VALIDITY OF CLINICAL SYMPTOMS
AND CHEST RADIOGRAPHY
IN PREDICTING PULMONARY TUBERCULOSIS AT THE
KENYATTA NATIONAL HOSPITAL, NAIROBI, KENYA.

A dissertation submitted in part fulfillment of the requirements for the degree of Master of Medicine in Internal Medicine by:

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University of Nairobi
2008
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I certify that this dissertation is my own original work and has not been presented for a degree at any other university.

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DEDICATION:
To my husband Tobias and our son Brian for their undying support.
To my parents, brothers, sisters and friends, whose tremendous encouragement has motivated me to keep at it.
To my God who has made it possible.
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TO NUMEROUS OTHER PERSONS WHO HAVE IN ONE WAY OR OTHER BEEN OF ENCOURAGEMENT TO ME.

I AM TRULY GRATEFUL.
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<td>Acid Fast Bacilli</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell Mediated Immunity</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly Observed Therapy-Short Course</td>
</tr>
<tr>
<td>DTC</td>
<td>Diagnostic Testing and Counseling</td>
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<tr>
<td>EPTB</td>
<td>Extra-Pulmonary Tuberculosis</td>
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<tr>
<td>ESRD</td>
<td>End Stage Renal Disease</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>IDU</td>
<td>Intravenous Drug Use</td>
</tr>
<tr>
<td>KNH</td>
<td>Kenyatta National Hospital</td>
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<tr>
<td>L-J</td>
<td>Lowenstein Jensen</td>
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<tr>
<td>MGIT</td>
<td>Mycobacterium Growth Indicator Tube</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry Of Health</td>
</tr>
<tr>
<td>MTB</td>
<td>Mycobacterium Tuberculosis Complex</td>
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<tr>
<td>NAA</td>
<td>Nucleic Acid Amplification</td>
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<td>NLTP</td>
<td>National Leprosy and Tuberculosis Programme</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PLWHA</td>
<td>People Living With HIV/AIDS</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified Protein Derivative</td>
</tr>
<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>SSA</td>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>ZN</td>
<td>Ziehl Neelsen stain for AFB</td>
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ABSTRACT

Background:
Tuberculosis (TB) incidence increases annually by 1% globally, and was declared a global emergency by the World Health Organization (WHO) in 1993. Diagnosis of TB infection is confirmed by microscopy of sputum smears for acid-fast bacilli (AFB) while suspicion of the infection is frequently based on clinical and radiological findings. However, sensitivity of the microscopic diagnosis in identifying all cases of TB is only 40-60%, and patients with negative sputum smears for AFB represent a diagnostic dilemma.

Therefore, the gold standard approach for TB diagnosis is to culture the organism from sputum or blood in a laboratory. Unfortunately this requires dedicated equipment and takes up to 8 weeks to yield results. It was, therefore, necessary to develop clinical and chest radiological algorithms that can be predictors for positive culture in Kenya.

Objective: To establish predictive value of clinical symptoms and chest radiography in the diagnosis of pulmonary tuberculosis.

Study Design: Prospective cross-sectional survey

Setting: Accident and Emergency department and general medical wards, Kenyatta National Hospital (KNH), Nairobi Kenya.

Study population: All patients seen in accident and emergency department, and admitted in the KNH medical wards within the study period with cough for more than two weeks.

Methodology:
Patients with cough for more than two weeks were screened and those who met the inclusion criteria were recruited into the study. Each patient was offered HIV testing after counseling. Three sputa were taken of which one was early morning sputum for examination for AFB. In addition, confirmatory sputum culture for
Mycobacterium tuberculosis complex was conducted on all patients and the patients informed about the results by their primary clinician. Chest radiographs was performed on all recruited patients at the time of recruitment. Two trained and experienced radiologists blinded to the laboratory diagnosis of TB, independently assessed the chest radiographs.

**Results:** A total of 271 were included into the study. Of these 126(46.5%) had culture proven TB. 55(44%) were HIV positive, 56(44%) were HIV negative and 15(12%) declined to be tested. Sputum smear microscopy had an overall sensitivity of 71% and specificity of 96%. Smear microscopy was frequently positive in patients without HIV infection 46(82%) compared to 33(60%) who were infected with HIV (p=0.019). Majority 68(54%) of patients with culture confirmed TB were males. The mean age was 32 years, range 15 to 63 years. The most prevalent symptoms in patients with TB were weight loss (52%), pleuritic chest pain (45%) and night sweats (40%). A combination of these three symptoms had 1.3 fold associations with culture proven infection. On univariate analysis, weight loss (p<0.001), pleuritic chest pain (p=0.001), night sweats (p<0.001), nodular alveolar infiltrates affecting upper zones (p<0.001) and cavitations affecting upper zones (p<0.001) were significantly associated with diagnosis of pulmonary tuberculosis. On multivariate analysis, weight loss (p=0.001), night sweats (p=0.001), chest pain (p=0.001), nodular infiltrates affecting upper zones (p<0.001) and cavitations (p=0.001) independently predicted diagnosis of pulmonary tuberculosis.

HIV positive patients with unintentional weight loss defined as 10% presumed or measured weight loss in the last one month, were six times more likely to have TB (95% CI, 2.73 to 14.5) while haemoptysis was significantly associated with HIV negative patients (p=0.009). Likewise HIV positive patients were less likely to have cavitations (p=0.003) and more likely to have intrathoracic adenopathy (p=0.043), miliary pattern (p<0.001), diffuse infiltrates (p=0.013) and normal chest radiographs (0.048) compared to HIV negative patients. HIV positive patients with positive sputum cultures were less likely to have had a positive sputum smear compared to HIV negative patients (p=0.019).
In patients with HIV/TB co-infection, mean CD4 count was 124 cells/mm³ with a median of 98 cells/mm³ and a range of (4-501). 32(58%) had CD4 counts of less than 100 cells/mm³ and were more likely to have intrathoracic adenopathy (p=0.67), miliary pattern (p=0.078), normal chest radiograph (p=0.17) and less likely to have upper lobe infiltrates (p=0.062) and cavitations (p=0.30).

**Conclusion:** Night sweats, weight loss and pleuritic chest pain were positive predictors of pulmonary tuberculosis and when combined had 1.3 fold association with culture proven TB. Cavitatory disease and nodular infiltrates affecting upper zones in the chest radiograph were still typical of TB infection. In the setting of an underlying HIV infection, chest radiographic findings tend to be more atypical and could present as normal or with minimal involvement and especially in those with advanced immunosuppression.
2.0. INTRODUCTION AND LITERATURE REVIEW

2.1: Introduction

Tuberculosis (TB) has afflicted the human race since the dawn of recorded history, remaining the leading cause of illness and death particularly in tropical countries. Despite the history of remarkable scientific achievement, TB has continued to pose an extra-ordinary threat to human health. *Tubercle bacillus*, the causative agent of TB and a member of *Mycobacterium tuberculosis* complex, was first isolated and described in 1882 by Robert Koch (1). Other members of the complex include *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium Carnetti*. *Mycobacterium tuberculosis* is the most important cause of morbidity and mortality in this complex.

*Tubercle bacilli* are aerobic, non-motile, non-sporing and often slightly curved rods 2-4 μm by 0.3-0.5μm in diameter. They retain aryl methane dyes on treatment with mineral acids, a property widely used to detect mycobacteria in clinical specimens by the light microscopy method of Ziel-Neelsen (ZN).

2.2: Background.

The World Health Organization (WHO) declared tuberculosis (TB) a global emergency in 1993 (2) with its incidence rising by 1% each year. The global and Kenya detection rate of TB was 60% and 43% respectively in 2005, falling short of the 70% target (3). Reasons cited for this under-detection of TB in high prevalence areas include failure of health workers to consider TB in patients with respiratory symptoms, resulting in diagnostic delays. These delays increase the risk of disease severity, mortality and transmission. Smear microscopy of sputum specimens remains the cornerstone of diagnosis of TB in most locations with a high burden of TB. Its sensitivity in identifying all cases of TB even in good centers is only 60% (4) Therefore patients whose sputum smears are negative for AFB represent a diagnostic dilemma. This is complicated further because HIV-TB co-infection broadens the differential diagnosis of smear negative PTB to include diseases such as PCP, pulmonary KS and gram-negative bacteraemia. A study done at Kenyatta National Hospital (KNH) by Siika et al. found PCP to
have been the most prevalent cause of chronic cough in HIV-infected adults with negative sputum smears for MTB (5). The gold standard for TB diagnosis is therefore to culture the organism in a laboratory, either from sputum or blood. This is both highly specific and highly sensitive but requires dedicated equipment and takes up to 8 weeks to yield results (6). In many cases, clinicians initiate treatment for Pulmonary TB (PTB) based on clinical and or chest radiographic findings.

2.3: Disease Burden.

The number of TB cases has been stable or falling in the five out of six WHO regions but growing in Africa where TB epidemics are still driven by the spread of HIV (3). TB prevalence fell from 297/100,000 pop globally in 1990 to 229/100,000 pop in 2005. Likewise TB mortality declined from 29/100,000 to 27/100,000 in 2005 (3). Case detection was 60% globally in 2005, still falling short of the 70% target (3). World health assembly target case detection, increased from 53% in 2004 to 60% in 2005, translating to an additional 350,000 smear positive cases (7). Case detection rate for all cases, changed little between 1995-2001 worldwide averaging 51% (3). Incidence of TB worldwide was 8.8 million of which 3.9 million were smear positive in 2005. Of this, 741,000 were adults living with HIV/AIDS. There was 14.6 million (229/100,000 pop) prevalent cases of which 6.1 million (95/100,000 pop) were smear positive. More than 80% of all the new cases in 2005 were in the African (23%), South East Asia (35%) and western pacific (25%) regions. An estimated 1.6 million (27/100,000) died from TB in 2005 including those co-infected with HIV (195,000).

In the African region, Nigeria with an incidence of TB of 283/100,000 pop/yr, South Africa (600/100,000 pop/yr) and Ethiopia (341/100,000 pop/yr) were ranked 4th, 7th and 8th respectively among the first 22 countries with high burden for TB. (3)
Kenya was ranked 10th among the first 22 countries with a high burden of TB worldwide in 2005. There were 108,401 new cases of TB diagnosed during that year, among whom 40,325 were smear positive, 43,794 smear negative, 15,176 extra pulmonary TB (EPTB) and 8,997 on retreatment for TB (3). Detection of smear positive TB was only 48% falling short of the expected 65-80%, and this was a drop from 56% in 1995 (3). The overall case detection rate was only 43%.

Incidence of TB in 2005 was 641/100,000 pop/yr, an increase from 108/100,000 pop/yr in 1990, smear positive of 276/100,000 pop/yr. with a trend in incidence rate of 5.5%/yr. The prevalence has been on the steady increase from 627/100,000 pop in 2000 to 936/100,000 pop in 2005 and mortality rate from 101/100,000 pop/yr to 140/100,000 pop/yr respectively, compared to prevalence of 167/100,000 pop and mortality of 22/100,000 pop/yr reported in 1990 (3). The peak age group was 25-34 years with a male to female ratio of 1.6:1 in these infections (8).

HIV prevalence in the incident TB case was 29% in adults aged between 15-45 years.

At autopsy TB has been indicated as the cause of death in 38-47% of adults with HIV infection although TB was diagnosed during life in only 50% of those autopsy proven disease (9-10).

The implementation of the global plan is expected to reverse the rise in the global incidence by 2015 and halve 1990 prevalence and death rates in most regions by 2015 though not in Africa and Eastern Europe (11). Many TB programmes are thus overwhelmed by the increase in patients. In Kenya as in other SSA countries, this increase is higher in patients with sputum smear negative and EPTB as compared to sputum smear positive cases (12).

2.4: HIV/TB Interaction.

Two thirds of the world's HIV infected individuals are in sub Saharan Africa (13), and an estimated 1.1 million people are living with HIV in Kenya alone (14) with a global prevalence of about 42 million people (13).

At present Africa accounts for 81% of the estimated 741,000 cases of TB among HIV positive people in the world, and only 4% were reported to have began ART
in 2003 (3). HIV Sero prevalence rates of greater than 40% are common among patients with TB in many African countries (15), and even higher rates have been observed among extra-pulmonary cases. Overall 30-40% of TB cases in Africa and the Caribbean countries are attributable to HIV (15).

There is a significant interaction between HIV and TB that accelerates development of both diseases (16). In this regard, HIV infection amplifies and accelerates the development of TB from infection to the disseminated form, and is the most important known risk factor associated with reactivation of a prior TB infection. Likewise TB reduces CD4+ lymphocytes, hence intensifying the immunosuppressant effect of HIV and potentially increasing viral activity (16). People Living with HIV and AIDS (PLWHA) have a ten-fold increase in the lifetime risk of TB (17). In Kenya, the prevalence of HIV infection among new cases of TB was 57% in 2005 and TB has been identified as the leading cause of death among PLWHA. (8, 14)

2.5: Pathophysiology of Tuberculosis.

*M. tuberculosis* is transmitted via airborne droplet nuclei that are produced when persons with pulmonary or laryngeal TB cough, sneeze, speak, or sing (18). The particles, which measure 1–5 μm in size, can be kept airborne by normal air currents for prolonged periods of time, resulting in dispersion throughout a room or building.

Infection occurs when a susceptible person inhales droplet nuclei that contain tubercle bacilli. As the distribution of inhaled droplet nuclei is determined by the ventilatory pattern and volumes of the various lung lobes, the site of implantation preferentially occurs in the middle and lower lung zones, although any lobe may be affected (19-20). Once lodged in the alveolus, *M. tuberculosis* is ingested by alveolar macrophages.

Resistance to establishment of tuberculous infection is known to be under genetic control (20), and the course of infection depends on the interaction between the inherent microbicidal power of the alveolar macrophage and the virulence of the ingested bacillus (21). If the alveolar macrophage cannot destroy or inhibit *M
tuberculosis, the bacilli multiply within its intracellular environment, causing the host macrophage or its progeny to burst. The cycle continues as released bacilli, are ingested by other alveolar macrophages and monocytes recruited from the blood. During this period of rapid growth, tubercle bacilli are spread through lymphatic channels to regional hilar and mediastinal lymph nodes and through the bloodstream to more distant sites in the body. The logarithmic phase of bacillary growth is arrested with the development of cell-mediated immunity and delayed-type hypersensitivity at 2–10 weeks after the initial infection (21-22).

Development of specific immunity is usually adequate to limit further multiplication of the bacilli; the host remains asymptomatic; and the lesions heal (22). Some of the bacilli remain dormant and viable for many years, and this condition—referred to as latent TB infection—may be detectable only by means of a positive purified protein derivative tuberculin skin test or radiologically identifiable calcification at the site of the primary lung infection or in regional lymph nodes(18). In approximately 5% of infected individuals, immunity is inadequate and clinically active disease develops within 1 year of infection (22); in another 5% of the infected population, endogenous reactivation of latent infection occurs remote from time of initial infection (22).

Co-infection with HIV and M tuberculosis is the strongest known risk factor for both immediate and delayed progression from infection to active TB (23). The risk of progression to disease for co-infected persons is 5%-10% per year compared with a 5%-10% lifetime risk for HIV-negative persons (1,24). Other known risk factors for development of active TB include conditions that are associated with defects in T-lymphocyte and/or macrophage function, such as malnutrition, drug and alcohol abuse, coexistent medical conditions (eg, chronic renal failure, diabetes mellitus, silicosis, jejunoileal bypass, and subtotal gastrectomy), and corticosteroid or other immunosuppressive therapy (25).

Post-primary TB occurs in a person who has previously been infected and has retained a degree of acquired immunity; it can result from endogenous reactivation or, less commonly, exogenous re-infection (26). Although delayed
progression of latent infection may occur at any seeded site in the body, lung foci account for the majority of cases (22). Predilection of post-primary disease to involve the upper lung zones is likely due to a combination of factors including the relatively higher oxygen tension and impaired lymphatic drainage in this region (27).

While cell-mediated immunity controls TB by activating macrophages to kill ingested bacilli, delayed-type hypersensitivity causes caseous necrosis that results in killing of bacilli-laden macrophages at the expense of destruction of nearby tissues (21). In primary and postprimary disease, the extent of necrosis and cavitation is dependent on the relative efficacy of each of these two immunologic processes in inhibiting multiplication of \textit{M tuberculosis}. Progressive primary TB refers to local progression of parenchymal disease with development of cavitation; this progression occurs in a small percentage of patients with primary disease and is similar in morphology and course to postprimary disease (27). Healing of TB occurs with resorption of caseous material accompanied by deposition of collagen (fibrosis). Dystrophic calcification occurs commonly at sites of caseous necrosis but is not a reliable marker for lesion sterility (27). Viable tubercle bacilli may persist, and in the preantibiotic era, \textit{M tuberculosis} could be grown from up to 20% of calcified lesions at autopsy (27).

Pleural involvement may occur at any time after the initial infection. In primary TB, effusions typically develop 3–6 months after infection and are believed to result from a hypersensitivity response to a small amount of tuberculoprotein released into the pleural space (22). Because of the paucity of organisms, pleural fluid will yield positive cultures in only 20%–40% of cases; a single closed needle biopsy of the pleura substantially increases the diagnostic yield to approximately 65%–75% (28). Pleural effusions are less commonly a manifestation of post primary disease in which a large number of organisms are spilled into the pleural space from rupture of a cavity or adjacent parenchymal focus. In true empyemas, acid-fast smears and mycobacterial cultures are usually positive (28).
Miliary spread of TB may also occur during either primary or post primary stages of disease. It results when a focal collection of tubercle bacilli discharges into a blood or lymph vessel, releasing a large number of viable bacilli that embolize to capillary beds in multiple organs. The lung is the most commonly involved organ.

2.6: Host response to infection.
The immunological response to initial infection with MTB may restrict its replication and spread in the majority of the people who are infected with it. However, if these mycobacteria continue to replicate, local dissemination via lymphatics and systemic spread throughout the body may occur via the bloodstream, creating new foci of infection. Many factors determine whether infection by MTB is contained or progress to overt disease. These include: extremes of age, immunosuppressive states, genetic factors, stress, environmental factors, and mycobacterial strain variation and virulence.

Both non-specific and specific effector mechanisms appear to play a role in protective immunity to TB. When MTB bacilli are inhaled, they reach the alveolae where they are phagocytosed by the alveolar macrophages, phagocytosis being facilitated by surfactant apoprotein A. This initial interaction can result in destruction of the organism or persistence and replication of the organism within the macrophage.

Protective T-cell mediated immunity involving CD4+ lymphocytes play a central role in immunity of TB. T cell responsiveness correlates inversely with disease progression in terms of low blastogenic responses to mycobacterium antigens in vitro and or absent skin tuberculin hypersensitivity seen in patients with advanced or uncontrolled disease. Further more, persons infected with HIV are extremely susceptible to TB.

In vivo Th 1 and Th 2 cells appear to act in concert with CD8+ cells, macrophages, B-cells and some stromal cells to give rise to cytokine release. Cytotoxicity from CD8+ T-cells also lead to release of mycobacteria from macrophages that have failed to kill them and enable their uptake by fresh activated cells.
2.7: Evasion of host immune responses.
A mycobacterium has evolved various strategies for avoiding killing by phagocytes. They inhibit acidification of the phagosome, modify intracellular trafficking of vesicles by interfering with maturation, blocking proton pump, and alter fusion pattern of the vesicle, and cause lipoarabinomannam (LAM) to insert into the glycosylphosphatidylinositol (GPI)-rich domains in the cell membrane.
LAM is itself a GPI of unusual glycan structure with the ability to modify numerous macrophage functions including the ability to respond to INFgamma and to present the antigen; hence the inability of macrophages containing mycobacteria to present antigen to CD4+ T cells.
Another mechanism involves blocking of apoptosis of macrophages, presumably because apoptosis also can lead to death of the contained bacteria. LAM also causes activation of SHP-1, a phosphotyrosine phosphatase intimately involved in cell signaling pathway.
Down-regulation of Fas together with increased expression of Fas ligand may lead the macrophage to signal apoptosis to Fas-positive T-cells thus leading to increased T-cell apoptosis.

2.8: Clinical presentation.
The clinical signs and symptoms of pulmonary TB in an infected adult are often nonspecific; complete absence of symptoms occurs in approximately 5% of active adult cases (29). Systemic manifestations include low-grade fever, anorexia, fatigue, night sweats, and weight loss that may persist for weeks to months (30).
Cough is the most frequent symptom referable to the site of lung infection (30). Early in the disease, it may be nonproductive, but subsequently there usually is production of mucoid or mucopurulent sputum. Hemoptysis may also occur. Inflammation adjacent to a pleural surface can cause pleuritic chest pain; dyspnea is unusual unless extensive lung involvement is present. Rarely, patients with miliary disease may present with symptoms of respiratory failure (31).
Specific clinical manifestations of TB are influenced by the age and immune status of the infected person (28). Diagnosis of TB in the elderly (≥65 years of age) is frequently delayed. In comparison to younger adults, the elderly are less likely to present with classic symptoms of cough, hemoptysis, fever, and night sweats (29). A cryptic presentation—fever of unknown origin often accompanied by pancytopenia or leukemoid reaction—is particularly common because of the greater frequency of hematogenous dissemination in this age group (29). The clinical features of TB in HIV-infected persons are dependent on the severity of their immunosuppression (32). Persons with relatively intact cellular immune function present with symptoms similar to the non–HIV-infected individuals, and TB generally remains localized to the lung. In persons with advanced HIV disease (CD4 T-lymphocyte count, <200/mm³), pulmonary TB is often accompanied by extra-pulmonary involvement, which most commonly takes the form of lymphadenitis or miliary disease (33). Depending on the sites of involvement, systemic or localized symptoms may predominate.

Radiology

Radiologic manifestations of pulmonary TB are dependent on several host factors, including prior exposure to TB, age, and underlying immune status. In persons with normal immune function, radiologic manifestations can be logically categorized into the two distinct forms of primary and postprimary disease.

**Primary disease:**

Lymphadenopathy is the radiologic hallmark of primary TB. While enlarged nodes occur in 83%–96% of pediatric cases (34), the prevalence of lymphadenopathy decreases with increasing age (34). Parenchymal involvement in primary pulmonary TB most commonly appears as an area of homogeneous consolidation, although patchy, linear, nodular, and mass like forms have also been described. Consolidation typically occurs in a segmental or lobar distribution; multifocal involvement is identified radiographically in 12%–24% and found at autopsy in 16% of the affected population (34).
Pleural effusion is an uncommon manifestation of primary TB in infants and young children (<2 years of age). The prevalence of effusion increases with age and is reported to be 6%-11% in children (34) and 29%-38% in adults (35). A pleural effusion usually develops on the same side as the site of initial tuberculous infection and is typically unilateral. Bilateral effusions occur in 12%-18% of cases with pleural involvement (34). Although usually observed in association with parenchymal and/or nodal abnormalities, pleural effusion is the only radiographic finding indicative of the presence of primary TB in approximately 5% of adult cases (35). The characteristic radiographic findings of miliary TB consist of innumerable, 1-3-mm, noncalcified nodules scattered throughout both lungs, with mild basilar predominance (36). A normal chest radiograph has a high negative predictive value for the presence of active TB. However, the frequency of false-negative examinations is approximately 1% in the adult immunocompetent population (29) and increases to 7%-15% in HIV-seropositive individuals (37-39).

Post Primary disease:
Parenchymal opacities situated in the apical and posterior segments of the upper lobes and the superior segment of the lower lobes, often associated with cavitation, are the characteristic radiographic manifestations of postprimary TB. Cavitation in single or multiple sites is evident radiographically in 40%-45% of cases of postprimary TB (41).

TB in acquired immunodeficiency syndrome.
The radiographic manifestations of HIV-associated pulmonary TB are dependent on the level of immunosuppression at the time of overt disease (40). Persons with relatively intact cellular immune function demonstrate radiographic findings similar to those of non-HIV-infected individuals (42). At severe levels of immunosuppression, 10%-20% of co-infected persons have normal radiographs (38-40) or demonstrate findings usually associated with primary disease or atypical manifestation of reactivation of TB (32).
2.9: Diagnosis.

2.9.1: Sputum microscopy.

Use is made of acid-fast property of mycobacteria to detect them in sputum. In ZN technique heat fixed smears of specimens are flooded with a solution of carbol fuschin and heated until steam rises. After washing with water the slide is flooded with dilute mineral acid and further washing with water a green or blue counter stain is applied. Red bacilli are seen against a contrasting background color using light microscopy. A minimum of 100 fields of ZN smear must be examined before reporting a negative result and this examination takes about 5-10 minutes (43). One sputum smear positive for AFB or two smear negative for AFB and chest radiography consistent with TB or smear negative culture positive sputum makes the diagnosis of pulmonary TB (6).

Fluorescence microscopy is based on the same principle of acid fastedness, however auramine-phenol staining is used and it only takes 1-2 minutes to read. The major disadvantages are; the need for a reliable electricity supply, the extra capital outlay (a fluorescence microscope is 4-5 times more expensive than a light microscope), and the additional maintenance (halogen lamps must be replaced after 200 hours of use) (44). About 5000-10,000 AFB per ml of sputum must be present for detection by smear, whereas culture requires only 10-100 viable organisms (45).

2.9.2: Sputum culture.

Sputum culture is the gold standard for diagnosis of tuberculosis. However, the mycobacterium is a slow growing organism and culture takes several weeks. In addition sputum culture for HIV-infected individuals requires more incubation time than for non-HIV infected patients. Tubercle bacilli are able to grow on a wide range of enriched media, but Lowenstein-Jensen (L-J) medium is the most widely used. It is an egg-glycerol based medium to which malachite green dye is added to inhibit growth of some contaminating bacteria and to provide contrasting color against which colonies of mycobacteria are easily seen. Sputum is decontaminated using petroff method whereby it is mixed with 4% sodium hydroxide for 15-30 minutes, neutralized with potassium hydroxide.
orthophosphate and centrifuged. The deposit is then inoculated on L-J slopes. Inoculated media are incubated at 35-37°C and inspected weekly for at least eight weeks. Any bacterial growth is stained by ZN method and if acid fast is sub cultured for further identification.

Agar based media or broths enriched with bovine serum albumin are also used particularly in automated culture system. BACTEC, MGIT 960, Mb/Bact, Septi-check and ESP, when combined with DNA probes for rapid species identification, are capable of producing a positive result in two weeks for a vast majority of smear positive specimens and within three weeks for smear negative specimens (46).

2.9.3: Chest radiograph.

Chest radiography plays a significant role in shortening delays in diagnosis and should be performed early in the course of investigation of the TB suspect whenever available (6).

However, sound clinical judgment is needed to put a serious ill patient with smear negative sputum on anti-tuberculous chemotherapy using only suggestive radiograph findings. Clinical response of patients has to be monitored and diagnosis confirmed preferably by culture. Existing limitations to the use of chest radiograph as a diagnostic tool are its non-availability at peripheral health facilities and difficulty in interpreting results.

2.9.4: Role of antibiotic trial.

There is little evidence for the use of empirical antibiotic treatment to rule out tuberculosis as a cause of cough in HIV infected persons. Although non-response to antibiotics increases the likelihood of tuberculosis, the converse is not true. Inappropriate use of broad-spectrum antibiotics, may also lead to drug resistance, treatment delay and death of patients because of prolonged symptoms.
2.9.5: Tuberculin skin Testing.
Austrian physician Clemens von Pirquet used the Koch phenomenon as an indication of bacterial allergy resulting from previous infection. Individuals with active TB were usually tuberculin positive but many of those with disseminated or rapidly progressive disease were negative. Solutions of PPD for mantoux are supplied as solutions of 1:10,000, 1:1000 and 1:100. Standard test dose is 10 IU but those suspected of TB may just be tested with 1 IU. Induration of greater than or equal to 5mm at 48-72 hours is considered to be positive. In developing countries, tuberculin skin testing is confounded by high coverage of BCG vaccination, asymptomatic TB infection, the presence of non-tuberculous mycobacteria and anergy due to HIV or malnutrition (47). TST, therefore, has no place in diagnostic algorithms in these settings.

2.9.6: Bronchoscopy.
Bronchoscopy for bronchoalveolar lavage and staining for AFB has been used in diagnosis. However, bronchoscopes are expensive and require on-going disinfections and maintenance. Bronchoscopy is also an invasive procedure with recognized complications. Daley et al; (1996), evaluated the role of brochoscopy among 237 patients in Tanzania with negative sputum smears for MTB and found that only 7% required bronchoscopy and a treatable disease was found in 3% (48). They concluded that bronchoscopy had little place in the investigation of smear negative TB patients in resource poor settings.

2.9.7: Nucleic acid amplification (NAA).
Currently two nucleic acid amplification (NAA) methods are available for commercial use. MTG (Gen probe) and Amplicor(Roche). MTG assay is an isothermal strategy for DNA amplification, and ampiclor kit uses polymerase chain reaction (PCR) to amplify unique nucleic acid targets that uniquely identify MTB in clinical specimens. Each test accurately diagnoses nearly every case of sputum smear positive and about half the cases of smear negative, culture positive PTB. NAA has sensitivity of 80-84%. At present this tests are expensive, cannot certainly replace culture and have not been validated in developing countries under field conditions (49).
3.0. JUSTIFICATION OF THE STUDY

The high prevalence of TB in Kenya has created an urgent need for rapid diagnosis and effective treatment of patients with this disease especially those with PTB who are responsible for infection transmission.

Sputum smear microscopy services are only available in 705 of 1,605 health units offering TB services under NLTP. Sputum cultures are only available in a few facilities in Nairobi and take up to 8 weeks to yield results.

In most hospitals the initial decision to isolate patients and treat is still based only on clinical symptoms and signs, physical examination and initial chest radiography.

Few prospective studies have tested extensively the diagnostic yield of clinical symptoms and chest radiographic findings in patients suspected to have pulmonary tuberculosis.

In hospitals such as KNH with very large numbers of patients at risk, it becomes important to establish the predictive values of these tests to diagnose tuberculosis and, therefore, minimize costs of treatment, hospital stay, morbidity and mortality.

4.0. RESEARCH QUESTION

Is it possible to reliably diagnose tuberculosis on the basis of clinical symptoms, and chest radiographic findings?
5.0. OBJECTIVES:
5.1: Broad objective.
To determine the predictive value of *clinical symptoms and *chest radiography, in the diagnosis of pulmonary Tuberculosis

5.2: Specific objectives
1. To determine the proportion of patients who have culture confirmed TB among those with cough for more than two weeks.
2. To determine the prevalence of other symptomatology in patients presenting with cough for more than two weeks.
3. To identify *clinical variables both singly and in combination, that best predict diagnosis of culture proven infection.
4. To determine the predictive value of *chest radiographic characteristics of culture proven infection.
5. To determine if HIV status of the patient influences the symptomatology and radiological features of pulmonary Tuberculosis.

Sputum cultures were used to validate the clinical symptoms* and the chest radiographic findings*.

* see study definitions in appendix I

6.0. METHODOLOGY
6.1: Site.
Accident and emergency department and adult medical wards, Kenyatta National Hospital (KNH): Nairobi, Kenya.

6.2: Study population.
All patients either seen in accident and emergency department or admitted to KNH adult medical wards with cough for two weeks or more and whose consent for inclusion was obtained.

6.3: Study design.
A prospective, cross-sectional hospital based survey.
6.4: Case definition

6.4.1: Inclusion Criteria

1. Above the age of 15 years
2. Cough for more than two weeks.
3. Written consent from patient or next of kin where the patient was unable to give consent and ability of the patient or the next of kin to respond to the questionnaire.

6.4.2: Exclusion Criteria

1. Patients who were currently receiving tuberculosis treatment.
2. Patients who were unable to produce quality sputum.
3. Age below 15 years
4. Very sick patients who were unable to follow the protocol.

A correctly diagnosed case was defined as a patient with at least one positive sputum culture out of three cultures while a patient with three negative cultures was regarded as not having tuberculosis.

6.5: Sampling Technique

Consecutive sampling of patients either seen in accident and emergency or admitted to the medical wards at KNH, who fulfilled the inclusion criteria was done until the desired sample size was achieved. Sampled patients underwent sputum smear examination for AFB and chest radiography. In addition, a sputum culture for *Mycobacterium tuberculosis* complex was carried out on all included patients. Once a positive sputum culture was obtained, the clinician in charge of the patient was informed and appropriate action taken.
6.6: Sample size

Sample size calculation was done using formula by Lwanga SK, Lemeshow W (1991) (50).

\[ n = \left( Z_{1-\alpha/2} \right)^2 \frac{p(1-p)}{d^2} \]

- **n**: Sample size
- **Z**: Standard normal deviate corresponding to 95% confidence interval, which is 1.96
- **α**: Level of significance set at 5%
- **P**: Estimated proportion of confirmed TB cases among patients with cough for three weeks or more. From a study done in Kenya this value was 56% (51).
- **d**: Error margin set at +/-0.06

Substituting the above values gave a minimum sample size of 263 patients.

6.7: Screening and recruitment

The principal investigator with the help of two study assistants reviewed patients both in accident and emergency department and admissions in the medical wards who had cough for more than two weeks. The study assistants consisted of an undergraduate medical student and a clinical officer who were trained by the PI on the requirements of the study.

A screening profoma was used to enter details of the patients. The aims of the study and what it entails was explained to the patients who fulfilled the inclusion criteria. Consent explanation was then done. It was clarified that refusal to give consent did not result in discrimination in care. Written informed consent was then sought from the patient or next of kin, where the patient was unable to give consent, prior to inclusion into the study. Only patients for whom consent was obtained were included.
6.9: Data Collection.
6.9.1. Clinical methods
A screening profoma was used to obtain data from patients presenting with cough for more than two weeks. It included the age, gender, HIV status of the patient, residence, occupation, level of education, history of alcohol intake or cigarette smoking, past medical history of TB treatment, TB contact, chemotherapy, malignancy, use of steroids, diabetes mellitus, exposure to silicon and duration of symptoms.

A study profoma was used to record further data on patients included into the study.

A complete medical history and physical examination with emphasis on past medical history of TB treatment, TB contact and examination of the respiratory system was carried out on all patients included in the study. Weight was measured once with a lever balance to the nearest 100 grams without shoes and in light garments.

The PI or the study assistants asked the patient to spontaneously expectorate the 1st sputum specimen known as the spot specimen, which was taken to KNH laboratory for ZN staining. The patient was instructed to cough up sputum samples from the lungs and not saliva, in a well-ventilated room or away from people and not in a confined space. At the same time the PI with the assistance of a trained counselor offered diagnostic testing and counseling (DTC) for HIV to all patients with unknown status. A pre-test counseling was done before testing. A rapid test consisting of both unigold and bioline methods was then done in parallel for those who consented, after which post-test counseling was done. However, those who declined to have the test were still included in the study and their status entered as unknown. Chest radiography was performed at the KNH radiology unit at the first contact with the patient.

The patient was then given a second container to collect an early morning specimen. For those seen as outpatient a specimen collection point was created at the accident and emergency department. For in-patients the 2nd sputum specimen was collected from the medical wards by the PI in the morning.
One more early morning sputum sample was taken to the central reference laboratory for culture. The containers used for sputum transport were; plastic and rigid to avoid crushing on transit, had watertight wide mouthed screw top to prevent leakage and contamination.

Before transport sputum samples were stored in a cool place and transported packed in material that absorbed any leakage caused by accidents. Patient’s data was entered into a form and the accompanying container labeled before being sent to the central reference laboratory.

6.9.2. Laboratory Methods

A. Sputum Microscopy.

At least two spontaneously expectorated sputa were collected into sterile, wide mouthed plastic containers with a secure lids. AFB smears were performed on sputum samples using ZN method. Each slide was processed separately to avoid contamination through transfer of bacilli from one smear to another. Two trained and experienced laboratory technologists independently read the smears. Any discrepant result was re-checked at the central reference laboratory by a third technologist. The technologist needed to identify greater than three AFB in the smear before reporting a positive test. Smear positive and negative controls were used to check each new batch of reagents and each staining run. A positive sputum culture was used to validate the results.

B: Sputum culture

Sputum samples were processed at the national central reference laboratory. 2.5ml of sputum sample was poured into 50ml falcon tubes. Decontamination was done by adding an equal volume of 4% sodium hydroxide, vortexing for two minutes, and standing for 15 minutes, then neutralizing with 6.8 potassium hydroxide orthophosphate and centrifuging at 3000 RPM for 10 minutes. The supernatant was then discarded and the sample re-suspended by vortexing. A smear was prepared from the deposit, stained by ZN method, examined and reported. The deposit was further inoculated onto three L-J slopes, one plain and two with pyruvate, and incubated at 37°C until growth of colonies was observed.
or until eight weeks. Inspection was done after 48 hours to exclude fast growing organisms and then weekly. Any bacterial growth was stained by ZN method and if acid fast (long, slender gently curving bacilli with eccentrically located beading) slowly growing on L-J media producing rough, dry, buff-colored colonies were tested for the presence of _mycobacterium tuberculosis_ complex with the use of, a positive niacin test; a positive nitrate reduction test and a positive p-nitro benzoic acid. Two independent, trained and experienced microbiologists were involved in interpreting the cultures. Where there was discrepancy, a third microbiologist re-examined the cultures. Date of appearance of the colonies was also recorded. Positive growth was quantitated as the total number of colony forming units (cfu). Only colonial morphology consistent with _M.tuberculosis_ complex was considered for the purposes of this study. Results of the sputum culture were then entered into the standard bacteriological examination form. If there was no growth after eight weeks or in case of contamination, the cultures were discarded and laboratory forms completed accordingly.

To maintain internal Quality control, a standard strain of _Mycobacterium tuberculosis_ was inoculated in each new batch of L-J medium. The external quality assurance of the central reference laboratory was maintained by CDC-Atlanta and Brisbane Australia.

**C. Chest Radiography**

Chest radiographs were performed on all included patients before taking the sputum for smear microscopy for AFB. The principal investigator with the assistance of two trained and experienced radiologists blinded to the laboratory diagnosis of TB independently assessed the chest radiographs. The radiologists reported the radiographs according to the categories listed in appendix I. The PI then entered the findings in the study profoma.
6.9.3. Data analysis

Data filled in the profoma was entered into data entry sheet. It was then cleaned and verified to ensure that quality was maintained. Statistical analysis was performed using Statistical Package for Social Sciences version 15 software for windows.

Chi Square test (and for small numbers, the Fischer's exact test) was used to analyze categorical variables such as sputum smear microscopy results, Sputum culture results, HIV status, gender, and radiological findings among patients who had pulmonary tuberculosis compared to those not infected.

Students' t-test was used to analyze continuous variables such as age.

Logistic regression models using backward selection technique to choose the final model were used to identify clinical and radiological features that independently or in combination predicted diagnosis of culture proven pulmonary tuberculosis.

2 × 2 tables were used to perform the predictive values of study outcome variables.

<table>
<thead>
<tr>
<th>Clinical Symptoms. e.g. Fever and Radiology e.g. pleural effusion</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True</td>
<td>False</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive (A)</td>
<td>Positive (B)</td>
</tr>
<tr>
<td>Negative</td>
<td>False</td>
<td>True</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative (C)</td>
<td>Negative (D)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gold Standard – sputum Culture.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV = A/A+B</td>
</tr>
<tr>
<td>NPV = D/C+D</td>
</tr>
<tr>
<td>Prev = A+C/A+B+C+D</td>
</tr>
</tbody>
</table>

PPV: Positive Predictive Value.
NPV: Negative Predictive Value.
Prev: Prevalence.

Data was then presented in tables, graphs, and pie charts.

A p-value of less than 0.05 was considered significant.
7.0. ETHICAL CONSIDERATIONS

The study was conducted after approval by the department of internal medicine, University of Nairobi and the Kenyatta National Hospital Scientific and Ethical Review Committee.

HIV testing was offered along with the sputum examination for AFB for all included patients. Pre-test counseling was done before doing the HIV test in patients with unknown status. A rapid test consisting of both bioline and unigold was done in parallel on those who consented. However if they declined to have the test done they were still included into the study and their status entered as unknown. For those who gave consent, post-test counseling was then done.

Patients received a written explanation of what the study entailed and its potential benefits and harms to them and the society from the principal investigator (PI). They were informed that the project involved research and the purpose of the research was explained. They also received an explanation on the study process, and the tests to be done in lay terms. They were informed that joining the study was voluntary and they would not be denied care should they decline participation. They were free to withdraw from the study without any penalty. They were assured that confidentiality would be strictly maintained and all data obtained would be securely stored. Consent forms were prepared in English. An interpreter was used for those patients who did not understand English. In the event that the patient was unable to give consent, their next of kin received the consent explanation on their behalf. Only consenting patients were enrolled into the study. The patients/ next of kin were requested to sign an informed consent form. All patients received the standard care for their illness and those with positive culture had their results communicated to their primary health care giver. Patients who declined to give consent were excluded from the study.

WHO guidelines for prevention of spillage and risk of infection to other patients, members of staff and the survey working team as explained were adhered to.
8.0. RESULTS

8.1: Recruitment

The study was carried out between September 2007 and February 2008. A total of 429 patients with cough for more than two weeks were recruited into the study. Out of these 271 were included into the study while 158 were excluded.
8.2 Demographic characteristics.

271 patients were included into the study, 126 (46.5%) had sputum culture confirmed PTB. Of these 68 (54%) were males and 58 (46%) were females. Male to female ratio was 1.2:1 (Table 1). There were more females with culture confirmed TB in the HIV positive group 30 (54.5%) compared with 20 (35.7%) in the HIV negative group.

The age distribution ranged from 15 to 63 years with majority of the patients falling in the 25-34 age brackets. 48 (87.3%) patients with HIV/TB co infection were aged between 15-49 years (figure 1). The mean age was 32 years with a median of 30 years.

Table 1: General characteristics of the 126 subjects with culture proven pulmonary Tuberculosis.

<table>
<thead>
<tr>
<th></th>
<th>Culture positive n=126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>58 (46%)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>55 (44%)</td>
</tr>
<tr>
<td>Negative</td>
<td>56 (44%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>46 (37%)</td>
</tr>
<tr>
<td>Married</td>
<td>65 (52%)</td>
</tr>
<tr>
<td>Widowed</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>separated</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>Nairobi</td>
<td>105 (83%)</td>
</tr>
<tr>
<td>Up-country</td>
<td>21 (17%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Primary</td>
<td>70 (56%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>37 (29%)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>46 (37%)</td>
</tr>
<tr>
<td>Employed</td>
<td>32 (25%)</td>
</tr>
<tr>
<td>unemployed</td>
<td>39 (31%)</td>
</tr>
<tr>
<td>Student</td>
<td>9 (7%)</td>
</tr>
</tbody>
</table>

Majority of the patients with culture confirmed TB were married 65(52%), had attained primary education 70(56%), resided in Nairobi 105(83%) and were either self employed 46(37%) or unemployed 39(31%)
8.3: Prevalence of risk factors associated with pulmonary tuberculosis.

Figure 1: Diagram showing risk factors associated with TB in the 126 patients

HIV infection was the most common risk factor associated with PTB (44%), followed by contact with an open case of TB (33%) and cigarette smoking (26%). Of the eight patients who had been previously treated for TB, six were HIV positive and two HIV negative.
8.4: Clinical symptoms

Figure 2: Prevalence of specific individual clinical symptoms among patients diagnosed with TB. n=126

Majority of the patients with cough for more than two weeks had associated weight loss (52%), drenching night sweats (40%) and pleuritic chest pain (45%).
8.4.1: Clinical predictors of culture positive TB in the 271 patients

Table 2: Individual clinical symptoms and their predictive value in the diagnosis of TB

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Culture positive TB n=126</th>
<th>Culture negative TB n=145</th>
<th>P value</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Yes 49(39%) se</td>
<td>46(32%)</td>
<td>0.218</td>
<td>52a</td>
</tr>
<tr>
<td></td>
<td>No 77(61%)</td>
<td>99(68%) sp</td>
<td></td>
<td>56b</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Yes 66(52%) se</td>
<td>41(28%)</td>
<td>&lt;0.001</td>
<td>65a</td>
</tr>
<tr>
<td></td>
<td>no 60(48%)</td>
<td>104(72%) sp</td>
<td></td>
<td>63b</td>
</tr>
<tr>
<td>Drenching Night sweats</td>
<td>Yes 50(40%) se</td>
<td>26(18%)</td>
<td>&lt;0.001</td>
<td>66a</td>
</tr>
<tr>
<td></td>
<td>No 76(60%)</td>
<td>119(82%) sp</td>
<td></td>
<td>61b</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Yes 22(17%) se</td>
<td>34(27%)</td>
<td>0.225</td>
<td>39a</td>
</tr>
<tr>
<td></td>
<td>No 104(83%)</td>
<td>111(73%) sp</td>
<td></td>
<td>52b</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Yes 28(22%) se</td>
<td>36(29%)</td>
<td>0.614</td>
<td>43a</td>
</tr>
<tr>
<td></td>
<td>No 98(78%)</td>
<td>109(71%) sp</td>
<td></td>
<td>53b</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>Yes 57(45%) se</td>
<td>38(26%)</td>
<td>0.001</td>
<td>60a</td>
</tr>
<tr>
<td></td>
<td>No 69(55%)</td>
<td>107(74%) sp</td>
<td></td>
<td>61b</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Yes 16(13%) se</td>
<td>16(11%)</td>
<td>0.672</td>
<td>50a</td>
</tr>
<tr>
<td></td>
<td>No 110(87%)</td>
<td>129(89%) sp</td>
<td></td>
<td>51b</td>
</tr>
</tbody>
</table>

P < 0.05 was considered statically significant

Se: sensitivity

Sp: specificity

a; positive predictive value

b: negative predictive value
In univariate analysis weight loss (p<0.001), OR 2.79 (95% CI, 1.68-4.61), drenching night sweats (p <0.0001) OR 3.01 (95% CI, 1.73-5.241) and pleuritic chest pain (p =0.001) OR 2.33 (95% CI, 1.39-3.87) were significantly associated with culture confirmed TB (Table 2).

Weight loss had PPV of 65% and NPV of 63%, while drenching night sweats and pleuritic chest pain had PPV of 66%, 60% and NPV of 61%, 61% respectively. The PPV of the combined three symptoms was 64% with NPV of 61%.

In the logistic regression model done using backward selection technique to choose a final model, Weight loss (p=0.001), OR 1.65 (95% CI, 1.26-2.17), drenching night sweats (p =0.001) OR 1.76 (95% CI, 1.30-2.38) and pleuritic chest pain (p =0.001) OR 1.73 (95% CI, 1.31-2.28) independently predicted diagnosis of TB.

**Table 3: Combination of clinical symptoms that best predicted diagnosis of TB in the 126 patients with culture confirmed TB.**

<table>
<thead>
<tr>
<th>Combination of symptoms</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea, night sweats, weight loss</td>
<td>0.068</td>
<td>2.28 (0.94-5.53)</td>
</tr>
<tr>
<td>Fever, weight loss, night sweat</td>
<td>0.928</td>
<td>1.01 (0.79-1.28)</td>
</tr>
<tr>
<td>Night sweats, chest pain, weight loss</td>
<td>0.046</td>
<td>1.28 (1.15-1.42)</td>
</tr>
<tr>
<td>Fever, night sweats</td>
<td>0.363</td>
<td>1.29 (0.73-2.29)</td>
</tr>
<tr>
<td>Weight loss, night sweats</td>
<td>0.688</td>
<td>0.88 (0.50-1.55)</td>
</tr>
<tr>
<td>Weight loss, chest pain</td>
<td>0.462</td>
<td>1.26 (0.67-1.63)</td>
</tr>
<tr>
<td>night sweats, chest pain</td>
<td>0.258</td>
<td>0.74 (0.45-1.24)</td>
</tr>
</tbody>
</table>

The combination of symptoms that best predicted diagnosis of TB included; night sweats, chest pain and weight loss (p= 0.046) OR 1.28 (95% CI, 1.15-1.42).
8.5: Chest radiographic findings

Table 4: predictive value of chest radiography in the diagnosis of TB among 271 patients

<table>
<thead>
<tr>
<th>Chest radiographic configuration</th>
<th>Culture positive TB n=126</th>
<th>Culture negative TB n=145</th>
<th>Predictive value (%)</th>
<th>P value</th>
<th>OR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular, alveolar infiltrates affecting upper zones</td>
<td>Yes 45(36%)se 19(13%)</td>
<td>126(87%)sp 61b</td>
<td>70a</td>
<td>&lt;0.001</td>
<td>3.7(2.0 to 6.7)</td>
</tr>
<tr>
<td></td>
<td>No 81(64%)</td>
<td>126(87%)sp</td>
<td>61b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitations affecting upper zones</td>
<td>Yes 36(29%)se 13(9%)</td>
<td>132(91%)sp 60b</td>
<td>74a</td>
<td>&lt;0.001</td>
<td>4.0(2.0 to 8.0)</td>
</tr>
<tr>
<td></td>
<td>No 90(71%)</td>
<td>132(91%)sp</td>
<td>60b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged hilar nodes or mediastinal shadows</td>
<td>Yes 13(10%)se 12(8%)</td>
<td>133(92%)sp 54b</td>
<td>52a</td>
<td>0.56</td>
<td>1.3(0.4 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>No 113(90%)</td>
<td>133(92%)sp</td>
<td>54b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonic lesion</td>
<td>Yes 24(19%)se 34(23%)</td>
<td>111(77%)sp 52b</td>
<td>41a</td>
<td>0.38</td>
<td>0.8(0.4 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>No 102(81%)</td>
<td>111(77%)sp</td>
<td>52b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>Yes 11(9%)se 11(8%)</td>
<td>134(92%)sp 54b</td>
<td>50a</td>
<td>0.73</td>
<td>1.2(0.5 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>No 115(91%)</td>
<td>134(92%)sp</td>
<td>54b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural exudates</td>
<td>Yes 24(19%)se 34(32%)</td>
<td>111(68%)sp 52b</td>
<td>41a</td>
<td>0.38</td>
<td>0.8(0.4 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>No 102(81%)</td>
<td>111(68%)sp</td>
<td>52b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Yes 9(7%)se 12(8%)</td>
<td>133(92%)sp 53b</td>
<td>43a</td>
<td>0.73</td>
<td>0.9(0.3 to 2.1)</td>
</tr>
<tr>
<td></td>
<td>No 117(93%)</td>
<td>133(92%)sp</td>
<td>53b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse reticulonodular infiltrates</td>
<td>Yes 6(5%)se 19(13%)</td>
<td>126(87%)sp 51b</td>
<td>24a</td>
<td>0.02</td>
<td>0.3(0.1 to 1.0)</td>
</tr>
<tr>
<td></td>
<td>No 120(95%)</td>
<td>126(87%)sp</td>
<td>51b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < 0.05 was considered statically significant

Se: sensitivity

Sp: specificity

a: positive predictive value (PPV)

b: negative predictive value (NPV)
In univariate analysis there was a significant difference between culture positive TB and culture negative TB patients in respect to nodular, alveolar infiltrates predominantly affecting upper zones (P<0.0001), cavitations affecting upper zones or the apical segments of the lower lobes (p<0.0001) and diffuse reticulonodular pattern (p=0.018) with PPV of 70%, 74%, 24% and NPV of 61%, 60%, 51% respectively. (Table 4)

In logistic regression model, nodular alveolar infiltrates predominantly affecting upper lobes (OR 1.43, 95% CI, 1.58-2.78), cavitations affecting upper zones (OR 1.54, 95% CI, 1.38-2.77) independently predicted diagnosis of TB.

8.6: Influence of HIV status on the symptomatology and radiological features.

Table 5: A comparison of individual clinical symptoms in HIV positive and HIV negative patients with culture confirmed TB

<table>
<thead>
<tr>
<th>symptom</th>
<th>HIV positive n=55</th>
<th>HIV negative n=56</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>23(39.2%)</td>
<td>24(41.5)</td>
<td>0.912</td>
<td>0.96(0.45-2.03)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>42(47.1%)</td>
<td>19(35.8%)</td>
<td>&lt;0.001</td>
<td>6.29(2.73-14.5)</td>
</tr>
<tr>
<td>Drenching night sweats</td>
<td>21(39.2%)</td>
<td>21(37.7%)</td>
<td>0.941</td>
<td>1.03(0.48-2.22)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>5(9.8%)</td>
<td>16(28.3%)</td>
<td>0.009</td>
<td>1.71(1.23-2.39)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>12(21.6%)</td>
<td>13(22.6%)</td>
<td>0.860</td>
<td>0.92(0.38-2.25)</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>22(37.4%)</td>
<td>25(45.3%)</td>
<td>0.621</td>
<td>0.82(0.39-1.76)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6 (11.8%)</td>
<td>9 (15.1%)</td>
<td>0.426</td>
<td>0.63(0.21-1.93)</td>
</tr>
</tbody>
</table>

Haemoptysis (p=0.009) was frequently observed in patients with TB who were HIV negative. Weight loss was significantly associated with culture confirmed TB in HIV positive patients (p<0.001). (Table 5)
Table 6: A comparison of chest radiographic findings in HIV positive and HIV negative patients with culture confirmed TB.

<table>
<thead>
<tr>
<th>Chest radiographic configuration</th>
<th>HIV positive n=55</th>
<th>HIV negative n=56</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular alveolar infiltrates predominantly affecting upper zones</td>
<td>16(29%)</td>
<td>24(43%)</td>
<td>0.131</td>
</tr>
<tr>
<td>Cavitations affecting upper zones</td>
<td>8 (14%)</td>
<td>22(39%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Enlarged hilar nodes or mediastinal shadows</td>
<td>8 (14%)</td>
<td>2(4%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Pneumonic lesion</td>
<td>6 (11%)</td>
<td>15(27%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Pleural exudates</td>
<td>15(27%)</td>
<td>9(16%)</td>
<td>0.152</td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>11(20%)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diffuse reticulonodular infiltrates</td>
<td>6(11%)</td>
<td>0</td>
<td>0.013*</td>
</tr>
<tr>
<td>Normal</td>
<td>6(11%)</td>
<td>1(2%)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

* Fischer’s exact test

P < 0.05 was considered statically significant

Comparing HIV positive patients to the HIV negative patients with TB, the former was significantly associated with enlarged hilar nodes or mediastinal shadows (p=0.043), miliary pattern (p <0.0001), diffuse reticulonodular infiltrates (p=0.013) and normal chest radiographs(p=0.048), while the later was significantly associated with cavitations(p=0.003) . (Table 6)
8.7: CD 4+ counts in HIV positive patients with culture confirmed TB.

Figure 3: diagram showing CD4+ cell count distribution in HIV positive patients with culture confirmed TB

Mean CD4 count was 124 cell/mm³ with a median of 98 cells/mm³ and a range of (4-501)
Chest radiographic findings in terms of CD4+ counts in HIV positive patients with culture confirmed TB

Table 7: Percentage of patients with CD4+ cell count (/mm³)

<table>
<thead>
<tr>
<th>Chest radiographic pattern</th>
<th>CD4+ counts cells/mm³</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All n=55</td>
<td>0-100 n=32</td>
</tr>
<tr>
<td>Nodular, alveolar infiltrates predominantly affecting upper zones</td>
<td>18</td>
<td>6%</td>
</tr>
<tr>
<td>Cavitations affecting upper zones</td>
<td>14</td>
<td>15%</td>
</tr>
<tr>
<td>Enlarged hilar nodes or mediastinal shadows</td>
<td>8</td>
<td>19%</td>
</tr>
<tr>
<td>Pneumonic lesion</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>Pleural exudates</td>
<td>13</td>
<td>19%</td>
</tr>
<tr>
<td>Milliary pattern</td>
<td>11</td>
<td>28%</td>
</tr>
<tr>
<td>Diffuse reticulonodular infiltrates</td>
<td>6</td>
<td>16%</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>13%</td>
</tr>
</tbody>
</table>

* Fischer’s exact test

P < 0.05 was considered statically significant

Enlarged hilar nodes, milliary pattern and normal chest radiograph were more frequently seen in patients with advancing levels of immune deficiency, CD4 less than 100cells/mm³ (19%, 28% and 13%) respectively while cavitations, pleural exudates and nodular infiltrates affecting upper zones were more frequent in patients with CD4 counts >300 cells/mm³ (38%, 21%, 38%) respectively. However none of these trends achieved statistical significance (Table 7)
Sputum smear microscopy by ZN method had sensitivity of 71% and specificity of 96%.

Smear microscopy was frequently positive in patients without HIV infection 46(82%) compared to 33(60%) who were infected with HIV (p=0.019).

Of the smear negative TB, 22(69%) were HIV positive and 10(31%) were HIV negative.

Smear microscopy had a sensitivity of 71% and specificity of 98% in the diagnosis of TB in patients with cough for 2-3 weeks. Sensitivity increased to 80% in patients with cough for more than 3 weeks with a specificity of 93%.
Table 8: A comparison of individual clinical symptoms between patients who were both smear and culture positive for TB and those who were smear negative, culture positive for TB.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Smear pos, culture pos n=94</th>
<th>Smear neg, culture pos n=32</th>
<th>P value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>48 (51%)</td>
<td>17 (53%)</td>
<td>0.225</td>
<td>0.61(0.28-1.35)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>45 (48%)</td>
<td>21 (66%)</td>
<td>0.397</td>
<td>0.71(0.32-1.56)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>34 (36%)</td>
<td>16 (50%)</td>
<td>0.490</td>
<td>0.76(0.35-1.66)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>19 (20%)</td>
<td>3 (9%)</td>
<td>0.088</td>
<td>2.9(0.81-10.64)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>21 (22%)</td>
<td>7 (22%)</td>
<td>0.635</td>
<td>1.26(0.48-3.29)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>42 (45%)</td>
<td>15 (47%)</td>
<td>0.610</td>
<td>1.22(0.56-2.67)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10 (11%)</td>
<td>6 (19%)</td>
<td>0.397</td>
<td>0.39(0.21-1.87)</td>
</tr>
</tbody>
</table>

There was no significant difference between patients who were both smear and culture positive for TB and those who were smear negative culture positive as regards to their clinical symptoms. However haemoptysis was more frequent among patients who were both smear and culture positive for TB (p=0.088) (Table 8)
Table 9: A comparison of chest radiographic findings between patients who were both smear and culture positive for TB and those who were smear negative, culture positive.

<table>
<thead>
<tr>
<th>Chest radiographic configuration</th>
<th>Smear pos, culture pos n=94</th>
<th>Smear neg, Culture pos n=32</th>
<th>P value</th>
<th>Odds ratio(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular alveolar infiltrates predominantly affecting upper zones</td>
<td>36 (38%)</td>
<td>9 (28%)</td>
<td>0.112</td>
<td>0.6(0.3-1.2)</td>
</tr>
<tr>
<td>Cavitations affecting upper zones</td>
<td>30 (32%)</td>
<td>6 (19%)</td>
<td>0.061</td>
<td>0.5(0.2-1.1)</td>
</tr>
<tr>
<td>Enlarged hilar nodes or mediastinal shadows</td>
<td>10 (11%)</td>
<td>3 (14%)</td>
<td>0.643</td>
<td>0.8(0.3-2.2)</td>
</tr>
<tr>
<td>Pneumonic lesion</td>
<td>17 (18%)</td>
<td>7 (22%)</td>
<td>0.943</td>
<td>1.0(0.5-2.0)</td>
</tr>
<tr>
<td>Pleural exudates</td>
<td>18 (19%)</td>
<td>6 (19%)</td>
<td>0.667</td>
<td>0.9(0.4-1.8)</td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>6 (6%)</td>
<td>5 (16%)</td>
<td>0.197</td>
<td>1.7(0.8-3.4)</td>
</tr>
<tr>
<td>Diffuse reticulonodular infiltrates</td>
<td>5 (5%)</td>
<td>1 (3%)</td>
<td>0.673*</td>
<td>0.6(0.1-3.5)</td>
</tr>
<tr>
<td>Normal</td>
<td>3 (3%)</td>
<td>6 (19%)</td>
<td>0.009</td>
<td>2.6(1.5-4.5)</td>
</tr>
</tbody>
</table>

Comparing patients with both smear and culture positive and those who were smear negative, culture positive, patients with smear negative TB were 2.6 fold likely to present with a normal chest radiograph (Table9).
Figure 5: Comparison of CD4 counts and smear microscopy in HIV positive patients with culture positive TB

Majority (32%) of culture confirmed smear negative pulmonary TB patients had CD4 counts of less than 100 cells/mm3 with very few (9%) having CD4 greater than 300 cell/mm3
The general prevalence of TB in this study was 46.5%. Earlier study done in Nairobi by Van Cleef et al reported a prevalence of 53% (51). This is consistent with a study done by Shungu et al in Zimbabwe who reported a prevalence of 43% (52). An Cohen et al in USA found a prevalence of 44% (53) while Tattevin in a French multi centre study reported a prevalence of 22% (54). This high prevalence of TB noted especially in sub-Saharan Africa implies that measures need to be put in place to curb transmission of TB if we are to achieve control of the disease.

Prevalence of HIV in the incident TB cases was 44% (table1) which is consistent to what has been observed elsewhere. In hospital based series in Zimbabwe, Botswana, Ivory Coast and Zambia, 40-65% of HIV infected patients with respiratory disease had TB (52, 55-57). Indeed there is an interaction between HIV and TB that accelerates development of both diseases. In this regard, HIV infection amplifies and accelerates the development of TB, and is the most important known risk factor associated with reactivation of a prior TB infection. Likewise TB reduces CD4+ lymphocytes, hence intensifying the immunosuppressant effect of HIV itself. Hence with such a large percentage of patients with TB/HIV co-infection, HIV would be a useful marker to trigger an evaluation of tuberculosis in patients admitted with pulmonary disease.

Males accounted for 54% of patients who had TB (Table1). Mean age was 32 years and median age of 30 years. This is consistent with a study done by Pedro et al in Brazil in which males accounted for 69.7% of all patients with TB with mean age of 37 years (58). Studies done in Zimbabwe and Sudan have reported median age of 33 and 32 years respectively (52, 59) and a predominance of TB in males. It has been suggested that chromosomal susceptibility may contribute to the excess of males with TB as observed in many different populations. However the presence of a biological factor conferring protection against infection or clinical development of tuberculosis in female subjects cannot be precluded, and deserves further investigation.
Females accounted for 55% of patients who were HIV/TB co-infected in this study. This is in contrast to what was reported by Perlam D et al in a prospective multicentre study trial for HIV related TB where females were only 23% (40). This finding was replicated by Keiper et al in a study in USA where females were 14% (60). One explanation for this difference is that in this population of patients studied by both Keiper et al and Perlam D et al, majority were either homosexuals or were intravenous drugs users. In this study, none of the patients had abused intravenous drugs nor was a confessed homosexual.

The most prevalent symptoms in patients with culture confirmed TB were weight loss 52% (p< 0.001), drenching night sweats 40% (p<0.0001) and pleuritic chest pain 45% (p=0.001) (Table 2). In the logistic regression model, drenching night sweats OR 1.53(95% CI, 1.39-2.72), pleuritic chest pain OR 1.59 (95% CI, 1.45-2.79) and weight loss OR 1.43(95% CI, 1.39-2.72) independently predicted diagnosis of TB. The presence of all the three symptoms increased the likelihood of TB 13 times compared to if none were present OR 12.7, 95% CI, 11.5-14.2) (Table2). These findings could form a basis for symptom screening in high risk settings such as emergency rooms, prisons and homeless shelters. Similarly, in a study done by Rene et al the most prevalent symptoms were, drenching night sweats (50%), weight loss (50%) and pleuritic chest pain (30%). The presence of these three symptoms independently predicted diagnosis of TB and increased likelihood of TB 17 times (61). This has been echoed by several other studies ( 53,59). In this study haemoptysis was frequently seen in patients who were smear positive compared to those who had TB and were smear negative (p=0.088) (Table8). Most of this patients were HIV negative (p=0.017) (Table5). This finding is consistent with the findings of Rathman et al in Gambia (62). Haemoptysis has been described as one of the typical symptoms of TB. However its absence does not rule out presence of tuberculosis.

Weight loss had a six fold association with HIV positive patients who had TB. One possible explanation for this could be the impact of both TB and HIV
infection in the individual. There was no difference between HIV positive and HIV negative with regard to fever, night sweats, pleuritic chest pain, dyspnoea and anorexia. (Table 5). This finding was consistent with that reported in a study done by Shungu et al to investigate causes of chronic cough in primary health care attendees and the impact of HIV in Harare (52). Therefore HIV status has very little impact on symptomatology and no combination of symptoms can be used to predict TB in HIV infected individuals.

The prevalence of TB in patients who had cough between 2-3 weeks in our study was 45%. Banda et al found a TB prevalence of 35% in patients presenting with cough 1-3 weeks unresponsive to a course of antibiotics (63). Likewise Scott et al reported a TB prevalence of 9% in patients who presented with acute pneumonia in Kenya (64). This clearly means that TB occurs even in patients with a short duration of cough. This supports the hypothesis that a significant proportion of patients with TB including those with pulmonary disease lack prolonged cough.

Sensitivity of smear microscopy in this study was 71% with a specificity of 96 % (figure 4). Several studies have reported similar findings (40, 52, 54). 29% of patients with TB were missed out by the sputum smear microscopy. It is therefore necessary to develop other methods with better sensitivity in order to minimize this number.

There was a significant difference in AFB smear sensitivity between HIV positive (60%) and HIV negative (82%) (p=0.019). This is consistent with what has been reported in Zambia (67). Kramer et al reported 61% positive AFB in the HIV infected group with culture proven TB as opposed to 84% positive smears in the HIV negative group (66). This finding suggests that, in the presence of HIV infection, the sputum smear results should be treated with caution. The presence of low bacillary load in the sputum of HIV positive patients could also suggest that they may be less infectious than those negative for HIV.
In the chest radiographic findings, there was a significant difference between culture positive TB and culture negative TB patients in respect to nodular and alveolar infiltrates predominantly affecting upper zones (P<0.0001) and cavitations affecting upper zones or the apical segments of the lower lobes (p<0.0001)) with PPV of 70%, 74% and NPV of 61%, 60% respectively. (Table 4). These findings were independent predictors of culture positive TB. These findings are the typical pattern of reactivation of TB. Findings of cavitations and fibro nodular or apical opacities are quite characteristic of tuberculosis, and their finding on chest radiography of patients should immediately raise the suspicion of tuberculosis. Both Cohen in USA and Tattevin in France reported similar findings (53-54).

Tuberculous pleural effusion was uncommon, did not occur in isolation in any patient and was associated with parenchymal disease in all but one patient. A possible explanation for this could be that most patients with pleural effusions had a dry cough and this group of patients was excluded from the study.

Comparing HIV positive patients to the HIV negative patients with culture positive TB, the former characteristically presented with a higher frequency of enlarged hilar nodes or mediastinal shadows (p=0.043), milliary pattern (p <0.0001), diffuse reticulonodular infiltrates (p=0.013) and normal chest radiographs (p=0.048), in contrast with localized or cavitatory disease in HIV negative patients (p=0.003) (Table 6). Similarly studies from Rwanda, Haiti and South Africa have documented that HIV sero positive patients have significant more hilar and mediastinal adenopathy and less cavitation and upper zone involvement when compared to sero negative patients (32, 37, 67). Pleural effusion was more common in HIV positive patients than HIV negative patients but the difference was not statistically significant (p=0.152) (Table 6). Batungwanayo in Rwanda, Abouya in Abidjan, and Aderaye in Addis Ababa reported that pleural effusion were more common in HIV positive patients than in HIV negative patients (32, 56,68). Since cell mediated immunity is necessary to control TB, it is possible that as the CD 4+ cells declines, the patient is unable to control to control the
infection and an atypical radiograph pattern develops. On the other hand the patient may have been recently infected and has primary disease.

Both Abouya in Ivory Coast and Aderaye in Addis Ababa reported miliary pattern to be commonly associated with HIV positive patients with TB compared to HIV negative patients (56, 68). A miliary picture usually depicts disseminated disease and is more common in the immunocompromised group as they are not able to contain the disease.

Unfortunately, the combination of negative smears for AFB and atypical chest radiographs, in the HIV positive patients with TB poses a challenge in diagnosis, treatment and overall control of tuberculosis. Therefore recognizing these peculiarities of chest radiographic patterns in HIV associated TB is important as it may minimize under-diagnosis and delay in initiation of treatment.

9(7%) of patients in this study with normal chest radiographs had culture proven infection. A normal chest radiograph was frequently seen in HIV positive patients than in HIV negative patients (p=0.048) (Table 6), and significantly in patients with smear negative TB (p=0.009) (Table 9). This finding has been replicated in other studies done in New York (14%), Addis Ababa (9.2%) and Rome(9.0%) and (40,67-68). The rising number of HIV infected symptomatic TB patients with normal chest radiographs has been the most challenging phenomenon observed recently. Even though the deficiency of sputum sampling is clearly defined, three out of the nine patients who had TB with normal chest radiographs were positive for AFB in the sputum. Therefore a normal chest radiograph does not exclude active PTB especially patients with HIV infection.

32(61%) patients with HIV/TB co-infection had CD4 counts of less than 100 cells/mm3 and constituted the majority of HIV infected patients with TB. (Figure 3). The median CD4 count was 98 cells/ml with mean of 124 cells/ml and range of (1-501). In contrast to this study, a study done by Alain et al in Co^te d'Ivoire reported a much lower prevalence (43%) of patients with CD4 counts of below 200cells/mm3. This could be due to the fact that patients in that study were mainly ambulant outpatients and were predominantly smear positive. (69)
Enlarged hilar nodes and a miliary pattern were more frequently seen in patients with advancing levels of immune deficiency (19%, 28%) respectively, while cavitations and nodular infiltrates affecting upper zones were less frequently seen (38% 21%) respectively (Table 7). The findings in this study are consistent with those of Abouya et al who reported hilar adenopathy in 20% of patients with CD4 <200cell/mm3 and 14% in patients with CD4 > 200cell/mm3 (p<0.05) and miliary pattern in 9% of patients with CD4<200 as opposed to 6% in patients with CD4 > 200, but this was not statistically significant. Cavitatory lesions were seen more frequently in patients with CD4 >200cells/mm3 (p<0.05) (56), Keiper et al in USA also reported a significant difference in the finding of cavitations between patients with CD4 above 200 cells/mm3 and those below 200cells/mm3 (69% vs. 29%) p<0.001 but no significant difference in hilar adenopathy (p=0.65). (60). Perlam et al did not find any significant difference in cavitations between the two groups (p=0.08) but hilar adenopathy had significant difference favoring lower CD4 counts (p=0.01) (40). The small number of patients in our study with cavitations n=8 may reflect the severe immunosuppression in this group (median CD4 count 98 cells/mm3). A normal chest radiograph was commonly seen in patients with CD4 counts of less than 200 cells/mm3 (13% vs. 7%) (Table 7). This trend has been reported by Greenberg et al (21% vs. 14%) and Perlam et al (9% vs. 3%) (40,42). Therefore pulmonary tuberculosis should be considered in HIV positive patients presenting with CD4 counts of less than 200cells/mm3 and atypical chest radiography. Appropriate infection control measures should be employed until diagnosis of tuberculosis has been reasonably excluded.
10.0: CONCLUSION

1. Weight loss, drenching night sweats and pleuritic chest pain were significant positive predictors of culture confirmed pulmonary tuberculosis.

2. The combination of night sweats, weight loss and pleuritic chest pain had a 1.3 fold association with culture positive tuberculosis.

3. Haemoptysis as a single factor was a significant positive predictor of pulmonary tuberculosis in patients who were HIV negative while weight loss had a six fold association with HIV positive patients with TB.

4. Infiltrates and cavitations affecting upper zones on the chest radiograph were significantly associated with TB in the immunocompetent host.

5. Intrathoracic adenopathy, miliary picture, diffuse infiltrates and a normal chest radiograph were more common in HIV positive patients with TB, and especially those with advanced immunodeficiency.

11.0: LIMITATIONS

1. The study did not look at extra pulmonary tuberculosis, which could also influence the prevalence of TB especially in HIV positive individuals.

2. Patients who were unable to produce sputum were excluded.

3. There was no correlation between TB infection and viral load in patients with HIV/TB co-infection.
12.0: RECOMMENDATIONS

1. In the background of cough for more than two weeks, a triad of weight loss, chest pain and drenching night sweats should be utilized in areas where both chest radiography and smear microscopy are not available, as positive predictors of pulmonary tuberculosis.

2. In the setting of cough for more than two weeks, weight loss, intrathoracic adenopathy and miliary pattern in patients with HIV infection, early isolation and treatment should be instituted until diagnosis of pulmonary tuberculosis has been reasonably excluded.

3. Findings of cough for more than two weeks, night sweats, weight loss and fever together with apical consolidation or cavitation on chest radiograph should prompt immediate evaluation for pulmonary tuberculosis.
APPENDICES

APPENDIX I – STUDY DEFINITIONS

Definition of clinical symptoms considered in the study was adapted from TB/HIV, A clinical Manual, 2nd Ed, WHO 2004.

- Cough for more than two weeks.
- Sputum Production.
- Un intentional weight loss defined as 10% presumed or measured weight loss in the last one month.
- Fevers defined as axillary temperature of greater than 37.5°C on any one occasion.
- Drenching night sweats defined as copious sweating during sleep.
- Anorexia defined as loss of appetite to food.
- Dyspnoea defined as shortness of breath
- Pleuritic chest pain: pain more marked on coughing.
- Haemoptysis: coughing up blood stained sputum even on one occasion irrespective of the amount.


- Nodular, alveolar infiltrates predominantly affecting upper zones
- Cavitations affecting upper zones or apical segment of the lower lobe
- Enlarged hilar nodes or mediastinal shadows
- Pneumonic lesion
- Miliary pattern
- Pleural exudates
- Normal
- Others (specify)
APPENDIX II - SCREENING PROFOMA

Study Number 

Name ___________________ Hospital No. ___________________

Age _______ Contact: address ___________________ Tel: ___________________

DOB ___________________

DERMOGRAPHICS

Gender 1 = male 2 = female 

Marital status 1 = single 2 = married 3 = divorced 4 = widowed 5 = separated

Usual residence ____________________________________________

Usual occupation 1 = self employed 2 = employed 3 = unemployed 4 = retired 5 = student/training

Level of education 1 = none 2 = Primary school 3 = secondary school 4 = tertiary 5 = other

Past medical history 1 = previous TB treatment 2 = TB contact 3 = chemotherapy 4 = malignancy 5 = diabetes mellitus 6 = use of steroids 7 = exposure to silicon

Social history 1 = cigarette smoking 2 = alcohol intake 3 = intravenous drug abuse 4 = incarceration/shelter

Duration of symptoms (weeks)
Cough [ ] Fever [ ] weight loss [ ] Night sweats [ ] haemoptysis [ ]
Shortness of breath [ ] pleuritic chest pain [ ] Others (specify [ ]

Consent to be included into the study: have you understood what the study is about? Are you willing to be included in the study, VALIDITY OF CLINICAL SYMPTOMS AND CHEST RADIOGRAPHIC CONFIGURATION IN PREDICTING PULMONARY TUBERCULOSIS Yes=1 NO=2

FOR OFFICIAL USE
Recruited into the study=1, excluded from study=2
If excluded: refused consent=1 one of the exclusion criteria=2 (indicate reason)
APPENDIX III: CONSENT EXPLANATION BEFORE RECRUITMENT

We would like to inform you/ your next of kin that we are conducting a hospital-based study on the accuracy of clinical symptoms and chest radiography in diagnosing patients suspected to have a disease called tuberculosis (TB) of the lungs, and that:

1. Joining the study is voluntary and no payment will be made or charges accrue due to participation in the study.
2. Participation in the study will not delay your treatment in any way.
3. You may decline to participate in the study or drop out at will and this will not lead to denial of treatment nor any form of care in this hospital.
4. If you have understood the information that we have given you and you are willing to participate in the study, you will be required to sign a form indicating your willingness to be recruited.

Study procedures; We will ask you or your next of kin some questions about your illness whose answers we will indicate in a form prepared for this activity after which you will give us at least two sputum samples one of which will be an early morning sample put in two separate plastic containers. This sputum samples will be taken to the national TB reference laboratory to be tested for the organism that causes TB. If your sputum grows the organism, we will communicate the results to you through your primary clinician. We will also take X-ray of your chest as required for the diagnosis of TB.

Purpose of the study; This study is being done to find out which symptoms and chest radiographic configuration best predict infection with tuberculosis of the lung.

Benefits of the study; The outcome of this study will help improve case detection of TB and therefore early initiation of treatment. This will lead to reduction of risk of severe infection with loss of lung function and mortality, and reduction of transmission of infection in the community.

Confidentiality; The information you have given us and the results of the tests will be kept confidential unless required by law. Any publications arising out of this study will not identify you or your next of kin in person.

Problem and/or questions; if you have any questions about this study, you may contact Dr. Francesca Akoth Odhiambo at the following address: P.O Box 6228-00300 Nairobi, Tel: 0722646783, and/ or KNH-Ethics and Research Committee: P.O Box 20723, Nairobi, Tel: 726300-9, Fax: 725272; E-mail: KNHplan@ken.Healthnet.org.
Statement of consent by the patient or the next of kin

The purposes of this study, procedure, study benefits and my rights/ patient’s rights have been fully explained to me. I hereby give my written consent to allow myself / my____________________ to participate in the study.

Name_________________________Sign/ thumb
print_________________________Date___________07

Witness_______________________Sign/ thumb
print_________________________Date___________07

Interviewers Statement

I have explained the purpose, procedure, and benefits of this study to the respondent. To the best of my knowledge and conviction he/she has understood and has given informed consent.

Interviewer_______________________Sign____________________Date________________
07.
APPENDIX V: STUDY PROFOMA

To be appended to screening profoma for included patients

1. Physical Examination

Weight [ ]  Height [ ]

Blood pressure (mmHG) [ ]  Chest findings [ ]

2. Sputum smear microscopy result

- Positive=1
- Negative=2

3. Chest radiographic configuration

- Nodular, alveolar infiltrates predominantly affecting upper zones=1
- Cavitations affecting upper zones or apical segment of the lower lobe=2
- Enlarged hilar nodes or mediastinal shadows =3
- Pneumonic lesion=4
- Miliary pattern=5
- Pleural exudates=6
- Normal=7
- Other specify=8

4. HIV status [ ]

- Positive=1
- Negative=2
- Unknown=3

5. CD 4+ counts if HIV positive [ ]

- 0-100 cells/mm³ = 1
- 101-200 cells/mm³ = 2
- 201-300 cells/mm³ = 3
- >300 cells/mm³ = 4
6. WHO stage if HIV positive
   ♦ stage I = 1
   ♦ stage II = 2
   ♦ stage III = 3
   ♦ stage IV = 4

7. Use of HAART if HIV positive
   ♦ none = 1
   ♦ ongoing = 2

8. Sputum culture
   ♦ Number of days to results = 1
   ♦ Positive = 2
   ♦ Negative = 3

9. Antibiotic taken before visit
   ♦ One course = 1
   ♦ Two courses = 2
   ♦ More than two courses = 3
   ♦ Unknown number = 4
References

17. The Kenya Demographic and Health Survey (KDHS); 2003


Ref: KNH-ERC/ 01/ 4524

Dr. Francesca A. Odhiambo
Dept. of Internal Medicine
School of Medicine
University of Nairobi

Dear Dr. Odhiambo

REVISED RESEARCH PROPOSAL: "VALIDITY OF CLINICAL SYMPTOMS AND CHEST RADIOGRAPHY IN PREDICTING PULMONARY TUBERCULOSIS AT K.N.H, NAIROBI, KENYA" (P105/5/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and approved your above revised research proposal for the period 4th July 2007 – 3rd July 2008.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. A.N. GUANTAI
SECRETARY, KNH-ERC

Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Internal Medicine UON
Supervisors: Prof. G.N. Lule, Dr. H.M. Irimu, Dr. J. Sitienei

4th July 2007