

High prevalence of tuberculosis among adults with fever admitted at a tertiary hospital in north-western Tanzania

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Abstract: Tuberculosis is a leading cause of death in developing countries where HIV is endemic. This hospital based study was done to estimate the magnitude of pulmonary and extra-pulmonary tuberculosis and to determine predictors of tuberculosis among febrile adults admitted at Bugando Medical Centre (BMC), Mwanza, Tanzania. A total of 346 adults febrile patients admitted in medical wards were studied. Sputum for AFB microscopy and chest X-rays was used to diagnose tuberculosis. Clinical features were collected using standardized data collection tool. HIV testing and CD4 counts were determined. Data were analyzed using STATA version 11 software. Of 346 febrile adults patients 116 (33.5%) were diagnosed to have tuberculosis; of which 79 (68.1%) and 37 (31.9%) had pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis, respectively. Smear negative PTB were more common in HIV positive than in HIV negative patients (50% vs. 18.5%, $p=0.007$). Extra-pulmonary tuberculosis was more common in HIV positive patients than pulmonary tuberculosis (86.4% vs. 13.6%), $p=0.0001$). On multivariate logistic regression analysis the predictors of tuberculosis were; age above 35 years (OR =2.38, $p=0.007$), cardinal symptoms (OR=37, $p<0.0001$), pleural effusion (OR=24, $p=0.0001$), and HIV status (OR =3.2, $p=0.0001$). Of 79 patients with PTB, 48 (60.7%) were AFB smear positive and 31 (39.3%) were AFB smear negative. HIV patients with smear negative tuberculosis had significantly lower CD4 count than HIV patients with smear positive tuberculosis (63.5 cells/ μ l versus 111.5 cells/ μ l) [Mann-Whitney test $p=0.0431$]. No different in mortality was observed between patients with TB and those without TB admitted in BMC medical wards (28.5% vs. 23.0%, $p= 0.1318$). Tuberculosis is the commonest cause of fever among adults patients admitted at BMC and is predicted by age above 35 years, positive HIV status, cardinal PTB symptoms, and pleural effusion. Routinely TB screening is highly recommended among adults with fever, cough, night sweating and wasting in countries where HIV is endemic.

Keywords: Tuberculosis, HIV/AIDS, fever, adults, Tanzania

Introduction

More than 11 million adults living with HIV/AIDS are also infected with tuberculosis (WHO 2007). In some sub-Saharan countries, one-third of patients with tuberculosis (TB) have HIV (WHO 2007). TB affects more than half of those infected with HIV (WHO 2007). In 2009 a total of 60,060 new TB cases (AFB+, AFB- and extrapulmonary) were reported in Tanzania. Out of

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these new cases 41.5% were smear positive. Of the total new TB cases 88% had known HIV status and 37% were found to be HIV positive (NTLP, 2009). The overlapping between tuberculosis and HIV epidemics has had a devastating impact on morbidity, mortality, and control, rendering tuberculosis the leading killer of HIV-positive people. More than 29% of global burden of TB is in Africa with 34% related deaths (WHO 2007). TB in adults causes fever, often lasting weeks, retrosternal discomfort or pain due to mediastinal lymph node enlargement and pleuritic pain (Bruchfeld *et al* 2003). Symptoms vary from a gradual insidious onset with anorexia, weight loss, fatigue and low-grade fever to acute onset with fever, night sweats, productive cough and dyspnoea (Nyirenda *et al* 2006). In Malawi among adults patient admitted with fever mycobacterium was the commonest isolate from the blood (Lewis *et al* 2003). Other study in Malawi found the prevalence of *Mycobacterium tuberculosis* blood stream infection in HIV endemic areas to range from 9-12% (Archibald *et al* 2000). In Tanzania 20.2% of HIV adult patients were found to be infected with TB compared to 1.3% of HIV negative (Lennox *et al* 1998). Diagnosis of TB in developing countries where HIV is endemic brings more challenges (Shea *et al.*, 2009).

Little is known about the magnitude of TB among febrile adults admitted in hospitals in Tanzania. This cross-sectional prospective study was conducted to determine the magnitude, predictors and case fatality rate of tuberculosis among febrile adults admitted at tertiary hospital in Northern-Western Tanzania.

Materials and Methods

Study design and sample size

A prospective cross-sectional hospital based study was conducted at Bugando Medical Centre (BMC) in Mwanza region in north-western Tanzania from June 2011 to December 2011. BMC is a tertiary hospital and University teaching hospital serving approximately 13 million people in the North-Western zone of Tanzania.

Sample size was estimated using Kish and Leslie formula (Kish, 1965) the proportion of 20% (Lennox *et al* 1998) was used in the formula; this is the prevalence of TB among HIV patients in Tanzania.

Patients' recruitment and laboratory procedures

All adults patients above 18 years with fever admitted in medical wards were enrolled into the study. Patients were asked to sign informed consent and were counselled for HIV testing. Sputum for acid fast bacilli (AFB) and blood for HIV testing and CD4 estimation were obtained as previously described (WHO 1998; Enarson *et al.*, 2000; IUATLD 2000; Bakari *et al* 2008).

Patient clinical history and physical examination findings were collected using standardized data collection tool. Chest X-ray was done in all patients suspected to have tuberculosis. HIV testing was done as per Tanzania National algorithm and CD4+ counts determined using FACS Calibur (BD UK).

Tuberculosis diagnosis

Smear positive tuberculosis was diagnosed if a patient had positive spot and early morning AFB smear or one positive smear with positive chest-X-ray findings (Bakari *et al.*, 2008). Smear negative tuberculosis were diagnosed if a patient had three negative smear (spot, early morning, spot), and failed to respond on 14 days antibiotic treatment, but improved when anti-TB is started. Extra pulmonary tuberculosis was defined as previously described (http://www.stoptb.org/wg/gli/assets/documents/TBcasedefinitions_20110506b.pdf).

Quality control

Adequate mucoid or mucopurulent sputum specimens were collected from TB suspects. The sputum specimens were transported immediately to the BMC laboratory and examined for the presence of AFB by experienced laboratory technician based on the standard operative procedures (Kubi & Kent, 1985). All the slides were checked again by the three investigators who are expert in the subject and no discrepancy was observed. All chest -x-ray were read by experienced radiologist in the hospital. All patients were seen after 2 weeks and assessed for clinical improvement.

Data analysis

Data collected were entered into a computer using Epidata version 3.1 (CDC, Atlanta, USA) and analyzed using STATA version 11 (College Station, Texas, USA). Data were summarized in form of proportions and frequent tables for categorical variables. To assess the significance of their distribution chi-square test was used. For non parametric continuous variables, we used medians to summarize them and Mann-Whitney test to test for the significance of the difference of the medians between two groups. To determine predictors of tuberculosis, logistic regression analysis was performed, starting with univariate then followed by multivariate logistic regression analysis with the dichotomous outcome being tuberculosis or no tuberculosis.

Odds ratio with 95% confidence interval was calculated to test for strength of association between predictor variables and tuberculosis. Predictors with p-value less than 0.05 on univariate analysis were then fitted into the multivariate regression analysis and predictors with a p-value of less than 0.05 were considered to have significant strength of association.

In the present study cough, night sweating and wasting were considered as cardinal symptoms of tuberculosis and were combined together and tested if they independently predict tuberculosis in multivariate analysis. We further analyzed the strength of HIV on predicting the two types of tuberculosis. We used multinomial logistic regression with the outcome being no tuberculosis, pulmonary tuberculosis and extra pulmonary tuberculosis. Based on patients with no tuberculosis as the reference group, relative risk ratio with 95% confidence interval was calculated to test for strength of association between HIV and tuberculosis type.

Ethical consideration

Ethical clearance and approval was obtained from a joint Catholic University of Health and Allied Sciences and Bugando Medical Centre Research and Publications Ethics Review Board. Written informed consent was obtained from each patient. If patient was unable to provide consent, written consent was obtained from their legal guardians.

Results

Demographic and other characteristics

Over the study period 1,552 patients were admitted to the medical wards at BMC and were screened for eligibility. A total of 417 (26.9%) met inclusion criteria of whom 346 (83%) were enrolled into the study. The median age was 35 (inter quartile range [IQR] 25-48) years and 179 (51.7%) were male. The median temperature was 38.5 with IQR of 38-39 °C. A total of 156 (45.1%) of the participants had HIV infection; of these 112 (71.8%) had WHO stage four. The median CD4 count among patients with HIV infection was 78 cells/ μ l.

Magnitude and predictors of Tuberculosis

Of 346 adult febrile patients 116 (33.5%) were confirmed to have tuberculosis; of which 79 (68.1%) and 37 (31.9%) had pulmonary tuberculosis and extra-pulmonary tuberculosis respectively. Of 79 patients with PTB, 48 (60.7%) were AFB smear positive and 31 (39.3%) were AFB smear negative. All 37 patients with extra-pulmonary tuberculosis had pleural effusion.

Table 1: Univariate analysis of predictors of TB among febrile adult patients

| Variable (N) | Response | Positive TB (N =116) | Odd ratio | 95% CI | P value |
|-------------------------|----------------------|----------------------|-----------|-------------|---------|
| <i>Age</i> | ≤35 year (179) | | | | |
| | >35 years (167) | 71 (42.5%) | 2.2 | 1.395-3.475 | 0.001 |
| <i>Sex</i> | Male (179) | 59 (32.9%) | 1 | | |
| | Female (167) | 57 (34.1%) | 1.05 | 0.674-1.64 | 0.818 |
| <i>Chronic Cough</i> | Absent (154) | 1 (0.65%) | 1 | | |
| | Present (192) | 115(59.9%) | 228 | 31.3-1667 | <0.0001 |
| <i>Night sweat</i> | Absent (299) | 81 (27.0%) | 1 | | |
| | Present (47) | 35 (74.5%) | 7.8 | 3.88-15.86 | <0.0001 |
| <i>Wasting</i> | Absent(254) | 56 (22.0%) | 1 | | |
| | Present(92) | 60 (65.2%) | 6.6 | 3.93-11.16 | <0.0001 |
| <i>Pleural effusion</i> | Absent (289) | 65 (22.5%) | 1 | | |
| | Present (57) | 51 (89.5%) | 29.3 | 12-71.31 | <0.0001 |
| <i>HIV status</i> | Negative(190) | 32 (16.8%) | 1 | | |
| | Positive(156) | 84 (53.9%) | 5.8 | 3.5-9.43 | <0.0001 |
| <i>WBC</i> | 4000-11000 (123) | 42 (34.2%) | 1 | | |
| | ≤4000/ μ l (74) | 39 (52.7%) | 2.14 | 1.19-3.87 | 0.011 |
| | >4000/ μ l (149) | 35 (23.5%) | 0.59 | 0.34-1.00 | 0.053 |
| <i>Anaemia</i> | ≥10g/dl (109) | 24 (22.0%) | 1 | | |
| | <10g/dl (237) | 92 (38.8%) | 2.24 | 1.33-3.79 | 0.002 |

WBC= white blood cells

On univariate logistic regression analysis night sweat, cough, wasting, positive HIV status, pleural effusion and anaemia were found to predict tuberculosis (Table 1). On multivariate logistic regression analysis the predictors of tuberculosis were; age above 35 years (OR =2.38, p=0.007), cardinal symptoms (OR=37, p=<0.0001), pleural effusion (OR=24, p=0.0001), and HIV status (OR =3.2, p=0.0001) (Table 2).

Table 2: Multivariate logistic regression analysis of predictors of tuberculosis among febrile adults

| Variable | Odds ratio | 95% CI | P value |
|-------------------|------------|---------------|---------|
| Age >35 years | 2.38377 | 1.2658-4.489 | 0.007 |
| Sex | 1.49688 | 0.8011-2.796 | 0.206 |
| Cardinal symptoms | 37.3454 | 7.695-181.243 | <0.0001 |
| Pleural effusion | 24.35281 | 9.297-63.789 | <0.0001 |
| HIV status | 3.2313 | 1.676-6.2289 | <0.0001 |
| Anaemia | 0.9612 | 0.4692-1.9693 | 0.914 |

HIV status and tuberculosis

Of 48 patients with smear positive TB, 22 (45.8%) were HIV positive and 26 (54.2%) were HIV negative. Smear negative PTB were more common in HIV positive than in HIV negative patients (83.9% vs. 16.1%, $p=0.007$) (Table 3). When compared to patients without tuberculosis as a reference group, HIV patients were much more likely to have extra pulmonary tuberculosis (RRR 14.0 [95% CI 5.3 - 37.5], $p<0.001$) than having pulmonary tuberculosis (RRR 4.2 [95% CI 2.5 - 7.3], $p<0.001$) (Figure 1). Though HIV predicts tuberculosis, HIV positive serostatus predicts more extra-pulmonary tuberculosis than it does for pulmonary tuberculosis.

The median CD4 counts of HIV patients with smear positive tuberculosis was 111.5 cells/ μ l compared to 63.5cells/ μ l of HIV patients with smear negative tuberculosis (Mann-Whitney test $p=0.0431$). HIV patients with smear negative tuberculosis had significantly lower CD4 count than HIV patients with smear positive tuberculosis.

Table 3: HIV status in relation to smear positive and smear negative pulmonary tuberculosis

| Variable | Pulmonary Tuberculosis | | Total |
|--------------|------------------------|----------------|-----------|
| | Smear positive | Smear negative | |
| HIV status | | | |
| Negative | 22 (81.5%) | 5 (18.5%) | 27 |
| Positive | 26 (50.0%) | 26 (50.0%) | 52 |
| Total | 48 | 31 | 79 |

Chi square 7.3876, $p=0.007$

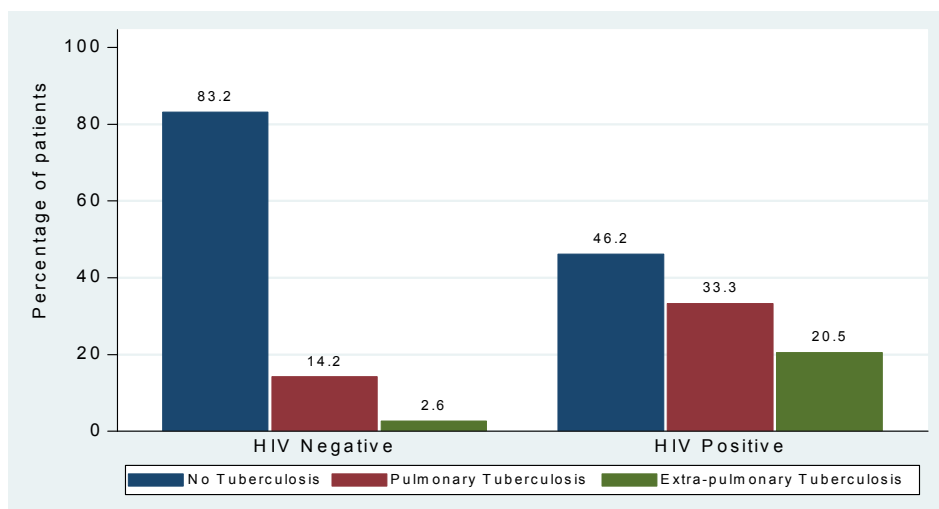


Figure 1: HIV status in relation to type of tuberculosis

HIV positive serostatus predicts more extra-pulmonary tuberculosis than it does for pulmonary tuberculosis. RRR 4.2 [95% CI 2.5 - 7.3] versus 14.0 [95% CI 5.3 - 37.5] all differences observed were statistically significant p-value <0.001.

Discussion

In this study, we have confirmed the high prevalence of tuberculosis in North-western Tanzania among HIV febrile adults. Overall the prevalence of tuberculosis observed in this study agrees with that of other studies in Africa (Corbett *et al.*, 2003; Dagnara *et al.*, 2011). Among TB patients 72% were co-infected with HIV. There have been several studies of the prevalence of HIV in TB patients in different parts of Africa ranges from 6.1% in Nigeria to 57.1% in Ethiopia (Anteyi *et al.*, 1996; Bruchfeld *et al.*, 2002). The prevalence of HIV in TB patients observed in this study is higher than 57.1% reported previously in the same area (Range *et al.*, 2007) and National TB and HIV co-infection of 37% (NTLP, 2009); this could be explained by the fact that this was a tertiary hospital based study.

Majority of HIV patients in our study were in WHO stage 4, this could be contributed by poor health seeking behaviour in developing countries. As reported previously patients with smear positive tuberculosis had higher median CD4+ count than HIV patients with smear negative tuberculosis (Rawat *et al.*, 2008; Sameer *et al.*, 2011; Mbwana *et al.*, 2011). HIV infected smear positive patient tend to secrete significant fewer organisms per ml than HIV negative patient (Long *et al.*, 1991). Our study has confirmed that smear negativity increases as immunosuppression increases (Shea *et al* 2009; Sameer *et al.*, 2011).

Various risk factors have been assessed in relation to tuberculosis in present study. Patient's risk factors associated with increased risk of tuberculosis includes chronic cough, wasting, advanced age, HIV status, Diabetes Mellitus, Malnutrition etc (Lewis *et al* 2003, David *et al* 2004). In the present study as in others studies (Bruchfeld *et al.*, 2003; Mtei *et al.*, 2005) factors found to predict tuberculosis on univariate logistic regression analysis were age above 35 years, cough more than 2 weeks, night sweats, severe wasting, present of pleural effusion, positive HIV status and anaemia. Independent risk factors found to predict tuberculosis on multivariate logistic regression analysis were cardinal symptoms of tuberculosis (chronic cough, night sweating and wasting); the risk of tuberculosis in patients with these three symptoms was more than 10 times compared to patient without these symptoms. Other factors found to predict tuberculosis on multivariate analysis were positive HIV status, presence of pleural effusion and age above 35 years. Clinicians should know these factors so that they can have high index of suspicion of tuberculosis diagnosis in patients presenting with these factors. In the present study HIV has been a statistically significant predict extra-pulmonary tuberculosis than it does for pulmonary tuberculosis. Previous studies have reported that extra-pulmonary disease is more common in HIV infected patients (Harries *et al.*, 1998).

The case fatality rate observed was 28.4%; this seems to be higher than previously reported in Tanzania (van den Broek *et al.*, 1998; Mtei *et al* 2005; Range *et al.*, 2007). This could be explained by the fact that majority of our patients with tuberculosis were HIV infected and WHO stage 4 with the evidence of severe immunosuppression based on CD4+ counts (Kiertiburanakul *et al.*, 2012).

The magnitude of tuberculosis in this cohort might be low due to the limitation of this study which was failure to perform sputum and blood culture for *Mycobacterium tuberculosis complex spp.*

In conclusion, sputum smear is still an important diagnostic tool among HIV patients with CD4 count more than 111.5cells/ μ l. Other techniques like routine culture, GeneXpert are urgently needed in our setting so that TB control can be assured and sustained. Strategies such as creating public awareness and the involvement of the private health sector, traditional practitioners and religious institutions in HIV and TB control should be emphasized in order to improve health seeking behaviour among HIV patients in developing countries.

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