Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga District, Malawi

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Objective To estimate the impact of cotrimoxazole prophylaxis on the survival of human immunodeficiency virus (HIV)-positive tuberculosis (TB) patients.

Methods A cohort study with a historical comparison group was conducted. End-of-treatment outcomes and 18-month survival were compared between TB patients registered in 1999 and patients registered in 2000 in Karonga District, Malawi. Case ascertainment, treatment and outpatient follow-up were identical in the two years except that in 2000 cotrimoxazole prophylaxis was offered to HIV-positive patients in addition to routine care. The prophylaxis was provided from the time a patient was identified as HIV-positive until 12 months after registration. Analyses were carried out on an intention-to-treat basis for all TB patients, and also separately by HIV status, TB type and certainty of diagnosis.

Findings 355 and 362 TB patients were registered in 1999 and 2000, respectively; 70% were HIV-positive. The overall case fatality rate fell from 37% to 29%, i.e. for every 12.5 TB patients treated, one death was averted. Case fatality rates were unchanged between the two years in HIV-negative patients, but fell in HIV-positive patients from 43% to 24%. The improved survival became apparent after the first 2 months and was maintained beyond the end of treatment. The improvement was most marked in patients with smear-positive TB and others with confirmed TB diagnoses.

Conclusion Survival of HIV-positive TB patients improved dramatically with the addition of cotrimoxazole prophylaxis to the treatment regimen. The improvement can be attributed to cotrimoxazole because other factors were unchanged and the survival of HIV-negative patients was not improved. Cotrimoxazole prophylaxis should therefore be added to the routine care of HIV-positive TB patients.

Keywords Trimethoprim-sulfamethoxazole combination/pharmacology; Tuberculosis /mortality/drug therapy; AIDS-related opportunistic infections/drug therapy; HIV infections; Treatment outcome; Survival analysis; Cohort studies; Malawi (*source: MeSH, NLM*).

Mots clés Triméthoprime-sulfaméthoxazole, Association/pharmacologie; Tuberculose /mortalité/chimiothérapie; Infections opportunistes liées SIDA/chimiothérapie; HIV, Infection; Evaluation résultats traitement; Analyse survie; Etude cohorte; Malawi (*source: MeSH, INSERM*).

Palabras clave Combinación trimetoprim-sulfametoxazol/farmacología; Tuberculosis/mortalidad/quimioterapia; Infecciones oportunistas relacionadas con el SIDA/quimioterapia; Infecciones por VIH; Resultado del tratamiento; Análisis de supervivencia; Estudios de cohortes; Malawi (*fuente: DeCS, BIREME*).

Arabic

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Voir page 361 le résumé en français. En la página 362 figura un resumen en español.

Introduction

Cotrimoxazole is effective against many of the opportunistic infections that occur in individuals with advanced HIV disease, and it has been used widely in high-income countries (*1–5*). A randomized placebo-controlled trial in HIV-positive patients with smear-positive pulmonary TB in Côte d'Ivoire found that cotrimoxazole prophylaxis significantly reduced both morbidity and mortality (*6*). A concurrent trial of individuals with early symptomatic HIV, also in Côte d'Ivoire, showed that patients in the cotrimoxazole-treated arm had lower morbidity (*7*).

In the trials conducted in Côte d'Ivoire, the levels of resistance to cotrimoxazole in the pathogens that caused morbidity were low (*8*), but resistance levels may be much higher in other parts of Africa. Consequently concern was expressed that the results obtained in Côte d'Ivoire might not be generalizable. New trials were started in Malawi, Senegal and South Africa, but the placebo arms were discontinued when WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued provisional guidelines recommending the widespread use of cotrimoxazole prophylaxis for individuals living with HIV in resource-poor countries (*9*). This recommendation has

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not yet been widely implemented, but in settings in which it has already been accepted it is no longer ethical to conduct placebo-controlled trials of cotrimoxazole prophylaxis. Alternative study designs are therefore required.

In Karonga District, Malawi, an operational study was conducted to test the effectiveness of cotrimoxazole prophylaxis in HIV-positive TB patients using historical controls as the comparison group. The study was done in parallel with two other studies in Malawi: one in Thyolo district and one in Blantyre. The two parallel studies followed substantially more TB patients than the study in Karonga, but the study in Karonga is the only one for which HIV test data are available for the historical control group and the only one that has followed up patients beyond the end of their treatment for TB. Researchers in Thyolo have recently reported that overall mortality at the end of treatment for TB was reduced from 36% to 28% when cotrimoxazole was provided to HIV-positive patients (*10*).

Methods

The research was conducted as part of the Karonga Prevention Study in Northern Malawi, in collaboration with the National TB Control Programme. The protocol was approved by the Malawi National TB Programme and the Health Sciences Research Committee of the Malawi Ministry of Health.

Staff of the Karonga Prevention Study see all TB patients registered in the district and the study is responsible for their outpatient care. Patients are diagnosed as having TB on the basis of sputum smears, cultures, chest X-rays, biopsies and clinical diagnosis. Patients with positive cultures, smears or biopsies were regarded as having confirmed TB, except those with a single scanty smear (fewer than 10 acid-fast bacilli) and no positive culture, who were regarded as having unconfirmed TB. Patients with only an X-ray or clinical diagnosis were also regarded as having unconfirmed TB.

Treatment follows National TB Control Programme guidelines (*11*). Since 1996 smear-positive patients have received 2 months of treatment with rifampicin, pyrazinamide, isoniazid, and streptomycin followed by 6 months of treatment with isoniazid and ethambutol; smear-negative patients with pulmonary TB and patients with extrapulmonary TB have received 1 month of treatment with isoniazid, streptomycin and ethambutol followed by 11 months of treatment with isoniazid and ethambutol; and retreatment (relapse) patients have received 2 months of treatment with rifampicin, pyrazinamide, isoniazid, streptomycin and ethambutol followed by 6 months of treatment with rifampicin, pyrazinamide, isoniazid and ethambutol. TB patients are tested for HIV after counselling and if consent is given (*12*), post-test counselling is given to those who wish to know their results.

The cotrimoxazole study started at the beginning of January 2000. In the course of HIV-counselling, patients were informed that they would be offered cotrimoxazole for 12 months if they were found to be HIV-positive, provided there were no contraindications. The contraindications were pregnancy, breast-feeding a child who was less than 2 months old, and a history of reaction to sulfa drugs. A special effort was made to counsel and test patients for HIV as soon as possible after their registration for TB treatment.

A dose of 960 mg/day of cotrimoxazole was given to patients with a positive HIV test result, starting on the date that the result of the HIV test was reported to the patient. Reduced doses were given to children: 6–12 years, 480 mg/day; 6 months–5 years, 240 mg/day, and 2–5 months, 120 mg/day. While the patients were in hospital, cotrimoxazole was distributed daily by a member of the study team. HIV-negative patients and others not participating in the study received multivitamins to avoid inadvertent disclosure of HIV status. At the end of the intensive phase of treatment, patients were discharged, and cotrimoxazole was then added to the patient's monthly supply of drugs where appropriate. Smear-positive patients were followed up monthly for the first 4 months after the end of treatment, so that cotrimoxazole could be provided for 12 months. Urine was tested for isoniazid to check compliance with TB treatment, and compliance with cotrimoxazole prophylaxis was assessed by counting the number of tablets that remained at the end of each month. Patients were advised to continue taking cotrimoxazole after TB treatment was completed, and were asked at the 18-month follow-up about continuation.

All analyses of the efficacy of cotrimoxazole were based on a comparison between patients registered in 2000 and patients registered in 1999. The case ascertainment procedures, TB treatment regimens and outpatient follow-up were the same during 1999 as during 2000, except that cotrimoxazole and multivitamins were not given to patients registered in 1999. Patients were seen monthly as outpatients for the continuation phase, and sputum examinations were performed at 5 and 8 months for smear-positive patients. All patients who were alive and still resident in the district at the end of TB treatment were sought in 2002 to obtain data on their survival status $\geqslant$18 months after being registered as TB patients.

The intervention was confined to HIV-positive TB patients, so it is this group for whom the findings are presented in most detail. Analyses including all TB patients were carried out to assess the impact of the intervention at the population level, and also to allow comparison with the parallel studies conducted in Thyolo and Blantyre. An analysis of HIV-negative patients was carried out to determine whether there was any change in mortality between patients registered in 1999 and in 2000 that was not attributable to the cotrimoxazole intervention, and the analysis of patients of unknown HIV status was presented for completeness. For each of these four groups, the analysis was further broken down by type of TB and certainty of diagnosis. For analyses restricted to HIV-positive patients, patients registered in 2000 were included irrespective of whether they received cotrimoxazole, as an intention-to-treat analysis. HIV test data collected >2 months after registration as a TB patient were not used in the analysis.

Two types of analysis were performed. First, outcome at the end of treatment (8 months for smear-positive TB patients, 12 months for smear-negative patients with pulmonary TB and patients with extra-pulmonary TB) was considered, following the WHO/ International Union against Tuberculosis and Lung Disease (IUATLD) guidelines (*13*). This analysis used only HIV test data that were available $\leqslant$16 days (half a month) after the patient was registered for TB treatment. The rationale for the tight restriction on the timing of HIV testing was the need to minimize survivorship bias (since patients had to survive beyond registration in order to have an HIV test), especially as the timing of HIV testing was on average earlier in 2000 than in 1999. An even tighter restriction was not possible: if the analysis were restricted to patients who were tested for HIV within 1 week of registration, fewer than 50 of the patients registered in 1999 could have been included.

Second, a survival analysis was done. Survival at 1, 2, 8, 12 and 18 months after registration as a TB patient was estimated. The timescale of the analysis was time since registration as a TB patient. Patients who transferred out or who were lost to follow-up were censored on the date they were lost to follow-up. Patients whose HIV status was known ⩽16 days after registration were included in the analysis as either HIV-positive or HIV-negative from the date of registration. All other patients were included in a group of unknown HIV status until the date of their HIV test. Entering these patients into the HIV-positive or HIV-negative group only on the date the HIV test was done, rather than on the date of registration, avoids survivorship bias in the analysis. Hazard ratios comparing the mortality rates in patients registered in 1999 with those registered in 2000 were calculated using Cox regression; this was done separately for the periods ⩽ 2 months (intensive phase), 3–12 months (until the end of cotrimoxazole prophylaxis for HIV-positive patients in 2000), and 13–18 months after registration as a TB patient. Crude analyses, and analyses adjusted for age, sex, presence of a bacille Calmette–Guérin (BCG) scar, area of residence and socioeconomic status were carried out.

Results

In 1999, 355 TB patients were registered, and in 2000, 362. End-of-treatment outcome data were available for all but five individuals. These five individuals were registered in 2000, were of unknown HIV status and were excluded from all analyses. The distributions of age, sex and area of residence, and the percentages of patients with different types of TB, were similar in patients registered in 1999 and in 2000, both overall and for HIV-positive patients (Table 1). Data on education were available for patients with confirmed TB, and the distributions of levels of education were similar in patients registered in 1999 and in 2000 (data not shown). Of the 254 patients examined for a BCG scar in 1999, and the 237 patients examined in 2000, 74% and 72%, respectively, had a scar. All but five of the patients with smear-positive TB had confirmed diagnoses, but the proportions with confirmed diagnoses were much lower for the other TB types: 10% (31/317) for smear-negative pulmonary TB and 24% (32/136) for extra-pulmonary TB.

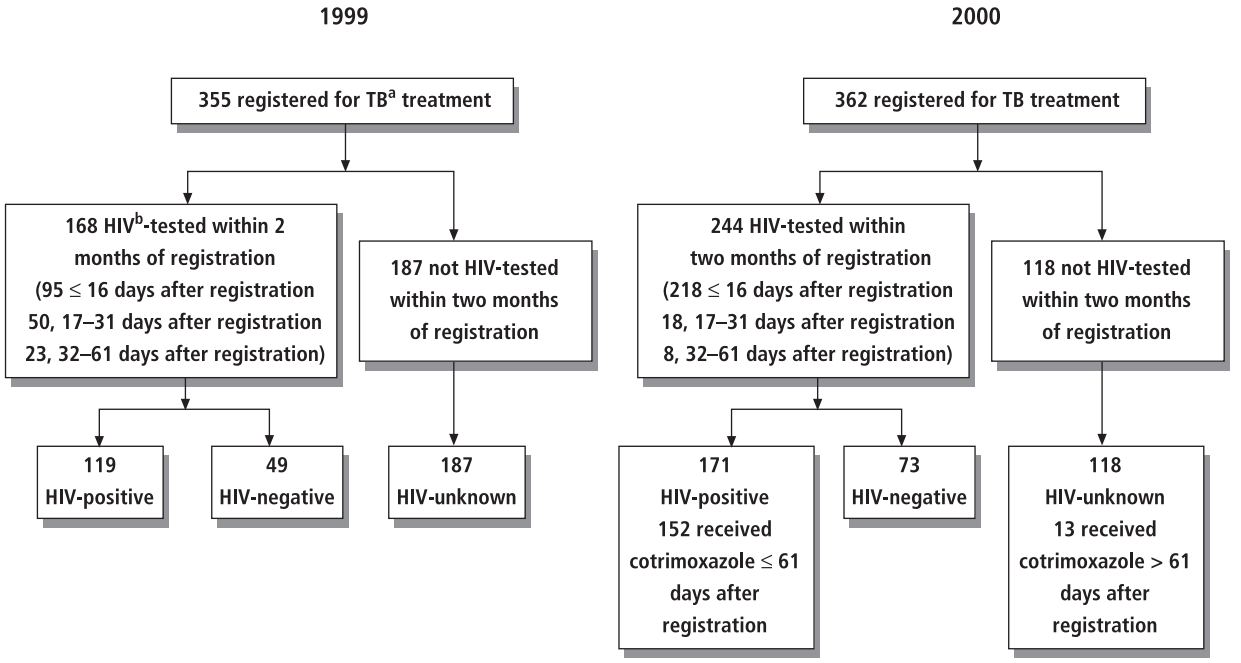
Fig. 1 summarizes the study profile. In 2000, 24% (86/357) of patients were not counselled. Of the 271 patients who were

Table 1. **Demographic characteristics, TB[a] type and HIV[b] status, by year of registration as a TB patient**

		1999		2000	
All TB patients					
Total number		355		357	
Age (years)	Mean (sd[c])	34	(15.8)	35	(16.1)
		n	%	*n*	%
Age	⩾15 years old	310	87	323	90
Sex	Male	184	52	173	48
Area of residence	Northern hills or northern lakeshore	111	31	99	28
	Southern hills	68	19	65	18
	District capital town	113	32	116	32
	Southern lakeshore	45	13	61	17
	Outside Karonga District	12	3	7	2
	Unknown	6	2	9	3
Type of TB	Smear + pulmonary	129	36	130	36
	Smear – pulmonary	159	45	158	44
	Extra-pulmonary	67	19	69	19
HIV	Tested ⩽16 days after registration as TB patient	95	27	218	61
	HIV[b] positive	67	71	153	70
HIV-positive patients					
Total number		67		153	
Age (years)	Mean (sd[c])	36	(10.1)	33	(11.6)
		n	%	*n*	%
Age	⩾15 years old	66	99	143	93
Sex	Male	35	52	62	41
Area of residence	Northern hills or northern lakeshore	15	22	43	28
	Southern hills	10	15	24	16
	District capital town	27	40	58	38
	Southern lakeshore	14	21	21	14
	Outside Karonga District	1	1	2	1
	Unknown	0	0	5	3
Type of TB	Smear + pulmonary	27	40	70	46
	Smear – pulmonary	30	45	66	43
	Extra-pulmonary	10	15	17	11

[a] TB = tuberculosis.
[b] HIV = human immunodeficiency virus.
[c] sd = standard deviation.

Fig. 1. **Study profile**



[a] TB = tuberculosis.

[b] HIV = human immunodeficiency virus.

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counselled, HIV test data were available for 244 <2 months after registration; a further 15 patients were tested for HIV >2 months after registration, and the remaining 12 were not tested for HIV. Data on numbers of patients counselled, reasons for not counselling, and reasons for patients who had been counselled refusing to be tested for HIV, were not available for patients registered in 1999.

In 2000, as a consequence of this study, testing for HIV was done soon after registration, resulting in 61% of patients being tested within 16 days of registration (compared to 27% of patients registered in 1999) and 67% within 2 months (compared to 47% of patients registered in 1999). Of those patients tested within 2 months of registration (Table 1 and Fig. 1), approximately 70% of those registered in each year were HIV-positive. The percentage who were HIV-positive did not vary by time of testing.

Prophylaxis with cotrimoxazole was started in 2000 for HIV-positive patients as soon as their HIV status was known, which was between 3 and 9 days after taking blood for an HIV test. Eighty-nine per cent of HIV-positive patients (152/171) started receiving cotrimoxazole within 2 months of registration. Random urine testing of 144 patients receiving cotrimoxazole showed that 121 (84%) were positive for isoniazid and four were weakly positive, and few individuals had any cotrimoxazole tablets left at the end of each month. These findings are consistent with good compliance. At the time of the 18-month follow-up, no patients reported that they were still taking cotrimoxazole daily, but 25% (19/75) reported that they had taken it during an episode of diarrhoea or when they had a cough.

End-of-treatment outcomes for all patients, irrespective of their HIV status, and those for HIV-positive patients only, are summarized in Table 2. Overall case fatality rates were higher in 1999 than in 2000 (37% compared with 29%, $P = 0.008$). The clearest evidence of a decrease in case fatality rates was seen in patients who were smear-positive and HIV-positive, in whom there was a decrease from 33% in patients registered in 1999 to 11% in those registered in 2000 ($P = 0.01$). For the HIV-negative patients, overall cure rates were 86% (24/28) and 78% (51/65) ($P = 0.43$), and overall death rates 11% and 11%, in patients registered in 1999 and in 2000, respectively. For patients of unknown HIV status, case fatality rates were also similar in patients registered in 1999 and in 2000, i.e. 39% and 42%, respectively.

The results of the survival analysis for all patients, irrespective of HIV status, and also of that for HIV-positive patients only, are summarized in Fig. 2. Mortality rates, hazard ratios and 18-month survival for HIV-positive patients are summarized in Table 3. The results from the crude analysis are presented because there was very little confounding of the 1999 versus 2000 comparison by the other risk factors studied. Results were also very similar when the analysis was restricted to adults (age ⩾15 years) (data not shown). There were too few children to allow them to be studied separately, and almost all HIV-positive individuals were adults (Table 1).

The percentage of patients who were alive at the end of treatment, but had left the district or could not be traced 18 months after registration, was quite small among patients of known HIV status: 19% (13/69) for HIV-positive and 16% (7/43) for HIV-negative patients registered in 1999, with corresponding figures for patients registered in 2000 of 9% (10/117) and 9% (5/58).

Survival at 2 months after registration was similar for patients registered in 1999 and in 2000: overall (81% versus 84%); in HIV-positive patients (89% versus 90%); in HIV-negative patients (94% versus 93%); and in those with unknown HIV status (76% versus 73%).

The improvement in survival in patients registered in 2000 compared to those registered in 1999 was restricted to the period 3–18 months after registration, and was confined to HIV-positive patients. Overall, survival at 8, 12 and 18 months was 62%,

Table 2. **Outcome at the end of TB[a] treatment, by TB type and year, for all TB patients and for HIV[b]-positive TB patients**

	Year	Cure[c]		Death[c]		Failure		Lost		Transfer		Total
All patients, irrespective of HIV status		%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	
All TB[a] types	1999	51	182	37	133	2	7	4	13	6	20	355
	2000	61	217	29	102	1	4	5	17	5	17	357
			$P = 0.012$		$P = 0.008$							
Smear + pulmonary	1999	60	77	23	30	4	5	4	5	9	12	129
	2000	75	97	15	20	2	3	4	5	4	5	130
			$P = 0.04$		$P = 0.06$							
Smear – pulmonary	1999	42	67	50	79	1	2	3	5	4	6	159
	2000	50	79	41	64	0	0	5	8	4	7	158
			$P = 0.14$		$P = 0.11$							
Extra-pulmonary	1999	57	38	36	24	0	0	4	3	3	2	67
	2000	59	41	26	18	1	1	6	4	7	5	69
			$P = 0.51$		$P = 0.29$							
HIV-positive patients												
All TB types	1999	49	33	43	29	4	3	1.5	1	1.5	1	67
	2000	67	103	24	36	0.6	1	5	8	3	5	153
			$P = 0.006$		$P = 0.004$							
Smear + pulmonary	1999	56	15	33	9	7	2	0	0	4	1	27
	2000	81	57	11	8	1	1	3	2	3	2	70
			$P = 0.007$		$P = 0.01$							
Smear – pulmonary	1999	43	13	50	15	3	1	3	1	0	0	30
	2000	50	33	39	26	0	0	6	4	5	3	66
			$P = 0.42$		$P = 0.43$							
Extra-pulmonary	1999	50	5	50	5	0	0	0	0	0	0	10
	2000	76	13	12	2	0	0	12	2	0	0	17
			$P = 0.22$		$P = 0.06$							

[a] TB = tuberculosis.
[b] HIV = human immunodeficiency virus.
[c] *P*-values calculated excluding patients who transferred out.

57% and 52%, respectively, in patients registered in 1999, and the corresponding figures for patients registered in 2000 were 72%, 62% and 58%.

Among HIV-positive patients, survival at 8, 12 and 18 months was 63%, 56% and 48%, respectively, for patients registered in 1999, and 77%, 63% and 58% for those registered in 2000. The difference in survival rates between patients registered in 1999 and in 2000 was evident for smear-positive patients with pulmonary TB in whom survival at 8, 12 and 18 months was 68%, 61% and 48%, respectively, in patients registered in 1999, and 89%, 70% and 62% in those registered in 2000. Eighteen-month survival was also higher in 2000 than in 1999 for other patients with a confirmed diagnosis of either smear-negative pulmonary or extra-pulmonary TB (Table 3).

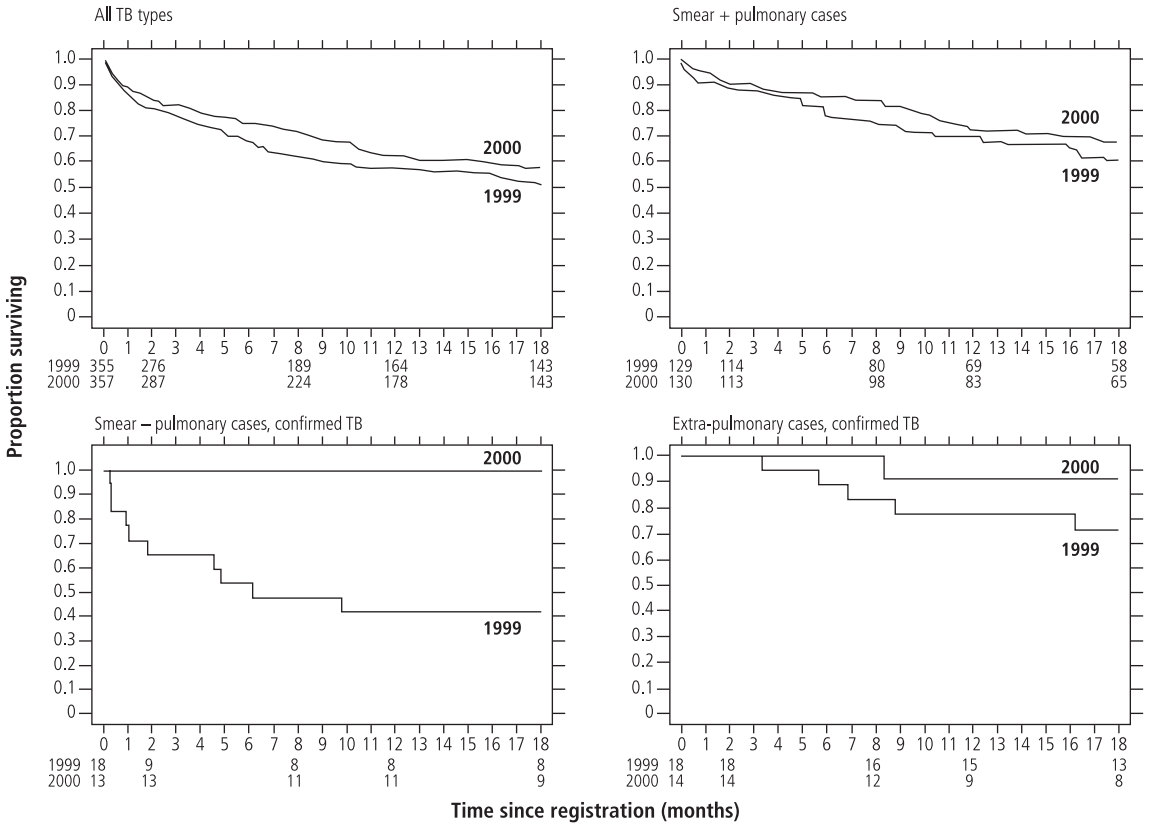
The hazard ratios for 3–12 and 13–18 months after registration were similar, and therefore a single hazard ratio was calculated for the period 3–18 months after registration (Table 3). Overall survival among HIV-positive patients 3–18 months after registration was significantly better in those registered in 2000 than in those registered in 1999 (hazard ratio for death = 0.67), and also for smear-positive patients (hazard ratio = 0.56). No deaths of smear-negative pulmonary patients with a confirmed diagnosis were recorded in 2000, and a log-rank test comparing death rates in 1999 and 2000 was statistically significant ($P = 0.029$). Patients with a confirmed diagnosis of extra-pulmonary TB also had improved survival in 2000, but this difference was not statistically significant. There was no evidence of a difference in survival between 1999 and 2000 for patients with an unconfirmed diagnosis. However, there was no firm evidence that the effectiveness of cotrimoxazole varied between smear-positive, smear-negative pulmonary, and extra-pulmonary TB patients (test for interaction, $P = 0.53$).

Hazard ratios were also calculated for HIV-negative patients and for those with unknown HIV status. There were no significant differences between patients registered in 1999 and in 2000. Overall survival for HIV-negative patients at 18 months was 86% in patients registered in 1999 and 85% for those registered in 2000, and for those with unknown HIV status survival was 48% in patients registered in 1999 and 41% in those registered in 2000.

The analysis was repeated for those HIV-positive patients who had been tested for HIV within the first 16 days after registration. The hazard ratios comparing 2000 with 1999 were lower (more extreme) than those reported above: hazard ratio 0.48 (95% confidence interval (CI) = 0.30–0.77) overall, and hazard ratio 0.41 (95% CI = 0.20–0.84) for smear-positive patients.

Fig. 2. **Survival after registration as a tuberculosis (TB) patient**

a) All TB cases, irrespective of human immunodeficiency virus (HIV) status



b) HIV-positive TB cases

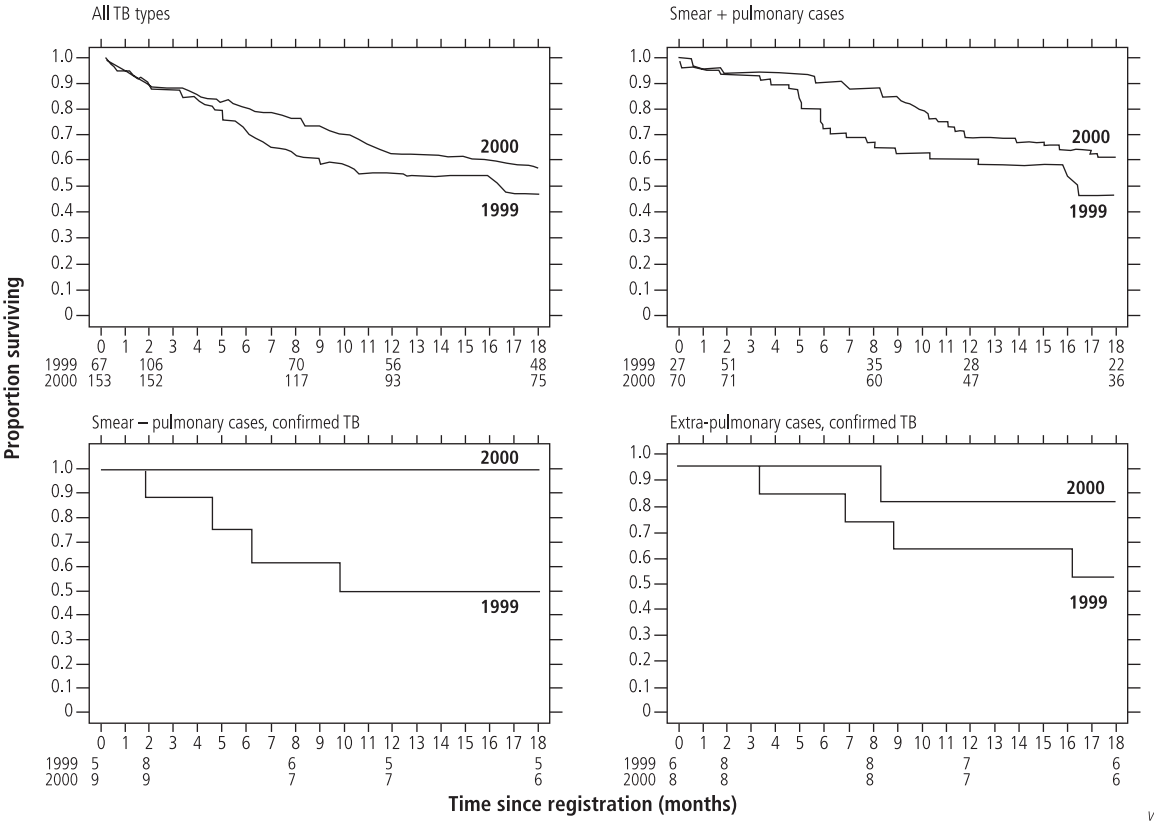


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Table 3. **Hazard ratios (HRs), in patients registered in 2000 and in 1999, overall and also separately for ⩽2 months (1–61 days) and 3–18 months (62–547 days) after registration as a TB[a] patient, and 18-month survival**

	Year	⩽2 months				3–18 months				0–18 months				18-month survival (%)
		deaths/ pyr[b]	HR	95% CI[c]	*P*-value	deaths/ pyr	HR	95% CI	*P*-value	deaths/ pyr	HR	95% CI	*P*-value	
All TB types	1999	10/14.8				46/91.2				56/106.0				48
	2000	16/25.3	0.94	(0.43–2.08)	0.88	49/145.5	0.67	(0.45–1.00)	0.048	65/170.8	0.72	(0.50–1.02)	0.068	58
Smear + pulmonary, all	1999	2/6.3				23/44.1				25/50.5				48
	2000	4/11.6	0.95	(0.17–5.26)	0.95	22/73.1	0.56	(0.31–1.00)	0.049	26/84.7	0.59	(0.34–1.02)	0.060	62
Smear – pulmonary, all	1999	7/6.2				17/32.8				24/39.0				46
	2000	11/10.6	0.97	(0.37–2.50)	0.94	23/51.8	0.87	(0.46–1.62)	0.65	34/62.4	0.90	(0.53–1.51)	0.68	49
Smear – pulmonary, confirmed diagnosis[d]	1999	1/1.1				3/6.5				4/7.6				50
	2000	0/1.5	0			0/9.0	0			0/10.5	0			100
Smear – pulmonary, unconfirmed diagnosis	1999	6/5.1				14/26.3				20/31.4				45
	2000	11/9.1	1.08	(0.40–2.92)	0.88	23/42.8	1.01	(0.52–1.97)	0.99	34/51.9	1.03	(0.59–1.80)	0.91	43
Extra-pulmonary, all	1999	1/2.3				6/14.3				7/16.5				54
	2000	1/3.1	0.69	(0.04–11.06)	0.79	4/20.6	0.47	(0.13–1.69)	0.25	5/23.7	0.51	(0.16–1.60)	0.24	73
Extra-pulmonary, confirmed diagnosis	1999	0/1.3				4/9.0				4/10.3				56
	2000	0/1.3	–			1/8.9	0.26	(0.03–2.36)	0.23	1/10.3	0.26	(0.03–2.36)	0.23	86
Extra-pulmonary, unconfirmed diagnosis	1999	1/1.0				2/5.3				3/6.3				54
	2000	1/1.8	0.51	(0.03–8.19)	0.63	3/11.7	0.77	(0.13–4.68)	0.77	4/13.4	0.68	(0.15–3.08)	0.62	65

[a] TB = tuberculosis.
[b] pyr = person–year.
[c] CI = confidence intervals.
[d] No deaths among patients registered in the year 2000, but log-rank test comparing year 2000 with year 1999 gives $P = 0.029$ for difference in survival between the 2 years.

Discussion

Our results show improved survival of HIV-positive TB patients following the addition of cotrimoxazole prophylaxis to routine care. The benefit was not apparent 2 months after registration, but emerged shortly afterwards. The improvement in survival persisted beyond the end of treatment and was still evident 18 months after registration.

Among the HIV-positive patients, the benefit was most evident in those who were smear-positive, but there was also some evidence of a benefit in patients with confirmed smear-negative pulmonary TB and extra-pulmonary TB. There was no evidence that survival of patients with unconfirmed TB diagnoses registered in 2000 was better than in those registered in 1999, but the confidence intervals were wide. The study was too small to establish whether effectiveness varies by TB type, and the lack of evidence that it varies suggests that most emphasis should be placed on the overall results.

The effect on survival in smear-positive, HIV-positive patients was similar to that observed in the study in Côte d'Ivoire. This is reassuring, because although the extent of resistance of pathogens to cotrimoxazole in this area of Malawi is unknown, several studies in southern Malawi have reported high levels of resistance (*14–17*) . However, whether cotrimoxazole prophylaxis reduced mortality in the present study because the level of resistance to the drug was low, or whether it reduced mortality despite resistance levels being high, is uncertain.

It is not clear why patients in whom the diagnosis of TB was unconfirmed did not appear to benefit from cotrimoxazole, although it could be a chance effect. It might be expected that these patients should benefit the most, because many of them probably do not have TB, but could have chest infections that are treatable with cotrimoxazole. However, patients for whom laboratory evidence of TB is lacking are registered for TB treatment only after having had at least one trial of broad spectrum antibiotics that has failed to improve their condition. Also, the survival of patients with pneumocystis pneumonia can be poor even when they receive appropriate treatment (*18*). We have previously found that patients with less certain diagnoses of TB have higher mortality, irrespective of their HIV status (*19*).

Although this was not a randomized trial, the profile and management of the TB patients registered in 1999 and in 2000 was similar, apart from the cotrimoxazole given to HIV-positive patients, and thus attribution of the improvement in outcome to cotrimoxazole is reasonable. This inference is supported by the similarity in outcomes for HIV-negative patients in both of the years studied. One difference between registration in 1999 and in 2000 was in the proportion of patients who were tested for HIV which was higher in patients registered in 2000 as a result of this study. Patients who were not tested had a high mortality rate, because severe disease and early death were reasons for not testing. A higher proportion of those individuals with severe disease who died shortly after registration as TB patients were tested for HIV in 2000 than in 1999, as a result of the special effort that was made in 2000 to test patients very soon after registration. Even among patients tested ⩽16 days after registration, the percentage tested within a few days of registration was much lower in 1999 than in 2000 (30% tested within 5 days in 1999 compared to 68% in 2000). It is also likely that patients registered in 2000 generally had more advanced HIV disease than those registered in 1999, as a result of being identified 1 year further into the epidemic. These two factors have probably led to the effect of cotrimoxazole being underestimated, and could explain our finding that cotrimoxazole had no apparent benefit in the first 2 months after registration.

Our findings support the overall results of the parallel study conducted in Thyolo District, Malawi (*10*). However, in that study the benefit of cotrimoxazole was confined to the patients with extra-pulmonary and smear-negative pulmonary TB. No analysis by HIV status or confirmation of diagnosis was possible, and the inclusion of HIV-negative patients (who account for a higher proportion of those who are smear-positive than of the other groups) will have diluted the effect of cotrimoxazole. When these results are considered together with those of the study in Côte d'Ivoire, which showed an effect in smear-positive patients, it would seem that cotrimoxazole prophylaxis is beneficial in HIV-positive patients with all types of TB.

In the present study, it was possible to provide counselling and testing and to start cotrimoxazole prophylaxis within 1 month of registration for most of the patients who were known to be HIV-positive. It is not clear how important early treatment with cotrimoxazole is, because the survival benefit was only evident after 2 months. However, as noted above, this could have been because a higher percentage of sick patients were included in 2000 than in 1999, and in Côte d'Ivoire the benefit was apparent from the time of starting cotrimoxazole (at 1 month after starting TB treatment in that study).

The evidence that cotrimoxazole reduces mortality in TB patients both in the Karonga and Thyolo Districts in Malawi and the high percentage of TB patients who are HIV-positive, suggests that voluntary counselling and testing, followed by cotrimoxazole prophylaxis for HIV-positive patients, should be implemented. This policy has been initiated in three districts in Malawi. A concern remains, however, that providing cotrimoxazole prophylaxis to TB patients could lead to increased levels of resistance to the drug, and it will be important to monitor this. ■

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Résumé

Le traitement préventif par le cotrimoxazole réduit la mortalité chez les patients tuberculeux positifs pour le virus de l'immunodéficience humaine dans le district de Karonga (Malawi)

Objectif Estimer l'impact du traitement préventif par le cotrimoxazole sur la survie des patients tuberculeux (TB) positifs pour le virus de l'immunodéficience humaine (VIH).

Méthodes Une étude de cohorte comportant un groupe de comparaison historique a été réalisée. L'issue en fin de traitement et la survie à 18 mois ont été comparées entre les patients TB enregistrés en 1999 et ceux enregistrés en 2000 dans le district de Karonga (Malawi). Le diagnostic, le traitement et le suivi en ambulatoire étaient identiques pour les deux années, mais en 2000 un traitement préventif par le cotrimoxazole a été proposé aux patients VIH-positifs en plus des soins courants. Ce traitement était administré dès le moment où le patient était identifié comme VIH-positif et jusqu'à 12 mois après son enregistrement. Les résultats ont été analysés selon l'optique de l'« intention de traiter » pour tous les patients TB, puis séparément selon le statut VIH, le type de tuberculose et le degré de certitude du diagnostic.

Résultats Parmi les patients TB, 355 ont été enregistrés en 1999 et 362 en 2000 ; 70 % d'entre eux étaient VIH-positifs. Le taux global

de létalité est tombé de 37 % à 29 %, c'est-à-dire que sur 12,5 patients TB traités, un décès a été évité. Les taux de létalité sont restés inchangés pendant les deux années considérées chez les patients VIH-négatifs, mais sont tombés de 43 % à 24 % chez les patients VIH-positifs. L'amélioration de la survie est devenue apparente au bout de deux mois de traitement et s'est maintenue jusqu'à la fin de celui-ci. L'amélioration était plus marquée chez les patients TB à frottis positif et chez ceux dont le diagnostic de tuberculose était confirmé.

Conclusion La survie des patients tuberculeux VIH-positifs s'est considérablement améliorée avec l'addition d'un traitement préventif par le cotrimoxazole au traitement standard. Cette amélioration a pu être attribuée au cotrimoxazole car les autres facteurs restaient inchangés et la survie des patients VIH-négatifs n'était pas améliorée. Le traitement préventif par le cotrimoxazole devrait donc être ajouté au traitement de routine des patients tuberculeux VIH-positifs.

Resumen

La profilaxis con cotrimoxazol reduce la mortalidad de los enfermos de tuberculosis VIH-positivos en el distrito de Karonga, Malawi

Objetivo Estimar el impacto de la profilaxis con cotrimoxazol en la supervivencia de los enfermos de tuberculosis (TB) VIH-positivos.
Métodos Se realizó un estudio de cohortes con un grupo de comparación histórico. Se procedió a comparar los resultados al final del tratamiento y la supervivencia a los 18 meses entre los enfermos de TB registrados en 1999 y los pacientes registrados en 2000 en el distrito de Karonga, Malawi. La confirmación de los casos, el tratamiento y el seguimiento ambulatorio fueron idénticos en esos dos años, con la salvedad de que en 2000 se administró profilaxis con cotrimoxazol a los pacientes VIH-positivos, además de la atención de rutina. La profilaxis se suministraba desde el momento en que se identificaba al paciente como seropositivo hasta 12 meses después del registro. Se hicieron análisis según la intención de tratar para todos los enfermos de TB, y también por separado según la serología VIH, el tipo de TB y la seguridad del diagnóstico.
Resultados En 1999 y 2000 se registró a 355 y 362 enfermos de TB, respectivamente; el 70% eran VIH-positivos. La tasa de letalidad general cayó del 37% a un 29%, es decir, por cada 12,5 enfermos tuberculosos tratados se logró evitar una muerte. Las tasas de letalidad se mantuvieron inalteradas entre los dos años en los pacientes VIH-negativos, pero en los positivos se redujeron del 43% al 24%. La mejora de la supervivencia se hizo patente después de los dos primeros meses y se mantuvo después de acabado el tratamiento. La mejoría más marcada fue la experimentada por los enfermos tuberculosos con frotis positivo y por otros con diagnóstico confirmado de TB.
Conclusión La supervivencia de los enfermos de TB VIH-positivos mejoró muy pronunciadamente al incluir en el régimen de tratamiento la profilaxis con cotrimoxazol. Dicha mejora puede atribuirse a este fármaco, pues no hubo ningún otro factor que se modificara, y la supervivencia de los pacientes VIH-negativos no mejoró. Así pues, la profilaxis con cotrimoxazol debería formar parte de la atención de rutina de los enfermos de tuberculosis VIH-positivos.

Arabic

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