the ACTG adherence questionnaire, particularly at an adherence rate cut-off value of 95%.

The rifampicin urine colour test classified more patients as non-adherent than the INH urine test. Since the orange urine colouration caused by rifampicin is of short duration and may be absent altogether, it is likely that the urine colour test misclassified some patients with yellow urine as non-adherent. Such misclassifications are difficult to confirm in a study population with high adherence rates.

The adapted ACTG adherence questionnaire yielded more favourable responses than the other self-report measures. Differences in wording in the questionnaires may account for this. While patients had to answer either “yes” or “no” to the questions in the Morisky scale, they could answer “often”, “sometimes”, “rarely”, or “never” to comparable questions in the ACTG adherence questionnaire. This wider range of choice options may have evoked more honest replies. The ACTG adherence questionnaire (and to a lesser extent the BMQ) has the added advantage of disclosing factors that cause non-adherence in the individual patient. These factors could be used to design tailored interventions for promoting adherence among non-adherent patients on community-based DOT. We therefore suggest using the triple combination consisting of the ACTG adherence questionnaire, refill visits plus pill counts, and urine colour test.
**Résumé**

**Suivi électronique de l’adhésion au traitement et validation de mesures d’adhésion alternatives des patients tuberculeux: une étude pilote**

**Objectif** Évaluer l’adhésion au traitement directement observé en milieu communautaire des patients tuberculeux tanzaniens, à l’aide du système de suivi des événements de médication (MEMS, Medication Event Monitoring System) et valider les mesures d’adhésion alternatives dans les configurations de ressources limitées utilisant le MEMS comme critère de référence.

**Méthodes** Il s’agissait d’une étude pilote longitudinale sur 50 patients recrutés consécutivement dans un hôpital rural, un hôpital urbain et deux centres de soins urbains. L’adhésion au traitement a été contrôlée par le système de suivi des événements de médication (MEMS) et validée par des mesures alternatives d’adhésion.

**Résultats** 632-639

**Conclusions** La validation des mesures alternatives d’adhésion au traitement a été réalisée par l’étude pilote. Les résultats ont montré des taux d’adhésion comparables entre les mesures alternatives et le système de suivi des événements de médication (MEMS). Cependant, les mesures alternatives peuvent être utilisées dans des contextes où le MEMS n’est pas disponible.

**Mots-clés** adhésion, suivi électronique, mesures alternatives, patients tuberculeux.
Резюме
Электронный мониторинг приверженности к лечению и проверка действенности альтернативных мер по контролю приверженности у больных туберкулезом (пилотовое исследование)

Цель Оценить приверженность к лечению, проводившемуся на базе общины, на основании наблюдения за течением лечения, у туберкулезных больных в Танзании с применением Системы электронного мониторирования выдачи препаратов (Medication Event Monitoring System, MEMS) и проверить участия альтернативных мер по контролю приверженности в условиях ограничения ресурсов, используя MEMS в качестве «золотого стандарта».

Методы Проведено пилотное исследование в течение 6 мес. на базе общины включившие в себя 50 пациентов, отобранных последовательно из сельской больницы, городской больницы и двух городских медицинских центров. Мониторинг приверженности к лечению осуществлялся с помощью MEMS; проводилась также проверка приверженности следующих мер по контролю приверженности: анализ мочи при приеме изониазида, контроль цвета мочи, применения шкалы Morisky, Краткого опросника по лекарственным препаратам (Brief Medication Questionnaire, BMQ) и адаптированного варианта «Опросника по приверженности» Группы клинических испытаний по СПИДу (ACTG), а также подсчет таблеток и посещения больных с целью пополнения запасов лекарств.

Результаты Средний показатель приверженности в исследуемой популяции составлял 96,3% (стандартное отклонение, СО: 7,7). У 70% больных показатель приверженности был ниже 100%, у 21% – ниже 95% и у 2% ниже 80%. При применении опросника ACTG и контроля цвета мочи достигалась максимальная чувствительность при минимальной специфичности. Применение шкалы Morisky и визитов для пополнения запаса лекарств давало максимальную чувствительность при минимальной специфичности. Использование в рутинной практике подсчета таблеток в сочетании с посещениями больных для пополнения запасов лекарств обеспечивали умеренную чувствительность и специфичность, однако при добавлении опросника ACTG чувствительность повысилась.

Вывод В данном исследовании пациенты, проходившие лечение под непосредственным наблюдением врача (DOT) на уровне общины, продемонстрировали высокий уровень приверженности. Для отслеживания приверженности больных к лечению в условиях, когда применение MEMS недоступно по финансовым причинам, можно применить подсчет таблеток, посещение больных с целью пополнения запаса лекарств и «Опросник по приверженности» ACTG. Полученные результаты, касающиеся приверженности к лечению и действенности простых мер контроля приверженности больных к лечению, необходимо подтвердить на примере более крупных популяций при широком разбросе значений показателя приверженности.

Resumen
Control electrónico del cumplimiento terapéutico de pacientes con tuberculosis y validación de medidas alternativas de cumplimiento: estudio piloto

Objetivo Evaluar el cumplimiento de los tratamientos observados directamente que están dirigidos a la comunidad por parte de los pacientes con tuberculosis en Tanzania, mediante el Sistema de vigilancia de la medicación (Medication Event Monitoring System [MEMS]) y validar medidas alternativas de cumplimiento para los entornos de recursos limitados, empleando los MEMS como método de referencia.

Métodos Se realizó un estudio piloto longitudinal con 50 pacientes seleccionados consecutivamente de un hospital rural, un hospital urbano y dos centros sanitarios urbanos. El cumplimiento terapéutico se controló con el MEMS y se evaluó la validez de las siguientes medidas de cumplimiento: detección de isoniazida en orina, prueba de color de la orina, test de Morisky, Cuestionario breve de medicación, cuestionario adaptado del cumplimiento terapéutico del Grupo de Ensayos Clínicos sobre el SIDA (ACTG), recuento de la medicación y visitas de aprovisionamiento de medicamentos.

Resultados La tasa media de cumplimiento en la población del estudio fue de un 96,3% (desviación estándar, DE: 7,7). El cumplimiento fue inferior al 100% en el 70% de los pacientes, inferior al 95% en el 21% de los pacientes e inferior al 80% en el 2% de los pacientes. El cuestionario de cumplimiento ACTG y la prueba de color de la orina registraron los niveles más elevados de sensibilidad y los más bajos de especificidad. El test Morisky y las visitas de aprovisionamiento de medicamentos obtuvieron los niveles más elevados de especificidad y los más bajos de sensibilidad. La combinación del recuento de medicamentos y las visitas de aprovisionamiento, empleada en la práctica habitual, registró una sensibilidad y una especificidad moderadas, si bien la sensibilidad aumentó cuando se añadió el cuestionario de cumplimiento ACTG.

Conclusión Los pacientes que siguieron un tratamiento observado directamente y dirigido a la comunidad mostraron un cumplimiento correcto.
en este estudio. La combinación del recuento de medicación, las visitas de aprovisionamiento de medicamentos y el cuestionario de cumplimiento ACTG podría emplearse para controlar el cumplimiento en entornos en los que el uso del sistema MEMS no resulte viable económicamente. Los resultados en cuanto al cumplimiento y a la validez de las medidas sencillas de cumplimiento podrían confirmarse en poblaciones más amplias con una mayor variabilidad de sus tasas de cumplimiento.

**References**


