INT J TUBERC LUNG DIS 6(12):1046–1050

Cotrimoxazole prophylaxis in HIV-infected individuals after completing anti-tuberculosis treatment in Thyolo, Malawi

R. Zachariah,* M. P. Spielmann,* A. D. Harries,† P. Gomani,‡ E. Bakali‡

*** Médecins Sans Frontières-Luxembourg, Thyolo, Thyolo District, † National Tuberculosis Control Programme/DFID, Lilongwe, Lilongwe, ‡ Thyolo District Health Services, Ministry of Health & Population, Thyolo, Thyolo, Malawi**

SUMMARY

SETTING: Thyolo, rural southern Malawi.

OBJECTIVES: To determine 1) the proportion who continue with cotrimoxazole prophylaxis for the prevention of opportunistic infections, and 2) the reasons for continuing or stopping prophylaxis, in human immunodeficiency virus (HIV) infected individuals with tuberculosis (TB) who complete anti-tuberculosis treatment.

DESIGN: A cross-sectional study.

METHODS: A questionnaire study of all HIV-infected TB patients who had been registered over a 3-month period to receive anti-tuberculosis treatment and cotrimoxazole prophylaxis and who had completed anti-tuberculosis treatment 3–6 months earlier.

RESULTS: Of 82 HIV-infected individuals who were alive at the time of interview, 76 (93%) were continuing with cotrimoxazole and wished to do so indefinitely. The most common reason for continuing the drug was to prevent illness associated with HIV, while the most common reason for stopping was long distances to the health facility. Ninety-six percent of patients received cotrimoxazole free of charge from a health centre. Of those who wished to continue indefinitely, the majority (63%) could not afford to pay for the drug.

CONCLUSIONS: In a rural setting, the great majority of HIV-infected individuals continued with cotrimoxazole after completing anti-tuberculosis treatment. Making the drug available and providing it free of charge is essential if it is to remain accessible for longer term prevention.

KEY WORDS: cotrimoxazole; HIV; tuberculosis; Malawi

PATIENTS INFECTED with the human immunodeficiency virus (HIV) and tuberculosis (TB) in sub-Saharan Africa have high death rates during and after anti-tuberculosis treatment.[1,2] Opportunistic infections are an important cause of the high morbidity and mortality experienced by these patients,[3–5] and it is believed that interventions to prevent these infections might improve survival. Prophylaxis with cotrimoxazole has been shown to reduce morbidity and mortality in HIV-infected patients with smear-positive pulmonary tuberculosis (PTB) in Côte d'Ivoire,[6] and in 2000, UNAIDS made provisional recommendations that cotrimoxazole prophylaxis be given to all persons living with HIV/AIDS in Africa.[7]

Since early 1999, Thyolo District, in rural southern Malawi, has been offering voluntary counselling and HIV testing (VCT) to all TB patients, followed by adjunctive cotrimoxazole treatment to those found to be infected with HIV. The district is currently assessing the feasibility and effectiveness of this intervention in reducing death rates.[8] During anti-tuberculosis treatment, HIV-infected TB patients receive anti-tuberculosis drugs as well as cotrimoxazole under the supervision of the TB control programme. This responsibility ceases at the end of anti-tuberculosis treatment, and patients are simply encouraged to continue with cotrimoxazole, the decision being left principally with the patient. Information as to whether patients are continuing with cotrimoxazole prophylaxis after anti-tuberculosis treatment, and possible factors that encourage or discourage continuation of prophylaxis would be useful to the general health services in planning for cotrimoxazole prophylaxis after anti-tuberculosis treatment. It might also give insight into the value of cotrimoxazole as perceived by the patient.

This study was conducted in a cohort of HIV-infected individuals 3 to 6 months after they had completed anti-tuberculosis treatment, in order to determine 1) the proportion of patients still taking cotrimoxazole prophylaxis, and 2) their reasons for continuing or stopping prophylaxis during the same period.

METHODS

Study setting

The study was carried out between February and March 2002 in Thyolo District, in rural southern

Correspondence to: Rony Zachariah, Médecins Sans Frontières-Luxembourg, Luxembourg 1617. Tel: (+352) 332515. Fax: (+352) 335133. e-mail: zachariah@internet.lu

Article submitted 1 June 2002. Final version accepted 31 July 2002.

[A version in French of this article is available from the IUATLD Secretariat in Paris.]

Malawi, which has a population of 450 000. The district has one government hospital, a mission hospital and 18 health centres involved in TB control activities. In this district, all patients (adults and children) diagnosed with TB are registered and started on standardised anti-tuberculosis treatment according to national guidelines.[9] Patients undergo VCT, and are offered cotrimoxazole prophylaxis if they are HIV-seropositive and there are no contraindications to the medication. Cotrimoxazole prophylaxis is offered at a dose of 480 mg (400 mg sulfamethoxazole and 80 mg trimethoprim) twice daily in adults and according to weight (kg) in two divided doses in children. The drug is taken throughout the whole course of anti-tuberculosis treatment and indefinitely thereafter. Early in the course of initiating cotrimoxazole in our setting, it was observed that several patients complained of severe nausea and vomiting when the drug was given once daily in the morning along with the anti-tuberculosis drugs. Twice-daily dosing was therefore introduced, and continued as patients experienced fewer reactions.

Anti-tuberculosis drugs and both daily doses of cotrimoxazole are administered by direct observation by the health worker during the initial phase of treatment. In the continuation phase, the anti-tuberculosis drugs and cotrimoxazole are given to patients at monthly intervals at their nearest health facility, and the drugs are self-administered.

At the end of anti-tuberculosis treatment, HIV-infected individuals can collect their cotrimoxazole for prophylaxis on a monthly basis from health centres, where a special stock is made available for this purpose, through nurses in areas where home-based care services exist, or from public pharmacies and vendors at a cost. The drugs provided by the health centres and home-based care services are free of charge.

Study population and data collection

All TB patients with known HIV infection who had been registered over a 3-month period to receive anti-tuberculosis treatment as well as cotrimoxazole prophylaxis and who had completed anti-tuberculosis treatment 3 to 6 months earlier were involved in the study.

TB treatment and counselling registers were used to gather information on patients who were alive at the end of their anti-tuberculosis treatment. A household visit was conducted for each patient known to be alive. After obtaining informed consent, interviewer-administered questionnaires which had been pre-tested on a different group of 10 HIV-infected TB patients were used to gather basic socio-demographic data and information related to cotrimoxazole prophylaxis. In the design of the questionnaire, patients were asked to give their main reasons for continuing or stopping cotrimoxazole after completing anti-tuberculosis treatment. In the case of children, the father or mother was interviewed. Cotrimoxazole availability at the patient's home was physically verified by requesting to see the tablet package. The interviews were conducted in the local language by experienced interviewers, and the same team was used throughout the study.

Analyses were performed using Epi-Info software (Centre for Disease Control and Prevention, Atlanta, GA).

RESULTS

Study population, VCT and adjunctive cotrimoxazole prophylaxis

A total of 219 TB patients were registered in the 3-month study cohort. Of these, 212 (97%) received pre-test counselling, 204 (93%) underwent HIV testing and 199 (91%) received post-test counselling. The HIV status was unknown for 15 patients: five refused HIV testing, six died, two were transferred out of the district and two had missed pre-test counselling (Figure).

Of the 204 TB patients who were HIV-tested (66 on standard treatment and 138 on short-course treatment), 149 (69%) were HIV-positive: this included 75 (65%) of 114 patients with smear-positive PTB, 41 (85%) of 48 with smear-negative PTB and 33

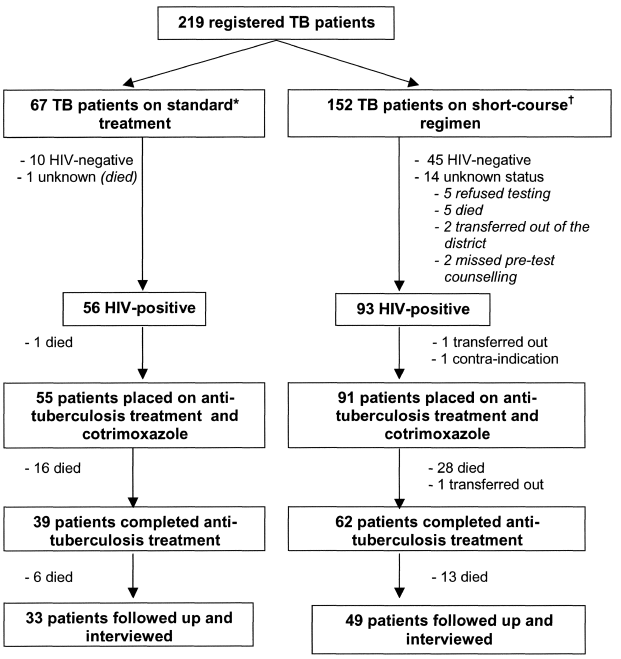

Figure Profile of the study cohort followed up after completing anti-tuberculosis treatment. * 35 smear-negative PTB and 32 EPTB cases on 1SEH/11EH; † 125 smear-positives and 13 severe smear-negatives/EPTB on 2SRHZ/6EH, six children on $2R_3H_3E_3$/6EH, and 8 relapses on 2 SRHZE/1RHZE/ $5R_3H_3Z_3E_3$. PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; S = streptomycin; E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide. (A regimen consists of two phases—an initial phase and continuation phase. Numbers before the letters indicate the duration of that phase in months; numbers in subscript indicate the number of doses of the drug(s) per week. If there is no subscript, the treatment with that drug is daily.)

(78%) of 42 patients with extra-pulmonary TB (EPTB). Of the 149 HIV-infected TB patients, 146 (98%) were given cotrimoxazole after VCT within a mean period of 2 days after registration (Figure).

Of those placed on anti-tuberculosis treatment and cotrimoxazole, 44 (20% of the registered cohort) died during the course of their anti-tuberculosis treatment, and 19 (9%) died after completing their treatment. One patient was transferred out during treatment and was lost to follow-up.

Of the 82 individuals on cotrimoxazole who were finally interviewed, there were 34 men, 47 (57%) women and one child. The median age was 32 years (range 5 to 58), and the median educational level was 6 years of schooling (range 0–14). Forty-nine (60%) patients were married and 33 were single (unmarried, divorced or widowed, or a child). The commonest occupations were farming in 46 (56%), unskilled work in 17 (21%), business in 10 (12%) and skilled work in six (7%) patients. Two patients had no form of employment and the child was aged 5 years. The majority of the patients (89%) resided in villages, with 62% earning less than the equivalent of US $4 in local currency per week.

Cotrimoxazole after anti-tuberculosis treatment

Eighty-two HIV-infected individuals were alive 3 to 6 months after completing anti-tuberculosis treatment; all of them gave consent for interview. Of these, 76 (93%) were continuing with cotrimoxazole prophylaxis and wished to do so indefinitely; 54 (71%) said they would continue the drug as they were HIV-positive and it would prevent them from getting ill, 10 (13%) felt their life depended on it, 10 (13%) wished to continue because it was free of charge and two (3%) because the doctor advised it.

Of the 76 patients taking cotrimoxazole, 73 (96%) were getting their drug from a health centre and the other three through home-based care nurses. When asked if they could afford to start purchasing cotrimoxazole for continuing prophylaxis, 26 (34%) were willing to try to pay up to US $0.50 for a month's supply, while 50 (66%) said they would have to stop the drug since they would not be able to afford it.

Six individuals stopped cotrimoxazole after completing anti-tuberculosis treatment, three because they moved to a different district that was too far away, one because he had started working and had no time, one felt he was fine and did not need to continue, and one individual had developed a skin allergy to the drug.

DISCUSSION

After completing anti-tuberculosis treatment, the great majority of HIV-infected TB patients in this study continued with cotrimoxazole prophylaxis and wished to do so indefinitely. There are a number of encouraging findings in this respect: first, the great majority of HIV-infected individuals came back of their own free will to the health centres to collect their cotrimoxazole. During the course of anti-tuberculosis treatment, activities linked to cotrimoxazole prophylaxis are integrated within the TB programme, and patient follow-up is the responsibility of the TB officers. The situation is not so clear once the patient has completed anti-tuberculosis treatment when, ideally, this responsibility should be taken over by the HIV programme. While efforts are still underway to try to integrate HIV and TB programme activities, making a stock of cotrimoxazole available at the health centres is an interim measure that will facilitate continuing prophylaxis without adding an undue burden for follow-up. Second, we demonstrated high compliance with cotrimoxazole prophylaxis in HIV-infected TB patients during the course of anti-tuberculosis treatment.[10] Our finding suggests that compliance remains high even after completion of anti-tuberculosis treatment. Third, the counselling process has clearly made HIV-infected TB patients aware of the potential benefits of cotrimoxazole in reducing morbidity and mortality. Emphasis placed on VCT in our setting and the value as perceived by the patient is likely to enhance compliance in the long term.

In Thyolo, cotrimoxazole is provided to patients free of charge both during and after anti-tuberculosis treatment. However, the question as to whether HIV-infected individuals on a country-wide scale should pay for cotrimoxazole or if it should be made available free of charge in Malawi has been raised. In a rural setting such as Thyolo, the majority of patients are either subsistence farmers or unskilled labourers earning less than US $4 per week. Furthermore, HIV-positive TB patients tend to be chronically ill, with a high prevalence of moderate to severe malnutrition.[11] Income generation capacity is low, and most patients end up destitute. Although patients might therefore desire to continue cotrimoxazole indefinitely, the majority would, quite understandably, be unable to afford the cost.

One of the discouraging findings in this study is that despite the fact that the great majority of HIV-positive TB patients were on cotrimoxazole prophylaxis, cohort mortality during anti-tuberculosis treatment remains high. Mortality after completing anti-tuberculosis treatment is also high, with about one in every five HIV-infected individuals dying within 6 months of completing anti tuberculosis treatment.

The National Tuberculosis Control Programme of Malawi has reported rising death rates in new TB patients, and in 1998 the country had the highest TB death rates reported in Africa.[12] Preventing early deaths in patients with TB remains a major challenge in resource-poor countries such as Malawi,[13] and apart from cotrimoxazole, additional effective and

affordable adjunctive interventions to reduce overall death rates, including the possibility of antiretroviral treatment, are urgently needed. Cotrimoxazole prophylaxis is nevertheless the most important adjunctive intervention currently available in resource-poor settings for reducing HIV-related opportunistic infections and promoting survival during and after anti-tuberculosis treatment. Making the drug available for HIV-infected individuals through existing health structures and providing the drug free of charge is essential to ensure that it remains accessible for longer term prevention of opportunistic infections.

Acknowledgements

We are very grateful to the staff and management of Thyolo and Malamulo hospitals for their collaboration and in particular to members of the TB support team namely D. Chilomo, A Mbanali, D Mbalume, T Store, R Kapangasa, and R Kwapatha.

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

The study was funded by Médecins sans Frontières-Luxembourg.

References

1 De Cock K M, Soro B, Coulibaly I M, Lucas S B. Tuberculosis and HIV infection in sub-Saharan Africa. JAMA 1992; 268: 1581–1587.
2 Raviglione M C, Harries A D, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS 1997; 11 (Suppl B): S115–S123.
3 Gilks C F, Brindle R J, Otieno L S, et al. Life-threatening bacteraemia in HIV-1-seropositive adults admitted to hospital in Nairobi, Kenya. Lancet 1990; 336: 545–549.
4 Brindle R J, Nunn P P, Batchelor B I F, et al. Infection and morbidity in patients with tuberculosis in Nairobi, Kenya. AIDS 1993; 7: 1469–1474.
5 Greenberg A E, Lucas S, Tossou O, et al. Autopsy-proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Cote d'Ivoire. AIDS 1995; 9: 1251–1254.
6 Wiktor S Z, Sassan-Morroko M, Grant A D, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1 infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 1999; 353: 1469–1475.
7 Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Geneva, Switzerland: UNAIDS, 2000.
8 Zachariah R, Harries A D, Spielmann M P, et al. Cotrimoxazole prophylaxis in HIV positive TB patients in a rural district of Malawi. Abstract TuOrB278. Durban, South Africa: XIII International AIDS Conference, 2000.
9 Manual of the National Tuberculosis Control Programme in Malawi. 1999 4th ed. Lilongwe, Malawi: Ministry of Health and Population.
10 Zachariah R, Harries A D, Arendt V, et al. Compliance with cotrimoxazole prophylaxis for the prevention of opportunistic infections in HIV-positive tuberculosis patients in Thyolo district, Malawi. Int J Tuberc Lung Dis 2001; 5: 843–846.
11 Zachariah R, Spielmann M P, Harries A D, Salaniponi F M L. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death. Trans Soc Trop Med Hyg 2002; 96: 291–294.
12 World Health Organization Communicable Diseases. WHO Report 2001. Global Tuberculosis Control. WHO/CDS/TB/2001.287. Geneva: WHO, 2001.
13 Harries A D, Hargreaves N J, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. Lancet 2001; 357: 1519–1523.

RÉSUMÉ

CADRE : Thyolo, Malawi rural du Sud.
OBJECTIFS : Déterminer, chez les patients infectés par le virus de l'immunodéficience humaine (VIH) et atteints de tuberculose (TB) qui ont achevé le traitement anti-tuberculose, 1) la proportion qui poursuit une prophylaxie au cotrimoxazole pour la prévention des infections opportunistes et 2) les raisons de prolongation ou d'arrêt de la prophylaxie.
SCHÉMA : Etude transversale.
MÉTHODES : Il s'agit d'une étude par questionnaire chez tous les patients TB infectés par le VIH qui ont été enregistrés pendant une période de 3 mois pour recevoir un traitement anti-tuberculose et une prophylaxie au cotrimoxazole et qui ont achevé le traitement anti-tuberculose de 3 à 6 mois plus tôt.
RÉSULTATS : Sur 82 individus infectés par le VIH, 76 (93%) qui étaient en vie au moment de l'entretien poursuivaient le traitement au cotrimoxazole et souhaitaient le faire indéfiniment. La raison la plus fréquente pour la poursuite de la médication a été la prévention de maladies associées au VIH, alors que la raison la plus fréquente pour son arrêt a été une distance importante du domicile au service de santé. Le cotrimoxazole a été administré gratuitement à 96% des patients dans un centre de santé. Parmi ceux qui souhaitaient poursuivre indéfiniment, la majorité (63%) n'étaient pas à même de payer le médicament.
CONCLUSION : Dans un contexte rural, la grande majorité des individus infectés par le VIH poursuivent le cotrimoxazole après avoir achevé le traitement antituberculeux. La mise à disposition de ce médicament et sa gratuité sont essentielles si l'on veut qu'il reste accessible pour une prévention de plus longue durée.

RESUMEN

MARCO DE REFERENCIA : Thyolo, región rural del sur de Malawi.
OBJETIVO : Determinar en los sujetos con tuberculosis (TB), infectados con el virus del inmunodeficiencia humana (VIH), que han completado el tratamiento antituberculoso : 1) la proporción que continúa con una profilaxis con cotrimoxazol para la prevención de las infecciones oportunistas y 2) las razones para continuar o suspender la profilaxis.
DISEÑO : Estudio transversal.

MÉTODO : Estudio por cuestionario de todos los pacientes con TB infectados con VIH, registrados durante un período de 3 meses como habiendo recibido tratamiento anti-tuberculosis y profilaxis con cotrimoxazol y que habían completado el tratamiento anti-tuberculosis 3 a 6 meses antes.

RESULTADOS : De 82 sujetos infectados con VIH, 76 (93%) que estaban vivos en el momento de la entrevista continuaban la profilaxis con cotrimoxazol y deseaban hacerlo indefinidamente. La razón más frecuente para continuar este tratamiento era la prevención de las enfermedades asociadas con el VIH, mientras que la razón más frecuente para suspenderlo era la distancia importante del domicilio al centro de salud. El 96% de los pacientes recibían el cotrimoxazol gratuitamente en el centro de salud. Entre aquéllos que deseaban continuar indefinidamente, la mayoría (63%) no podían hacer frente al pago del medicamento.

CONCLUSIÓN : En un contexto rural, la gran mayoría de los sujetos infectados con VIH continuaban con cotrimoxazol después de haber completado el tratamiento anti-tuberculosis. Asegurar la disponibilidad de este medicamento y entregarlo gratuitamente es esencial si se pretende que permanezca accesible para una prevención de más larga duración.