Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi

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Objectives: To assess the feasibility and effectiveness of voluntary counselling, HIV testing and adjunctive cotrimoxazole in reducing mortality in a cohort of tuberculosis (TB) patients registered under routine programme conditions in a rural district of Malawi.

Design: 'Before' and 'after' cohort study using historical controls.

Methods: Between 1 July 1999 and 30 June 2000 all TB patients were started on standardized anti-TB treatment, and offered voluntary counselling and HIV testing (VCT). Those found to be HIV-positive were offered cotrimoxazole at a dose of 480 mg twice daily, provided there were no contraindications. Side-effects were monitored clinically. End-of-treatment outcomes in this cohort (intervention group) were compared with a cohort registered between 1 July 1998 and 30 June 1999 in whom VCT and cotrimoxazole was not offered (control group).

Findings: A total of 1986 patients was registered in the study: 1061 in the intervention group and 925 in the control cohort. In the intervention group, 1019 (96%) patients were counselled pre-test, 964 (91%) underwent HIV testing and 938 (88%) were counselled post-test. The overall HIV-seroprevalence rate was 77%. A total of 693 patients were given cotrimoxazole of whom 14 (2%) manifested minor dermatological reactions. The adjusted relative risk of death in the intervention group compared with the control group was 0.81 ($P < 0.001$). The number needed to treat with VCT and adjunctive cotrimoxazole to prevent one death during anti-TB treatment was 12.5.

Interpretation: This study shows that VCT and adjunctive cotrimoxazole is feasible, safe and reduces mortality rates in TB patients under routine programme conditions.

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Keywords: HIV, tuberculosis, sub-Saharan Africa, voluntary counselling and HIV testing, cotrimoxazole

Introduction

Death rates in patients treated for tuberculosis (TB) in sub-Saharan Africa have risen in the last 10–15 years, the most important reason being concomitant HIV infection [1]. Between 20 and 30% of HIV-infected

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patients with smear-positive pulmonary TB (PTB) die within 12 months of starting treatment, with even higher death rates reported in those with smear-negative PTB and extrapulmonary TB (EPTB) [1].

Infections are an important cause of the high morbidity and mortality experienced by HIV-positive TB patients during treatment [2–4], and it is believed that interventions to prevent these infections might improve survival. Between 1995 and 1998, a cotrimoxazole (sulphamethoxazole trimethoprim five/one) placebo controlled trial in HIV-positive smear-positive PTB patients in Cote d'Ivoire showed a 48% reduction in deaths in the cotrimoxazole group [5]. The results of this study were an important factor in persuading WHO/UNAIDS to issue provisional recommendations that cotrimoxazole be given to all patients in Africa living with AIDS (by definition this includes HIV-positive patients with TB) [6].

Malawi, a small country in central-southern Africa, is currently experiencing a severe epidemic of HIV infection, linked to which is a twin epidemic of TB. In 2000, a countrywide survey found that 77% of new patients registered with TB were HIV-seropositive [7]. The National Tuberculosis Control Programme (NTP) has reported rising death rates in new patients with smear-positive PTB, and in 1998 the country had the highest death rates reported in Africa [8]. Despite the encouraging results from Cote d'Ivoire, it is uncertain whether cotrimoxazole will have the same efficacy in Malawi because of differing resistance profiles of commonly occurring pathogens [9]. The NTP in consultation with the Ministry of Health and Population concluded that there needed to be more evidence to support a policy of widespread implementation of adjunctive cotrimoxazole for patients with AIDS, including those with TB.

The recommendations from WHO/UNAIDS [6] have made it difficult to ethically justify further efficacy studies using placebo controls. A district initiative was therefore planned with the aim of assessing the feasibility and effectiveness of voluntary counselling, HIV testing and adjunctive treatment with cotrimoxazole in reducing death rates in TB patients, who are registered and treated under routine conditions. The objectives of the study were: (i) to assess the feasibility of introducing voluntary counselling and HIV testing (VCT) within a TB control programme setting; (ii) to determine whether adjunctive cotrimoxazole is safe; (iii) to measure death rates in a cohort of patients offered the package of VCT followed by adjunctive cotrimoxazole to those who were HIV-seropositive (intervention group); and (iv) to compare results with those obtained in a cohort of patients registered for TB in the previous year when no VCT or cotrimoxazole was offered (control group).

Methods

Setting and study design

The study was carried out in Thyolo District, in Southern Malawi, with a population of 650 000. The district has one government hospital, a mission hospital, and 18 health centres which are involved in TB control activities. The design was a 'before' and 'after' cohort study measuring end-of-treatment death rates in a group of TB patients offered an intervention package compared with historical controls who were not offered the intervention package in the previous year.

Diagnosis, registration and treatment of patients with TB

The same standardized methods of diagnosing, registering and treating patients with TB were used for the intervention and control groups. Diagnosis, registration and treatment of TB was carried out according to National guidelines [10]. The different anti-TB treatment regimens and their indications are shown in Table 1. The initial phase of treatment was always administered in hospital, and the continuation phase in the community.

Integrated voluntary counselling and testing services

In order to set-up voluntary counselling and HIV testing services, a new counselling unit (comprising a reception room, two counselling rooms and a waiting area) was constructed. Four full-time counsellors and an additional laboratory technician were also employed. The necessary consumables for performing rapid HIV tests were made available on a continuing basis.

Study populations

Intervention group

Between 1 July 1999 and 30 June 2000, all TB patients who were registered in Thyolo district, at either the government hospital or the mission hospital, were enrolled into the VCT and adjunctive cotrimoxazole treatment study. This cohort of patients was known as the 'intervention group'. All patients were registered and started on standardized anti-tuberculosis treatment, and referred to the hospital HIV-voluntary counselling and testing unit. Patients were offered pre-test counselling, and those who accepted HIV testing were offered post-test counselling. All blood samples were screened for HIV-1 and HIV-2 using a combination of the Capillus (Cambridge Diagnostics Ltd, Galway, Ireland) and HIV-Spot (Genelabs Diagnostics, Singapore Science Park, Singapore) tests. Any discordant sample was retested, and if it remained discordant was sent for ELISA testing at the referral hospital in Blantyre.

Patients who tested HIV-seropositive were offered adjunctive cotrimoxazole, provided there were no contraindications to the medication. Contraindications

Table 1. Tuberculosis (TB) treatment regimens and indications.

TB treatment regimens	Drugs and duration[a]	Indication
Short course regimen	2SRHZ/6EH	New smear-positive PTB and severe smear-negative PTB or extrapulmonary TB
Standard regimen	1SEH/11EH	New smear-negative PTB and less severe forms of extrapulmonary TB
Retreatment regimen	$2SRHZE/1RHZE/5R_3H_3Z_3E_3$	Retreatment of smear-positive PTB relapses and failure cases
Meningitis regimen	$2SRHZ/7RH$	TB meningitis in adults and children
Paediatric regimen 1	$2R_3H_3Z_3E_3/6EH$	Children with smear-positive PTB and severe smear-negative PTB (new cases)
Paediatric regimen 2	$2R_3H_3Z_3/6EH$	Children with less serious extrapulmonary TB and smear-negative PTB (new cases)

[a]A regimen consists of two phases: initial phase and continuation phase; the number before a phase is the duration of that phase in months; a number in subscript after a letter is the number of doses of that drug per week (if there is no subscript, the treatment with that drug is daily). S, Streptomycin; E, ethambutol; H, isoniazid; R, rifampicin; Z, pyrazinamide; PTB, pulmonary TB.

included known allergies to sulpha-containing drugs, pregnancy, breast-feeding until 2 months and children aged less than 2 years (because of uncertainty about HIV-serostatus). Cotrimoxazole was given at a dose of 480 mg (400 mg sulphamethoxazole and 80 mg trimethoprim) twice daily for the whole course of anti-TB treatment and indefinitely thereafter. Anti-TB drugs and both daily doses of cotrimoxazole were administered by direct observation during the initial phase of treatment. In the continuation phase, anti-TB drugs and cotrimoxazole were given to patients at monthly intervals from their nearest health facility and the drugs were self-administered. Patients received enough pills for 33 days, which included a 3-day safety stock in case the patient was unable to attend the health facility on the specified follow-up date.

Compliance with self-administered cotrimoxazole was assessed in a cohort of TB patients who were attending four of the TB follow-up centres during the continuation phase (months 4–6) of anti-TB treatment [11]. Urine trimethoprim was measured using gas chromatography and mass spectrometry, and was detected in 87 (94%) of 93 TB patients in the cohort.

Side-effects of cotrimoxazole were monitored clinically. A protocol for monitoring side-effects was developed, and all health personnel were trained on how to manage side-effects. A standard reporting form was also available at all health facilities in the district.

Control group

Between 1 July 1998 and 30 June 1999, all TB patients who were registered in the same two hospitals in the district were started on the same standardized anti-TB treatment, and this cohort of patients was known as the 'control group'. This group was not offered VCT or cotrimoxazole prophylaxis, as the intervention had not commenced during this period.

Treatment outcomes

All patients were followed to the end of treatment, and outcomes were recorded according to standard guidelines [12]. Death was defined as a death at any time during the 8–12 months of treatment from whatever cause. Month of death, default or transfer-out was recorded in the file. End-of-treatment outcomes were classified after cross-verification of information contained in TB registers, laboratory registers, medication registers and treatment cards. Reliability of treatment outcomes was verified by conducting independent household visits on a random sample of 40 TB patients from the intervention and control groups. All these outcomes were confirmed correct.

In 160 TB patients (88 in the control group and 72 in the intervention group), information on treatment outcomes was incomplete and cross-verification was not

possible for the following reasons: the treatment register was not properly completed; the treatment card had been misplaced at the health centre; the date of treatment outcome was not indicated. In these patients, an independent household visit was conducted at the end of the study period in order to obtain a reliable end-of-treatment outcome.

Statistical analysis

A previous cohort study in Zomba district, Southern Malawi, had shown an end-of-treatment mortality of 30% in patients with all types of TB [13]. A sample size of 748 patients in each group was calculated to achieve a power of 90%, and to detect a 25% reduction in end-of-treatment mortality (from 30 to 22.5%) with a type I error rate of 5%. This calculation formed the basis of using a 12-month recruitment period for each group.

Data was entered and analysed using EPI-INFO 6.0 and 2000 (Centre for Disease Control and Prevention, Atlanta Georgia, USA). Baseline characteristics of patients in the intervention and control groups were compared using the chi-squared test for categorical variables. Analysis of treatment outcome was carried out between the intervention and control groups according to the intention-to-treat principle. All patients were included in the intervention group regardless of whether they were treated with cotrimoxazole or not. Differences in end-of-treatment outcomes between intervention and control groups were compared using the chi-squared test. The relative risk of death was stratified for type and category of TB as well as anti-TB treatment using the Mantel–Haenszel chi-squared test. Hazard ratios were also used to compare death rates in the two groups per 100 person-months of follow-up, and were stratified in the same way. Overall survival distributions for both groups were estimated using the Kaplan–Meier method and compared using the Cox–Mantel (log-rank) test. All P values were two sided, and the level of significance was set at $P = 0.05$ or less. 95% Confidence intervals (CI) were used throughout.

Results

Characteristics of the study population

A total of 1986 patients was registered in the study: 1061 in the intervention group and 925 in the control group. Characteristics of the two groups are shown in Table 2. The age, sex and hospital at which the patients were registered were similar between the two groups, but the groups differed in terms of type and category of TB, and in terms of anti-TB treatment.

Occupation and physical status on admission were recorded in the intervention group only. The most common occupations were farming in 625 (59%), unskilled work in 173 (16%), business in 71 (7%) and skilled work in 60 (6%) patients. On admission, 231 (22%) patients were moribund (bedridden and unable to stand without support), 703 (66%) felt ill due to clinical symptoms linked to TB/HIV, 87 (8%) felt well and the physical status was unknown in 40 (4%) patients.

Table 2. Characteristics of patients in the intervention (cotrimoxazole) and control groups.

	Cotrimoxazole [n (%)]	Control [n (%)]	P[a]
Total	1061	925	
Median age (years)	32 (range 1–93)	31 range (1–85)	
Age-group (in years)			
1–14	85 (8)	81 (9)	0.5
15–44	783 (74)	689 (74)	0.7
45–64	169 (16)	141 (15)	0.7
> 64	24 (2)	14 (2)	0.2
Male	505 (48)	472 (51)	0.1
Site of registration			
District Hospital	616 (58)	569 (62)	0.1
Mission Hospital	445 (42)	356 (38)	0.1
TB type			
Smear-positive PTB	464 (44)	340 (37)	< 0.01
Smear-negative PTB	282 (26)	288 (31)	0.02
EPTB	315 (30)	297 (32)	0.2
TB category			
New TB case	967 (91)	897 (97)	< 0.01
Relapse	39 (4)	22 (2)	0.09
Other	55 (5)	6 (1)	< 0.01
Type of TB treatment			
Short-course	542 (51)	400 (43)	< 0.01
Standard treatment	350 (33)	416 (45)	< 0.01
Retreatment	77 (7)	24 (3)	< 0.01
TB meningitis	21 (2)	11 (1)	0.2
Paediatric	71 (7)	74 (8)	0.3

[a]Chi-squared test. TB, Tuberculosis; PTB, pulmonary TB; EPTB, extrapulmonary TB.

VCT and adjunctive treatment with cotrimoxazole

Of 1061 patients registered for TB in the intervention group, 1019 (96%) were counselled pre-test, 964 (91%) underwent HIV testing and 938 (88%) were counselled post-test (Fig. 1). Of the 964 TB patients who were tested for HIV, 740 (77%) were HIV positive: this included 294(68%) patients with smear-positive PTB, 223 (86%) with smear-negative PTB and 223 (82%) with EPTB.

Six-hundred and ninety-three patients, comprising 93% of all known HIV positive cases and 65% of all registered TB patients, were given cotrimoxazole after a median of 4 days (range, 1–57 days) from registration. Two-hundred and eighty-three (61%) of 464

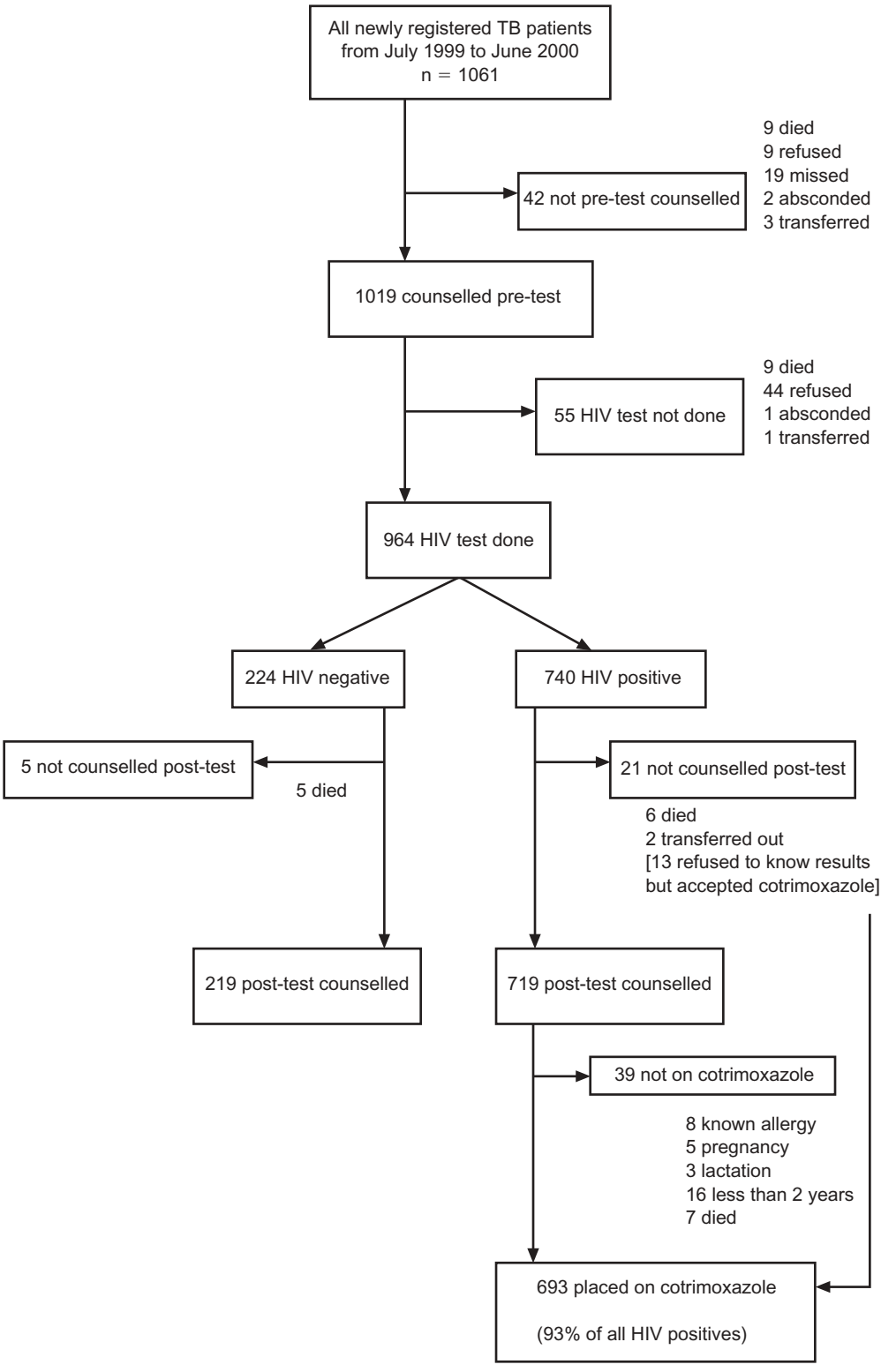

Fig. 1. Study profile of tuberculosis patients in the intervention (cotrimoxazole) group.

registered patients with smear-positive PTB, 200 (71%) of 282 patients with smear-negative PTB and 210 (67%) of 315 patients with EPTB were given cotrimoxazole.

Reactions to cotrimoxazole

Of 693 patients on cotrimoxazole, 14 (2%) had a dermatological reaction. No reactions were serious or involved mucosal membranes, and all were reversible on

discontinuing treatment. All dermatological reactions occurred in the first 2 months of treatment, with 9 (64%) occurring during the first month. In 13 patients cotrimoxazole was discontinued indefinitely, and in one patient it was re-started (by mistake) without problems.

End-of-treatment outcomes and mortality rates

End-of-treatment outcomes in the intervention and control groups – death, treatment success and other outcomes – for all patients and in relation to type, category of TB and treatment regimen are shown in Table 3. Treatment outcomes were known for all except seven patients in the control group.

Death was significantly decreased for all patients in the intervention group, and also for those with smear-negative PTB, new TB and those on standard treatment. Treatment success was also significantly increased for all patients in the intervention group, and for those with smear-negative PTB, EPTB, new TB and those on standard anti-TB treatment. For smear-positive PTB patients, neither death nor treatment success were significantly different between the intervention and the control groups. Other outcomes were similar between the two groups for all patients except those with new TB. The crude relative risk (RR) of death by the end of treatment in the intervention compared with the control group was 0.78 (95% CI, 0.69–0.89; $P < 0.001$). Adjusted for type and category of TB as well as anti-TB treatment, the RR was 0.81 (95% CI, 0.75–0.87; $P < 0.001$).

Death rates per 100 person-months of follow-up and the hazard ratios (HR) in the two groups for all patients and in relation to type, category of TB and anti-TB treatment were also calculated. Results were similar to those obtained using death at the end of treatment as the measurable outcome. The death rate for all registered TB patients was 4.0 per 100 person-months of follow-up in the intervention group and 5.3 in the control group, which corresponds to a 25% reduction in risk of death (95% CI, 12.3–35.8). Adjusted for type and category of TB as well as anti-TB treatment, the HR was 0.76 (95% CI, 0.69–0.83).

Survival curves for both intervention and control groups are shown in Fig. 2. By the end of the first month of treatment, 113 (38%) of 299 deaths had occurred in the intervention group which was not different from the 130 (39%) of 333 deaths in the control group. These results were similar in patients with different types of TB. A significant difference in the survival curve between the intervention and control groups became apparent from 4 months of anti-TB treatment (Log-Rank test, $P = 0.05$), and the overall end-of-treatment survival probability was higher in the intervention group compared with the control group.

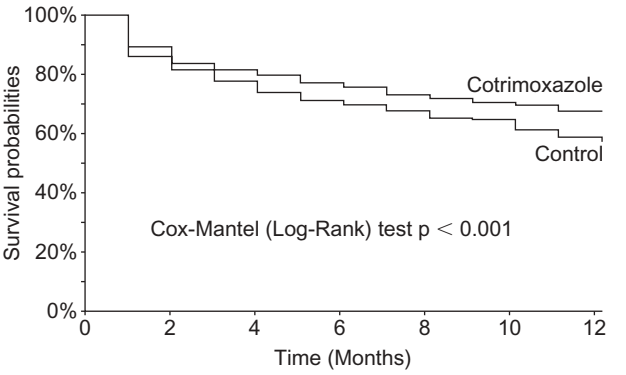

Fig. 2. Kaplan–Meier survival probability in the intervention (cotrimoxazole) and control groups.

In the intervention group receiving VCT and cotrimoxazole 299 deaths (28% of 1061) occurred, whereas 333 deaths (36% of 925) occurred in the control group. The number of TB patients needed to treat with a package of VCT and adjunctive cotrimoxazole to prevent one death during the course of anti-TB treatment is 12.5.

Discussion

This study shows that a package of VCT and cotrimoxazole given as adjunctive treatment to those who were HIV-positive reduced the overall mortality in a cohort of TB patients registered under routine programme conditions in a rural district in Malawi. The intervention appeared to be safe with minimal side-effects. The protective effectiveness of this intervention package was seen mainly in new patients (who comprised $> 90\%$ of patients in both groups), and in patients with smear-negative PTB and EPTB. There was no significant benefit in patients with smear-positive PTB.

This was an operational research study using historical controls as the comparison group, as a randomized control trial was not possible. The use of historical controls inevitably leads to problems in deciding what really caused the reduction in mortality. Was it the package of VCT, cotrimoxazole, increased enthusiasm of the programme, the possibility that HIV-positive patients look after themselves better than patients who do not know their HIV-serostatus or that poverty indicators were better in the intervention year compared with the control year? We do not think that poverty, care or programme enthusiasm were any different between the two years, but we do not have firm data to substantiate this.

Although the historical control group was similar in age and sex to the intervention group, there were

Table 3. End-of-treatment outcomes in intervention (cotrimoxazole) and control groups.

	Death [n/total (%)]			Treatment success [n/total (%)][a]			Other [n/total (%)][b]		
	Cotrimoxazole	Control	*P*[c]	Cotrimoxazole	Control	*P*[c]	Cotrimoxazole	Control	*P*[c]
All TB patients	299/1061 (28)	333/925 (36)	< 0.001	701/1061 (66)	524/925 (57)	< 0.001	61/1061 (6)	68/925 (7)	0.1
TB type									
Smear-positive PTB	91/464 (20)	74/340 (22)	0.5	358/464 (77)	253/340 (74)	0.4	15/464 (3)	13/340 (4)	0.7
Smear-negative PTB	105/282 (37)	140/288 (49)	< 0.01	151/282 (54)	122/288 (42)	< 0.01	26/282 (9)	26/288 (9)	0.9
EPTB	103/315 (33)	119/297 (40)	0.05	192/315 (61)	149/297 (50)	< 0.01	20/315 (6)	29/297 (10)	0.1
TB category									
New TB case	267/967 (28)	326/897 (36)	< 0.001	646/967 (67)	505/897 (56)	< 0.001	54/967 (5)	66/897 (8)	0.1
Relapse	11/39 (28)	3/22 (14)	0.2	25/39 (64)	18/22 (82)	0.1	3/39 (8)	1/22 (4)	1
Other	21/55 (38)	4/6 (67)	0.2	30/55 (55)	1/6 (16.5)	0.1	4/55 (7)	1/6 (16.5)	0.4
TB treatment									
Short course	114/542 (21)	98/400 (24)	0.2	403/542 (74)	283/400 (71)	0.2	25/542 (5)	19/400 (5)	0.9
Standard	130/350 (37)	198/416 (48)	< 0.01	193/350 (55)	180/416 (43)	< 0.01	27/350 (8)	38/416 (9)	0.5
Retreatment	25/77 (33)	5/24 (21)	0.3	47/77 (61)	18/24 (75)	0.2	5/77 (6)	1/24 (4)	1
TB meningitis	13/21 (62)	9/11 (82)	0.2	8/21 (38)	1/11 (9)	0.1	0/21 (0)	1/11 (9)	0.3
Paediatric	17/71 (24)	23/74 (74)	0.3	50/71 (70)	42/74 (57)	0.09	4/71 (6)	9/74 (12)	0.2

[a]Includes all patients who have completed treatment, with or without sputum smear-negative results. [b]Includes patients who have defaulted, transferred, failed, or with unknown outcome (seven, all in the control group). [c]Chi-squared test. TB, Tuberculosis; PTB, pulmonary TB; EPTB, extrapulmonary TB.

differences in the proportions of patients according to type and category of TB. Towards the beginning of the intervention period, the NTP had found that patients with recurrent smear-negative TB were being misclassified as new cases of TB [14]. These mistakes were rectified, and this probably explains the increase in TB cases registered as 'other'. The increase in proportion of patients with smear-positive PTB in the intervention group reflects the on-going training and supervision of all TB programme staff around Malawi in improving the diagnosis of TB by sputum smear examination.

Otherwise, the methods of diagnosing and registering TB patients and the anti-TB treatment regimens were the same in both study periods. HIV sero-status was not measured in historical controls. Malawi has witnessed escalating rates of HIV infection in its registered TB patients during the 1990s [7]. Thus, if anything, HIV-seroprevalence might have been higher in the intervention group, which would have had the effect of increasing mortality rates.

The strengths of this study are that a large number of patients were registered in each of the study groups. Rigorous attempts were made to accurately determine end-of-treatment outcomes and month of death/default or transfer-out. End-of-treatment outcomes were known for all patients, except seven in the control group. Default and transfer-out rates were low and in general were similar in the two groups. The study also used the routine district health services for implementation of activities, and the results are therefore relevant, practicable and probably replicable in other parts of the country.

The benefit of cotrimoxazole was seen in the whole cohort of TB patients, but when subgroup analysis was performed the benefit was only apparent in those with smear-negative PTB and EPTB. The lack of effect in patients with smear-positive PTB appears to conflict with the results of the Cote d'Ivoire study [5]. There are several possible reasons for these differences. First, only 61% of smear-positive PTB patients were given cotrimoxazole compared with 71% of patients with smear-negative PTB. This might reduce the cohort benefit of cotrimoxazole in the smear-positive PTB patients. Second, in Cote d'Ivoire, cotrimoxazole had the most significant effect on mortality in those most immunosuppressed [5]. This effect has also been shown in other parts of Africa [15]. HIV-infected patients with smear-negative PTB may be more immunosuppresed than those with smear-positive PTB [16], and thus might be expected to benefit more from cotrimoxazole. Third, patients in our study were offered cotrimoxazole as soon as possible after registration and starting anti-TB treatment. This contrasts with the design in Cote d'Ivoire [5] where patients were offered

cotrimoxazole 1 month after starting anti-TB treatment. We have already documented high early mortality rates in TB patients in Malawi, with nearly 40% of deaths countrywide occurring in the first month of anti-TB treatment [17]. In the current study, a similar high proportion of deaths in both intervention and control groups occurred during the first month, which would negate the overall benefit of cotrimoxazole. Finally, differing patterns of HIV-related disease and differing rates of cotrimoxazole resistance may reduce the efficacy of cotrimoxazole in our patients. There are high rates of *in vitro* cotrimoxazole resistance to a wide range of pathogens in Malawi [9]. Unfortunately we have limited data on the pattern of HIV-related pathogens in Malawi [18], and this aspect was not investigated in our study.

In addition to providing HIV-positive patients with an effective prophylactic intervention, this study also shows that HIV-counselling and testing is feasible under routine conditions in a rural district and has a high patient acceptance rate. HIV-counselling and testing has been shown in sub-Saharan Africa to promote behaviour change and safer sexual practices, and it appears to be a cost-effective intervention to reduce sexual transmission of HIV [19,20]. Patient compliance with cotrimoxazole prophylaxis in the continuation phase of anti-TB treatment (where the drug is self-administered) was found to be encouragingly high [11]. Since June 2000, the package of VCT and cotrimoxazole prophylaxis has continued in Thyolo district, and good links have been established between the hospital counselling services and community care groups. Although cotrimoxazole had a significant benefit, the death rates in patients offered this intervention were still high. The feasibility and effectiveness of other interventions to reduce early mortality (for example, improving access to care, empirical use of antibiotics to treat presumptive bacteraemia and use of corticosteroids) and to improve overall survival, including the possible use of antiretroviral treatment, needs to be explored [21].

For every 12.5 TB patients in our setting, that were offered the package of VCT plus cotrimoxazole, there was one preventable death during the course of anti-TB treatment. Assuming the same level of uptake of VCT countrywide, if the intervention package was adopted by the NTP there might be just over 2000 prevented deaths during anti-TB treatment. In addition, VCT might lead to changes in sexual behaviour and a reduction in HIV transmission. It has, however, been suggested that widespread use of cotrimoxazole for HIV-positive TB patients may increase the risk of drug resistance for the treatment of acute respiratory infections in children (cotrimoxazole is first-line therapy) and for treatment of malaria (sulphadoxine-pyrimethamine is first-line therapy) [22]. The policy debate about whether to introduce the intervention package will have to take into account these considerations. Other issues include: given the high HIV-seroprevalence, whether adjunctive cotrimoxazole should be provided to all TB patients if widespread implementation of VCT is slow; whether the intervention should include all TB patients or just those with smear-negative PTB and EPTB; and who has responsibility for drug administration, adherence and costs after anti-TB treatment.

Whatever the outcome of this debate, providing VCT and adjunctive cotrimoxazole to TB patients is an essential step to reduce the high mortality associated with HIV infection in sub-Saharan Africa. Our findings have important public health implications for TB control in Malawi and in other high HIV-TB burden countries of sub-Saharan Africa.

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