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Review

Tuberculosis associated mortality in a prospective cohort in Sub Saharan Africa: Association with HIV and antiretroviral therapy

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ABSTRACT

OBJECTIVE: Nine out of ten tuberculosis deaths occur in tuberculosis-burdened countries, particularly Sub Saharan Africa. In these setting mortality has not been fully described. We describe the magnitude and pattern of TB mortality in Tanzania.
METHODS: A multicenter prospective cohort study was conducted among HIV infected and uninfected pulmonary tuberculosis patients from time of anti-TB treatment initiation to completion. Patients were censored at the time of treatment completion, or at their last visit for those who did not complete TB treatment. Kaplan-Meier curves were used to estimate time to death; cox proportional hazards model was used to examine risk factors for mortality.
RESULTS: A total of 58 deaths out of 1696 patients (3.4%) occurred, two thirds (n = 39) during the first two months of treatment. Compared to HIV un-infected TB patients, mortality risk for TB/HIV co-infected patients was least when antiretroviral therapy (ART) was initiated after 14 days of anti-TB (RR = 3.55; 95% CI: 1.44, 8.73 $p < 0.0001$) and highest when ART was initiated 90 days or less prior to anti-TB and within the first 14 days of anti-TB therapy (RR = 10; 95% CI: 3.28, 30.54; $p < 0.0001$).
CONCLUSION: Meticulously planned and supervised antiretroviral therapy reduces mortality among TB/HIV patients. Among patients with TB/HIV naïve of ART, withholding ART until the third week of anti-tuberculosis therapy will likely reduce TB mortality in Tanzania. Patients on ART and later develop tuberculosis should be closely monitored.

Contents

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INTRODUCTION

About 1.5 million tuberculosis (TB) deaths occurred worldwide in 2014, with nine of ten of the deaths happening in Sub Saharan Africa (SSA) and South East Asia.[1] Tanzania reported 65,732 TB cases of all forms (smear positive, smear negative and re-treatment) in 2013.[2] About four percent (1048) of newly diagnosed smear positive PTB patients died.[2] HIV co-infection is a major driver of TB in Tanzania[2–4] while multi drug resistance is less frequently encountered.[5,6]

TB and HIV co-infection complicates management of both diseases. Certainly, antiretroviral (ART) has tremendously improved survival of patients with TB/HIV.[7–10] Consequently earlier initiation of ART is recommended among patients with TB/HIV confection.[11] On the other hand, clinicians need to be aware that benefits of initiation of ART at HIV diagnosis presents yet other challenges including increased risk for immune reconstitution inflammatory syndrome (IRIS) among those with sub clinical TB.[12,13] TB/IRIS is a well-recognized phenomenon which occurs within three months (90 days) of initiating ART.[13]

Few studies have reported mortality among TB patients in Eastern SSA.[14,15] As a result, global TB mortality estimates are based on surveys and surveillance systems in developed countries and a few high burden countries.[16] This might not only underestimate the burden of TB mortality but also reflect a poor understanding of the associated risk factors. With the universal HIV "test and treat" policy there is need to disentangle mortality risks relative to timing of ART and anti-TB therapy. We undertook this study to determine the burden and risk factors for TB mortality among HIV infected and uninfected TB patients initiating anti-TB treatment in Dar es Salaam, we also explore mortality risks with respect to ART initiation relative to initiation of anti-TB therapy.

Methodology

Design and Setting

This study was part of a multi-center prospective observational study conducted in Dar es Salaam city, Tanzania between 2010 and 2011, as published previously.[3]

Study population

Eligibility included; age (15 years or above), confirmed pulmonary TB (at least one sputum specimen positive for acid fast bacilli (AFB)), initiating TB therapy in one of the 14 selected study sites. Patients who were previously treated with anti-TB drugs, or who intended to move out of Dar es Salaam before completing TB therapy were excluded. Study clinicians recruited consenting patients consecutively until the desired sample size was attained. Direct observed therapy (DOT) with isoniazid, rifampicin, ethambutol and pyrazinamide was instituted daily according to the national TB treatment policy for six months. According to Tanzanian guidelines, newly HIV diagnosed patients within TB treatment services are offered ART as soon as they tolerated TB drugs, preferably within 2–8 weeks of initiating TB treatment, however, patient with CD4 $<$ 50cells/μL are initiated ART within two weeks of anti-TB.[17]

Study procedures

Data were collected at three time points, day one, at two and five months of TB treatment, coinciding with patient regular clinic appointments as stipulated in the National TB guidelines.[17] On day one, the attending clinicians obtained demographic characteristics from patients, and performed clinical evaluation concurrently with routine care. An additional sputum specimen was collected for culture and anti-TB drug sensitivity testing (DST). After two and five months of TB treatment, sputum specimens were collected and re-examined for AFB and vital status was also established. Patients missing clinic visits were followed by telephone calls or home visits by trackers. Some patients who missed their visits moved to different locations and did not respond to telephone calls, they are reported missing in this report. Heath care trackers or patients' treatment supervisors reported events of death, which were then recorded on patients' files and clinic TB register. Other missing information was collected from HIV database using unique HIV identifier recorded on patients' TB card. The vital registration in the country does not allow for linkage between clinic and death records.

Laboratory tests

The following tests were employed; sputum culture for *M.tb* and drug susceptibility testing (DST) using Mycobacteria Growth Indicator Tube (MGIT) – (Beckton-Dickinson) or Löwenstein Jensen (LJ) medium. HIV infection followed the National HIV screening algorithm.[18] serial testing with DetermineTM HIV-1/2 (Inverness Medical Japan Co. Ltd, Japan) and Uni-GoldTM HIV-1/2 (Trinity Biotech, Wicklow, Ireland). Complete blood count (CBC) was performed using the ACT5 DIFF hematology analyzer according to the instructions of the manufacturer (Beckman Coulter, Miami, Florida).

Data collection, management and analysis

Patients demographic, clinical and laboratory information were recorded in case record forms by the study clinicians and laboratory personnel, respectively. Information on ART use was obtained from the clinic registers. Data were double entered into Epi6 database by trained data clerks. SAS version 9.3 (SAS Institute, Cary, NC) statistical software was used for statistical analysis.

Categorical data were summarized using proportions, and these were compared using the Chi square test. Kaplan-Meier curves were used to estimate the cumulative incidence of death. The associations between various patient characteristics with mortality were examined using the Cox proportional hazards model with time since the initiation of anti-TB therapy as the time scale. Patients were censored at the end of study if they were event free or at their last visit for those who did not complete TB treatment. Relative risks (RRs; hazard ratios), 95% confidence intervals (CIs), and corresponding p values were obtained from the models adjusting for potential confounders. The criterion for significance for all the analyses was a P value $<$0.05 and all p values were two-tailed.

Outcome of interest is all cause mortality, as defined by WHO any death occurring during TB therapy is regarded as TB death.[1] The explanatory variable of interest was HIV and timing of ART relative to initiation of anti-TB therapy as a compound variable

with five categories. **(Category 1)** HIV-uninfected TB patients were the control/reference group. Bearing in mind the risk of TB/IRIS within 3 months of ART, we separated TB/HIV patients on ART before anti-TB therapy into two groups: **(Category 2),** HIV infected on ART more than 90 days before initiating anti-TB, **(Category 3),** HIV infected and ART initiated 90 days or less prior to anti-TB initiation. **Category 3** also include patients who initiated ART within 14 days of initiating anti-TB also; **Category 4** are patients who initiated ART after 14 days of anti-TB therapy; and lastly **category 5 are HIV/TB co-infected patients who did not have** ART throughout the entire duration of their observation.

Other possible confounding variables included in the multivariate analyses (MVA) models were variable with known association with TB mortality or were significantly associated with mortality at $P<0.20$ in univariate analyses. Therefore, multivariate estimates were adjusted for age (15-<30, 30-50, and >50), sex (male vs female), median monthly income in USD (≥100, <100**),** illicit substance use (never, vs current or past),, resistance to INH or rifampicin (no vs yes). The missing indicator method was used for missing data in all categorical covariates.

Ethical considerations

Patients provided written informed consent. Minors assented to participate in the study before guardians/parents signed consent forms on their behalf. The research protocol was approved by Muhimbili University of Health and Allied Sciences (MUHAS) ethical review board (Ref. No. MU/DRP/AEC/Vol.XIII/2008). Hospitals and Municipals management teams granted permits to conduct the study. Patients with multidrug-resistant TB (MDR-TB) were put on second line therapy as soon as result became available. Mono drug resistance was treated on case by case in combination with clinical response and smear conversion results.

RESULTS

During the study period 1805 patients were recruited, of these 109 (6%) were excluded, due to missing; outcome status or survival time (88) or HIV status (10) or age (11). This study reports analysis of a total of 1696 patients who started treatment at the selected facilities. Patients included in this analysis (n = 1696) and those excluded (n = 109) did not differ with respect to age ($p = 0.76$), education ($p = 0.20$), income ($p = 0.41$), hemoglobin ($p = 0.95$), HIV status ($p = 0.55$), ART use ($p = 0.21$) resistance to rifampicin or INH ($p = 0.85$), data not shown here. However, excluded patients were more likely to be males (80% Vs 67%; $p < 0.01$) and have higher proportion using illicit drugs (15% vs 6% $p < 0.01$).

Table 1 provides baseline demographic and clinical characteristics of the study population. The patients were relatively young, 40% aged less than thirty years; two thirds were males. The median monthly income was approximately 100 US dollars (Table 1). Alcohol, cigarette smoking and use of addictive drugs were not uncommon in this study population. Twenty-nine (3.3%) of the patients who had anti-sensitivity test had resistance to either isoniazid or rifampicin. Thirty percent of the patients (514) were infected with HIV, of whom 285 (50%) were not on any ART until end of their follow up. About one in ten of patients (n = 49) with TB/HIV co-infection were on ART more than 90 day before initiation of TB therapy, eight percent (n = 39) initiated ART within 90 before anti-TB commenced or within 14 days after commencement of anti-TB. Majority of those on ART during anti-TB therapy initiated ART after 14 days of anti-TB therapy (n = 141; 27%). (Table 1)

Table 1
Baseline characteristics of Pulmonary TB Patients receiving anti-tuberculosis treatment in Dar es Salaam, Tanzania.

Characteristics	Missing n (%)	N	%
Age (years)	0		
15-29		682	40.21
30-50		868	51.18
>50		146	8.61
Sex	0		
Male		1138	67.10
Female		558	32.90
Income/month (USD)	362 (21.34)		
≥100		746	55.92
<100		588	44.08
Cigarette smoking	24 (1.42)		
Never		1223	73.15
Current or past		449	26.85
Alcohol use	37 (2.18)		
Never		1064	64.14
Current or past		595	35.86
Illicit drug use	56 (3.30)		
Never		1542	94.02
Current or past		98	5.98
HIV infection status			
HIV uninfected	0	1182	69.69
HIV infected		514	30.31
Timing of antiretroviral initiation in respect to initiation of anti-TB therapy			
>90 days prior to anti-TB started	0	49	9.53
90 days prior to anti-TB up to 14 days of starting anti-TB		39	7.89
>14 days post anti-TB initiation		141	27.43
No ART at any time during anti-TB		285	50.19
Anemia[a]	234 (13.80)		
No		202	13.82
Yes		1260	86.18
Isoniazid or rifampicin resistance	816 (48.11)		
No		851	96.70
Yes		29	3.30

[a] Hemoglobin <12 g/dl for women and <13 g/dl for men; ART = Antiretroviral status.

Table 2
Crude mortality pattern in according to HIV infection and antiretroviral status of the patients.

	No of deaths	No at risk	Crude mortality risk	Median time to death in days (IQR)*
TB only	17	1182	1.4	46 (32,62)
TB/HIV; ART >90 days prior to anti-TB	5	49	10.2	79 (33,96)
TB/HIV; ART 90 days prior to anti-TB to 14 days after ART	4	39	10.3	56 (28, 72)
TB/HIV; ART >14 days post anti-TB	7	141	5.0	52 (45,89)
TB/HIV; No ART	25	285	8.8	37 (26,59)
Total	**58**	**1696**	**3.4**	**46 (30,72)**

* IQR = interquartile range.

Table 3
Factors associated with mortality among Pulmonary TB Patients receiving treatment in Dar es Salaam, Tanzania.

	Unadjusted				Adjusted			
	No of deaths	HR	95% CI	P	HR	95% CI		P
HIV infection and ART use				**<0.001**				**<0.001**
HIV uninfected	17/1182	1.00			1.00			
HIV infected; ART >90 days prior to anti-TB therapy	5/49	7.00	2.58	18.96	8.26	2.89	23.64	
HIV infected; ART 90 days prior to anti-TB and within 14 days of anti-TB therapy initiation	4/39	7.55	2.54	22.44	10.00	3.28	30.54	
HIV infected; ART >14 days post anti-TB therapy initiation	7/141	3.43	1.42	8.26	3.55	1.44	8.73	
HIV infected; No ART at any time during anti-TB therapy	25/285	6.34	3.42	11.74	6.46	3.41	12.24	
Isoniazid or rifampicin resistance				**0.01**				**0.02**
No	21/851	1.00			1.00			
Yes	3/29	4.50	1.34	15.10	4.24	1.24	14.48	
Age (years)				**0.08**				**0.60**
15-29	16/682	1.00			1.00			
30-50	36/868	1.76	0.98	3.17	1.11	0.60	2.06	
>50	6/146	1.74	0.68	4.45	1.29	0.49	3.40	
Sex				**0.95**				**0.20**
Male	39/1138	1.00			1.00			
Female	19/558	0.98	0.57	1.70	1.46	0.82	2.62	
Monthly income (USD)				**0.07**				**0.03**
≥ 100	21/746	1.00			1.00			
<100	28/588	1.70	0.97	3.00	1.91	1.07	3.39	
Illicit substance use				**0.09**				**0.09**
Never	48/1542	1.00			1.00			
Current or past	6/98	2.06	0.88	4.82	2.14	0.90	5.12	

Table 2 describes the mortality pattern during the study duration. A total of 58 deaths occurred among the patients with TB, equivalent to a cumulative mortality incidence of 3.4% within six months of follow up. In the worst scenario if all 109 patients excluded in this study are considered dead then the maximum mortality in this cohort would be 9.3%. Patients with TB/HIV co-infection were more likely to die. However, patients who initiated ART therapy before anti TB were had highest mortality while patients who initiated ART after 14 days of anti-TB therapy had lower mortality (5%). Patients exhibited an accelerated mortality during the early phase of TB treatment; the overall median time to death is 46 days. (Table 2)

As shown in Table 3, HIV infection, resistance to INH or rifampicin and low monthly income; were independent mortality predictors. Compared to HIV un-infected TB patients mortality risk was tenfold among TB/HIV co-infected who initiated ART 90 days or less prior to and within the first 14 days of anti-TB therapy. (RR = 10; 95% CI: 3.28, 30.54; $p < 0.0001$) while, patients who initiated ART after 14 days of anti-TB had a threefold mortality risk (RR = 3.55; 95% CI: 1.44, 8.73 $p < 0.0001$). Further examination of categories of TB/HIV co-infected patients is provided in Table 4. Patients who initiated ART more than 90 days prior to anti-TB had median CD4+ 263 cell/μL while those who initiated ART after first 14 days of anti-TB therapy had the lowest CD4 counts 151 cells/μL. Patients who were not on ART during the entire period of observation had relatively higher median CD4+ counts (331 cells/μL) Table 4.

Patient with TB infected with mycobacteria resistant to INH or rifampicin had a fourfold increased mortality risk (RR = 4.24; 95% CI: 1.24, 14.48; $p = 0.02$). Monthly income lower than 100 USD was

Table 4
Comparison of patients with TB/HIV according to CD4 and body mass index (BMI).

	Median CD4 (IQR)	Median BMI (IQR)
HIV infected; ART started more than 90 days before starting anti-TB therapy	263 (181, 422)	18.8 (17.0, 21.5)
HIV infected; ART started 90 days before starting or up to 14 days after starting anti-TB therapy	168 (79, 221)	17.4 (15.4, 19.6)
HIV infected; ART started more than 14 days and up to 180 days after starting anti-TB therapy	151 (69, 220)	18.7 (16.9, 21.2)
HIV infected; not on ART at any time or ART initiated more than 180 days after starting anti-TB therapy	331 (158, 471)	18.1 (16.5, 20.4)

associated with an approximately 91% increased mortality risk (RR = 1.91; 95%CI 1.07, 3.39; P = 0.03) Table 3.

DISCUSSION

This study describes mortality among patients with TB in general, and TB/HIV co-infected patients, who were on the HIV care and treatment programme after scale up of ART services in Tanzania.[14] Of particular note, the composition of our current study population mirrors the most recent reported country's TB population; male predominance, young adults being more affected and almost one third of patients with TB and HIV coinfection.[2] To the best knowledge of the authors, it is the first to report mortality among patients with TB within treatment duration, after wide spread of ART in the country.[14,15]

We observed an overall low cumulative mortality incidence of 3.4% among patients with newly diagnosed open TB during the course of TB treatment. However due to failure to account for 109 patients, the highest mortality possible would be 9.3% if we assume all missing patients had died. We note a precipitous mortality within intensive phase of anti-TB therapy. HIV co-infection, ART as well as resistance to either INHor rifampicin and low income were associated with increased mortality risk in this cohort.

Mortality rate in our current cohort is similar to that reported by national cohort, 4% (1048/24,241) of patients with newly diagnosed smear-positive TB in 2013,[2] and is comparatively low compared with TB-associated mortality rates in high endemic countries (4-18%) (14-18). These differences could be varying degrees in drug resistance as well as co-morbidities such as HIV co-infections, anemia, diabetes mellitus, malignancies and renal failure, among other reasons,[15,19–22] duration of illness as well as well adherence to TB treatment.[23–25] In Tanzania, HIV is main driver of tuberculosis disease.[14,26] Unlike in countries with high burden of MDR-TB, properly administered ART and anti-TB therapy would reduce TB/HIV mortality. Further, adherence to anti-TB therapy is key to a successful treatment program; highly efficient DOTS system in Tanzania that ensure adherence of 96%[27] might contribute to lower mortality in our setting.

Our results do show that TB/HIV co-infection is a spectrum of disease that may not be taken as one entity. HIV was an independent predictor for mortality and ART reduces mortality among patients with HIV and TB co-infection. These findings are in keeping with the findings of a large South African TB program showing a 5 times increased case fatality rate among TB/HIV positive patients compared to HIV-negative patients with TB,[28] and is consistent with the observed benefits of early initiation of ART in decreasing TB disease events[29,30] and deaths.[7–10] Two thirds of the deaths in this cohort occurred during the intensive phase of anti-TB treatment, which is in keeping with the findings of previous studies, being (24-26), and could be due to treatment complications linked to immune reconstitution inflammatory syndrome.[31] Indeed, in our cohort, the highest mortality risk was among patients treated with ART 90 days before anti-TB therapy and within the first 14 days of anti-TB therapy. TB/IRIS is a recognized phenomenon within this period.[13] Drug to drug interaction might have complicated treatment and result in fatal side effect, evaluation of mortality causes would be advantageous to this end. Further evaluation of factors associated with death during the intensive TB treatment phase is essential.

The highest mortality among patients with TB/HIV co-infection occurred among those who initiated ART 90 or less days before anti-TB drugs or within the first 14 days of anti-TB therapy. This category of patients are likely to have had an advanced HIV disease at the time of presentation as demonstrated with their median body mass index (BMI) 17.4 kg/m^2. Secondly, due to their low CD4 + levels (168 cells/μL), these patients may have or had sub-clinical TB, which was unmasked and associated with the recovery of T-cell function.[32–34] Severe immune deficiency has been associated with increased risk of both poor immunological recovery, TB/IRIS and mortality associated with TR/IRIS.[35,36] The other category of patients who have been on ART well in advance of diagnosis and treatment with anti-TB therapy are clearly not well suppressed (CD4+ 268 cells/μL) as shown in the result section. In addition, three out of the five patients in this category had CD4 less than 200 cells/μL. Treatment failure, due to prior ART adherence or drug resistance is speculated as cause of mortality in this group. Data on drug resistance pattern and viral load could assist in this matter. On the other hand, postponing ART among TB/HIV+ individuals, even when CD4 level were relatively high (331 cells/μL), was detrimental for the category five patients, i.e TB+/HIV+ patients who did not have ART until they either died or completed the anti-TB drug treatment regiment. Together our results and previous reports[7,10] lends support that concomitant ART and anti-TB treatment significantly reduced mortality when properly instituted. Among ART naïve TB patients, withholding ART for the first until after first two week of TB therapy would be prudent.

The main weakness of this study is the exclusion of 109 (6%) of the study participants due to missing outcomes or exposure of interest. However we found no substantial difference between excluded and included patients except for sex and illicit drug use. It is likely that mortality estimates, presented in this report, are underestimation since both male sex and illicit drug use are known factors associated with poor TB outcome. Should this be the case the true mortality would between 3.4% and 9.3% at its highest. Nonetheless our study has several strengths. First, it was conducted in the region with highest TB notifications in Tanzania. Second, mortality and HIV rates in our population mirrors that of the national cohort[2] and in addition to reporting mortality were able to examine associated risk factors among patients with TB and HIV co-infection or without makes our study very unique. We hope this strength makes it possible to generalizable findings from this study into working policies in Tanzania and other countries within SSA with similar TB dynamics.

In conclusion, despite low overall mortality among open TB cases in Dar es Salaam, most of the deaths occur during the early during anti-tuberculosis treatment. Delay of ART initiation until third week of anti-TB therapy is recommended for ART naïve TB/HIV co-infected patients. This study therefore supports the WHO recommendation for "test and treat" HIV infected individuals despite CD4+ count while careful monitoring their immunological recovery.

Conflict of Interest

None.

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