High mortality among tuberculosis patients on treatment in Nigeria: a retrospective cohort study

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Abstract

Background: Tuberculosis (TB) remains a leading cause of death in much of sub-Saharan Africa despite available effective treatment. Prompt initiation of TB treatment and access to antiretroviral therapy (ART) remains vital to the success of TB control. We assessed time to mortality after treatment onset using data from a large treatment centre in Nigeria.

Methods: We analysed a retrospective cohort of TB patients that commenced treatment between January 2010 and December 2014 in Aminu Kano Teaching Hospital. We estimated mortality rates per person-months at risk (pm). Cox proportional hazards model was used to determine risk factors for mortality.

Results: Among 1,424 patients with a median age of 36.6 years, 237 patients (16.6%) died after commencing TB treatment giving a mortality rate of 3.68 per 100 pm of treatment in this cohort. Most deaths occurred soon after treatment onset with a mortality rate of 37.6 per 100 pm in the 1st week of treatment. Risk factors for death were being HIV-positive but not on anti-retroviral treatment (ART) (aHR 1.39(1.04–1.85)), residence outside the city (aHR 3.18(2.28–4.45)), previous TB treatment (aHR 3.48(2.54–4.77)), no microbiological confirmation (aHR 4.96(2.69–9.17)), having both pulmonary and extra-pulmonary TB (aHR 1.45(1.03–2.02), and referral from a non-programme linked clinic/centre (aHR 3.02(2.01–4.53)).

Conclusions: We attribute early deaths in this relatively young cohort to delay in diagnosis and treatment of TB, inadequate treatment of drug-resistant TB, and poor ART access. Considerable expansion and improvement in quality of diagnosis and treatment services for TB and HIV are needed to achieve the sustainable development goal of reducing TB deaths by 95% by 2035.

Keywords: Tuberculosis, Mortality, Risk factors, Adults, Nigeria, Retrospective cohort
HIV-positive TB death rate (44 per 100,000) [5, 10]. Reports indicate that TB prevalence and deaths have been underestimated and the 2015 TB mortality rates in Nigeria may even be higher than the 1990 estimates [5, 10, 11]. TB deaths after treatment has been initiated remain high and occur within the first few months of treatment [12–16]. Burden of drug-resistant TB is high in Nigeria, with an estimated 29,000 (16 per 100,000) new cases in 2015 [17]. Treatment and microscopy services are provided free in 5,728 treatment centres and 1,765 microscopy sites across the country, though coverage is disproportionately higher in urban areas [18]. Among an estimated 3.4 million people living with HIV in Nigeria, less than 800,000 are on antiretroviral therapy [19].

Although there are studies describing TB treatment outcomes in Nigeria, [20–27] there is paucity of information on mortality in HIV negative and HIV positive cohorts. Additionally, the Boko Haram insurgency in the North-eastern part of the country since 2009, has led to a population of internally displaced persons from communities often with no access to healthcare who may be at a higher risk of disease and death. For instance, a survey of multi-drug resistant TB in North-east states affected by this conflict showed a prevalence of up to 35.7% in most affected state (Borno) [28]. Consequently, in this study we evaluate mortality and factors associated with time to death in a large treatment centre.

Methods
Study setting
Kano state in Northern Nigeria is one of the most populous in the country with over 12 million residents and has the third highest number of TB cases notified to the National TB programme [18]. Aminu Kano Teaching Hospital (AKTH), is a large federal government run university hospital, established in 1988, which caters for populations from Kano and neighbouring states. It has a turnover of about 400,000 out-patients and over 19,000 in-patient admissions reported in 2013.

The AKTH TB-DOTS clinic provides TB screening, diagnosis and treatment services to both children and adults. Patients enrolled in the DOTS service come from a variety of sources and include suspected and confirmed TB cases, referred from other clinics within the hospital and other hospitals including private health facilities. Other services provided are HIV counselling and testing, contact tracing, and provision of isoniazid prophylaxis to children in close contact with active TB cases.

Patients diagnosed with TB receive treatment based on the existing national guidelines. Prior to 2014, category 1 treatment (CAT 1) was given to new patients which comprised 2 months of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) followed by 6 months of EH (up to 2012) or 4 months of RH (from 2013); and CAT 2 regimen for re-treatment patients, comprised 2 months of RHZE and Streptomycin (S), 1 month of RHZE and 5 months of RHE. However, from 2014, the guideline recommended the same regimen 2RHZE and 4RH for both new and re-treatment cases with the exception of central nervous system TB which requires longer treatment. Treatment is also occasionally extended if final investigations such as sputum smear or X-ray are not available. Guidelines for investigation (including a GeneXpert machine in the TB lab), management and referral of multi-drug resistant TB became available from 2014.

TB Treatment is observed by the health worker in the clinic once weekly during the intensive phase, and once monthly in the continuation phase. Daily supervision is undertaken by a designated guardian.

TB/HIV services are co-located and integrated. Patients with unknown HIV status at enrolment are routinely counselled and screened for HIV. Patients with HIV are followed up in the same clinic. Anti-retroviral treatment (ART) is based on existing National guidelines, and eligibility is based largely on clinical staging of HIV disease and CD4 count. However, for co-infected patients that are newly diagnosed with HIV or those diagnosed with TB before commencement of ART, guidelines recommend commencement of ART irrespective of HIV disease stage or CD4 count. Though only ART status at beginning of TB treatment is usually recorded in the TB registers.

Study design data sources
Patients 15 years and above enrolled in the clinic for treatment from January 2010 to December 2014 were included in the cohort. Data were collected from a combination of clinic-based sources - patient treatment cards and TB treatment registers. A treatment card is opened for each patient upon registration in the clinic on treatment commencement, and each patient is assigned a unique identification number. Patient and treatment information including treatment outcome are recorded in both.

Information available included: age, gender, residence, sputum smear status, site of disease, HIV status at treatment onset, previous TB treatment, ART status at treatment onset, date of treatment onset, treatment outcome, and date of censor. Age was categorised into the following bands: 15–24, 25–34, 35–44, 45–54 and ≥65 years. HIV/ART status was determined from HIV and ART status at treatment onset and grouped in to HIV-negative, HIV-positive on ART, HIV-positive not on ART and Unknown HIV status. Site of disease was classified in to pulmonary (disease affecting lungs only), extra-pulmonary (disease affecting organs other than the lung) and both (disease affecting the lungs and any other organ) and
patients were also group into bacteriologically-confirmed (sputum-smear or culture confirmed) or clinically diagnosed (smear-negative and physician-confirmed through other means). Residential status includes Kano residents (primarily residing within Kano metropolis) and outside Kano.

Subjects entered the cohort on the day treatment commenced and remained in the cohort until any one of the following occurred; i) end of treatment ii) death before end of treatment iii) loss to follow-up from default or unknown treatment outcome status. The time between treatment onset and death was the primary outcome which included all causes based on the WHO 2013 definitions for treatment outcome [29].

Statistical analysis
We described numbers and proportions for categorical variables and means (with standard deviation, SD) or medians (with interquartile range) for quantitative measures for all patients. To inform the analyses, follow-up time was time from treatment commencement to date of censor which was expanded into person-months (pm) at risk. Mortality rates over time per 100 pm at risk were estimated and plotted by time since treatment commencement. Covariate stratum-specific mortality rates were also determined. Kaplan-Meier analysis and log-rank tests were used to compare survival curves stratified by previous TB treatment and HIV/ART status. To estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI), Cox proportional hazards modelling was fitted and used to determine risk factors for mortality. Covariates that were associated with each outcome measure (adjusting for age) with \( p < 0.2 \) were included in the multivariable analysis. Variables were included in models if they resulted in >10% change-in-estimate or a change in log likelihood with \( p \)-value < 0.2. Variables that resulted in change in coefficient standard errors of already included variables by >20% were assumed to be collinear and excluded from the model.

All analyses were done using Stata 14 (Stata Corp, College Station, TX, USA).

Results
Among 1,484 eligible patients, 1,424 (96.0%) were followed-up for analysis (Fig. 1). More than half of the patients were men (56.9%) and the mean age was 36.6 ± SD14.4 years. The study cohort characteristics and treatment outcomes are shown in Table 1. About a quarter (342) had reported a history of being previously treated for TB. Out of the 568 (40%) participants that were HIV positive at treatment onset, only 90 (15.8%) were on ART. Nearly 22% of deaths occurred in HIV positive individuals, however, HIV-positive patients who were on ART at treatment onset had the lowest crude mortality rates (1.52:95% CI – 0.72–3.19).

Kaplan-Meier survival curves show differences in survival between sub-groups (Fig. 2). When stratified by previous TB treatment, survival was lower for patients with previous TB treatment (\( p < 0.0001 \)). When stratified by HIV/ART status, survival was lowest among HIV-infected but not on ART (\( p = 0.001 \)). Analysis of mortality from time since treatment onset (Table 4) showed that most deaths occurred within the 1st week of treatment, with a crude mortality rate of 37.6 (95% CI – 31.4–44.9) per 100 person-months of treatment. Death rates rapidly declined over treatment period.

Multivariable analysis
After adjusting for age, sex, and other covariates, risk of death was still markedly higher in the 1st week of treatment and declined steadily over treatment period.
Multivariable analysis (Table 5) showed that, compared to patients aged 15–24 years, those between 45 and 54 years had over twice the risk of death (aHR 2.37; 95% CI – (1.44–3.92)). Risk factors for death were being HIV-positive but not on ART (aHR 1.39; (1.04–1.85)), residence outside the city (aHR 3.18 (2.28–4.45)), previous TB treatment (aHR 3.48 (2.54–4.77)), no microbiological confirmation (aHR 4.96 (2.69–9.17)), having both pulmonary and extra-pulmonary TB (aHR 1.45 (1.03–2.02)), and referral from a non-programme linked clinic/centre (aHR 3.02 (2.01–4.53)). Calendar period also had a strong effect on risk of death in both univariable and multivariable models, such that patients enrolled at the later periods (2013 and 2014) had lower risks of death compared to those enrolled earlier (2010–2011).

### Table 1 Description of study cohort

| Variable          | Frequency | Percent |
|-------------------|-----------|---------|
| Age group (years) |           |         |
| 15–24             | 260       | 19.5    |
| 25–34             | 396       | 30.0    |
| 35–44             | 335       | 25.1    |
| 45–54             | 185       | 13.9    |
| 55–64             | 87        | 6.5     |
| > 65              | 72        | 5.4     |
| Missing           | 93        |         |
| Gender            |           |         |
| Male              | 81        | 56.9    |
| Female            | 614       | 43.1    |
| Residence         |           |         |
| Within Kano       | 1,014     | 71.2    |
| Outside Kano      | 410       | 28.8    |
| Referral facility |           |         |
| DOTS-linked facility | 624     | 45.7    |
| Non DOTS-linked facility | 740 | 54.3 |
| Missing           | 60        |         |
| TB diagnosis      |           |         |
| Bacteriological   | 468       | 32.9    |
| Clinical          | 956       | 67.1    |
| TB site           |           |         |
| Pulmonary         | 936       | 67.4    |
| Extra-pulmonary   | 229       | 16.5    |
| Both              | 223       | 16.1    |
| Missing           | 36        |         |
| HIV/ART status    |           |         |
| HIV-              | 683       | 48.0    |
| HIV+ on ART       | 90        | 6.3     |
| HIV+ not on ART   | 478       | 33.6    |
| Unknown HIV status| 173       | 12.2    |
| Previous TB treatment |       |         |
| No                | 1,082     | 76.0    |
| Yes               | 342       | 24.0    |
| Year of diagnosis |           |         |
| 2010–2011         | 413       | 29.0    |
| 2012              | 321       | 22.5    |
| 2013              | 450       | 31.6    |
| 2014              | 240       | 16.9    |
| Treatment outcome |           |         |
| Successful        | 745       | 52.3    |
| Lost to follow-up | 366       | 25.7    |
| Died              | 237       | 16.6    |
| Failed            | 33        | 2.3     |
| Transferred-out   | 43        | 3.0     |

### Table 2 Characteristics of 60 patients excluded from analysis

| Variable          | Freq (%) |
|-------------------|----------|
| N                 | 60       |
| Age group (years) |           |
| 15–24             | 15 (25.0)|
| 25–34             | 13 (21.7)|
| 35–44             | 16 (26.7)|
| 45–54             | 7 (11.7) |
| 55–64             | 6 (10.0) |
| > 65              | 3 (5.0)  |
| Gender            |           |
| Female            | 27 (45.0)|
| Male              | 33 (55.0)|
| Residence         |           |
| Within Kano       | 42 (70.0)|
| Outside Kano      | 18 (30.0)|
| TB diagnosis      |           |
| Bacteriological   | 2 (3.3)  |
| Clinical          | 58 (96.7)|
| TB site           |           |
| Pulmonary         | 29 (82.9)|
| Extra-pulmonary   | 5 (14.3) |
| Both              | 1 (2.9)  |
| HIV/ART status    |           |
| HIV-              | 25 (41.7)|
| HIV+ on ART       | 0 (0.0)  |
| HIV+ not on ART   | 17 (28.3)|
| Unknown HIV status| 8 (13.3) |
| Previous TB treatment |       |
| No                | 56 (93.3)|
| Yes               | 4 (6.7)  |
This study has identified a high case fatality rate among a cohort of TB patients on treatment in Nigeria. The majority of deaths in this young cohort occur shortly after treatment onset. We have compared mortality across different risk factors. Factors associated with mortality included HIV infection without ART, residence outside the city, extrapulmonary and pulmonary disease, prior TB treatment, the absence of microbiological confirmation of TB and periods proximal to treatment onset.

Deaths among patients on TB treatment reported from different regions of Nigeria are much lower (<10%) than figures observed in this study (16.6%), except for some that involved rural health facilities (13.1%) [30], tertiary health facility (14.8%) [31], elderly (12.3%) [32] and MDR-TB (15%) [33]. However, following the Boko Haram insurgency, Kano state is home to a large
number displaced and vulnerable populations that may also have accounted for high mortality. Case fatality reported from other sub-Saharan Africa ranged between 4 and 9% in HIV-uninfected, lower than our finding and 16–35% among HIV-infected, comparable to our observed 20% in this cohort [34]. Case fatality during treatment from outside Africa were lower, other than in some Asian countries where the cohorts are much older. For example, in a population-wide studies in Taipei Taiwan, case fatality was 17.8% for all adults (mean age 65 years) [35] and 25% in another study of elderly persons aged 65 or more years (mean age 80 years) [36], compared to a mean age of 36.6 years in our study. In Singapore, a nationwide study found a case fatality of only 11.9%, even though their population was much older and HIV prevalence was very low (0.6%) [37]. In India, case fatality was also much lower (6%), even though the age distribution was similar to ours (mean = 36 years) [13] possibly due to a lower HIV prevalence and better access to care. In South Africa, where burden of HIV and drug-resistant TB are high, case fatality among platinum miners was 12.2% [12].

About half of the deaths occurred within the 1st week of treatment, and over three-quarters within the first month. This is higher than what was obtained in Malawi hospital based study, where 40% of deaths occurred within the 1st month of treatment [38]. Early deaths or clinical worsening after treatment onset have been associated with disease progression from additional co-morbid illnesses, drug toxicity and poor adherence [14, 15, 39–43]. The high death rates observed so soon after treatment onset may be attributable to delays in TB diagnosis and/or initiation of anti-TB and antiretroviral treatment; severe disease; and undiagnosed drug-resistant TB or co-morbidities.

Delays could be in health care-seeking, diagnosis, treatment or a combination of them all [44, 45]. In a review of 45 studies across 17 Asian countries, consultation with a public hospital was associated with lower risk of treatment delay [46]. A systematic review of diagnosis and treatment delays in India showed that use of Government health care providers was a risk factor for patient-related delays while use of private health care providers were associated with health system delays [45]. Reports from sub-Saharan Africa indicate that delay was associated with prior consultation of traditional healers, private or rural public facilities [47–49]. Although sputum smear microscopy is provided to patients free by the National TB programme, additional investigations for diagnosis of TB such as radiographs and histology, and other co-morbidities such as diabetes have to be paid for by the patient and may also contribute to delays and disease progression [50–53]. In a study of platinum miners in South Africa, although high death rates were also observed in the first month of treatment irrespective of HIV/ART status and previous treatment, death rates were still lower than present study. However, the miners were covered by a free comprehensive medical care including HIV care, reducing the likelihood of diagnostic and treatment delays and possibly improving early likelihood of detecting and managing co-existing conditions. The majority of treatment services in Nigeria are provided by lower cadre health workers at the primary care level, with limited capacity for diagnosis of sputum-
negative and extra-pulmonary TB. This may have wors-ened diagnostic delay. Although the literature suggests that access to public hospitals lowers the risk of delay, a large tertiary hospital may represent a different experience within the TB programme due to the extreme of spectrum of disease. It is therefore possible that early deaths in this cohort are reflective of more severe disease

Decrease in mortality rates we observed over calendar period could be reflective of changes in treatment pol-icies which include switch from 8 months (2RHZE/6EH) to 6 months (2RHZE/4RH) treatment regimen; use of same regimen for re-treatment cases; revision of CD4 cell count threshold for ART initiation; and introduction of drug-susceptibility testing. This decrease in mortality could also be as a result of maturity of the DOTS programme within the hospital and country at large, as such delays in diagnosis and treatment may have reduced over time; and detection and management of drug-resistant TB may have improved.

Residing outside Kano city was also associated with in-creased mortality. Distance from health centre, coexisting untreated or undiagnosed co-morbid chronic illnesses, un-availability of health/treatment centres at place of residence, poor access to ART, and shortage or interrupted supply of drugs can also contribute to deaths [46, 54, 55]. Additionally, rural areas have fewer TB treatment and ART services further decreasing access. Delayed treatment initiation has been shown to be associated with increased periods of infectiousness, disease severity, treatment failure and mortal-ity [56]. Poor treatment outcomes may reflect socio-economic conditions including poor awareness and rural residence which influence access to overall health care [45, 46, 57]. Poor health access may also indicate unrecog-nised co-morbidities, which can increase risk of death.

About a quarter of the cases were on TB re-treatment, therefore, it is possible that previous failed treatment and drug-resistant TB contributed to the poor outcomes [58, 59]. There were no guidelines or protocol for man-agement of drug resistant TB in the country during the initial period covered by this study, and empirical treat-ment with 1st line anti-tuberculous agents was recom-mended. A study in AKTH, Kano reported MDR-TB prevalence of 10.6% [60]. Applying this figure to our cohort implies that inadequate treatment of drug-resistant TB may have increased risk of mortality.

Consistent with previous reports, higher mortality risk was observed among HIV-infected patients not on ART, while those who were already on ART when TB treat-ment was started did not have any excess mortality risk [61]. Though some studies have shown higher mortality risk among TB/HIV co-infected soon after initiating ART, use of ART for at least 6 months has been shown to reduce mortality [62, 63]. Integrated ART at time of TB treatment initiation has been shown to reduce mor-tality [61, 64–66]. The integration of TB-HIV services in this centre with active clinical screening for TB, could have resulted in early diagnosis and timely TB treatment among patients already enrolled in the HIV clinic [67]. Our findings indicate that only 15.8% of HIV-infected were on ART at the time of TB treatment. This figure however does not take into account patients who may receive ART during TB treatment, as well as duration of ART treatment, CD4 count and HIV disease stage be-cause these were not updated in the clinic registers. This may have resulted in under-estimation of the effect of ART. The observed effect of HIV on risk of death over time was lower than in other studies across sub-Saharan Africa [12, 20, 65, 68].

Misdiagnosis of other diseases, especially among HIV-infected persons as smear-negative or extrapulmonary TB may partly explain the high mortality rates observed in clinically-diagnosed patients [44, 69, 70]. For instance, a study in South Africa found a strong association between certainty of diagnosis and mortality [12]. Though studies have shown that autopsy-confirmed causes of deaths attributed to TB are lower than those clinically diagnosed, autopsies performed on patients whose deaths had been attributed to other causes have also shown a substantial proportion of missed TB cases [12, 65, 71, 72].

### Table 4 Mortality from time since treatment commencement

| Time since treatment onset | Number of deaths | Proportionate mortality (%) | Person-months | Mortality rate per 100 pm (95%CI) | Crude HR (95% CI) | Adjusted HR (95% CI)* |
|---------------------------|------------------|-----------------------------|---------------|----------------------------------|-------------------|-----------------------|
| 1st week                  | 120              | 50·6                        | 319·3         | 37·6 (31·4—44·9)                | 1                 | 1                     |
| 2nd week                  | 32               | 13·5                        | 265·9         | 12·0 (8·5—17·0)                | 0·34 (0·23—0·53)  | 0·49 (0·31—0·78)      |
| 3rd week                  | 23               | 9·7                         | 253·2         | 9·1 (6·0—13·7)                 | 0·31 (0·19—0·49)  | 0·57 (0·34—0·96)      |
| 4th week                  | 13               | 5·5                         | 245·9         | 5·3 (3·1—9·1)                  | 0·18 (0·10—0·32)  | 0·31 (0·17—0·60)      |
| 2nd month                 | 21               | 8·9                         | 936·8         | 2·2 (1·5—3·4)                  | 0·08 (0·05—0·12)  | 0·18 (0·10—0·30)      |
| 3rd month                 | 12               | 5·1                         | 885·2         | 1·4 (0·8—2·4)                  | 0·04 (0·02—0·08)  | 0·13 (0·07—0·26)      |
| 4th month+                | 16               | 6·7                         | 3530·0        | 0·5 (0·3—0·7)                  | 0·01 (0·06—0·02)  | 0·05 (0·03—0·08)      |

*Adjusted for age, gender, residence, calendar period, HIV/ART status, previous TB treatment, TB site, referring source, and diagnosis
The major strengths of this study include the availability of information allowing time to event analysis which is usually lacking from programme-level data. Findings should be interpreted in light of a number of limitations. First, some deaths in this study may not be TB deaths and would be more appropriately grouped as deaths during TB treatment. Thus, we may have over-estimated TB mortality. Conversely, we might have underestimated the overall mortality in this population as many deaths will likely occur before contact with the health system or the TB programme. Second, although, patients or their next of kin are usually contacted on reasons for default, a number of patients who had been lost to follow-up may have died at home [73]. This may have further underestimated mortality. Additionally, death rates among the 60 patients excluded may be different, and

| Variable                     | Crude HR (95% CI) | P value | Adjusted HR (95% CI) | p value |
|------------------------------|-------------------|---------|----------------------|---------|
| Age group (years)            |                   |         |                      |         |
| 15–24                        | 1                 |         | 1                    |         |
| 25–34                        | 1·62 (1·01–2·58)  | 1·18 (0·73–1·89) |
| 35–44                        | 1·57 (0·97–2·53)  | 1·07 (0·65–1·77) |
| 45–54                        | 3·79 (2·37–6·07)  | 2·37 (1·44–3·92) |
| 55–64                        | 1·85 (0·96–3·57)  | 1·43 (0·73–2·80) |
| >65                          | 3·60 (2·03–6·38)  | <0·001  | 1·64 (0·90–2·99)    | 0·001   |
| Gender                       |                   |         |                      |         |
| Female                       | 1                 | 0·06    | 1                    |         |
| Male                         | 1·28 (0·99–1·67)  | 0·94 (0·71–1·25) |
| Residence                    |                   |         |                      |         |
| Within Kano                  | 1                 |         | 1                    |         |
| Outside Kano                 | 6·74 (5·13–8·86)  | <0·001  | 3·18 (2·28–4·45)    | <0·001  |
| Referral facility            |                   |         |                      |         |
| DOTS-linked facility         | 1                 |         | 1                    |         |
| Non DOTS-linked facility     | 5·85 (4·07–8·42)  | <0·001  | 3·02 (2·01–4·53)    | <0·001  |
| TB diagnosis                 |                   |         |                      |         |
| Bacteriological              | 1                 |         | 1                    |         |
| Clinical                     | 10·72 (6·12–18·76)| <0·001  | 4·96 (2·69–9·17)    | <0·001  |
| TB site                      |                   |         |                      |         |
| Pulmonary                    | 1                 |         | 1                    |         |
| Extra-pulmonary              | 1·46 (1·00–2·14)  | 1·08 (0·72–1·63) |
| Both                         | 4·86 (3·68–6·42)  | <0·001  | 1·45 (1·03–2·02)    | 0·09    |
| HIV/ART status               |                   |         |                      |         |
| HIV-                         | 1                 |         | 1                    |         |
| HIV+ on ART                  | 0·43 (0·21–0·92)  | 1·51 (0·60–3·78) |
| HIV+ not on ART              | 1·42 (1·09–1·86)  | 1·39 (1·04–1·85) |
| Unknown HIV status           | 0·54 (0·32–0·93)  | <0·001  | 0·77 (0·44–1·33)    | 0·05    |
| Previous TB treatment        |                   |         |                      |         |
| No                           | 1                 |         | 1                    |         |
| Yes                          | 6·43 (4·95–8·35)  | <0·001  | 3·48 (2·54–4·77)    | <0·001  |
| Year of diagnosis            |                   |         |                      |         |
| 2010–2011                    | 1                 |         | 1                    |         |
| 2012                         | 1·17 (0·86–1·60)  | 1·10 (0·78–1·56) |
| 2013                         | 0·48 (0·36–0·68)  | 0·47 (0·32–0·69) |
| 2014                         | 0·45 (0·29–0·70)  | <0·001  | 0·45 (0·27–0·74)    | <0·001  |

*Adjusted for all variables in the table
this may have resulted in either under- or over-estimation of mortality in this cohort. Third, our findings are from a single treatment centre, therefore, generalisability may be somewhat limited. However, we believe that our findings represent the experience of many treatment centres within tertiary-level health facilities in the country which tend to see more of severe disease. Fourth, due to the retrospective nature of this study, we could not account for the effect of other co-morbidities such as diabetes on the risk of death as this information is not recorded in the clinic registers.

Conclusion

The high TB mortality observed in a tertiary health centre may reflect marked delays in diagnosis; poor access to care among vulnerable populations; and unrecognised co-existing morbidities. Data from our high-TB burden low-resource setting illustrates the difficulties related to diagnosis and treatment of smear negative and extrapulmonary TB, low ART coverage, poor access to comprehensive healthcare and the limitations of passive case-finding. TB programmes in Africa have focused on passively detecting and treating smear-positive disease despite evidence of increasing burden of smear-negative TB including HIV-related TB [34]. To attain the End TB strategy’s target of zero deaths and suffering from TB, aggressive strategies need to be employed to actively find and promptly treat all cases; and make TB care more comprehensive in order to recognise and adequately manage other co-morbidities. Wider access to ART among HIV infected persons will also be critical to the TB and HIV control effort. Considering the limitations of the historical nature of this study, future prospective studies should aim to differentiate deaths due to TB from coincidental deaths from other causes to adequately define TB burden; and identify co-morbidities and their contribution to risk of death among patients with TB.

Abbreviations

AKTH: Aminu Kano Teaching Hospital; ART: Anti-retroviral treatment; CI: Confidence intervals; DOTS: Directly observed treatment short-course; HIV: Human immuno-deficiency virus; HR: Hazard ratio; MDR: Multi-drug resistant; TB: Tuberculosis; WHO: World Health Organization

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Availability of data and materials

Data supporting findings are available in Tables. However, additional data cannot be made publicly available as we do not have permission to share data containing HIV-status of participants.

Authors’ contributions

ALA and IA contributed to study design. MG, ISA, AMJ, MMB, AUG, and MMB were involved in data acquisition. ALA did the statistical analysis of the data with input from IA. ALA and IA did the initial data interpretation. ALA wrote the first draft of the manuscript. ALA, IA, MG, ISA, AMJ, MMB, AUG and BMB revised the manuscript critically for important intellectual content. All authors approved the final draft of the manuscript. All authors read and approved the final manuscript.

Competing interests

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Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethical approval was obtained from the Research Ethics Committee of AKTH (NHREC/21/08/2008/AKTH/EC/1562). As this was a retrospective study and data were obtained from records of patients, patient consent was not required by the ethics committee. The committee provided permission to use the patient clinic records for this study.

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