Does antiretroviral treatment reduce case fatality among HIV-positive patients with tuberculosis in Malawi?

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_____ S U M M A R Y

SETTING: Thyolo district, Malawi.

OBJECTIVES: To report on 1) case fatality among human immunodeficiency virus (HIV) positive tuberculosis (TB) patients while on anti-tuberculosis treatment and 2) whether antiretroviral treatment (ART) initiated during the continuation phase of TB treatment reduces case fatality.

DESIGN: Retrospective cohort analysis.

METHODS: Comparative analysis of treatment outcomes for TB patients registered between January and December 2004.

RESULTS: Of 983 newly registered TB patients receiving diagnostic HIV testing, 658 (67%) were HIV-positive. A total of 132 (20%) patients died during the 8-month course of anti-tuberculosis treatment, of whom 82 (62%) died within the first 2 months of treatment when ART was not provided (cumulative incidence 3.0, 95%CI 2.5–3.6 per 100 person-years). A total of 576 TB patients started the continuation phase of anti-tuberculosis treatment, 180 (31%) of whom were started on ART. The case-fatality rate per 100 person-years was not significantly different for patients on ART (1.0, 95%CI 0.6–1.7) and those without ART (1.2, 95%CI 0.9–1.7, adjusted hazard ratio 0.86, 95%CI 0.4–1.6, $P = 0.6$)

CONCLUSIONS: ART provided in the continuation phase of TB treatment does not have a significant impact on reducing case fatality. Reasons for this and possible measures to reduce high case fatality in the initial phase of TB treatment are discussed.

KEY WORDS: Malawi; HIV/AIDS; TB; ART; case fatality

HUMAN IMMUNODEFICIENCY VIRUS (HIV) positive patients with tuberculosis (TB) in sub-Saharan Africa have high death rates during and following anti-tuberculosis treatment.[1–3] Case-fatality rates (deaths during treatment) have a negative impact on cure rates and challenge the credibility of TB control programmes amongst patients, health care staff and the community. Effective adjunctive interventions to reduce case-fatality rates in sub-Saharan Africa are urgently needed.

HIV-positive patients with TB in our setting are all potentially eligible for antiretroviral treatment (ART), either because they are in World Health Organization (WHO) Clinical Stage 3 (pulmonary TB, PTB) or in WHO Clinical Stage 4 (extra-pulmonary TB, EPTB).[4] The WHO recommends that where CD4 testing services are not yet available (or feasible), all individuals classified as WHO stage 3 or 4 could be considered eligible for ART.

In principle, HIV-positive TB patients should benefit from ART, with a reduction in HIV-related case fatality and episodes of recurrent TB. Reports on small numbers of patients treated in Asian countries, such as Taiwan[5] and Thailand,[6] point to good overall outcomes for HIV-positive TB patients treated with ART.

To our knowledge, there have been no reports on the impact on case-fatality rates in HIV-infected TB patients treated with ART in the routine health system in sub-Saharan Africa, where these rates are among the highest in the world.

Every year, Thyolo District, in rural Malawi, registers a large number of HIV-positive TB patients who are all systematically offered ART. A proportion of these individuals accept the offer during anti-tuberculosis treatment while others do not, thus allowing an observation of death rates between the two cohorts. Under routine conditions of health service delivery in this district, we report on 1) case-fatality rates among HIV-positive TB patients while on anti-tuberculosis treatment and 2) whether ART initiated during the continuation phase of anti-tuberculosis treatment reduces case fatality.

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METHODS

Design

The study was a retrospective analysis of standardised anti-tuberculosis treatment outcomes in HIV-positive TB patients registered between 1 January and 31 December 2004 who were further divided into those who received ART during the continuation phase of treatment and those who did not choose ART.

Study setting and management of TB

The study was conducted in Thyolo District, a rural region of southern Malawi with a population of about 550 000. The great majority of inhabitants in this district are farmers. The main public hospital in the district (Thyolo Hospital), which registers and treats the majority of TB patients, was involved in the study.

TB patients are diagnosed, registered and treated according to national guidelines, using a standardised approach[7] and following WHO guidelines.[8] New patients are treated with a 2-month initial phase of rifampicin (RMP), isoniazid (INH) and pyrazinamide (with additional ethambutol [EMB] for sputum smear-positive patients), followed by a 6-month continuation phase of INH and EMB. Drugs and investigations for TB are free of charge and, since early 1999, all TB patients undergo diagnostic counselling and HIV testing. HIV-positive patients are managed for opportunistic infections and offered cotrimoxazole preventive treatment (CPT), provided there are no contraindications.[9]

ART for TB patients

The first-line ART regimen in Malawi is a fixed-dose combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP). In case of side effects, zidovudine (AZT) and efavirenz (EFV) are alternatives to d4T and NVP, respectively. ART for HIV-positive TB patients is deferred until the continuation phase of anti-tuberculosis treatment (2 months after the start of TB treatment) because of concerns about pill burden, immune reconstitution syndrome in patients not yet stabilised on anti-tuberculosis treatment and drug-drug interactions between RMP and NVP.[10]

Once the patient has been started on the continuation phase of anti-tuberculosis treatment (INH and EMB), the patient is eligible to start ART. TB patients who are started on ART are followed up monthly, and attend the TB clinic for anti-tuberculosis medication and a separate clinic for ART drugs. ART was started in Thyolo in April 2003 and is offered free of charge.

Study population, data collection and statistical analysis

The study included all newly diagnosed HIV-positive TB patients registered between 1 January and 31 December 2004. Only TB patients offered HIV testing for the first time following a diagnosis of active TB were included in the study. Patients who were on ART and were diagnosed with TB thereafter were not included in the analysis. The counselling register, district TB register, TB patient cards, ART Patient Master Cards and ART Register[11] were reviewed to gather information on demography, HIV status, ART uptake and outcomes of anti-tuberculosis treatment. The cumulative number of deaths that occurred during the entire course of anti-tuberculosis treatment among HIV-positive TB patients was determined. All deaths that occurred during the first 2 months of the initial phase of anti-tuberculosis treatment were then excluded, and the outcomes between those who chose to be initiated on ART and those who chose not to be initiated on ART while in the continuation phase of anti-tuberculosis treatment were compared.

Thyolo has a well-developed network of community volunteers and nurses who ensure consistent follow-up, including home visits for non-reporting patients. Reliable ascertainment of deaths and other treatment outcomes was thus possible, thereby avoiding misclassifications, in particular case fatality as default.

Differences between groups were compared using the χ^2 test for categorical variables or the Student's t-test for continuous variables. Crude relative risks and hazard ratios (HR) (per 100 person-years [py] of follow-up) were used to compare death rates in the intervention and control groups. HRs were adjusted using a Cox regression model. Survival estimates were determined using the Kaplan-Meier method and compared using the Cox-Mantel (log-rank) test. The level of significance was set at $P \leqslant 0.05$, and 95% confidence intervals (CI) were used throughout. Data were analysed using STATA 8.2 software (Stata Corporation, College Station, TX, USA).

Ethical approval

General measures are provided in the Thyolo ART facility to ensure patient confidentiality, consent for HIV testing, and counselling and support for those who receive a positive HIV test result. The Malawi National Health Science Research Committee provides general oversight and approval for the collection and use of routine programmatic data for monitoring and evaluation, and does not require formal submission for ethical approval for the type of study conducted in this paper.

RESULTS

Characteristics of the study population

A total of 983 new TB patients were registered during the study period, of whom 658 (67%) were found to be HIV-positive. This included 270 (41%) men and 388 women, with a mean age of 33 years. There were 297 (45%) cases of smear-positive PTB, 203 (31%)
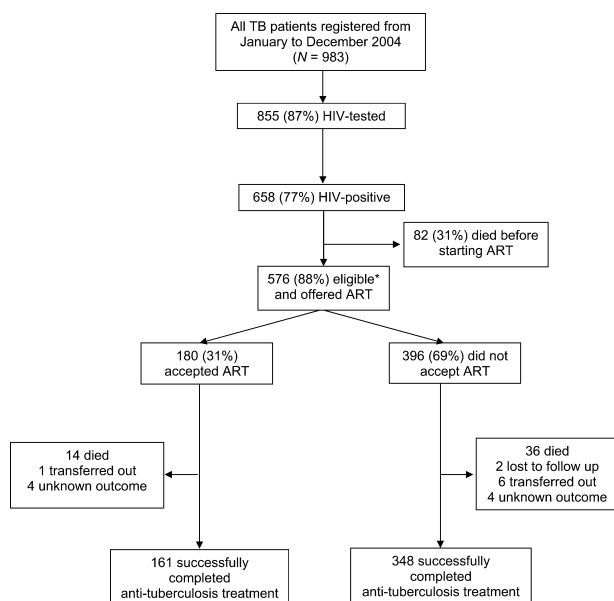
Figure 1 Deaths and acceptance of ART among HIV-positive TB patients in Thyolo, Malawi. *ART is initiated only after patients have completed their initial 2-month phase of anti-tuberculosis treatment. ART = antiretroviral treatment; HIV = human immunodeficiency virus; TB = tuberculosis.

smear-negative PTB and 158 (24%) EPTB cases. A total of 401 (61%) HIV-positive TB patients were receiving CPT, usually started within 1 week of commencement of anti-tuberculosis treatment. Of the 658 HIV-positive TB patients, 576 (88%) completed the initial 2-month phase of anti-tuberculosis treatment, and all were offered ART. One hundred and eighty (31%) of these individuals accepted and were started on ART (Figure 1). ART was started a median of 88 days (inter-quartile range 66–125 days) after initiation of anti-tuberculosis treatment.
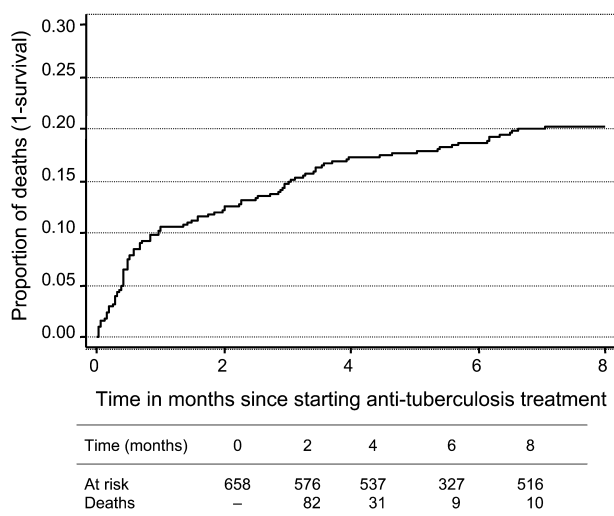

Figure 2 Cumulative incidence of death among HIV-positive TB patients during anti-tuberculosis treatment, Thyolo, Malawi. HIV = human immunodeficiency virus; TB = tuberculosis.

Deaths among HIV-positive TB patients

A total of 132 (20%) deaths occurred among HIV-positive TB patients during the 8-month course of anti-tuberculosis treatment. The cumulative incidence of death among HIV-positive TB patients, whether they received ART or not, during the 8-month period of treatment was 3.0 (95%CI 2.5–3.6) per 100 py of follow-up (Figure 2). Eighty-two (62%) deaths occurred during the first 2 months of treatment before ART was offered to patients.

Characteristics and death rates in relation to ART

The Table shows the characteristics and anti-tuberculosis treatment outcomes ($n = 576$) in patients started on ART and those not started on ART, after excluding the 82 deaths that occurred during the first 2 months of anti-tuberculosis treatment when patients were not offered ART. Characteristics and standardised end of treatment outcomes were not significantly different between those who started ART and those who did not. The case-fatality rate per 100 py among those who accepted ART (1.0, 95%CI 0.6–1.7) was not significantly different from that of patients who

Table Characteristics and treatment outcomes of TB patients who started the continuation phase of anti-tuberculosis treatment, Thyolo, Malawi ($n = 576$)*

Variable	Accepted ART n (%)	Did not accept ART n (%)	P value†
Total ($N = 576$)	180 (31)	396 (69)	—
Sex			
Male	67 (37)	172 (43)	0.4
Female	113 (63)	224 (57)	0.3
Age, years, mean (range)	32 (2–74)	33 (1–74)	0.9
Type of TB			
Smear-positive PTB	89 (49)	177 (45)	0.4
Smear-negative PTB	54 (30)	126 (32)	0.9
EPTB	37 (21)	93 (24)	0.5
Treatment outcomes			
Death			
All TB types	14 (7)	36 (9)	0.8
Smear-positive PTB	8 (9)	12 (7)	0.8
Smear-negative PTB	5 (9)	13 (10)	0.7
EPTB	1 (3)	11 (12)	0.2
Treatment success‡			
All TB types	161 (89)	348 (87)	0.2
Smear-positive PTB	79 (89)	162 (92)	0.6
Smear-negative PTB	47 (87)	107 (85)	0.8
EPTB	35 (95)	79 (85)	0.8
Other outcomes§			
All TB types	5 (3)	12 (3)	0.6
Smear-positive PTB	2 (2)	3 (2)	0.5
Smear-negative PTB	2 (4)	6 (5)	0.9
EPTB	1 (3)	3 (3)	0.8

* Deaths that occurred during the first 2 months of anti-tuberculosis treatment (initial phase) were excluded.
† P value based on χ² test.
‡ Treatment success includes treatment completed with negative smears (cured) and treatment completed with no smears done.
§ Other outcomes includes loss to follow-up ($n = 2$), transfers out to another registration facility and outcome not reported ($n = 7$) and outcomes unknown ($n = 8$).
TB = tuberculosis; ART = antiretroviral treatment; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis.
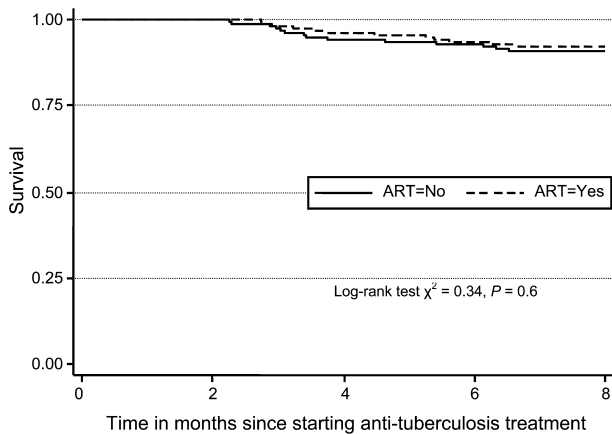
Figure 3 Survival probability in relation to ART during the continuation phase (months 2–8) of anti-tuberculosis treatment, Thyolo, Malawi. HIV = human immunodeficiency virus; TB = tuberculosis; ART = antiretroviral treatment.

did not accept ART (1.2, 95%CI 0.9–1.7). The crude HRs for death comparing those with and without ART was 0.83 (95%CI 0.5–1.5, $P = 0.5$). After adjustment for type of TB, sex and age, this remained non-significant (0.86, 95%CI 0.4–1.6, $P = 0.6$). Figure 3 shows the probability of survival in patients on ART and patients not on ART during the continuation phase of anti-tuberculosis treatment.

DISCUSSION

This study shows that about six of every 10 deaths among HIV-positive TB patients occur very early (within the first 2 months) in the course of anti-tuberculosis treatment, and that ART introduced after this period has no significant impact on case-fatality rates.

There are a number of possible explanations for the limited effect observed with ART in routine settings. First, as the great majority of deaths occurred during the initial phase of anti-tuberculosis treatment and ART is only introduced in the continuation phase, the critical period when most deaths occur is simply missed. Second, it is possible that patients who die in the first 2 months are those with HIV infection and severe immunodeficiency (low CD4 counts). Survivors who start the continuation phase of anti-tuberculosis treatment are therefore those with less severe immunodeficiency (healthy cohort effect), in whom ART is likely to have less impact in reducing case-fatality rates in the presence of both anti-tuberculosis treatment and CPT, as it takes time for ART to result in a significant increase in CD4-lymphocyte counts. Third, acceptance rates of CPT were relatively high, and as this intervention alone has a significant effect in reducing case fatality,[9] it might have reduced the additional effect of ART during the course of anti-tuberculosis treatment. Fourth, we compared case-fatality rates and survival over a relatively short period of anti-tuberculosis treatment. The longer term

survival benefit of ART is well known,[12–14] and in Malawi it has been shown that fewer than 20% of HIV-positive TB patients remain alive 7 years after being diagnosed with TB.[2] Despite our findings in the short term, offering ART to TB patients is therefore likely to have a favourable impact on long-term survival.[15]

The strengths of this study were that a large number of TB patients were studied, deaths were reliably ascertained, the loss to follow-up was low and, as the data come from a programme setting, the findings reflect the operational reality on the ground. There were, however, also a number of limitations. 1) Although there were two cohorts of TB patients, those taking ART were self-selected, and hence the comparison is not between two equal cohorts; a randomised controlled trial design would have been preferred, but this was not ethically possible. 2) Despite the fact that all HIV-positive TB patients are potentially eligible for ART in our setting, only 27% (about 1 in 3) actually took up the offer; there are several possible reasons for this relatively low acceptance rate and these have been discussed previously.[15,16] 3) Potential differences in social or economic status between those who accepted ART and those who did not might have had an influence on case fatality, but we do not have data in this regard. 4) Baseline CD4-lymphocyte counts were not recorded, and we therefore do not know if there were any immunological differences between the groups; however, the proportion of patients by 'type of TB' (likely to be a proxy of immune status) was similar between those who did and those who did not accept ART.

Reducing high early case-fatality rates during anti-tuberculosis treatment in sub-Saharan Africa continues to be a major challenge. There are several potential reasons for early deaths among patients with TB: for example, delayed presentation of patients and thus advanced TB and HIV/AIDS, late diagnosis of TB within health services, life-threatening HIV-related complications such as anaemia and bacteraemia,[17,18] the occurrence of a Herxheimer-type reaction (paradoxical reaction) due to rapid killing of tubercle bacilli by anti-tuberculosis drugs or immune reconstitution.[19] In rural settings such as Thyolo, moderate to severe malnutrition, perhaps by further compromising host immunity and predisposing to life-threatening nutritional deficiencies and superadded infection, adds to the risk of death.[20] More recently, multi- and extremely drug-resistant TB have been shown to be associated with high case fatality in South Africa,[21] and we do not know as yet if this is also a problem in Malawi.

There are a number of possible ways of addressing the problem of high early case fatality. First, increasing community awareness, improving health seeking behaviour linked to HIV/AIDS and TB, and addressing access issues in terms of both diagnosis and treatment might prevent patients from presenting 'too late'. Second, efforts need to be made to reduce diagnostic

and treatment delays linked to smear-negative PTB and EPTB by introducing the recently recommended standardised diagnostic and treatment algorithms.[22] This does not, however, replace the urgent need for access to simpler and more efficient TB diagnostic tools for use in resource-limited settings. Third, identification of bacteraemia in many African hospitals is very difficult because of a lack of access to blood culture facilities, and HIV-positive TB patients might need to be offered an empirical course of broad spectrum antibiotics to treat commonly occurring but potentially lethal infections due to *Streptococcus pneumoniae* and non-typhoidal *Salmonella*.[17,18] Fourth, corticosteroids have been suggested as one way of reducing early deaths due to Herxheimer-type reactions by reducing the toxicity of the disease.[19] Prospective controlled trials have shown a treatment benefit of corticosteroids in TB meningitis and pericardial and pleural disease.[23] However, trials on the use of corticosteroids, particularly in ill HIV-positive TB patients, have yet to be carried out and published, but they might be warranted. Fifth, intensive nutritional rehabilitation and use of micronutrients among malnourished TB patients by improving cell-mediated and humoral immunity might be of benefit. Finally, there is the question of the optimal time to start ART in HIV-positive TB patients. This study clearly identified the first 2 months of TB treatment as the time of greatest mortality. Starting ART earlier, particularly with EFV-based regimens, would seem to be an option that needs serious attention. Its impact on morbidity and mortality and issues related to co-management needs to be studied further in an operational setting. The associated risks might include additive adverse drug reactions, drug-drug interactions and a higher incidence of immune reconstitution disease.[24]

The findings from this study provide ample ground for discussion and most of all the much needed impetus to urgently address the issue of high early case fatality in TB patients through relevant interventions and operational research while waiting for the results of randomised controlled trials.

The results of this study also highlight the urgent need to improve TB-HIV co-management and better collaboration between TB and HIV programmes.

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RÉSUMÉ

CADRE : District de Thyolo, Malawi.

OBJECTIFS : Faire un rapport sur 1) la létalité chez les patients tuberculeux (TB) séropositifs pour le VIH au cours du traitement anti-tuberculeux ; et 2) la question de la réduction de la létalité par la mise en route du traitement antirétroviral (ART) au cours de la phase de continuation du traitement TB.

SCHÉMA : Analyse rétrospective de cohorte.

METHODS : Analyse comparative des résultats du traitement chez les patients TB enregistrés entre janvier et décembre 2004.

RÉSULTATS : Sur 983 nouveaux cas de TB enregistrés ayant bénéficié d'un test VIH, 658 (67%) étaient séropositifs pour le VIH. Au total 132 patients (20%) sont décédés au cours des 8 mois du traitement antituberculeux, parmi lesquels 82 (62%) sont décédés au cours

des 2 premiers mois du traitement en l'absence d'ART (incidence cumulative = 3,0 ; IC95% 2,5–3,6 pour 100 années-personne). La phase de continuation du traitement anti-tuberculeux a été démarrée chez 576 patients TB, dont 180 (31%) ont reçu l'ART. Le taux de létalité par 100 années-personne n'a pas été significativement différent entre les patients sous ART (1,0 ; IC95% 0,6–1,7) et sans ART (1,2 ; IC95% 0,9–1,7 ; risque relatif ajusté 0,86 ; IC95% 0,4–1,6 ; $P = 0.6$).

CONCLUSIONS : L'administration d'ART pendant la phase de continuation du traitement anti-tuberculeux n'a pas un impact significatif sur la réduction de la létalité. Les raisons de ce fait et les mesures possibles pour réduire la létalité élevée dans la phase initiale du traitement TB font l'objet de la discussion.

RESUMEN

MARCO DE REFERENCIA : Distrito de Thyolo, Malawi.

OBJETIVOS : Comunicar sobre 1) la mortalidad de los pacientes con tuberculosis (TB) e infección por el VIH durante el tratamiento antituberculoso ; y 2) el efecto del tratamiento antirretrovírico (ART) durante la fase de continuación del tratamiento antituberculoso en términos de reducción de la mortalidad.

DISEÑO : Estudio retrospectivo de cohortes.

MÉTODOS : Análisis comparativo del desenlace terapéutico de pacientes con TB registrados entre enero y diciembre de 2004.

RESULTADOS : Se registraron 983 casos nuevos de TB, todos recibieron la prueba diagnóstica de la infección por el VIH y en 658 (67%) el resultado fue positivo. Un total de 132 pacientes (20%) falleció durante los 8 meses del tratamiento antituberculoso, de los cuales

82 (62%) en los primeros 2 meses, antes de comenzar la administración del ART (incidencia acumulada 3,0/100 años-persona ; IC95% 2,5–3,6). De los 576 pacientes con TB que comenzaron la fase de consolidación del tratamiento antituberculoso, 180 (31%) iniciaron también el ART. La diferencia de la tasa de mortalidad por 100 años-persona entre los pacientes con ART (1,0 ; IC95% 0,6–1,7) y sin él (1,2 ; IC95% 0,9–1,7) no fue estadísticamente significativa (cociente ajustado de riesgos instantáneos 0,86 ; IC95% 0,4–1,6 ; $P = 0,6$).

CONCLUSIONES : El ART suministrado en la fase de continuación del tratamiento antituberculoso no tuvo un efecto significativo sobre la reducción de la mortalidad. En el artículo se comentan las razones de este resultado y las medidas que podrían reducir la alta tasa de mortalidad durante la fase inicial del tratamiento antituberculoso.