Epidemiology and control of tuberculosis and sexually transmitted infections in Thyolo District, Malawi

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CHAPTER 3

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Compliance with cotrimoxazole prophylaxis for the prevention of opportunistic infections in HIV-positive tuberculosis patients in Thyolo district, Malawi

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OBJECTIVE: To verify compliance with cotrimoxazole prophylaxis in human immunodeficiency virus (HIV) infected tuberculosis (TB) patients during the continuation phase of anti-tuberculosis treatment, and to assess the sensitivity, specificity and positive predictive values of verbal verification and pill counts as methods of checking compliance.

DESIGN: Cross-sectional study.

METHODS: Cotrimoxazole compliance was assessed in a cohort of TB patients who were attending four TB follow-up centres during the continuation phase of anti-TB treatment between months 4 and 6. Verbal verification of drug intake, physical verification of pill count balance, and urine trimethoprim detection by gas chromatography and mass spectrometry were used for assessing compliance.

RESULTS: Using urine trimethoprim detection as the gold standard for compliance, trimethoprim was detected in 82 (94%) of 87 patients in the cohort. Verbal verification of cotrimoxazole intake and objective pill count balances showed high sensitivity and positive predictive values compared with the gold standard of urine trimethoprim detection.

CONCLUSIONS: In a rural district in Malawi, compliance with cotrimoxazole as an adjunct to anti-tuberculosis treatment in HIV-infected TB patients was good, and can be assessed simply and practically by verbal verification and pill counts.

KEY WORDS: cotrimoxazole; compliance; HIV infection; tuberculosis; Malawi

HUMAN IMMUNODEFICIENCY VIRUS (HIV) positive patients with tuberculosis (TB) in sub-Saharan Africa have high death rates during and following anti-tuberculosis treatment.1,2 These death rates have a negative impact on cure rates, and challenge the credibility of TB control programmes amongst patients, health care staff and the community. Effective and affordable adjunctive interventions to reduce death rates in sub-Saharan Africa are urgently needed. Tuberculosis is also an early HIV-related opportunistic infection which often brings persons with HIV to medical attention, and it is therefore an opportunity for intervention.

In Abidjan, Cote d'Ivoire, a randomised placebo-controlled trial of cotrimoxazole prophylaxis in HIV-positive patients with smear-positive pulmonary tuberculosis (PTB) showed a significant reduction in morbidity and mortality during anti-TB treatment.3 Similar encouraging results were reported from Cape Town, South Africa,4 and UNAIDS has made provisional recommendations that cotrimoxazole prophylaxis be used in those with symptomatic HIV-related disease or persons with CD4 counts of less than 500 in Africa.5 However, it is uncertain whether the beneficial effect of cotrimoxazole seen in Abidjan and Cape Town will be replicated widely and elsewhere in sub-Saharan Africa because of the differing patterns of HIV-related opportunistic infections and the different prevalence of cotrimoxazole resistance among commonly occurring pathogens.

In view of these uncertainties, the National TB Control Programme (NTP) in Malawi is currently carrying out operational research in two districts to assess the efficacy and feasibility of cotrimoxazole prophylaxis to reduce mortality in patients being registered and treated for TB. This research is being conducted within the routine conditions of district TB control programmes. In assessing whether cotrimoxazole is effective or not, it is important to know that patients are actually taking the drug. The present study was carried out in one of the districts to determine 1) compliance with cotrimoxazole prophylaxis in HIV-positive TB patients during the continuation phase of anti-

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tuberculosis treatment, 2) factors associated with compliance, and 3) the sensitivity and predictive values of verbal verification and pill counts as methods of checking compliance.

METHODS

Study population, data collection and specimens

This operational research study of cotrimoxazole prophylaxis, which is still being implemented, examined a cohort of TB patients registered in the Thyolo district of the southern region of Malawi. In the cotrimoxazole study, all registered TB patients are started on standardised anti-tuberculosis treatment according to national guidelines. Patients undergo voluntary counselling and HIV testing, and are offered cotrimoxazole prophylaxis if they are HIV-seropositive and if there are no contraindications for the medication. Cotrimoxazole prophylaxis is given at a dose of 480 mg (400 mg sulfamethoxazole and 80 mg trimethoprim) twice daily during the whole course of anti-tuberculosis treatment and indefinitely thereafter. Anti-tuberculosis drugs and both daily doses of cotrimoxazole are administered by direct observation during the initial phase of treatment. In the continuation phase of treatment, a sufficient supply of anti-tuberculosis drugs and cotrimoxazole is given to patients at monthly intervals, and the drugs are self-administered. All patients receive enough pills for 33 days of cotrimoxazole prophylaxis (which includes 3 days of safety stock), and are expected to report at the follow-up clinic on a fixed day at the end of 30 days of treatment to collect further supplies of anti-tuberculosis drugs and cotrimoxazole.

Cotrimoxazole compliance was assessed in patients attending four TB follow-up centres during the continuation phase of treatment between months 4 and 6. Compliance was assessed as follows. There was a verbal (subjective) verification of cotrimoxazole intake in the previous 24 hours, an objective verification of pill count balance and a record made of the reasons for pill count differences (as explained by the patient). Pill count balances were classified for the purposes of this study as exact (100% correct), satisfactory (one, two or three tablets higher or lower than the expected pill balance) or unsatisfactory (pill balances showing a difference of more than three tablets). The three-tablet cut-off point was used because this signifies one and half days of prophylaxis, which for the purposes of this study was designated as an operationally acceptable difference that can be verified on follow-up visits with respect to the prescribed dose of two tablets daily. A 15 ml sample of urine was also collected for detection of trimethoprim. Urine specimens were stored at −20°C and transported under cold chain to the National Laboratory of Health, Department of Toxicology in Luxembourg for urine trimethoprim detection by gas chromatography/mass spectrometry (set as the gold standard for this study).

Gas chromatography and mass spectrometry (GC/MS) analysis

The GC/MS system combines a separation technique (gas chromatography) and a highly sensitive and specific identification technique (mass spectrometry). Detection of the trimethoprim component of cotrimoxazole (the combination of sulfamethoxazole and trimethoprim) was done by identifying its characteristic fragmentation pattern and retention times. Calibration curves were obtained by spiking drug-free urine specimens with trimethoprim at different concentrations using methanol as an internal standard at constant concentration (1 mg/L). Creatinine levels were determined on a Cobas Mira instrument using Merck reagents. Trimethoprim concentrations in urine were standardised and expressed for 1 g of creatinine, although no reference values for trimethoprim levels in urine are available. Trimethoprim is detectable in urine up to 24 hours after the last intake of cotrimoxazole.

Statistical analysis

Data were analysed using Epi-Info (Centers for Disease Control and Prevention, Atlanta, GA). Crude odds ratios with 95% confidence intervals were used to assess whether social and clinical factors were associated with compliance, with the level of significance set at \( P = 0.05 \) or less.

Sensitivity, specificity and positive predictive values of verbal verification and pill counts were calculated using urine trimethoprim detection as the gold standard.

RESULTS

Demographic characteristics of the study cohort

Of 93 TB patients who should have attended for follow-up in the four main centres during the period of the compliance study, data are available for 87 (94%): two patients did not turn up on the appointed day, two submitted an insufficient amount of urine for analysis and in two patients the specimen bottles leaked during field and international transport, respectively. Of the 87 patients, there were 38 men and 49 women, with an age range of 32 years. Forty-three patients had smear-positive PTB, 16 had smear-negative PTB and 28 had extra-pulmonary TB. The majority of patients were farmers (57), followed by unskilled employees (15), small scale business people or vendors (12) and skilled employees, students and children (3).

Cotrimoxazole compliance

Trimethoprim was detected in 82 (94%) of the urine samples. The median urine concentration of trimethoprim was 22.7 mg/gm of creatinine (range 0.2-233 mg/gm creatinine). In five urine samples no trimethoprim was detected. Table 1 shows the results of
**Table 1** Verbal verification and pill count balances compared to urine trimethoprim detection (gold standard)

<table>
<thead>
<tr>
<th>Trimethoprim in urine</th>
<th>n (%)</th>
<th>Absent n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal verification (n = 87)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole intake in last 24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>82 (96.5)</td>
<td>3 (3.5)</td>
<td>85</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>2 (100)</td>
<td>2</td>
</tr>
<tr>
<td>Pill count balance (n = 87)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exact*</td>
<td>51 (60.2)</td>
<td>2 (2.4)</td>
<td>53</td>
</tr>
<tr>
<td>Satisfactory†</td>
<td>24 (28)</td>
<td>0 (0)</td>
<td>24</td>
</tr>
<tr>
<td>Unsatisfactory‡</td>
<td>7 (7.8)</td>
<td>3 (3.3)</td>
<td>10</td>
</tr>
</tbody>
</table>

* Exact balance  † 1-3 pills more or less than expected balance  ‡ >3 pills more or less than expected balance

Verbal verification and pill count balance compared to the results of urine trimethoprim detection. Of 85 patients who verbally stated that they had taken cotrimoxazole in the last 24 hours, three (4%) had no trimethoprim detected in the urine. Of 77 patients in whom pill count balances were exact or satisfactory, two (3%) had no trimethoprim detected in the urine. Sensitivity and positive predictive values for verbal verification, pill count balance and both assessments together, using urine trimethoprim as the gold standard, were high (Table 2).

Two patients stated that they had not taken cotrimoxazole in the previous 24 hours as they had run out of pills, and 10 patients had unsatisfactory pill count balances. The mean number of pills in excess or deficit from the exact balance was 4.3 (range 0–6). Reasons for unsatisfactory balances included giving some pills out to a sick child, family member or friend (6), losing some pills (2), forgetting to take some doses (1) and not knowing (1). There were no statistically significant social or clinical factors associated with compliance based on urine trimethoprim results, verbal verification or pill count balances.

**DISCUSSION**

Using urine trimethoprim detection measured by gas chromatography/mass spectrometry as the gold standard for determining cotrimoxazole compliance, the degree of compliance in our TB patients who were taking cotrimoxazole and anti-tuberculosis drugs under routine conditions was high. Similar good results were obtained under research conditions in Abidjan, Cote d’Ivoire. These results are reassuring for the conduct of the operational study in Thoyo, particularly when it comes to assessing the efficacy of this adjunctive intervention. Although the method of detecting trimethoprim in urine is reliable and objective, it is sophisticated and expensive, and is therefore unsuitable as a routine way of assessing cotrimoxazole compliance. Verbal verification, pill count balance and both methods together proved acceptable and robust as alternative ways of assessing compliance, and under routine conditions these are simple and practical to use.

In a rural district such as Thoyo where the majority of patients are farmers, it is understandable that some patients will use cotrimoxazole for treating sick members of the family, will forget to take tablets or will be unable to report at the treatment centre on the exact day of the follow-up appointment. Providing patients with a 3-day excess stock of pills provides a safety net for continued prophylaxis, and in the present study this was not associated with undue abuse of the system.

In the cotrimoxazole operational research study which aimed to recruit TB patients during the course of 12 months, over 1000 patients have been registered for treatment of whom nearly 700 have been started on cotrimoxazole prophylaxis. End of treatment outcomes compared with those observed in historical controls within the same district will help the NTP make a decision about the efficacy or not of this intervention in reducing death rates.

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This study received ethical approval from the National Health Sciences Research Council of Malawi.

**References**

OBJECTIFS : Vérifier l’adhésion à une prophylaxie au cotrimoxazole chez les patients tuberculeux (TB) infectés par le virus de l’immunodéficience humaine (VIH) au cours de la phase de continuation du traitement antituberculeux, et apprécier la sensibilité, la spécificité et la valeur prédictive positive d’une vérification verbale et des décomptes de comprimés comme méthodes de contrôle de l’adhésion.

SCHEMA : Etude transversale.

MÉTHODES : L’adhésion thérapeutique au cotrimoxazole a été appréciée dans une cohorte de patients TB qui fréquentaient quatre centres de suivi de TB au cours de la phase de continuation du traitement antituberculeux entre les mois 4 et 6. La vérification verbale de la prise des médicaments, la vérification physique de l’équilibre des décomptes de comprimés et la détection du triméthoprim dans les urines par chromatographie gazeuse et spectrographie de masse ont été utilisées pour apprécier l’adhésion.

RÉSULTATS : Si l’on utilise la détection de triméthoprim dans les urines comme « gold standard » pour l’adhésion, le triméthoprim a été détecté chez 82 (94%) des 87 patients de la cohorte. La vérification verbale de la prise de cotrimoxazole et l’équilibre des décomptes de comprimés ont révélé une sensibilité et une valeur prédictive positive élevée par comparaison au gold standard de détection de triméthoprim dans les urines.

CONCLUSION : Dans un district rural du Malawi, l’adhésion à la prise de cotrimoxazole comme complément à un traitement antituberculeux chez les patients TB infectés par le VIH s’est avérée bonne et peut être appréciée rapidement et d’une façon pratique par une vérification verbale et le décompte des comprimés.

RESUMEN

OBJETIVO : Verificar la adhesión a la profilaxis con cotrimoxazol en pacientes con TB infectados por el virus de la inmunodeficiencia humana (VIH) durante la fase de continuación del tratamiento antituberculoso y evaluar la sensibilidad, especificidad y valor predictivo positivo de la verificación verbal y del conteo de cápsula como métodos de control.

DISEÑO : Estudio transversal.

MÉTODO : Se evaluó la adhesión al cotrimoxazol en una cohorte de pacientes con TB que asistían a cuatro centros, en la fase de continuación del tratamiento antituberculoso, entre los meses 4 a 6. Para evaluar la adhesión se utilizaron la verificación verbal de la toma de drogas, control de la toma de comprimidos y la detección urinaria de trimetoprima por cromatografía gasosa y espectrometría de masa.

RESULTADOS: Cuando se utiliza la detección de trimetoprima urinaria como el criterio estándar para la adhesión, se detectó la misma en 82 (94%) de 87 pacientes en la cohorte. La 'verificación verbal' de la toma de cotrimoxazol y el 'balance del conteo de píldoras' mostró una gran sensibilidad y un valor predictivo comparados con el criterio estándar de la detección de la trimetoprima en orina.

CONCLUSIÓN: En un distrito rural de Malawi, la adhesión al cotrimexazol como un agregado al tratamiento anti-tuberculoso en los pacientes infectados por el VIH, fue bueno y puede ser evaluado en forma simple y práctica a través de la verificación verbal y del conteo de las píldoras.