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Clinical Manifestations and CD4 Counts of Tuberculosis in Human Immunodeficiency Virus-infected and Un-infected among Newly Diagnosed Patients in Mombasa, Kenya

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SAY and MFO did the study design and wrote the protocol. Authors RRS and SAY did the statistical analysis and literature searches while analyses of study was done by authors SAY, SSN and RRS. All authors read and approved the final manuscript.

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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.

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Aim: This study was at aimed assessing clinical manifestations and CD4 counts of TB patients with or without HIV co-infection.
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 Mikindani 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, Lowestein 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/mm^3 accompanied by night sweats. Tuberculosis patients had statistically significant higher mean CD4+T cell counts ($t=5.6$, $df=461$, $p<0.05$) and higher leukocyte counts ($t=3.8$, $df=472$, $p<0.05$) than HIV/AIDS tuberculosis co-infected patients.
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. CDT+T cell counts were significantly elevated in TB patients than TB-HIV co-infection.

Keywords: Kenya; clinical manifestations; tuberculosis; HIV; CD4+T cells.

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.

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

The spread of the human immunodeficiency virus (HIV) has also contributed dramatically tothe re-emergence of TB infection. HIV infection is recognized as a powerful risk factor for the development of active and often lethal TB and for the reactivation of latent TB infection to active disease [9,10]. The HIV infection affects cell mediated immunity and individuals infected with *Mycobacterium tuberculosis* are at risk of developing active disease after being infected with HIV [11,12]. According to WHO about a third of the 40 million people with HIV/AIDS are co-infected with *Mycobacterium tuberculosis*. In a population, the lifetime risk of developing active TB once infected in absence of HIV infection is about 10% [13]. However, it increases tenfold in HIV infected individuals and this has resulted in a large increase in the number of TB cases [14].

The proportion of smear-negative pulmonary TB (PTB) and extra-pulmonary TB (EPTB) is higher among HIV co-infected TB patients [15].

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

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

2. MATERIALS AND METHODS

2.1 Study Area

The study was conducted in Mombasa County which has a population of 1,031,266 by the year 2012. The population is steadily growing due to rural-urban migration and immigration from unstable countries. The total area Mombasa is 109 Km^2 with about 60% of the people living overcrowded informal settlements in the form of shelters. Residents are of mixed ethnicity and are engaged in low-income generating activities, mainly informal sector and small trading. The County has rapid population growth and is characterized by low socio-economic indicator. This creates huge demands on health facilities and inability to keep pace with the environment, continued economic prosperity, public health and quality of life of residents. Tuberculosis and HIVAIDS are the leading causes of deaths in the area representing 50%.

2.2 Study Site

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

2.3 Study Design

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

2.3.1 Inclusion and exclusion criteria

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

2.3.2 Sampling frame

Mombasa County was purposively sampled because of high cases of TB and HIV co-infection. The sampling frame consisted of all the public health facilities within the study area. After the selection of the study sites, each was allocated a proportionate number of study subjects based on the level of health care

delivery system and the average client attendance in the past one month before embarking on the study. To minimize bias in selecting study subjects, consecutive sampling was used hence every alternate TB suspect who satisfied the inclusion criteria was selected for the study. Patients were suspected of having TB if they had cough of more than two weeks and not responding to antibiotic 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 50 ml 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. Sputum samples were decontaminated using the modified Petroff´s method and concentrated by centrifugation at 3000g for 15 minutes. 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 appropriate post-test counseling.

2.4.3 CD4+T cell determination

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

2.4.4 Microscopic examinations and isolation of *Mycobacterium tuberculosis*

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

2.4.5 Radiological examination

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

2.4.6 Categories of tuberculosis

Category I: New PTB+ patients, new PTB patients who are seriously ill and seriously ill EPTB patients. Category II TB: PTB+ relapses, PTB+ treatment failures and PTB+ returns after default. Category III TB: new adult patients with PTB and new adult patients with EPTB.

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 (χ^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 (χ^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 kg/m^2. This was more pronounced and frequent among HIV-positive TB patients as compared to HIV negative ones. Severe malnutrition (BMI<15.9 kg/m^2), moderate malnutrition (BMI=16-16.9 kg/m^2) and mild malnutrition (BMI=17.18.5 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±198.8 cells/mm^3) than TB-HIV co-infection patients (265.1.±158.4 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 (χ^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 EPTB were diagnosed in 96.2% (202/210) and 3.8% (8/210) of the patients respectively.

3.2 Clinical Symptoms of Tuberculosis in HIV Positive and Negative Patients

Table 2 shows clinical symptoms and physical findings of the patients by HIV serostatus. The common clinical symptoms cough 105 (50%), constitutional symptoms like fatigue, malaise and anorexia 89 (42.3%), fever 83 (39.5%) and weight loss 66 (31.4%). Breathlessness 39 (18.6%), Hemoptysis 35 (16.7%), symptoms of MI 20 (9.5%) and headache 10 (4.8%). In relation to HIV-status, the following symptoms were predictors of TB-HIV co-infection. Hemoptysis 3.8% (OR=0.14; 95% CI: 012-4;13; p=0.001), breathlessness 26.9% (OR=2.33; 95% CI: 1.12-3.01 p=0.017), constitutional symptoms 70.5% (OR=7.17; 95% CI: 2.24-15.2; p=0.001), significant weight loss 44.9% (OR=2.65; 95% CI: 1.23-5.65; p=0.001) and gastro-intestinal symptoms (GI) 6.4% (OR=8.97; 95% CI: 3.45-23.41; 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.

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.

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%)

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

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*

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

*T-test for numerical variables and Yates corrected chi-square test for categorical variables: OR = Odds ratio; *Statistically significant association; CNS = Central nervous*

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	20 (25.6%)	13 (16.7%)	2 (2.6%)
Prolonged fever	16 (20.5%)	11 (14.1%)	1 (1.3%)
Coughs	4 (5.1%)	5 (6.4%)	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%)	0 (0.0%)	0 (0.0%)
Breathlessness	21 (26.9%)	0 (0.0%)	0 (0.0%)
Symptoms of MI	3 (3.8%)	0 (0.0%)	0 (0.0%)
Night Sweats	18 (38.5%)	8 (10.3%)	2 (2.6%)
Neck swelling	1 (1.3%)	0 (0.0%)	0 (0.0%)

3.4 Clinical Outcomes Observed in TB-HIV Co-infection Based on CD4+ Cells

Majority of the respondents with CD4+cells<200 presented with seizers 42.3%, constitutional symptoms 41.0%, night sweats 38.5% and weight loss 25.6%. Prolonged fever 23.1% was also common in patients with CD4+T lymphocyte range 201-500 cells/mm^3 followed by weight loss 21.8%, constitutional symptoms 15.4%, coughs 12.8% and night sweats 12.8%. In bivariate logistic regression analysis, breathlessness, prolonged cough, night sweats and weight loss were associated with CD4+T <200 cells/mm^3. The significant symptoms/signs persistently predicting CD4+T count<200 cells/mm^3 at a multivariate model were coughs (OR=5.9; 95% 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 (OR=2.8; 95% CI:1.3-6.7, 0.011). There was a statistically significant difference between TB-HIV co-infection and the degree of immune

suppression-CD4+T cell counts in relation to clinical outcomes (p<0.05) as shown in Table 4.

3.5 Symptoms and Signs Predictive of the Need to Start HAART (CD4+T Count<200

The study conducted an analysis to determine the symptoms and signs that predict the need for HAART initiation in this study population. In a univariate logistic regression analysis, cough>1 month, oral thrush, herpes zoster, general body malaise, dehydration and generalized skin rash were associated with CD4+T <200 cells/mm^3. The significant symptoms/signs persistently predicting CD4+T count <200 cells/mm^3 at a multivariate model were dehydration (OR= 14.6), skin rash (OR = 3.6), candida/oral thrush (OR =2.6), cough> 1 month (OR =2.6) and history of generalized body rash (OR = 2.9) as shown in Table 5.

3.6 Immunological Markers in Tuberculosis and HIV Co-infection

The mean absolute CD4+T count in males and females combined was 276.44±142.71 cells/mm^3.Mean in males was 265.12.±158.35 cells/mm^3 and females 289.64±128.67 cells/mm^3. Combined CD8+T lymphocyte count in males and females were 796.46±265.69 cells/mm^3. The mean CD8+T cells in males were 780.19±288.07 cells/mm^3 and females 802.98±247.96 cells/mm^3. The mean CD4+/CD8+ ratio in both males and females was 0.387±0.269 cells/mm^3. The mean CD4+T cells count in males was lower than for females but the difference was not statistically significant (t=0.754, df=76, p>0.05). The mean haemoglobin levels in males and females combined was 11.09±9.44 gm/dl and the in males was 12.51±13.74 gm/dl and females 9.88±1.69 gm/dl respectively.

3.7 Mean CD4$^+$, CD8$^+$, BMI and HB in Different Study Groups

Tuberculosis patients had statistically significant lower mean CD4+T counts 474.5±198.8 cells/mm^3 than the reference value found in this population (1054.9 ± 156.1 cells/mm^3, t=34.6, df=485, p=0.001) and lower haemoglobin level (11.16±5.9 gm/dl) than the reference value for this population (12.8 ±13 g/dl, t=27.5, df=453 p=0.002). Tuberculosis patients had statistically significant higher CD4+T counts (474.5±198.8 cells/mm^3) than HIV/AIDS patients (333.3±150.6, t=4.6, df=47, p=0.001) and

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

Clinical indicator	CD4<200 (%) N=30	CD4≥200 (%) N=48	Measures of association OR (95% CI)	p-value	Adjusted measure of association OR (95% CI)	p-value
On history						
Pain or difficulty with swallowing	9 (30.0)	30 (62.5)	0.6 (0.3-1.2)	0.173	0.4 (0.2-1.2)	0.095
Fever>1 month	16 (45.7)	12 (34.3)	1.9 (0.5-7.2)	0.329	0.3 (0.1-4.6)	0.415
Cough>1 month	4 (13.3)	6 (12.5)	2.5 (1.2-5.3)	0.014	2.6 (1.2-5.6)	0.017
History of TB	7 (23.3)	5 (10.4)	2.2 (0.9-5.4)	0.081	1.7 (0.5-5.7)	0.355
Night sweats>1 month	18 (60.0)	10 (20.8)	1.5 (0.6-4.20	0.405	0.8 (0.2-4.4)	0.866
History of generalized body rash	8 (26.7)	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 (10.0)	2 (4.2)	3.2 (0.8-13.3)	0.102	0.6 (0.1-13.6)	0.725
Diarrhoea>1 month	3 (10.0)	2 (4.2)	3.2 (0.8-13.3)	0.102	4.9 (1.4-50.7)	0.179
On examination						
Oral thrush (candida)	7 (23.3)	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 (36.7)	15 (31.3)	1.3 (0.6-2.60	0.492	0.9 (0.4-2.5)	0.955
Substantial unintentional wt loss	20 (66.7)	15 (31.3)	1.7 (0.6-5.4)	0.228	1.3 (0.1-45.6)	0.873
Fatigue	4 (13.3)	2 (4.2)	4.4 (1.2-15.9)	0.025	4.9 (1.4-18.1)	0.015
Pallor	2 (6.7)	3 (6.3)	3.2 (0.6-17.8)	0.184	1.1 (0.1-26.9	0.931
Dehydration	2 (6.7)	1 (2.1)	12.9 (1.2-144.3)	0.038	14.6 (1.3-163.8)	0.030
Generalised skin rash	4 (13.3)	2 (4.2)	4.2 (1.3-13.3)	0.014	3.6 (1.1-11.8)	0.034

Table 6. Immunological markers in tuberculosis and HIV co-infection

Gender	N	Median	2.5^{th}-97.5^{th}	Mean ± SD	95% CI	P-value
Absolute CD4 T cells						
Male	36	283.5	169.00 - 368.50	265.12.±158.35	236.06 - 343.22	t=0.75
Female	42	249.5	168.00 - 349.50	289.64±128.67	225.02 - 305.22	df=76
Total	78	254.5	168.75 - 362.50	276.44±142.71	244.26 - 308.61	p=0.45
Absolute CD8 T cells						
Male	36	786.5	462.00 - 983.50	780.19±288.07	682.73 - 877.66	t=0.375
Female	42	811.5	699.50 - 972.25	802.98±247.96	725.71 - 880.25	df=76
Total	78	786.5	628.75 - 362.50	796.46±265.69	732.56 - 852.36	p=0.708
Absolute CD4/CD8 T cells ratio						
Male	36	0.365	0.217 - 0.472	0.339±0.320	0.315 - 0.532	t=1.103
Female	42	0.308	0.223 - 0.441	0.356±0.216	0.289 - 0.423	df=76
Total	78	0.327	0.223 - 0.468	0.387±0.269	0.326 - 0.448	p=0.273
Haemoglobin						
Male	36	10.5	9.125 - 11.500	12.51±13.74	7.859 - 17.158	t=1.230
Female	42	10.1	8.725 - 11.125	9.88±1.69	9.355 - 10.407	df=76
Total	78	10.2	9.05 - 11.23	11.09±9.44	9.05 - 11.23	p=0.233

Table 7. Mean $CD4^+$, $CD8^+$, BMI and HB in different study groups

Immuno-haematological variables	HIV+/TB+ (N=78) (Mean ± SD)	HIV-/TB+ (N=210) (Mean ± SD)	HIV-/TB- (N=500) (Mean ± SD)	P-value
CD4+T cells/mm^3	265.1±158.4	474.5±198.8	1054.9 ± 156.1	0.001
CD8+T cells/mm^3	796.5±265.7	614.8±247.5	679.1± 697.7	0.000
CD3+T cells/mm^3	1165.2±343.3	1271.0±350.7	1907.4 ± 1982.2	0.000
HB gr/dl	11.1±9.4	11.2±5.9	12.7± 12.9	0.002
BMI kg/m^2	16.9±2.2	19.7±2.4	22.7 ±1.3	0.000

CD4+=Cluster differentiation T-lymphocyte no.4; CD8+=Cluster differentiation T-lymphocyte no.8; BMI=Body mass index; SD=standard deviation; P-value=level of marginal significance; Yates corrected chi-square test for categorical variables

HIV/AIDS patients not on treatment (290±184, t=7.6, df=58, p=0.05). Tuberculosis patients had significant lower mean haemoglobin level (11.2±5.9 gm/dl) than HIV/AIDS patients (11.3±1.5, t=3.4, df=47, p=0.001).Patients with tuberculosis were significantly malnourished (BMI 19.7±2.4 kg/m^2) as compared to the reference value for this population (BMI 22.7±1.3, t=8, df=465, p<0.05). HIV/AIDS patients had significantly higher BMI (19.9±2.2 kg/m^2) than tuberculosis HIV/AIDS co-infected patients (BMI 16.9±2.2, t=0.70, df=58, p<0.021) and lower compared to values obtained for control subjects (p<0.003) (Table 7 above).

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/mm^3. 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 ml^3), 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/mm^3 [8].

Our study was conducted in an area with high PTB and HIV prevalence. The differences described in the clinical presentation of patients with confirmed PTB who are or are not coinfected with HIV could be used to identify patients who are more likely to be coinfected. These patients may benefit from an early referral for pre-test counselling, 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 [26].

In this study the identified clinical indicators for CD4+T cell count <200 cells/mm^3 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. Another study 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%), $p=0.02$). [28] studied 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/mm^3) and mean viral load (79,433 copies/ml) ($p<0.001$). In this current study generalized skin rash remained significant at both CD4+T count threshold of 200 and 350 cells/mm^3 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/mm^3 in this study population. Although it featured in adjusted analyses it was based on small number of patients [30,31]. 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 [32]. In this study oral thrush was identified to predict CD+T counts at both threshold of <200 and <350 cells/mm^3. In the study by [33] among homosexual men, the occurrence of oral thrush at a CD4+T count>200 cells/mm^3 signifies that oral thrush remained an important risk factor underlining the predictive value of clinical signs at CD4+T count 200 cells/mm^3. Their study showed no correlation between CD4+T count and oral candidiasis although they report a high prevalence of oral candida colonization [34,35,36]. In this study the haemoglobin level was lower in tuberculosis patients (11.2±5.9 gm/dl) than the reference values established for this population (12.8±1.3, $t = 27.5$, $df = 461$, $p<0.05$) which was statistically significant. Reasons for this could be insufficient dietary intake because of poor appetite or anaemia due to chronic infections. This is also supported by findings in this current study which showed significantly lower BMI in tuberculosis patients than in healthy subjects and in HIV/AIDS patients without tuberculosis. Patients with tuberculosis were significantly malnourished as compared to the normal values for this population. (BMI 22.7±1.3, $t = 8$, $p<0.05$). Malnutrition is normally associated with impaired immunity and it has been reported that malnourished individuals at a risk of acquiring tuberculosis [37]. This study found no significant difference between males and females with regards to nutritional status ($p>0.05$).

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/mm^3 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. All newly diagnosed TB and TB-HIV co-infection patients should be exposed to immunehaematological counts to monitor their immune system.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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