INT J TUBERC LUNG DIS 11(10):1121–1128

Population differences in death rates in HIV-positive patients with tuberculosis

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SUMMARY

SETTING: Randomised controlled clinical trial of *Mycobacterium vaccae* vaccination as an adjunct to anti-tuberculosis treatment in human immunodeficiency virus (HIV) positive patients with smear-positive tuberculosis (TB) in Lusaka, Zambia, and Karonga, Malawi.

OBJECTIVE: To explain the difference in mortality between the two trial sites and to identify risk factors for death among HIV-positive patients with TB.

DESIGN: Information on demographic, clinical, laboratory and radiographic characteristics was collected. Patients in Lusaka (667) and in Karonga (84) were followed up for an average of 1.56 years. Cox proportional hazard analyses were used to assess differences in survival between the two sites and to determine risk factors associated with mortality during and after anti-tuberculosis treatment.

RESULTS: The case fatality rate was 14.7% in Lusaka and 21.4% in Karonga. The hazard ratio for death comparing Karonga to Lusaka was 1.47 (95% confidence interval [CI] 0.9–2.4) during treatment and 1.76 (95%CI 1.0–3.0) after treatment. This difference could be almost entirely explained by age and more advanced HIV disease among patients in Karonga.

CONCLUSION: It is important to understand the reasons for population differences in mortality among patients with TB and HIV and to maximise efforts to reduce mortality.

KEY WORDS: tuberculosis; HIV; mortality; sub-Saharan Africa

MORTALITY in human immunodeficiency virus (HIV) infected patients with tuberculosis (TB) is high in the absence of antiretroviral treatment (ART). Many of these deaths are probably from causes not related to TB.[1] Case-fatality rates (CFR) recorded in this group vary greatly, ranging from less than 10% to more than 40%, in studies from sub-Saharan Africa.[2–14]

These differences may be explained to some extent by the stage and severity of the HIV epidemic: as the epidemic matures, the proportion of TB patients who are HIV-infected, the average duration of HIV infection, the degree of immunosuppression among these patients, and the burden on the health services all increase. This is illustrated in Figure 1, which shows a strong correlation between HIV prevalence in TB patients and the CFR of those with HIV co-infection (r^2 0.38, $P = 0.02$). Whether there are other reasons for the differences observed between populations is unclear.

In-depth comparisons of outcomes between sites are difficult: treatments, duration of treatment, losses to follow-up and patient mix all vary. Using data from a trial of *Mycobacterium vaccae* vaccination[15] which had been proposed as an adjunct to TB therapy, we had the opportunity to explore outcomes in Lusaka, Zambia, and Karonga District, Malawi. *M. vaccae* had no effect on survival or treatment outcome, but it was noted that survival rates were much lower in Karonga than in Lusaka (Figure 2). As the data were collected in the same way in both sites, a detailed comparison was possible.

METHODS

The original study was a two-centre randomised, double-blind, placebo-controlled clinical trial of *M. vaccae* immunotherapy in adult patients with smear-positive TB co-infected with HIV.[15] Patients with newly diagnosed previously untreated smear-positive pulmonary TB were recruited between September 1996 and October 1998 at the two trial sites: the University Teaching Hospital in Lusaka, Zambia, and the Karonga Prevention Study in Karonga, a rural district of northern Malawi. Patients were randomly allocated

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Article submitted 21 December 2006. Final version accepted 18 June 2007.

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.iuatld.org]

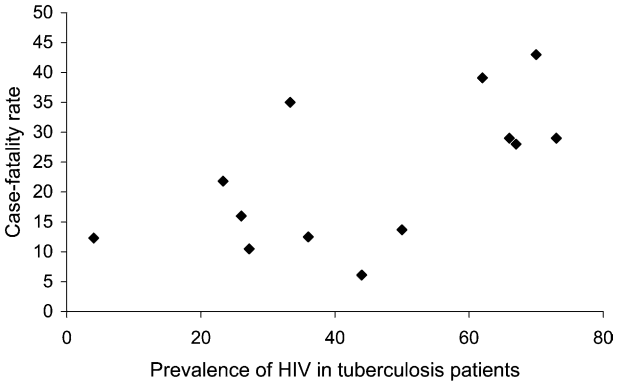

Figure 1 Case-fatality rates of patients with tuberculosis co-infected with HIV, compared to HIV prevalence among tuberculosis patients in different settings in sub-Saharan Africa. Each diamond represents a different study.[1–13] HIV = human immunodeficiency virus.

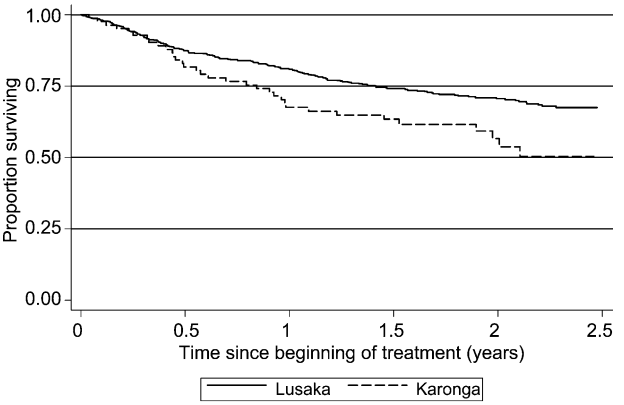

Figure 2 Kaplan-Meier survival curve, comparing survival of HIV-positive patients with smear-positive pulmonary tuberculosis in Lusaka, Zambia (solid line) and Karonga, Malawi (dashed line).

to receive either a single dose of killed *M. vaccae* or placebo within the first 14 days of initiating anti-tuberculosis treatment.

Patients received standard short-course anti-tuberculosis treatment according to the current country guidelines. Antiretrovirals, cotrimoxazole or isoniazid (INH, H) prophylaxis were not available at the time at either site. Patients in Lusaka received 2 months of INH, rifampicin (RMP, R), pyrazinamide (PZA, Z) and ethambutol (EMB, E), followed by 6 months of HE (2HRZE/6HE). Drugs were given on an out-patient basis and self-administered throughout treatment. Patients in Karonga received HRZ and streptomycin (SM, S) for 2 months in hospital, followed by 6 months of HE as out-patients (2HRZS/6HE).

At baseline, the history and presence of HIV-related signs and symptoms were recorded, weight and height were measured, blood samples were taken for HIV serology and haemoglobin levels, chest radiography was performed and an additional sputum sample was taken for sputum culture.

At each follow-up visit (every 4 weeks during treatment and every 12 weeks thereafter), patients were examined, signs and symptoms of HIV-related illnesses were recorded and sputum samples were taken for smear and culture. Chest X-rays (CXRs) were taken at the end of treatment and at months 12 and 18.

CXRs were reviewed by an independent blinded assessor as part of the multi-centre study to assess the effect of *M. vaccae* immunotherapy on radiographic healing in TB.[16] For each radiograph, the assessor recorded the number of zones affected, aggregated extent of pulmonary disease, and presence of cavitation, hilar/mediastinal adenopathy, miliary TB, pleural effusion and infiltration.

Statistical analysis

Patients were assigned a World Health Organization (WHO) HIV clinical stage[17] according to the signs and symptoms recorded at the beginning and at the end of anti-tuberculosis treatment (week 32/34). At the beginning of treatment, the following signs and symptoms were included in the categorisation: minor mucocutaneous manifestations, history of herpes zoster in last 5 years, unexplained chronic diarrhoea for more than one month, oral candidiasis, herpes simplex virus infection and Kaposi's sarcoma. Signs and symptoms typical of TB (prolonged fever, weight loss and wasting syndrome) as well as current or previous TB were excluded. The categorisation at the end of treatment was done independently of the staging assigned at baseline, using the same criteria but also including prolonged fever, weight loss and wasting syndrome.

The data were analysed using STATA™ 9.2 software (Stata Corporation, College Station, TX, USA). The CFR was calculated as the number of deaths during anti-tuberculosis treatment divided by the number of patients initiating treatment. Death rates were calculated by dividing the number of deaths by the person-years (py) of observation, calculated from the date of beginning treatment until the end of follow-up or time of death. Patients lost to follow-up were censored at the time of their last visit.

Cox proportional hazard models were used to compare mortality rates between the two sites. The proportional hazards assumption was checked by visual inspection of Nelson-Aalen plots and by performing tests for interaction with time. All analyses were performed for the whole follow-up period and separately for the time during and after anti-tuberculosis treatment.

We used univariate Cox regression to assess the effect of each risk factor on the death rate for each site separately. With bivariate Cox regression we examined the possible confounding effect of each risk factor on the hazard ratio (HR) of death in Karonga compared to Lusaka. We used multivariate Cox regression to explain the difference between the two sites. In addition, we used data from both sites to determine risk factors associated with mortality of HIV-positive patients during and after anti-tuberculosis treatment.

Ethical approval

This analysis was approved by the London School of Hygiene & Tropical Medicine Ethics Committee. The original study was approved by review boards at the University Teaching Hospital, the University of Zambia School of Medicine, the Health Sciences Research Committee of the Ministry of Health, Malawi, and the London School of Hygiene & Tropical Medicine.

RESULTS

Between September 1996 and October 1998, 1442 patients with pulmonary TB were screened, 1184 in Lusaka and 258 in Karonga, and respectively 996 and 149 were randomised into the trial. The main reasons for exclusion were lack of bacteriological confirmation of TB ($n = 78$), previous anti-tuberculosis treatment ($n = 49$), ineligible age or area of residence ($n = 66$), pregnancy ($n = 10$) and not giving consent ($n = 48$). Four patients in Lusaka and 21 in Karonga were deemed too ill. In Lusaka, 67% (667/996) were HIV-positive, and in Karonga 56% (84/149). Patients were followed up for an average of 1.56 years in Lusaka and 1.59 years in Karonga; the maximum follow-up time was 3.13 years.

Overall, 230 patients died; of these, 216 were HIV-positive. In Lusaka, the CFR was 14.7% in HIV-positive patients and 0.6% in HIV-negative patients, and in Karonga, 21.4% in HIV-positive and 1.5% in HIV-negative patients. Mortality rates are shown in Table 1. The overall mortality rate among HIV-positive patients was 18.2/100 py in Lusaka and 30.0/100 py in Karonga. Increased mortality was observed in Karonga both during and after treatment. The mortality rates also differed among HIV-negative patients, but the number of deaths was small and the confidence interval wide. Further analysis is therefore restricted to HIV-positive patients.

Patient characteristics

Table 2 shows the characteristics of the HIV-positive patients. Compared to the patients in Lusaka, the patients in Karonga were older, a higher proportion had a body mass index (BMI) in the lowest group (severely malnourished) and a higher proportion had HIV-related signs and symptoms, both at the beginning and at the end of anti-tuberculosis treatment. Patients in Karonga were less likely to have cavities on CXR and more likely to have hilar/mediastinal lymphadenopathy.

Risk factors for mortality

The associations between patient characteristics and mortality throughout the period of follow-up are shown in Table 3. Mortality rates increased with age but were similar in men and women. Low BMI, low level of haemoglobin and more advanced clinical stage of HIV at baseline were strong predictors of mortality. Clinical stage at the end of anti-tuberculosis treatment was strongly associated with subsequent mortality.

Patients with cavitation or a larger proportion of lungs affected on the baseline CXR had lower mortality rates (Table 3). Patients at highest risk were those with no radiological changes.

Comparing Lusaka and Karonga

In the bivariate proportional hazards analysis, the overall HR of 1.60, comparing mortality at the two sites (Table 1), was reduced by adjusting for age (adjusted HR [aHR] 1.40, 95% confidence interval [CI] 1.0–2.0) and clinical stage at the beginning of treatment (aHR 1.47, 95%CI 1.0–2.1), but was not changed by adjusting for any other demographic or clinical factor. Among those with CXRs available, the overall HR comparing the sites was 1.74 (95%CI 1.2–2.6). The only radiological feature that explained some of the difference between sites was absence of cavitation (aHR 1.56, 95%CI 1.0–2.3). Age, baseline HIV stage

Table 1 Mortality rates and hazard ratios comparing Lusaka and Karonga throughout the follow-up period, during anti-tuberculosis treatment and after treatment

	Lusaka			Karonga				
	py	Deaths *n*	Rate (95%CI)	py	Deaths *n*	Rate (95%CI)	HR (95%CI)	*P* value*
All patients								
Overall	1559.7	192	12.3 (10.7–14.2)	236.5	38	16.1 (11.7–22.1)	1.29 (0.9–1.9)	0.15
During treatment	598.5	100	16.7 (13.7–20.3)	91.9	19	20.7 (13.2–32.4)	1.23 (0.7–2.0)	0.40
After treatment	961.3	92	9.6 (7.8–11.7)	144.6	19	13.1 (8.4–20.6)	1.36 (0.8–2.2)	0.22
HIV-positive								
Overall	999.7	182	18.2 (15.7–21)	113.4	34	30.0 (21.4–42.0)	1.60 (1.1–2.3)	0.01
During treatment	394.5	98	24.8 (20.4–30.3)	49.0	18	36.7 (23.1–58.3)	1.47 (0.9–2.4)	0.13
After treatment	605.2	84	13.9 (11.2–17.2)	64.4	16	24.9 (15.2–40.6)	1.76 (1.0–3.0)	0.04
HIV-negative								
Overall	560.0	10	1.8 (1–3.3)	123.1	4	3.2 (1.2–8.6)	1.82 (0.6–5.7)	0.31
During treatment	204.0	2	1.0 (0.2–3.9)	42.9	1	2.3 (0.3–16.6)	2.42 (0.2–26.7)	0.47
After treatment	356.0	8	2.2 (1.1–4.5)	80.2	3	3.7 (1.2–11.6)	1.67 (0.4–6.3)	0.45

* *P* value from Wald test.
py = person-years; HR = hazard ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Table 2 Demographic and clinical characteristics of HIV-positive patients with tuberculosis in Zambia and Malawi at baseline and at the end of treatment (32 weeks)

Risk factor	Lusaka (n = 676) n (%)	Karonga (n = 84) n (%)	P value
Sex			
Male	353 (52.2)	40 (47.6)	
Female	323 (47.8)	44 (52.4)	0.43
Age, years			
<35	343 (50.7)	30 (35.7)	
35–45	242 (35.8)	35 (41.7)	
>45	91 (13.5)	19 (22.6)	0.01
BMI, kg/m^2			
<16	127 (18.9)	21 (25.9)	
16–18.5	302 (44.9)	36 (44.4)	
>18.5	243 (36.2)	24 (29.6)	0.26
Haemoglobin, g/dl			
<8	89 (13.6)	16 (19.5)	
8–10	222 (33.9)	17 (20.7)	
>10	343 (52.5)	49 (59.8)	0.04
HIV clinical stage*			
1	543 (80.3)	58 (69.1)	
2	35 (5.2)	10 (11.9)	
3	78 (11.5)	11 (13.1)	
4	20 (3.0)	5 (6.0)	0.03
Presence of cavity			
No	218 (37.5)	38 (54.3)	
Yes	363 (62.5)	32 (45.7)	0.007
Hilar/mediastinal adenopathy			
Absent	515 (88.6)	59 (84.3)	
Present	66 (11.4)	11 (15.7)	0.29
Miliary TB			
No	577 (99.3)	69 (98.6)	
Yes	4 (0.7)	1 (1.4)	0.50
Pleural effusion			
0	510 (87.8)	57 (81.4)	
>1/3	71 (12.2)	13 (18.6)	0.13
Infiltration			
No	40 (6.9)	7 (10.0)	
Yes	541 (93.2)	63 (90.0)	0.34
Area of lungs affected			
<1	177 (30.5)	25 (35.7)	
1–2	293 (50.4)	27 (38.6)	
3–6	111 (19.1)	18 (25.7)	0.16
HIV clinical staging week 32†			
1	444 (89.3)	35 (63.6)	
2	7 (1.4)	7 (12.7)	
3	36 (7.2)	8 (14.6)	
4	10 (2.0)	5 (9.1)	<0.001

* Excluding TB and signs and symptoms related to it.
† Based on symptoms at week 32. X-rays of all patients were not available.
HIV = human immunodeficiency virus; BMI = body mass index; TB = tuberculosis.

and absence of cavitation on CXR were the main factors explaining the increased mortality rate in Karonga, both during and after treatment. The largest single risk factor explaining the difference in mortality after the end of treatment was HIV stage at week 32 (reducing the HR from 1.76 to 1.20, 95%CI 0.6–2.2).

The overall HR for death in Karonga compared to Lusaka was reduced to 1.22 (95%CI 0.8–1.8) after adjusting in the multivariate model for age, HIV stage at baseline and absence of cavitation on CXR. The HR for death during treatment fell from 1.64 (in those with CXR available) to 1.19 (95%CI 0.6–2.2) adjusting for the same factors. For death after treatment the HR fell from 1.76 to 0.81 (95%CI 0.4–1.6) after adjusting for age, HIV stage at baseline and HIV stage at the end of treatment.

Multivariate analysis of risk factors for mortality

The risk factors that were found to be significantly associated with mortality in multivariate analyses are shown in Table 4. Study site was retained in the model a priori.

Age was a strong risk factor for mortality during both time periods. Low BMI, low level of haemoglobin and absence of cavitation on CXR were strong risk factors for death during anti-tuberculosis treatment. HIV stage at the beginning of treatment was no longer a significant risk factor once adjusted for other variables. After treatment, HIV stage and haemoglobin levels at baseline and HIV stage at the end of treatment were important risk factors for mortality.

DISCUSSION

The difference in mortality between Karonga and Lusaka appears to be attributable largely to differences in age (patients in Karonga were older) and stage of HIV infection: patients in Karonga had more advanced HIV disease both at the beginning and at the end of anti-tuberculosis treatment, and were less likely to have cavitation on CXR.

Age and stage of HIV disease have been identified as risk factors for death in HIV-positive TB patients in previous studies.[3,6,14,18,19] Clinical stage is difficult to assess in patients with active TB. We excluded those signs and symptoms that overlapped with signs and symptoms of TB to be able to detect differences in HIV disease (if not, the majority of patients would fall in WHO stage 3) but misclassification is likely. In the multivariate analysis, other risk factors (BMI, haemoglobin and absence of cavitation on CXR) were better predictors of mortality during treatment, probably because they were better correlates of immune deficiency. Low BMI has been identified as an independent risk factor for mortality in HIV-positive patients[20] and an important predictor of early death of patients on anti-tuberculosis treatment in an area with high HIV prevalence.[21] Anaemia has been previously identified as a risk factor for HIV-associated mortality,[22] independently of viral load or CD4 count.[23] Atypical features on CXR indicating impaired immune response, including absence of cavitation, have been associated with HIV,[24] and are more common among patients with more severe CD4 depletion.[25]

The LUSKAR trial was not designed to compare differences between the two trial sites, and as only 13% of the patients in the trial were recruited in

Table 3 Mortality rates for HIV-positive patients with tuberculosis throughout the follow-up period in Lusaka and Karonga

	Lusaka			Karonga		
Risk factor	Deaths *n*	Rate (95%CI)	HR	Deaths *n*	Rate (95%CI)	HR
Sex						
Female	85	17.0 (13.7–21.0)	1	18	29.6 (18.7–47.0)	1
Male	97	19.4 (15.9–23.7)	1.13 (0.8–1.5)	16	30.4 (18.6–49.6)	1.04 (0.5–2.0)
Age, years						
<35	64	11.7 (9.2–15.0)	1	12	30.3 (17.2–53.3)	1
35–45	75	21.8 (17.4–27.4)	1.84 (1.3–2.6)	11	20.5 (11.3–37.0)	0.69 (0.3–1.5)
>45	43	38.7 (28.7–52.1)	3.13 (2.1–4.6)	11	55.0 (30.4–99.3)	1.88 (0.8–4.3)
BMI, kg/m^2						
<16	49	29.0 (21.9–38.4)	1	11	48.6 (26.9–87.8)	1
16–18.5	74	16.4 (13.0–20.6)	0.57 (0.4–0.8)	15	27.8 (16.7–46.1)	0.60 (0.3–1.3)
>18.5	57	15.2 (11.7–19.7)	0.53 (0.4–0.8)	8	24.3 (12.1–48.6)	0.51 (0.2–1.3)
Haemoglobin, g/dl						
<8	53	60.2 (46.0–78.8)	1	8	47.8 (23.9–95.6)	1
8–10	68	21.8 (17.2–27.6)	0.39 (0.3–0.5)	11	53.5 (29.6–96.5)	1.16 (0.5–2.9)
>10	56	9.9 (7.6–12.9)	0.18 (0.1–0.3)	14	19.1 (11.3–32.3)	0.42 (0.2–1.0)
HIV stage						
1	121	14.8 (12.3–17.6)	1	19	23.3 (14.8–36.6)	1
2	11	17.9 (9.9–32.4)	1.28 (0.7–2.4)	6	51.8 (23.3–115.3)	2.15 (0.8–5.4)
3	37	40.5 (29.3–55.9)	2.65 (1.8–3.8)	8	64.6 (32.3–129.2)	2.70 (1.2–6.2)
4	13	47.3 (27.5–81.5)	3.19 (1.8–5.6)	1	12.5 (1.8–89.0)	0.58 (0.1–4.3)
Presence of cavity						
No	82	26.0 (20.9–32.3)	1	21	43.4 (28.3–66.6)	1
Yes	66	11.9 (9.4–15.2)	0.47 (0.4–0.6)	9	16.8 (8.4–33.6)	0.39 (0.2–0.9)
Hilar/mediastinal adenopathy						
0	116	14.9 (12.4–17.9)	1	25	30.4 (20.6–45.0)	1
>1	32	35.4 (25.0–50.0)	2.37 (1.6–3.5)	4	29.0 (10.9–77.2)	0.96 (0.3–2.8)
Miliary tuberculosis						
No	147	17.1 (14.5–20.0)	1	28	29.8 (20.6–43.2)	1
Yes	1	13.8 (1.9–97.9)	0.84 (0.1–6.0)	1	47.5 (6.7–337.2)	1.44 (0.2–10.7)
Pleural effusion						
Absent	131	16.9 (14.2–20.0)	1	22	28.5 (18.7–43.2)	1
Present	17	18.4 (11.4–29.5)	1.08 (0.6–1.8)	7	37.5 (17.9–79.7)	1.38 (0.6–3.2)
Infiltration						
No	16	26.6 (16.3–43.4)	1	5	62.7 (26.1–150.6)	1
Yes	132	16.3 (13.7–19.3)	0.61 (0.4–1.0)	24	27.3 (18.3–40.7)	0.46 (0.2–1.2)
Area of lungs affected						
<1	66	26.3 (20.7–33.5)	1	14	43.76 (25.9–73.9)	1
1–2	59	12.6 (9.7–16.2)	0.49 (0.3–0.7)	9	25.2 (13.1–48.4)	0.57 (0.2–1.3)
3–6	23	15.4 (10.2–23.1)	0.58 (0.4–0.9)	6	21.3 (9.5–47.3)	0.48 (0.2–1.3)
HIV stage week 32*						
1	55	9.9 (7.6–13)	1	5	12.4 (5.2–29.8)	1
2	3	38.1 (12.3–118.3)	3.65 (1.1–11.7)	2	23.6 (5.9–94.4)	1.94 (0.4–10.0)
3	14	45.6 (27.0–77.0)	4.53 (2.5–8.2)	4	42.8 (16.1–114.1)	3.23 (0.9–12.1)
4	4	41.7 (15.6–111.1)	4.37 (1.6–12.1)	2	63.5 (15.9–253.8)	6.31 (1.1–34.7)

* Mortality rates after the end of treatment are shown.
HIV = human immunodeficiency virus; CI = confidence interval; HR = hazard ratio; BMI = body mass index.

Karonga the power of the comparison is limited. The mortality rates among the HIV-negative patients also differed by site, but there were a few deaths and this could be due to chance.

Although the same protocol was in place in both sites, there were differences in the selection of patients: in Karonga, 8% of screened patients were excluded because they were too ill (unlikely to survive 2 weeks), compared to only 0.3% in Lusaka. This may explain the similar survival patterns during the first few months of treatment. However, whereas all available patients were screened in Karonga, patients were pre-screened at peripheral clinics and then referred to the hospital in Lusaka, so some very ill patients may have been excluded at this stage. There may also have been differences in assessing clinical signs and symptoms between sites, although the CXRs were read blind to site. Slightly different treatment regimens were used in the two sites, but the efficacies of EMB and SM as part of the standard regimen have been shown to be similar.[26]

The proportion of patients lost to follow-up was small, but differed between the sites. By 12 months, the outcome was unknown for 11.7% of patients in Lusaka and 6% in Karonga. In a study elsewhere in Malawi, a third of all TB patients with unknown outcome were found to have died;[27] this could be higher

Table 4 Hazard ratios for deaths in HIV-positive patients with tuberculosis during and after the anti-tuberculosis treatment

Risk factor	Adjusted HR (95%CI)	*P* value
During treatment		
Study site	1.24 (0.7–2.2)	0.46
Age (per 1 year increase)	1.07 (1.0–1.1)	<0.001
Presence of cavity	0.41 (0.3–0.6)	<0.001
BMI 16–18.5 kg/m^2	0.47 (0.3–0.8)	0.004
BMI >18.5 kg/m^2	0.35 (0.2–0.6)	<0.001
Haemoglobin 8–10 g/dl	0.63 (0.4–1.1)	0.08
Haemoglobin >10 g/dl	0.22 (0.1–0.4)	0.001
After treatment		
Study site	0.97 (0.5–2.0)	0.93
HIV clinical stage 2	2.38 (1.1–5.2)	0.03
HIV clinical stage 3	2.17 (1.1–4.1)	0.02
HIV clinical stage 4	2.51 (1.0–6.1)	0.05
HIV clinical stage 2 at week 32	0.94 (0.3–3.0)	0.92
HIV clinical stage 3 at week 32	3.31 (2.0–6.2)	<0.001
HIV clinical stage 4 at week 32	5.45 (2.2–13.7)	<0.001
Age (per 1 year increase)	1.04 (1.0–1.1)	0.03
Haemoglobin 8–10 g/dl	0.32 (0.2–0.6)	0.001
Haemoglobin >10 g/dl	0.25 (0.1–0.5)	<0.001

HR = hazards ratio adjusted for other factors in that model; HIV = human immunodeficiency virus; CI = confidence interval; BMI = body mass index.

among HIV-positive patients, so the mortality rate in Lusaka may have been underestimated.

Although several risk factors were examined, there is probably considerable residual confounding. CD4 counts, which would better measure the degree of immune suppression than clinical signs and symptoms alone, were available for only a subset of patients in Lusaka and were not included in the analysis. Socioeconomic status was not recorded. Karonga being a rural district, the majority of the population are subsistence farmers, while Lusaka is a capital city; socioeconomic differences between patients at the two sites are therefore likely. Information on delay of treatment was not collected, and it is likely that access to health care in Karonga was more difficult.

It is not clear why HIV-infected patients with smear-positive TB in Karonga should have more advanced HIV disease than similar patients in Lusaka. In both sites, the most common type of HIV is subtype C.[28,29] The HIV epidemic peaked later in Karonga than in Lusaka: in Lusaka, 77% of TB patients were HIV-infected by 1989,[2] whereas in Karonga the proportion increased from 21.3% in 1989 to 38.4% in 1993 and to 70% in 1999/2000.[30] This would be expected to lead to a higher proportion of patients with HIV infections of longer duration in Lusaka. It is possible that in Lusaka non-tuberculosis antibiotics are more easily available or more readily used by patients as soon as they have signs of infection. Several studies have shown reductions in mortality among HIV-infected patients with TB who were taking cotrimoxazole prophylaxis.[7,31–34] Even if ad-hoc treatment of established infections is not as efficient as prophylaxis, it is probably better than nothing.

As we have shown in our analysis, mortality rates differ even between trial settings. The main preventable reason for the increased mortality in Karonga was advanced HIV disease. It is therefore of utmost importance to maximise efforts to slow the advance of HIV disease by making ART available and also by providing other interventions known to reduce mortality among patients co-infected with HIV[35] and *M. tuberculosis*, such as cotrimoxazole prophylaxis. This is now beginning to happen in Malawi[36] and elsewhere.

Acknowledgements

The authors wish to thank Prof Chintu and the members of the LUSKAR Trial Group, the patients and staff at the University Teaching Hospital, Lusaka, and at the Karonga Prevention Study (supported by the Wellcome Trust and LEPRA) and the Ministries of Health of Zambia and Malawi. The original trial was supported by grant RD344 from the UK Department for International Development. JRG is supported by the UK Department of Health (Public Health Career Scientist Award).

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RÉSUMÉ

CONTEXTE : Essai clinique contrôlé randomisé d'une vaccination par *Mycobacterium vaccae* comme complément au traitement antituberculeux chez les patients séropositifs pour le virus de l'immunodéficience humaine (VIH), atteints d'une tuberculose (TB) à bacilloscopie positive des crachats à Lusaka, Zambie et Karonga, Malawi.

OBJECTIF : Expliquer la différence de mortalité entre les deux sites d'essai et identifier les facteurs de risque de décès chez les patients séropositifs pour le VIH atteints de TB.

SCHÉMA : On a recueilli des informations sur les caractéristiques démographiques, cliniques, de laboratoire et de radiographie. On a suivi les patients à Lusaka (n = 667) et à Karonga (n = 84) pendant une durée moyenne de 1,56 années. Les analyses proportionnelles de risque de Cox ont été utilisées pour évaluer les différences de survie entre les deux sites et pour déterminer les facteurs de risque en association avec la mortalité au cours du traitement ou après traitement antituberculeux.

RÉSULTATS : Le taux de létalité des cas était de 14,7% à Lusaka et de 21,4% à Karonga. Le ratio de risque de décès comparant Karonga à Lusaka est de 1,47 (IC95% 0,9–2,4) au cours de traitement et de 1,76 (IC95% 1,0–3,0) après traitement. Cette différence pourrait être presque entièrement expliquée par un âge plus avancé et une maladie VIH plus avancée chez les patients de Karonga.

CONCLUSION : Il est important de comprendre les raisons des différences de mortalité entre populations chez les patients atteints de TB et d'infection par le VIH et d'accroître au maximum les efforts de réduction de la mortalité.

RESUMEN

MARCO DE REFERENCIA: Estudio clínico comparativo aleatorizado de la vacunación con *Mycobacterium vaccae* como medida complementaria al tratamiento antituberculoso en pacientes con serología positiva para el virus de la inmunodeficiencia humana (VIH) y tuberculosis (TB) con baciloscopia positiva en Lusaka, Zambia y Karonga, en Malawi.

OBJETIVO: Explicar la diferencia de mortalidad entre dos centros del estudio y determinar los factores de riesgo de muerte en los pacientes con TB y serología positiva para el VIH.

MÉTODO: Se recopiló información sobre las características demográficas, clínicas y radiográficas. Se practicó el seguimiento de 667 pacientes en Lusaka y 84 en Karonga durante un promedio de 1,56 años. Se aplicaron los modelos de riesgos instantáneos proporcionales de Cox, con el fin de evaluar las diferencias de supervivencia entre los dos centros y determinar los factores de riesgo asociados con la mortalidad durante el tratamiento antituberculoso y después del mismo.

RESULTADOS: El índice de letalidad fue 14,7% en Lusaka y 21,4% en Karonga. Comparando Karonga con Lusaka, el cociente de riesgos instantáneos de muerte fue 1,47 (IC95% 0,9–2,4) durante el tratamiento y 1,76 (IC95% 1,0–3,0) después del mismo. Esta diferencia se podría explicar casi totalmente por la mayor edad y el estado más avanzado de la enfermedad por el VIH de los pacientes de Karonga.

CONCLUSIÓN: Es importante comprender el origen de las diferencias entre las poblaciones con respecto a la mortalidad de los pacientes con TB e infección por el VIH y maximizar los esfuerzos tendientes a reducir esta mortalidad.