

Original Research Article

Coinfection and Clinical manifestations of tuberculosis in human immunodeficiency

Abstract

Background: Tuberculosis is a disease with protean manifestations. The clinical presentation of tuberculosis can mimic several diseases and can be a diagnostic problem even in endemic areas. Virulence and dose of the infecting mycobacterium, the immune status of the host, the organ systems(s) involved, all influence the clinical manifestations of tuberculosis.

Aim: This study was aimed assessing clinical manifestations of tuberculosis HIV sero-positive and sero-negative patients in Mombasa Kenya.

Study design: Hospital and laboratory based cross-sectional study was carried between May 2011 and November 2013 in Coast General Referral hospital, Tudor, Port-Reitz, Mlaleo, Likoni and Mikandani districts and Sub-districts hospitals.

Methodology: Tuberculosis was diagnosed following standard clinical bacteriological and radiological procedures. Sputa from 500 tuberculosis suspects underwent mycobacteriologic evaluation using Ziel-Nelsen smear microscopy, Lowenstein and Jensen and BACTEC MGIT 960 culturing. Consenting participants were screened for HIV infection by enzyme -linked immunosorbent assay. Data collected from group were compared using univariate and multivariate analysis. The level of significance was set at $p < 0.05$ and for each statistically significant, odds ratios and confidence interval were computed

Results: A total of 210/500 (42%) of the tuberculosis suspects had mycobacterial disease and 78/210 (37.1%) were HIV co-infected. Most presenting symptoms in TB patients with or without HIV was cough 50%, constitutional symptoms 42.3%, fever 29.5% and weight loss 31.4%.and night sweats (90.9%). Regarding clinical signs, pallor 50.4%, night sweats 35.2% and respiratory signs 16.7 % were common and significantly associated with HIV -positive serology. Oral thrush (OR=11.04; 95%CI: 3.01-17.20), Gastro intestinal symptoms (OR=8.97; 95% CI: 3.45-23.41) and constitutional symptoms (OR=7.17; 95% CI: 2.24-15.2) were independent predictors of HIV-positive serology. Majority of the patients with TB-HIV co-infection had CD4+T cell count < 200 cells/mm³ accompanied by night sweats.

Conclusion: Co-infection with HIV was very high in patients with TB. The presence of chronic cough more than one month, night sweats, fever and pallor may assist in identify TB patients with HIV infection. Physicians should be aware of this pattern of presentation and the atypical findings on investigation for early diagnosis and treatment.

Key words: Mombasa Kenya, Clinical manifestations; Tuberculosis; HIV; CD4+T cells

1. INTRODUCTION

Tuberculosis is a communicable disease resulting from infection with *Mycobacterium tuberculosis* whose principal reservoir is man and also, but infrequently with other mycobacterium belonging to the *Mycobacterium tuberculosis* complex [1]. In 1993, the world organization (WHO) declared TB a global emergency [2]. It is estimated that between years 2009-2025 nearly one billion people will be newly infected, 200 million people will get TB and 40 million are likely to die from it if control programs do not improve [3].

43 Tuberculosis is a disease of the poor and under privileged. With improved socio-economic
 44 conditions and availability of effective drugs, spread of TB infection has been effectively
 45 controlled in many parts of the world [4]. In industrialized countries this disease is generally
 46 associated with identified high risk groups such as the elderly, immigrants from TB high
 47 prevalence areas, the homeless, drug and alcohol addicts [5, 6, 7, 8].

48 The spread of the human immunodeficiency virus (HIV) has also contributed dramatically
 49 to the re-emergence of TB infection. HIV infection is recognized as a powerful risk factor for
 50 the development of active and often lethal TB and for the reactivation of latent TB infection
 51 to active disease [9, 10]. The HIV infection affects cell mediated immunity and individuals
 52 infected with *Mycobacterium tuberculosis* are at risk of developing active disease after being
 53 infected with HIV [11, 12]. According to WHO about a third of the 40 million people with
 54 HIV/AIDS are co-infected with *Mycobacterium tuberculosis* [21]. In a population, the
 55 lifetime risk of developing active TB once infected in absence of HIV infection is about 10%
 56 [13]. However, it increases tenfold in HIV infected individuals and this has resulted in a large
 57 increase in the number of TB cases [14]. The proportion of smear-negative pulmonary TB
 58 (PTB) and extra-pulmonary TB (EPTB) is higher among HIV co-infected TB patients [15]

59 Kenya ranks 13th on the list of 22 high burden tuberculosis countries in the world [16]. Kenya
 60 had more than 162,000 new TB cases and an incidence rate of 180 new sputum smear
 61 positive cases per 100,000 populations. World Health Organization estimates around 5000
 62 cases of multidrug-resistant (MDR-TB) in Kenya in 2009. In Mombasa county, tuberculosis
 63 and HIV co-infection ranks first among the ten most common disease morbidity and
 64 mortality and accounts for 47% of the patients [17]. There were 600 people in every 100,000
 65 in Mombasa county suffering from multi- drug resistant tuberculosis and 14,750 newly
 66 diagnosed tuberculosis patients in 2009. The county is contributing 28.4% of all cases of
 67 tuberculosis in country. The increased burden of the disease has been attributed to poor

68 housing, high population and poverty.

69 Clinical features of HIV/AIDS and tuberculosis are difficult to separate since both diseases
70 present wasting and persistent fever and this makes the clinical diagnosis difficult in many
71 cases. Human immunodeficiency virus (HIV) infection and the acquired immunodeficiency
72 syndrome (AIDS) have a profound impact on the clinical presentation of tuberculosis.
73 Clinical presentation of tuberculosis in patients with HIV infection depends on the severity of
74 immuno-suppression [18]. In patients with earlier stages of HIV disease, the clinical
75 presentation of tuberculosis tends to be similar to that observed in persons without HIV
76 infection. Pulmonary disease is most common often with focal infiltrates and cavities. When
77 the immuno-suppression is more marked (CD4 count $<200\text{ml}^3$), the features of tuberculosis
78 are a typical with a much greater frequency of extra-pulmonary involvement, especially of
79 the lymph nodes [19]. Few studies in Kenya have focused on the prevalence of tuberculosis
80 but there are no studies done on tuberculosis- HIV co-infection and clinical outcomes. This
81 study was carried out to assess the clinical features of TB in HIV sero-positive and sero-
82 negative TB patients at the chest clinics in Mombasa Kenya.

83 **2. MATERIALS AND METHODS**

84 **2.1 Study area**

85 The study was conducted in Mombasa County which has a population of 1,031,266 by the
86 year 2012. The population is steadily growing due to rural-urban migration and immigration
87 from unstable countries. The total area Mombasa is 109 Km^2 with about 60% of the people
88 living overcrowded informal settlements in the form of shelters. Residents are of mixed
89 ethnicity and are engaged in low-income generating activities, mainly informal sector and
90 small trading. The County has rapid population growth and is characterized by low socio-
91 economic indicator. This creates huge demands on health facilities and inability to keep pace
92 with the environment, continued economic prosperity, public health and quality of life of
93 residents. Tuberculosis and HIVAIDS are the leading causes of deaths in the area

94 representing 50%.

95 **2.2 Study site**

96 The study was done at done at Ganjoni clinic, Coast provincial General hospital (CPGH),
97 Mlaleo Health and Mikindani Health Centers, Likoni, Portreizi and Tudor district hospitals.
98 These hospitals were selected because they serve populations at high risk for TB due to high
99 HIV prevalence or social-cultural practices that favour TB transmission. These hospitals like
100 all others at their levels have chest clinics where TB patients obtain health care respectively.

101 **2.3 Study design**

102 This was hospital and laboratory based descriptive cross-sectional study carried out between
103 May 2011 to
104 November 2013. It was aimed at assessing the clinical features of TB in HIV-seropositive
105 and sero-negative TB patients.

106 **2.3.1 Inclusion and exclusion criteria**

107 All adult patients 18 years and above suspected of having TB and resident in Mombasa
108 County for at least six (6) months, not on anti-TB chemotherapy and consented to participate
109 in the study were recruited. Tuberculosis suspects who were below 18 years, not lived in
110 Mombasa County for the last six (6 months), unwilling to participate in the study and not
111 meeting the above inclusion criteria were excluded.

112 **2.3.2 Sampling frame**

113 Mombasa County was purposively sampled because of high cases of TB and HIV co-
114 infection. The sampling frame consisted of all the public health facilities within the study
115 area. After the selection of the study sites, each was allocated a proportionate number of
116 study subjects based on the level of health care delivery system and the average client
117 attendance in the past one month before embarking on the study. To minimize bias in
118 selecting study subjects, consecutive sampling was used hence every alternate TB suspect
119 who satisfied the inclusion criteria was selected for the study. Patients were suspected of
120 having TB if they had cough of more than two weeks and not responding to antibiotic
121 treatment.

2.4 Collection of demographic data

Counselling and collection of demographic data were done by clinicians/nurses running the adult TB clinics. A structured and pre-tested questionnaires were used to obtain the demographic data. The data collected included age, gender and HIV status.

2.4.1 Collection of sputum

A specialist medical doctor working in the TB clinic performed the necessary clinical and diagnostic work. Diagnostic was made based on the combined evaluation of clinical, radiological and laboratory features. Three sputum specimens (spot, early morning, spot) were collected from 500 TB suspects under the supervision of trained and competent medical staff. The patients were advised to rinse their mouth twice with water before producing the specimen and this helped to remove food and any contaminating bacteria in the mouth. They were instructed to take two breaths, coughed vigorously and expectorated the material in into the sterile 50ml blue cap screw-capped bottle. This process allowed sputum to be produced from deep in the lungs. The TB suspects were asked to hold the sputum container close to the lips and spit into it gently after a productive cough. The safety for research assistants and healthcare workers during collection and handling of sputum specimens was ensured by observing the WHO guideline.

2.4.2 Collection of blood samples and HIV screening

HIV counseling and testing was done for two hundred and ten (210) TB patients who consented. Test was also done according to manufacturer's instruction. About 5ml of venous blood was collected from each patient and delivered into vacutainer Brand STERILE interior ethylene diaminetetra-acetic acid (EDTA) tubes. Blood samples were tested for HIV antibodies according to the Kenyan national testing algorithm for voluntary counseling and testing. Testing for HIV infection was done by screening serum/plasma by using Determine HIV1/2 (Abott laboratories, Japan co. LTD), Capillus HIV1/2 (The Trinity Biotech, Ireland) and Unigold H1/2 rapid test kits. Positives were confirmed with the enzyme linked immunosorbent assay. Patients were informed of the results of the HIV serology test after

149 appropriate post-test counseling.

150 **2.4.3 CD4+T cell determination**

151 The CD4 count was done by cytoflow method whereby the CD4+ cells were stained with
152 fluorochrome and when they become energized through the laser beam, the CD4 cells were
153 scattered, and with the help of the photomultiplier tube (PMT) they were displayed as
154 numbers or as histograms, and the result was read. When 50µl of EDTA blood was dispensed
155 into a Partec test tube, 10µl of CD4 antibody was added, mixed and incubated in the dark for
156 10 to 15 min. After incubation, 800µl of diluted buffer was added and vortexed. The mixture
157 was then passed via the suction pipe and the result was obtained as histograms on computer
158 read out system.

159 **2.4.4 Microscopic examinations and isolation of *Mycobacterium tuberculosis***

160 Sputum smears were examined for acid-fast bacilli (AFB) after staining following ZN
161 method. The degree of ZN smear positivity was quantified as 1+ for 10-100 AFBs per 100
162 fields, 2+ for 1-10 AFBs per field (50 fields) and 3+ for >10 AFBs per field (20 fields). For
163 less than 10 AFBs per 100 fields, the exact number of AFBs was indicated. A suspect was
164 considered to be ZN smear positive if at least one specimen was positive. Using sterile 1ml
165 disposable pipette, 0.5ml of the sediment (sputum) obtained after centrifuging was inoculated on two
166 Lowenstein Jensen (LJ) slopes/ or MGIT, one with glycerol (0.75%) and one without glycerol, but
167 supplemented with 0.5% pyruvate. The caps were labelled with lab serial number of the specimen and named as
168 1 and 2. All Lowenstein-Jensen media slopes were incubated at 37°C. The slopes were examined weekly for any
169 visible growth and negative culture tubes discarded after 8 weeks.

170 **2.4.5 Radiological Examination**

171
172 Chest X-Ray (CXR) was taken for all patients irrespective for their HIV status. For
173 tuberculosis patients, the X-Ray was taken before commencing anti-TB drugs. Chest X-Rays
174 were taken in anterior-posterior view and read by the Radiologist. The X-Ray was reported as
175 unilateral/bilateral infiltration with/without cavities, infiltration with hilar lymph node
176 enlargement and unilateral/bilateral pleural effusion. The radiological findings were used

together with clinical information such as chronic cough for more than two weeks, weight loss and chronic fever to make diagnosis of smear/culture negative pulmonary tuberculosis. For the smear/culture positive pulmonary cases, chest X-Ray were not considered in making the diagnosis.

2.5 Data management and analysis

Demographic data were confidentially obtained from the TB suspects by clinicians / nurses running the chest clinics. Results of ZN smear microscopy, culture, and HIV tests were confidentially sent to the respective clinicians / nurses. Provisions of these data were made available to the clinicians/ nurses for the purpose of managing the patients. Data was recorded on questionnaires, register books, ELISA reader print-outs and species evaluation sheets. The data was coded, entered into MS Excel 8.0 and processed using a statistical package for social sciences (SPSS) version 16.5 software for windows. The chi-squared (χ^2) test was used to compare categorical data and logistics regression to avoid the confounder effect and to calculate risk ratio. Odds ratio (OR) and 95% interval (CI) were used to measure the strength of an association. *p* values of <0.05 were considered statistically significant.

2.5.1 Ethical issues

The proposal for this study was approved by Kenyatta University Ethical Review Committee (No PKU018/115). It was approved by the ministry of education, Science and Technology (MOEST). Clearance was also obtained from respective district health authorities and hospital administrations. The purpose of the study was explained participants in English, Kiswahili or local language before consent was sought. The study was conducted in accordance with the declaration of Helsinki. Code numbers rather than names were used to identify candidates in order to maintain confidentiality. The study did not expose candidates to any unusual risks as competent hospital staff obtained sputum and blood specimens from candidates using standard procedures.

3. RESULTS

3.1 Socio-demographic Characteristics of the Sample Population

A total of five hundred (500) participants suspected of having TB were enrolled into the study, 45.8% (229) were males and 54.2% (271) females. The majority (43.2%) of the participants were in the age 25-34 age-group, followed by those in the 35-44 (24.4%), 45-54 (9.8), 18-24 (19.2%) and 55+ (3.4%) age categories respectively. Most respondents (53.2%) had attained secondary education, 31.8% college level, 14.6% primary and 0.4% no formal education. Most respondents were self-employed (29.2%), 25% jobless, 24.2% Government employees, 9.4% others, 6.6% house wife and 4.8% engage in farming (Table 1). The calculated overall TB prevalence in tuberculosis suspects included in the study was 42.0% (210/500) and was higher in females (45.9%) than males (38.7%) which was statistically significant ($\chi^2=3.391$, $df=1$; $p<0.001$). Tuberculosis and HIV co-infection in the population was 39.7% (78/210). There was significant difference between the TB-HIV co-infection rate and age ($\chi^2=18.395$, $df=4$; $p<0.001$). Analysis of body mass index (BMI) indicated that 70% of the patients had a BMI of $<18.5 \text{ kg/m}^2$. This was more pronounced and frequent among HIV-positive TB patients as compared to HIV negative ones. Severe malnutrition ($\text{BMI}<15.9 \text{ kg/m}^2$), moderate malnutrition ($\text{BMI}=16-16.9 \text{ kg/m}^2$) and mild malnutrition ($\text{BMI}=17.18-5 \text{ kg/m}^2$) were observed in 18.4%, 14.5% and 23.2% of patients respectively. Tuberculosis patients had statistically significant higher CD4+T cell counts ($474.5 \pm 198.8 \text{ cells/mm}^3$) than TB-HIV co-infection patients ($265.1 \pm 158.4 \text{ cells/mm}^3$). Out of 200 patients who had productive sputum, 88.1% (185/210) were found to be positive for AFB. Among these, 25.6% (20/78) were HIV-seropositive 74.5% (58/78) were HIV-negative TB patients. The sputum smear positivity did not show statistically significant association with HIV sero-status ($\chi^2=1.077$; $df=1$; $p>0.05$). The lungs were the most common site of the disease in both HIV-positive and HIV-negative patients. The most common extrapulmonary involvements were lymph nodes and pleura. PTB and EPTBM were diagnosed in 96.2% (202/210) and

230 3.8% (8/210) of the patients respectively.

231 **Table 1: Socio-demographic Characteristics of the TB suspects (n=500)**

Characteristic	Female (n=229)	Male (n=271)	Total (n=500)
Age in Years			
18 – 24	44 (19.2%)	52 (19.2%)	96 (19.2%)
25 – 34	101 (44.1%)	115 (42.4%)	216 (43.2%)
35 – 44	53 (23.1%)	69 (25.5%)	122 (24.4%)
45 – 54	21 (9.2%)	28 (10.3%)	49 (9.8%)
55 +	10 (4.4%)	7 (2.6%)	17 (3.4%)
Mean age	32.84 ± 9.90	32.75 ± 9.64	32.79±9.75
Level of Education			
No Education	1 (0.4%)	1 (0.4%)	2 (0.4%)
Primary	39 (17.0%)	34 (12.6%)	73 (14.6%)
Secondary	112 (48.9%)	154 (56.8%)	266 (53.2%)
College	77 (33.6%)	82 (30.3%)	159(31.8%)
Marital Status			
Unmarried	89 (38.9%)	103 (38.0%)	192 (38.4%)
Married	122 (53.3%)	159 (58.7%)	281 (56.2%)
Divorced	2 (0.9%)	4 (1.5%)	6 (1.2%)
Widowed	16 (7.0%)	5 (1.9%)	21 (4.2%)
Employer			
Jobless	59 (25.8%)	66 (24.4%)	125 (25.0%)
Government	55 (24.0%)	66 (24.4%)	121 (24.2%)
Self Employed	79 (34.5%)	67 (24.7%)	146 (29.2%)
Farmer	15 (6.6%)	9 (3.3%)	24 (4.8%)
House wife	6 (2.6%)	27 (10.0%)	33 (6.6%)
Student	2 (0.9%)	2 (0.7%)	4 (0.8%)
Others*	13 (5.7%)	34 (12.6%)	47 (9.4%)

232 *Other occupations include daily labourers, commercial sex workers and house hold servants

233
234 **3.2 Clinical symptoms of tuberculosis in HIV positive and negative patients**

235 Table 2 shows clinical symptoms and physical findings of the patients by HIV serostatus.The

236 common clinical symptoms cough 105 (50%), constitutional symptoms like fatigue, malaise

237 and anorexia 89 (42.3%), fever 83 (39.5%) and weight loss 66 (31.4%). Breathlessness 39

238 (18.6%), Hemoptysis 35 (16.7%), symptoms of MI 20 (9.5%) and headache 10 (4.8%). In

239 relation to HIV-status, the following symptoms were predictors of TB-HIV co-infection.

240 Hemoptysis 3.8% (OR=0.14; 95% CI: 0.012-4.13; p=0.001), breathlessness 26.9%

241 (OR=2.33;95%CI: 1.12-3.01 p=0.017), constitutional symptoms 70.5% (OR=7.17; 95% CI:

242 2.24-15.2; p=0.001), significant weight loss 44.9% (OR=2.65; 95% CI: 1.23-5.65;

243 p=0.001)and gastro-intestinal symptoms (GI) 6.4% (OR=8.97; 95% CI: 3.45-23.41;

244 p=0.018). Patients with gastrointestinal symptoms (GI) were 8.9 times more likely to have

HIV than those without infection with GI symptoms. Irrespective of HIV sero-status, most patients had fever, breathlessness, constitutional symptoms and weight loss.

Table 2: Clinical symptoms of Tuberculosis in HIV positive and negative patients (n=210)

Symptoms	TB+/HIV+ (N=78)	TB+/HIV- (n=132)	Total	Significance test (χ^2)	OR (HIV+)
Cough	10 (12.8%)	95 (72.0%)	105	68.61, p=0.001	0.06*
Hemoptysis	3 (3.8%)	32 (24.2%)	35	13.20, p=0.001	0.14*
Breathlessness	21(26.9%)	18 (13.6%)	39	5.72, p=0.017	2.33*
Fever	28 (35.9%)	55 (41.7%)	83	0.68, p=0.409	0.78
Constitutional symptoms	55 (70.5%)	34 (25.8%)	89	41.71, p=0.001	7.17
Significant weight loss	35 (44.9%)	31(23.5%)	66	10.406,p=0.001	2.65*
Headache	3 (3.8%)	7 (5.3%)	10	0.229, p=0.632	0.71
Symptoms of MI	7 (9.0%)	13 (9.9%)	20	0.026,p=0.873	1.09
Neck swelling	1 (1.3%)	6 (4.5%)	7	0.645, p=0.422	0.42
GI symptoms	5 (6.4%)	5 (2.3%)	8	5.644, p=0.018	8.97*

OR=Odds ratio; *statistically significant association; Constitutional symptoms include-malaise, anorexia, fatigue and lack of appetite.

3.3 Clinical signs of Tuberculosis in HIV positive and negative patients

Table 3 shows a wide spectrum of clinical signs on examination among the patients. The common signs were pallor 105 (50.4%), night sweats 74 (35.2%) night 62(29.5%) respiratory signs, Lymphadenopathy 35 (16.7%) and oral thrush 26 (12.4%). The following were independent predictors of HIV; pallor (OR=2.72; 95% CI: 1.2-4.1; p=0.001) Jaundice 17.9% (OR=3.90; 95% CI; 1.24-10.25;p=0.003), oedema 9.0% (OR=6.41; 95% CI: 1.45-20.25; p=0.010), Lymphadenopathy 26.9% (OR=3.37; 95% CI: 1.01-6.91; p=0.001). Oral thrush was seen in 26.9% of patients (OR=11.04; 95% CI; 3.01-17.2; p=0.001), per abdomen signs (PA signs) 19.2% (OR=5.00; 95% CI: 1.1-13.30; p=0.001). Patients with oral thrush were 11.03 more likely to have HIV co-infection than those without.

264 **Table 3: Clinical signs of tuberculosis in HIV positive and negative patients (n=210)**

Signs	TB+/HIV+ (N=78)	TB+/HIV- (N=132)	TOTAL	Significance test of association (χ^2)	OR (HIV+)
Pallor	52 (66.7%)	54 (40.9%)	106	11.74, p=0.001	2.73*
Jaundice	14 (17.9%)	8 (6.1%)	22	8.71, p=0.003	3.91*
Night sweats	28 (35.9%)	46 (34.8%)	74	0.02, p=0.878	1.05
Oedema	7 (9.0%)	4 (3.0%)	11	6.65, p=0.010	6.41*
Skin infections	5 (6.4%)	5 (3.8%)	10	0.58, p=0.443	1.73
Lymphadenopathy	21 (26.9%)	14 (10.6%)	35	10.53, p=0.001	3.37*
Oral thrush	21 (26.9%)	5 (3.8%)	26	24.76, p=0.001	11.03*
Respiratory signs	20 (25.6%)	42 (31.8%)	62	1.324, p=0.250	0.69
PA Signs	15 (19.2%)	8 (6.1%)	23	11.74, p=0.001	5.00*
CNS signs	8 (10.3%)	9 (6.8%)	17	0.77, p=0.37	1.56

265 T-test for numerical variables and Yates corrected chi-square test for categorical variables:
 266 OR=Odds ratio; *statistically significant association; CNS=central nervous

267

268 **3.4 Clinical outcomes observed in TB-HIV co-infection based on CD4+ cells**

269 Majority of the respondents with CD4+cells<200 presented with night sweats 79.5%,
 270 constitutional symptoms 70.5%, seizures 42.3%, weight loss 329.9%, prolonged fever 35.9%
 271 and coughs 12.8%. Prolonged fever 23.1% was also common in patients with CD4+T
 272 lymphocyte range 201-500 cells/mm³ followed by weight loss 21.8%, constitutional
 273 symptoms 15.4%, coughs 12.8% and night sweats 12.8%. Fewer patients 2.6% with >500
 274 CD4+T cells count showed weight loss and night sweats respectively. In bivariate logistic
 275 regression analysis, breathlessness, prolonged cough, night sweats and weight loss were
 276 associated with CD4+T <200 cells/mm³. The significant symptoms/signs persistently
 277 predicting CD4+T count<200 cells/mm³ at a multivariate model were coughs (OR=5.9; 95%
 278 CI: 1.2-5.6, p<0.017), prolonged fever (OR=4.5; 95% CI: 0.5-7.2, p<0.015) and weight loss
 279 (OR=2.8; 95% CI:1.3-6.7, 0.011). There was a statistically significant difference between
 280 TB-HIV co-infection and the degree of immune suppression-CD4+T cell counts in relation to
 281 clinical outcomes (p<0.05) as shown in table 4. .

282

283 **Table 4: Clinical features observed in TB-HIV co-infection based on CD4+cells (n=78)**

Clinical presentation	Degree of Immune-deficiency (CD4-counts/mm ³)		
	<200	201-500	>500
Weight loss	31 (39.7%)	17 (21.8%)	2 (2.6%)
Prolonged fever	28 (35.9%)	18 (23.1%)	1 (1.3%)
Coughs	10 (12.8%)	10 (12.8%)	1 (1.3%)
Constitutional symptoms	32 (41.0%)	12 (15.4%)	0 (0.0%)
Seizures	33 (42.3%)	2 (2.6%)	1 (1.3%)
Hemoptysis	3 (3.8%)	3 (3.8%)	0 (0.0%)
Breathlessness	21 (26.9%)	1 (1.3%)	0 (0.0%)
Symptoms of MI	3 (3.8%)	0 (0.0%)	0 (0.0%)
Night Sweats	30 (38.5%)	10 (12.8%)	2 (2.6%)
Swelling	6 (7.7%)	3 (3.8%)	1 (1.3%)

284 **3.5 Symptoms and signs predictive of the need to start HAART (CD4+T count<200**

285 The study conducted an analysis to determine the symptoms and signs that predict the need
 286 for HAART initiation in this study population. In a univariate logistic regression analysis,
 287 cough > 1 month, diarrhea>1 month, oral thrush, herpes zoster, general body malaise,
 288 dehydration and generalized skin rash were associated with CD4+T <200 cells/mm³. The
 289 significant symptoms/signs persistently predicting CD4+T count <200 cells/mm³ at a
 290 multivariate model were dehydration (OR= 14.6), skin rash (OR = 3.6), candida/oral thrush
 291 (OR =2.6), cough> 1 month (OR =2.6) and history of generalized body rash (OR = 2.9) as
 292 shown in table 5.

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 294
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Table 5: Symptoms and signs predictive of the need to start HAART (CD4+T count<200 (n=78)

OR=Odds ratio; *statistically significant association; CI=confidence interval; CD4+=Cluster differentiation T-lymphocyte no.4.

Clinical Indicator	CD4<200 (%) N=35	CD4≥200 (%) N=48	Measures of Association OR(95% CI)	p-value	Adjusted Measure of Association OR(95% CI)	p-value
<u>On History</u>						
Pain or difficulty with swallowing	9(25.7)	30(62.5)	0.6(0.3-1.2)	0.173	0.4(0.2-1.2)	0.095
Fever>1 month	3(8.6)	4(8.3)	1.9(0.5-7.2)	0.329	0.3(0.1-4.6)	0.415
Cough>1month	11(31.4)	7(14.6)	2.5(1.2-5.3)	0.014	2.6(1.2-5.6)	0.017
History of TB	7(20.0)	5(10.4)	2.2(0.9-5.4)	0.081	1.7(0.5-5.7)	0.355
Night sweats>1month	4(11.4)	7(14.6)	1.5(0.6-4.20)	0.405	0.8(0.2-4.4)	0.866
History of generalized body rash	8(22.9)	10(20.8)	2.5(1.2-5.5)	0.018	2.9(1.3-6.7)	0.011
Persistent genital oral sores >1 month	3(8.6)	2(4.2)	3.2(0.8-13.3)	0.102	0.6(0.1-13.6)	0.725
Diarrhoea>1 month	3(8.6)	2(4.2)	3.2(0.8-13.3)	0.102	4.9(1.4-50.7)	0.179
<u>On Examination</u>						
Oral thrush(candida)	7(20.0)	11(22.9)	2.9(1.2-7.4)	0.022	2.6(1.1-6.9)	0.047
Swollen glands in the neck or axillae	11(31.4)	15(31.3)	1.3(0.6-2.60)	0.492	0.9(0.4-2.5)	0.955
Substantial unintentional wt loss	10(28.6)	12(25.0)	1.7(0.6-5.4)	0.228	1.3(0.1-45.6)	0.873
Fatigue	4(11.4)	2(4.2)	4.4(1.2-15.9)	0.025	4.9(1.4-18.1)	0.015
Pallor	2(5.7)	3(6.3)	3.2(0.6-17.8)	0.184	1.1(0.1-26.9)	0.931
Dehydration	2(5.7)	1(2.1)	12.9(1.2-144.3)	0.038	14.6(1.3-163.8)	0.030
Generalised skin rash	4(5.7)	2(4.2)	4.2(1.3-13.3)	0.014	3.6(1.1-11.8)	0.034

3.6 Tuberculosis recurrences and HIV- infection

A total of 30 (14.3%) of the TB cases were recurrences, having previously been treated for TB and declared cured. No treatment or default failures cases were observed in this study. Males constituted 56.7% (17/30) and females 43.3% (13/30) of the recurrent cases. A total of 8 (26.7%) of the TB recurrent cases were ZN smear positive of which 6 (20%) were culture positive and 22 (73.3%) cases were smear negative and 4 (13.3%) were culture positive. A total of 13 (43.3%) of these cases were HIV sero-positive and 17 (56.7%) were HIV sero-negative. The majority (43.3%) of the recurrences were in the 21-30 age-group followed by the 35-44 age group with 21.9%. There was no statistically differences in TB recurrences between the genders (OR=1.02; 95% CI: 0.66-1.37; p=0.54) and HIV status (OR=0.39; 95% CI: 0.22-1.10; p=0.17) as shown in Figure 1 below.

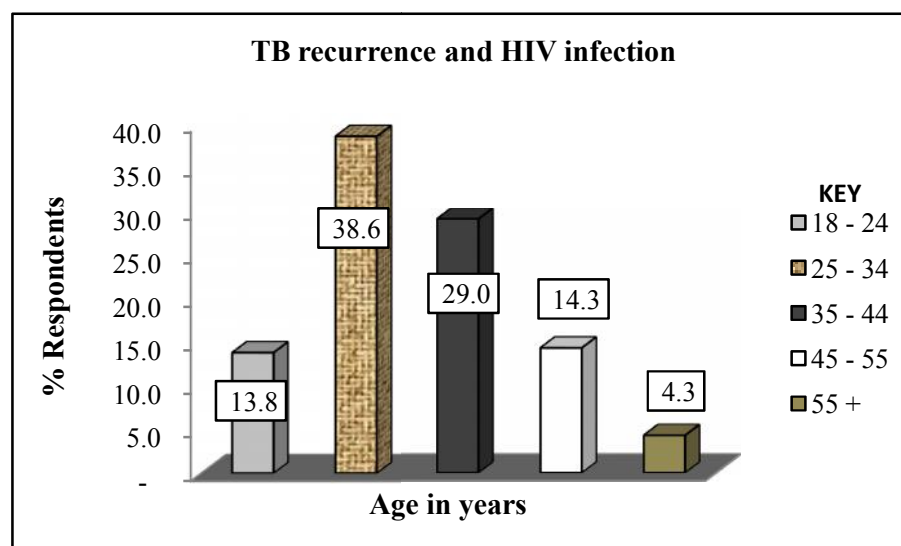


Figure 1: Tuberculosis recurrence and HIV infection

4. DISCUSSION

Diagnosing active TB in people with HIV is challenging in developing countries where resources, laboratory facilities are often limited. Most symptoms of TB and X-ray findings are indistinguishable from those caused by other respiratory conditions. In addition, HIV pandemic poses a serious diagnostic and therapeutic challenge as a co-infection [4]. In this

study, the most presenting symptoms of TB among those who are HIV negative were cough (72.0%), Fever (41.7%) and weight loss (23.5%). Patients with tuberculosis normally present with fever which develops in the late afternoon or evening [20]. The fever is usually low grades at the onset and may become high grade with progression of disease [8]. The diagnosis of pulmonary tuberculosis is influenced by the patient's illness, HIV/AIDS status and the level of care services available. In this study, Symptoms like weight loss (53%) and constitutional (62%) were strongly associated TB-HIV co-infection patients [21]. These clinical findings means that screening of tuberculosis in HIV co-infected patients by using symptoms of fever, cough, weight loss and chest radiography with features suggestive of tuberculosis would detect only 25% of the HIV positive co-infected with tuberculosis. This is expected as TB which is a chronic debilitating disease is coexisting with another debilitating disease (HIV). Studies by Corbett [12] on HIV-1 co-infection in children hospitalized with tuberculosis in South Africa revealed that clinical features of cough, fever and night sweats or TB contact were similar between HIV-infected and non-infected children. World health organization has developed a clinical staging system (originally for prognosis), based on clinical criteria and the definition of symptoms, signs and diseases is according to clinical judgment [16]. Clinical condition or performance score whichever is the higher, determines whether a patient is at clinical stage 1, 2, 3 or 4 which is an important criteria for starting anti-retroviral (ARV) therapy [22]. In this study 88.1% of the sputum specimen were smear positive while 11.9% sputum smear-negative. This concurred well with tuberculosis reports of 2010 which showed a treatment success rates of 85.86% for new sputum smear-positive pulmonary TB cases, 78% for sputum smear-positive retreatment relapse cases, 79% for smear positive retreatment failure cases and 83% for new sputum smear-negative PTB cases [23]. This figure is much higher than the global target of 70% [16] and that reported from Addis Abba [24], where all PTB cases, less than 20% were sputum smear-positive.

In this study, Patients had a wide spectrum of clinical signs on examination with 66.7% of the patients with pallor being sero-positive compared to 40.9% sero-negative and this was statistically significant ($p<0.05$). Oral candidiasis was also occurring in 26.9% of the HIV-positive cases [19]. Night sweats, skin infections and respiratory signs did not have any statistically significant association with sero positivity ($p>0.05$). Signs like pallor and oedema were common in tuberculosis co-infected patients. This study demonstrates that the clinical signs of TB were comparable in HIV sero-positive and sero-negative TB patients, as both groups had similar complaints of pallor, night sweats skin infections and respiratory signs. The absence of any difference in most of the clinical signs between the HIV sero-positive and sero-negative TB patients might be due to the chronic nature of TB, leading to protracted ill-health and wasting [18].

In this study majority of the respondents with CD4+ cells <200 presented with night sweats 79.5% and constitutional symptoms 70.5%. Prolonged fever 23.1% and weight loss 21.8% were also common in patients with CD4+T count range 200-500 cells/mm³. There was a statistically significant difference between TB and HIV co-infection and the degree of immune suppression ($p<0.05$). It has been observed that when the immune suppression is more marked (CD4 count <200 ml³), the features of tuberculosis are a typical with a much greater frequency of extra-pulmonary involvement, especially the lymph nodes [25]. A study in Malaysia General Hospital showed that prolonged insidious symptoms found in majority of patients consisting of weight loss, prolonged low grade fever and nocturnal sweat may delay diagnosis. This classical picture of pulmonary TB is seen mainly in less immunocomprised patients with CD4 count > 200 cells/mm³ [8].

Our study was conducted in an area with PTB and HIV prevalence. The differences described in the clinical presentation of patients with confirmed PTB who are or are not coinfectd with HIV could be used to identify patients who are more likely to be coinfectd. These patients

may benefit from an early referral for pre-test counselling for HIV screening and culture sputum, as they will be more likely to have smear negative microscopy. Excess transmission of tubercle bacilli in the community, caused by increased number of HIV-associated tuberculosis cases will be contained only to the extent that patients with infectious tuberculosis are swiftly identified and properly treated and cured.

In this study the identified clinical indicators for CD4+T cell count<200 cells/mm³ after adjusting for all factors were generalized skin rash, dehydration and oral thrush (candida). Patients likely to seek care for these conditions may not know their HIV status and these conditions are strong predictors of need for treatment. ²⁶also identified exactly the same symptoms and signs among hospitalized HIV positive patients in Hindu-Mandal Hospital in Dares-Salaam Tanzania, consistent with the findings of this current study. The finding of a non-specific generalized skin rash on examination was associated with low CD4+count (OR=4.2, 95% CI: 1-13). This is consistent with a study by [27] among 716 police officers in Dares-Salaam, Tanzania. HIV-infected police officers had significantly higher prevalence of skin diseases than HIV-uninfected police officers (42% vs 26%), p=0.02). ²⁸studied the patterns of skin manifestations and their relationships with CD4+ counts among HIV/AIDS patients and found that the patients presented with at least one type of skin problem. Generalized purigo, oral candidiasis, herpes zoster and vaginal candidiasis were the most skin problems associated with mean CD4+ count (128 ± 85 cells/mm³) and mean viral load (79,433 copies/ml) (p<0.001). In this current study generalized skin rash remained significant at both CD4+T cell count threshold of 200 and 350 cells/mm³ confirming its importance in immunosuppressed persons. The possible explanation for skin manifestation being common at low CD+T cell count is due to altered normal flora alongside immunodeficiency. Other mechanisms could be auto immune phenomena like vitiligo and alopecia which are predominantly due to immune dysregulation seen in TB and HIV co-infection at low CD+T

cell count [8]. The other explanation could be a systemic immune dysfunction as seen in HIV infection where the influx of CD4+T lymphocytes to the perifollicular regions of the skin when the CD4/CD8 ratio is low leads to skin inflammation [29]. Dehydration was an additional clinical feature not strictly in WHO criteria but was found to be significant in predicting CD+T count <200 cells/mm³ in this study population. Although it featured in adjusted analyses it was based on small number of patients. The possible explanation for dehydration in TB and HIV co-infection is due to anorexia, dysphagia and chronic diarrhea. Oral thrush was found to predict both CD4+T counts <200. It is marker of HIV infection that is bound to occur especially during advanced stage of immunosuppression [25]. Oropharyngeal candidiasis is the most common fungal and opportunistic infection in TB and HIV co-infection affecting nearly 90% of subjects at some stage during the course of infection. In this study oral thrush was identified to predict CD+T counts at both threshold of <200 and <350 cells/mm³. In the study by [18] among homosexual men, the occurrence of oral thrush at a CD+T count >200 cells/mm³ signifies that oral thrush remained an important risk factor underlining the predictive value of clinical signs at CD4+T count 200 cells/mm³. Their study showed no correlation between CD4+T count and oral candidiasis although they report a high prevalence of oral candida colonization.

In this study, thirty patients (14.3%) had recurrent TB. In the official 2012 DLTLTD annual report, retreatment cases contributed 9% of the TB cases of which 3% were classified as PTB relapse category. The rest were recurrent smear negative PTB and EPTB (4%), Treatment failures (0.1%) and return after a default (1.4%). The 2011 annual report published by DLTLTD shows a smear positive relapse rate of 3% and a combined recurrent smear negative pulmonary TB and extra pulmonary TB rate of 5%. Many national TB control programmes in sub-Saharan African countries have no capacity to distinguish between relapse (endogenous reactivation) from (exogenous) re-infection TB which constitute recurrent tuberculosis. It is

not clear how the DLTLD identified TB relapse case given their annual reports. This is because diagnosis and treatment of new TB cases in most health facilities in Kenya is based on clinical symptom, Ziehl-Neelsen (ZN) smear microscopy and occasionally augmented with chest X-Ray in some health facilities.

In this study males dominated females (56.7%) in the number of recurrent tuberculosis cases. The majority (43.3%) of the recurrences were in the 25-34 year age group which is the most productive segments of society. There was no statistical difference in TB recurrence rates between gender and HIV status ($p>0.05$). Kenya has been fully under directly observed therapy short counts (DOTs) programme since 1998 [16]. However it cannot be concluded categorically that DOTs functions as maybe expected on basis of its naming. In this current study, patients in Mombasa County were provided with drugs to take at home for at least two weeks and adherence is not routinely checked. Therefore it is unknown what the degree of compliance is and it can only be determined if differentiation between relapse and re-infection is established.

5. CONCLUSION

The prevalence of HIV in TB patients was very high. Clinical features of fever, night sweats and weight loss were common in both TB and TB-HIV co-infection patients. Except for oral thrush, constitutional and GI symptoms which were significantly associated with HIV-positive serology, most of the clinical presentations of TB were comparable in both HIV-sero-positive and sero-negative patients. The presence of such features may assist in identifying TB patients with HIV infection. Co-infection with CD4+T cell count <200 cells/mm³ accompanied by night sweats were predictors to start HAART. Thus, identification and curative treatment of sputum-smear positive tuberculosis patients is still the most cost-effective intervention, irrespective of the HIV sero-status of the patient.

List of abbreviations: TB-Tuberculosis, PTB-Pulmonary tuberculosis, WHO-World Health

Organization, MTB-*Mycobacterium tuberculosis*, HIV-Human immunodeficiency virus,
HAART-Highly active anti-retroviral treatment, MDR-TB-Multidrug resistant tuberculosis.

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