ADDIS ABABA UNIVERSITY

COLLEGE OF NATURAL AND COMPUTATIONAL SCIENCE DEPARTMENT OF BIOLOGY

(GRAGUATE PROGRAMME)

Prevalence of HIV – co infection and multiple Drug Resistance of Pulmonary tuberculosis among patients attending Debre Markos Referral Hospital, Ethiopia

By:

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Addis Ababa

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Atnafu Temesgen Fenta

A Thesis submitted to the School of Graduate Studies of Addis Ababa University in partial fulfillment of the requirements for the degree of Master of Sciences in Biology.

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Declaration

This thesis is my original work and has not been presented for a degree in any other Universities and that all sources of information used for the thesis have been fully acknowledged.

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Date of Submission: 14/09/2016

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Abbreviations

AFB- Acid Fast Bacilli

AIDS-Acquired Immune Deficiency Syndrome

ARV-Anti-Retrovirus

CDC-Center for Disease Control and prevention

DOTS-Directly Observed Treatment Short-course

EPTB-Extra Pulmonary Tuberculosis

FMHE- Federal Ministry of Health Ethiopia

HIV-Human Immunodeficiency Virus

IRIS-Immune Reconstitution Inflammatory Response

MDR- Multi-drug resistant

MODS- Microscopic Observation Drug Susceptibility

PTB-pulmonary Tuberculosis

TB-Tuberculosis

TLCP- Tuberculosis Leprosy Control Program

WHO-World Health Organization

Abstract

Tuberculosis is a wide spread infectious disease caused by *Mycobacterium tuberculosis* which typically attack the lungs. There is a close association of tuberculosis (TB) infection with human immunodeficiency virus (HIV) co-infection. This, together with multiple drug resistance of the pathogen, makes it very difficult to control. This necessitates a survey of TB, multiple drug resistance and HIV co-infection on outpatients in order to evaluate the status and control of the disease. The main objective of the study was to assess the prevalence, HIV co-infection and multi drug resistance(MDR) of pulmonary tuberculosis among patients attending Debremarkos referral hospital. Descriptive cross sectional study design was conducted to investigate pulmonary tuberculosis (PTB) burden in the study site on secondary data source from recorded cases with complete socio demographic information. Data were analyzed using SPSS version 20 software. The study period was from January 2011- December 2015.

From a total of 2886 PTB patients 1722 (59.7%) were males and 1164 (40.3%) were females. PTB decreased in the recent three years (2013, 2014 and 2015)compared with the previous two years (2011 and 2012). The burden of PTB was also high in 16-30 age groups (44.3%) than the other age groups such as the above 60 age groups (4.9%). In addition 84.8% were from rural area and 15.2% from urban dwellers. PTB decreased by 7.58% in the recent three years (2013, 2014,and,2015) than in (2011and 2012).The prevalence of HIV/PTB co infection among PTB cases was 18.8%. Co infection was highin males, and the same in active age groups of 16-30, rural area, and smear negative TB cases than the other groups. The trends of co infection decreased from 5.9% (2011) to 2.0% (2015). The prevalence of MDR-TB was 2.3%. Most MDR-TB cases were observed in males, 16-30 age groups and rural dwellers. Previous treatment showed strong association with the emergence of MDR-TB. The trend of MDR-TB was rapidly increasing from 0.0% to 0.9% across 2011-2015 that needs to be addressed urgently.

Key words/phrases: assessment, DOTS, PTB, secondary data

1. INTRODUCTION

Communicable diseases are caused by infectious agents of bacteria, viruses, fungi, and parasites. These diseases remain a major cause of death and are responsible for worsening the living conditions of many millions of people around the world especially in the developing countries, despite decades of dramatic progress in their treatment and prevention, (Getachewet *al*.2006).

Tuberculosis (TB) is one of the infectious diseases caused by *Mycobacterium tuberculosis*(Kumar *et al*, 2007*)*. It is the second-most common cause of death from infectious disease (after those due to acquired immune deficiency syndrome (AIDS) (Dolin, 2010), and more common in developing countries; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the United States population test positive (Kumar,2007). TB typically attacks the lungs, but can also affect other parts of the body. It spreads when people with active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. However, most infections with *M. tuberculosis* do not cause TB disease and 90–95% of infections remain asymptomatic (CDC, 2011; Skolnik, 2011).

The Word Health Organization (WHO) estimates that TB in 2010 reached 12 million cases, corresponding to rates of 169 per 100,000 population worldwide and to 303 per 100,000 in Africa (WHO,2013). The Centers for Disease Control (CDC) point out that worldwide, approximately one third of persons are infected with *M.tuberculosis* (Dokubo, et al 2013) underscoring the enormity of the global burden of TB. In 2010, 8.8 million new cases of TB were diagnosed, and 1.20–1.45 million deaths occurred, mostly in developing countries. Of these1.45 million deaths, about 0.35 million occur in patients co infected with HIV (WHO, 2011).In 2012, an estimated 8.6 million chronic cases were recorded (WHO, 2013). Although Africa contributes to 11% of the world's population, it carries 29% of the global burden of tuberculosis cases and 34% of related deaths, Chaisson*et al*. (2008).

According to WHO (2014), there are 22 "high-burden" countries in the world that contributes to 80% of cases as well as 83% of deaths of TB. Accordingly, Ethiopia ranked seventh among

these high burden countries, with overall prevalence of TB 211 per 100, 000 populations. In addition, it is one of the five most affected countries in Africa, WHO (2014). According to WHO 2013 report, the prevalence, incidence, and mortality rates in the country were 224/100,000, 247/100,000, and 18/100,000 populations, respectively. The same report showed that 1.6% of new TB patients and 12% of previously treated patients had multi drug resistant tuberculosis (MDR-TB). Determining the proportion of drug resistance among new cases is vital in the assessment of the effectiveness of national TB control program. According to the Ethiopian Ministry of Health report, TB is the leading cause of morbidity, the third leading cause of hospital admission, and the second cause of death in Ethiopia (MOH, 2008).

Ethiopia is one of the high TB/HIV and MDR-TB burden countries. Among TB patients with known HIV status, about 11% were HIV co-infected (Alemie and Gebreselassie 2014). According to the recent national TB drug resistance surveillance report, 2.3% of new TB cases and 17.8% of previously treated TB cases were estimated to have MDR (WHO, 2014).

The idea of totally controlling the disease has been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s (Lawn,2011).A recent Ethiopian National TB/HIV Survey showed that the prevalence of HIV among the TB patients registered was 20% (EFMOH, 2013).

MDR-TB has become a major public health problem and presents new barriers to the control of TB (WHO, 2013).MDR-TB is defined as *M.tuberculosis* strains that are resistant to at least isoniazid and rifampicin, the two key first line drugs in short course TB chemotherapy. The WHO (2010) Global MDR-TB report estimated that there were 440,000 MDR-TB cases and 150,000 deaths due to MDRTB worldwide in 2008 (WHO, 2010). According to a WHO (World Health Organization/International Union against Tuberculosis and Lung Disease) survey of 20 countries with the highest rates of MDR-TB among previously treated cases, 14 were in the European Region (WHO, 2004).

According to Federal Ministry of Health of Ethiopia (2009), Ethiopia is one of the 27 high MDR-TB countries; it ranks 15th with more than 5000 estimated MDR-TB patients each year, and nearly half a million cases ofMDR-TB emerge every year, but only 3% of them get

treatment and 110,000 die annually. The problem of drug resistant TB exists in different parts of Ethiopia, and data on patterns of resistance among Ethiopian isolates is in the range of 2% and 21% for isoniazid, and between 2% and 20% for streptomycin and between 14% and 15% for any of the drugs tested (Abate, 2002).

According to the above-mentioned reports, the prevalence and MDR pattern of *M.tuberculosis* varies from region to region and from time to time. Eastern Gojjam is known for its high TB case load and the use of multiple drugs to treat tuberculosis. Patients with resistant TB are treated in the directly observed treatment short-course (DOTS) clinic of DebreMarkos Referral Hospital. However the prevalence and multidrug resistance of TB has not been assessed in DebreMarkos Referral Hospital and there is no adequate information that show the recent status of the problem. Assessment of the prevalence of PTB, TB and HIV co-infection and MDR of *M.tuberculosis* is very important for the planning, resource allocation, prevention and control activities.

Therefore, this study was conducted to measure the prevalence of PTB among patients attending DebreMarkos hospital; to assess the TB-HIV co-infection at the study site; to determine MDR pattern of *M.tuberculosis* among TB patients; to assess the associated factors with PTB, PTB and HIV co-infection and drug resistant of *M.tuberculosis* and to determine whether the burden of PTB, PTB/HIV co infection and MDR-TB has fallen from 2011-2015.

1.1 The research questions

1. What is the prevalence of PTB registered at DOTS clinic of DebreMarkos hospital?

2. What is the prevalence of PTB-HIV co- infection at the study site?

3. What is the prevalence of MDR among PTB patients?

4. Has the burden of PTB, PTB/HIV co-infection and MDR-TB fallen from 2011-2015?

5. What are the associated factors with PTB, PTB /HIV co-infection and MDR of *M. tuberculosis*?

1.2 objective of the study

The main objective of the study was to assess the prevalence, HIV- co infection and multi drug-resistance of pulmonary tuberculosis among patients attending Debremarkos referral hospital.

Moreover, the specific objectives of the study were, therefore:

1 To measure the prevalence of PTB among patients attending DebreMarkos referral hospital.

2. To determine the prevalence of PTB-HIV co- infection.

3. To measure the prevalence of MDR among PTB patients.

4. To assess whether the burden of PTB, PTB /HIV co infection and MDR disease has fallen from2011-2015at the study site.

5. To determine the associated factors with PTB, PTB/HIV co-infection and MDR of *M. tuberculosis*.

1.3 Significance of the study

The study will contribute to the process of identification of more affected socio demographic characteristics (sex, age group and residences) and associated factors with the emergence of pulmonary TB, PTB/HIV co infection and MDR-TB. In addition, the study will serve as the basis for comprehensive update of estimates of PTB burden whether it is stable, increasing, or decreasing (trends) for TB control and prevention. Since reliable baseline information is essential for TB control program, the findings of this survey will be of great importance for the overall management of the National TB control Program particularly for planning, policy and decision making. It may also serve as a base line for the researchers who want to assess similar problem.

1.4. Limitation of the study

Data was collected by using secondary data source from already recorded documents instead of using primary data and the study includes data only for five years (2011-2015).

2. REVIEW OF RELATED LITERATURE

2.1. Epidemiology

WHO (2003) tuberculosis is one of the most prevalent diseases in the world. About one-third of the world's population is infected with tuberculosis and thus at risk of developing active disease (TB). It is estimated that 8.4 million people develop active TB every year and 2.3 million die. More than 90 % of TB cases and deaths occur in developing countries and 75 % of cases are in the most economically productive age group.

TB has been recognized as major cause of morbidity and mortality in Ethiopia. According to a report from Ministry of health (2008) TB is 3rd leading cause of hospitalization and 1st leading cause of Hospital death. WHO Estimates Incidence of TB in Ethiopia is 356 per 100,000 /yr and the incidence Smear positive TB is 155 per 100,000/year.

In the year 2001 the TB leprosy control program (TLCP) registered 94,957 cases of TB from DOTS implementing areas. Co infection with HIV significantly increases the risk of developing active TB, and HIV has become the most important risk factor to develop active TB. In HIV- infected persons the risk of developing TB is increased by more than 10 times compared to those who are HIV negative. It is estimated that about 40% of adult TB cases in urban areas are HIV positive.

The incidence and prevalence of tuberculosis, in recent years has doubled or tripled because of the HIV pandemic, especially in developing countries. It is also shown that active tuberculosis can result in rapid progression of HIV infection in a patient. Multi-drug resistant TB which often results from poor management is becoming a serious concern in many countries (WHO, 2004).

2.2 Etiologic Agent

Tuberculosis (TB) is an infectious disease caused by strains belonging to the Mycobacterium tuberculosis complex. The *M. tuberculosis* complex includes: *M. tuberculosis, M. bovis*, *M. africanum*, *M. canetti*, and *M. microti(Van, 1997).M. africanum* is not widespread, but it is a significant cause of tuberculosis in parts of Africa (Niobe, 2003). *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has largely eliminated

this as a public health problem in developed countries (Kumar, 2007). Acton (2011) *M. canetti* is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants. *M. microti* is also rare and is mostly seen in immune deficient people, although the prevalence of this pathogen has possibly been significantly underestimated. But of all, M.tuberculosis is by far the commonest. Tuberculosis usually affects the lungs but almost all organs can be affected. *Pulmonary TB (PTB)*: accounts for 80% of all TB cases and*Extra-pulmonary TB (EPTB)*: accounts for 20% of all TB cases (Getachew, 2006).

Mycobacterium tuberculosis is a small, non motile, rod-shaped, non-spore-forming, thin aerobic bacterium measuring about 0.5µm by 3µm. The bacterium is demonstrated by acid fast staining technique. The high lipid content of this pathogen accounts for many of its unique clinical characteristics (Southwick, 2007). It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour (Jindal, 2011). Mycobacteria have an outer membrane lipid bi layer. If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall. MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured in the laboratory (Parish, 1999).

According to WHO (2011) number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Of people without HIV who are infected with tuberculosis, about 5–10% develop active disease during their lifetimes; in contrast, 30% of those co infected with HIV develop the active disease.

HIV promotes the progression of infection with Mycobacterium tuberculosis to active TB, both in people with recently acquired infections and those with latent infections. Undeniably, HIV is the most powerful risk factor known for activation of latent M. tuberculosis infection. For an HIV-infected person co infected with M. tuberculosis, the risk of developing active TB reaches 5–10% annually, instead of the 5–10% lifetime risk for an individual not infected with

HIV. This discrepancy is clearly linked to the immunodeficiency caused by HIV. Furthermore, HIV infection increases the rate of recurrent TB, which can be due to either endogenous reactivation or exogenous re infection (Lienhardt et al, 1997).

Lawn (2011) tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty. Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients.

Chronic lung disease is another significant risk factor. Silicosis increases the risk about 30-fold. Those who smoke cigarettes have nearly twice the risk of TB compared to nonsmokers. Other disease states can also increase the risk of developing tuberculosis. These include alcoholism and diabetes mellitus (three-fold increase) (Lawn, 2011).

2.3 Transmission

Cole (1998) indicates that tuberculosis is most commonly transmitted by inhalation of infected droplet nuclei which are discharged in the air when people with active pulmonary TB cough, sneeze, speak, or sing, they expel infectious aerosol droplets 0.5 to 5.0 μm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (the inhalation of fewer than 10 bacteria may cause an infection).

People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year. Transmission should occur from only people with active TB – those with latent infection are not thought to be contagious (Kumar, 2007). The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain, the level of immunity in the uninfected person, and others (CDC, 2011). Detection of the most infectious cases of tuberculosis – sputum smear-positive pulmonary cases – is an essential component of the control of tuberculosis. Contacts of smear-positive tuberculosis

patients are at high risk of getting infection and developing tuberculosis, thus justifying active case detection in these individuals. Examination of contacts, particularly of contacts of sputum smear-positive patients, is therefore recommended to identify and treat additional tuberculosis cases and to provide preventive treatment to those at highest risk, such as children and people infected with HIV (FMHE,2008). The cascade of person-to-person spread can be circumvented by effectively segregating those with active ("overt") TB and putting them on anti-TB drug regimens. After about two weeks of effective treatment, subjects with nonresistant active infections generally do not remain contagious to others (Ahmed, 2011).

According to Federal Ministry of Health Ethiopia (FMHE) (2008)consumption of raw milk containing *M.bovis*is also a possible way of getting infected by TB, though it is much less frequent. TB affects individuals of all ages and both sexes. There are, however, groups, which are more vulnerable to develop the disease: Poverty, malnutrition and over-crowded living conditions have been known for decades to increase the risk of developing thedisease. HIV infection has been identified as a major risk factor for developing tuberculosis. The age group mainly affected is between 15 and 54 years, andthis leads to grave socio-economic consequences in a countrywith a very high prevalence of the disease(FMHE, 2008)..

TB is one of the most common infections in HIV-infected people, especially in high TB prevalence areas. HIV greatly increases the number of TB patients, which in turn increases TB transmission from family members (the highest TB transmission risk is from household contacts, such as children and HIV-positive partners) and community members (through contact in work-places, schools and hospitals) where there is a risk of nosocomial infections from both patients (whether HIV-positive or -negative) and health care workers. Moreover, the risk of MDR-TB transmission may be increased if effective and uninterrupted TB treatment is not ensured (Girardi et al*).*

If someone does become infected, it typically takes three to four weeks before the newly infected person becomes infectious enough to transmit the disease to others.

2.4 Pathogenesis

According to Kumar (2007) TB infection begins when the mycobacterium reach the pulmonary alveoli, where they invade and replicate within endoscopes of alveolar macrophages. Macrophages identify the bacterium as foreign and attempt to eliminate it by phagocytosis. During this process, the bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called aphagosome. The phagosome then combines with a lysosome to create a phagolysosome. In the phagolysosome, the cell attempts to use reactive oxygen species and acid to kill the bacterium. However, *M. tuberculosis* has a thick, waxy mycolic acid capsule that protects it from these toxic substances. *M. tuberculosis* is able to reproduce inside the macrophage and will eventually kill the immune cell.

As indicated in Tortora et al (2010) tubercle bacilli that reach the alveoli of the lung are ingested by macrophages, but often some survive. Infection is present, but no symptoms of disease. Tubercle bacilli multiplying in macrophages cause a chemotactic response that brings additional macrophages and other defensive cells to the area. These form a surrounding layer and, in turn, an early tubercle. Most of the surrounding macrophages are not successful in destroying bacteria but release enzymes and cytokines that cause a lung damaging inflammation. After a few weeks disease symptoms appear as many of the macrophages die, releasing tubercle bacilli and forming a caseouscenterin the tubercle. The aerobic tubercle bacilli do not grow well in this location. However, many remain dormant {latent TB} and serve as a basis for later reactivation of the disease. The disease may be arrested at this stage and the lesions become calcified.

In some individuals, disease symptoms appear as a mature tubercle is formed. The disease progresses as the caseous center enlarges in the process called liquefaction. The caseous center now enlarges and forms an air-filled tuberculouscavityin which the aerobic bacilli multiply outside the macrophages. Liquefaction continues until the tubercle ruptures, allowing bacilli to spill into a bronchiole and thus be disseminated throughout the lungs and then to the circulatory and lymphatic systems (Tortora et al, 2010).

Kumar (2007) TB mainly affects the lungs. The primary site of infection in the lungs, known as the "Ghon focus", is generally located in either the upper part of the lower lobe, or the

lower part of the upper lobe. Tuberculosis of the lungs may also occur via infection from the blood stream. This is known as a Simon focuses and is typically found in the top of the lung. This hematogenous transmission can also spread infection to more distant sites, such as peripheral lymph nodes, the kidneys, the brain, and the bones.

2.5. Clinical features

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis). Extra pulmonary TB occurs when tuberculosis develops outside of the lungs, although extra pulmonary TB may coexist with pulmonary TB, as well (Dolin, 2010).

2.5.1 Pulmonary

Lawn (2011) if a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases). About 25% of people may not have any symptoms (i.e. they remain "asymptomatic"). According to Federal Ministry of Health of Ethiopia (FMHE**)** **(**2008)the common Symptoms include persistent cough for two weeks or more.Cough is usually with expectoration, with or without bloodstained sputumand can be accompanied by one or more of thefollowing symptoms: Weight loss;Chestpain;Shortness of breath;Intermittentfever;Nightsweats;Loss of appetite;Fatigue and malaise. Moreover, any person who for any other medical reasons has gota chest x-ray examination and whose chest x-ray findings aresuggestive of PTB must be dealt with as a TB-suspect.

Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones (Dolin, 2010).

2.5.2 Extra pulmonary

Golden (2005) in 15–20% of active cases, the infection spreads outside the lungs, causing other kinds of TB. These are collectively denoted as "extra pulmonary tuberculosis". Extra pulmonary TB occurs more commonly in immune suppressed persons and young children. In those with HIV, this occurs in more than 50% of cases. Notable extra pulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in

tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott disease of the spine), among others. When it spreads to the bones, it is also known as "osseous tuberculosis", a form of osteomyelitis (Kumar, 2007).Sometimes, bursting of a tubercular abscess through skin results in tuberculous ulcer. An ulcer originating from nearby infected lymph nodes are painless, slowly enlarging and has an appearance of "wash leather". A potentially more serious, widespread form of TB is called "disseminated" TB, commonly known as miliary tuberculosis. Miliary TB makes up about 10% of extra pulmonary cases (Dolin, 2010).

Ministry of Health of Ethiopia (2008) the signs and symptoms of *extra pulmonary Tuberculosis* (*EPTB)* depend mainly on the organ(s) involved**.** The most common forms and their respective presentations are:

Tuberculous lymphadenitis: Slowly developing and painless enlargement of lymph nodes, followed by matting and eventual drainage of pus.

Tuberculous pleurisy: Pain while breathing in, dull lower chest pain, intermittent cough, breathlessness on exertion.

TB of bones and/or joints: Localized pain and/or swelling, discharge of pus, muscle weakness, paralysis, stiffness of joints.

*Intestinal TB:*Loss of appetite and weight, abdominal pain, diarrhoea or constipation, mass in the abdomen, fluid in the abdominal cavity (ascites).

Tuberculousmeningitis: Headache, fever, vomiting, neck stiffness and mental confusion of insidious onset.

2.6 Diagnosis

According to Federal Ministry of Health of Ethiopia (2008) all suspects of any form of TB must be examined according to the standardized diagnostic procedures of which the microscopic examination of sputum is the most important and reliable. By rank of importance the diagnostic methods to confirm/exclude TB are: Microscopic examination of sputum smears; Radiological investigation; AFB culture; and Histo-pathology.

According to the latest recommendation by WHO and the national AFB microscopy laboratory manual, Sputum microscopy is the most efficient way of identifying sources of tuberculosis infection, and the primary tool for diagnosing TB; it is easy to perform at the peripheral laboratories, not expensive and specific. It can be used for diagnosis, monitoring and defining cure. Therefore, this is the key diagnostic tool used for case detection. Every individual suspected of having tuberculosis must have an examination of 3 sputum smears, to determine whether or not they have infectious tuberculosis. PTB+ is confirmed when at least 2 out of three smear resultsare positive for AFB. PTB + is also confirmed when one sputum specimen is positive for AFB in additiontoradiographic abnormalities consistent with active PTB. In HIV-positive patients (or in presence of a strong clinicalsuspicion of HIV-infection), only one positive smear result isnecessary to make diagnosis of smear-positive pulmonary TB.

2.6.1 Latent Tuberculosis Diagnosis

Screening and treatment for latent *M. tuberculosis* infection are indicated for groups in which theprevalence of latent infection is high (e.g., foreign bornpersons from regions in which tuberculosisis endemic), those in whom the risk of reactivateddisease is high (e.g., patients with HIV infectionor diabetes and patients receiving immunosuppressivetherapy), and those with both factors(e.g., recent contacts of patients with tuberculosis) (Horsburgh, 2011). Latent infection can be diagnosed witheither a tuberculin skin test or an interferon-gamma release assay. Specific guidelines from the Centers for Disease Control and Prevention in the United States (2010) recommend the use of the interferon- gamma release assay and tuberculin skin test for screening for latent *M. tuberculosis* infection in various age and risk groups. The tuberculin skin test is less expensive and is therefore preferred in low-income regions. It is as sensitive as the interferon- gamma release assay but less specific (McNerney et al, 2012).

2.6.2 Active Tuberculosis Diagnosis

A diagnosis of TB should be considered in those with signs of lung disease or constitutional symptomslasting longer than two weeks. A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation Escalante (2009). Sputum microscopy and culture in liquid medium with subsequent drug-susceptibility testing are currently recommended as standard methods for diagnosing active tuberculosis. The use of solid culture medium is more cost-effective in resource poor countries. Interferon-gamma release assays and tuberculin skin tests have no role in the diagnosis of active disease (WHO, 2010).Nucleic acid amplification tests, imaging, and histo-pathological examination of biopsy samples supplement these evaluations. In resource-constrained settings with a high prevalence of tuberculosis and HIV infection, an estimated 30% of all patients with tuberculosis and more than 90% of those with multidrug- resistant and extensively drug-resistant tuberculosis do not receive a diagnosis (WHO, 2012).

A new molecular diagnostic test called Xpert MTB/RIF assay detects *M. tuberculosis* complex within 2 hours, with an assay sensitivity that is much higher than that of smear microscopy. In HIV infected patients, the test has a rate of case detection that is increased by 45%, as compared with smear microscopy. This molecular assay has the potential to improve the performance of national tuberculosis programs and is currently being implemented in district-level laboratories in 67 countries with a high prevalence of tuberculosis (WHO, 2012)

2.6.3 Drug-Resistant Tuberculosis Diagnosis

The current standard for first-line drug-susceptibility testing is an automated liquid culture system, which requires 4 to 13 days for results. Commercial molecular line-probe assays can yield results in 24 hours, once they have been validated against automated liquid culture (WHO, 2008). Within 2 hours, the Xpert MTB/RIF assay concurrently gives results on rifampin resistance, a proxy of multidrug-resistant tuberculosis in settings in which there is a highprevalence of drug resistance, since rifampin resistance in the absence of isoniazid resistance is uncommon. Other screening tests for drug resistance include the microscopic-observation drug-susceptibility (MODS) assay, the nitrate reductase assay, and colorimetric reductase methods. The MODS assay simultaneously detects *M. tuberculosis* bacilli, on the

basis of cording formation, and isoniazid and rifampin resistance (WHO,2012).Since most of these methods are not currently available in countries in which tuberculosis is highly endemic, it is estimated that only 10% of cases of multidrug-resistant tuberculosis are currently diagnosed worldwide and only half of them receive appropriate treatment (WHO, 2012).

2.7 Treatment

2.7.1 Latent TB Treatment

Persons with latent *M. tuberculosis* infection who are at increased risk for active tuberculosis require preventive treatment (WHO, 2010 and 2012).The preferred regimen is isoniazid alone for 9 months or for a longer duration in HIV-infected persons in areas with a high prevalence of tuberculosis (WHI, 2011).Recently, directly observed weekly administration of isoniazid and rifampicin for 12 weeks has been shown to be as effective as isoniazid alone in adults without HIV infection in countries with a low burden of tuberculosis. This regimen was associated with fewer serious adverse events than 9 months of isoniazid alone, although treatment discontinuation because of an adverse event was more common.The trial is continuing to assess safety and effectiveness in children and HIV-infected persons (Sterling, 2011).

WHO (2011) guidelinesrecommend that all HIV-infected persons with positive or unknown results on the tuberculin skin test and without active tuberculosis who are living in resource constrained, high-burden countries receive preventive therapy with isoniazid for at least 6 months. Three regimens are effective for the prevention of active tuberculosis in HIV-infected persons: daily isoniazid for 6 to 9 months, daily rifampicin and isoniazid for 3 months, and rifampicin and isoniazid twice weekly for 3 months. Rifampincontaining regimens have higher rates of drug toxicity than those that do not include rifampicin. WHO(2011) the difficulty of diagnosing active tuberculosis in patients with HIV co-infection accounts in part for the slow adoption of isoniazid preventive therapy in clinical practice. Only patients with a positive tuberculin skin test who are receiving preventive therapy with isoniazid have decreased rates of active tuberculosis and death, and protection against tuberculosis wanes within a few months after cessation of isoniazid therapy.

2.7.2 Drug Sensitive Active TB Treatment

WHO(2012) effective tuberculosis treatment requires accurate and early diagnosis, screening for drug resistance and HIV, the administration of effective regimens under supervision, and the provision of support to patients for compliance throughout the course of treatment. Chemotherapy regimens that are used for the treatment of all types of TB are classified as first- and second-line anti-TB drugs. First-line anti-TB drugs include isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (STM). INH and RMP are the two most commonly used drugs for treatment of TB. First-line anti-TB drugs are safe and effective if used correctly WHO(2013).The current standard four-drug treatment regimen of first-line drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) achieves cure rates of more than 95% in trial conditions and more than 90% in treatment under the oversight of tuberculosis-control programs.Abdool (2011) treatment requires a minimum of 6 months in two phases: 2 months of all four drugs in the intensive phase and 4 months of isoniazid and rifampin in the continuation stage. Risk factors for relapse include cavitation, extensive disease, immunosuppression, and a sputum culture that remains positive at 8 weeks. If any of these risk factors is present, therapy may be extended for up to 9 months. Challenges with current therapy include inconsistent drug quality, the need to ensure that drug administration is directly observed and that other support is provided to patients, treatment interruptions and changes in regimen because of side effects, toxic effects, pharmacokinetic interactions (particularly with antiretroviral therapy in patients with HIV coinfection), and compliance issues owing to the lengthy treatment period. Several trials in progress are adding or substituting fluoroquinolones or testing higher doses of rifamycins in an attempt to shorten standard therapy to 4 months.

2.7.3 MDR-Tuberculosis Treatment

The treatment of multidrug-resistant tuberculosis is based on expert opinion and requires the creation of combination drug regimens chosen from five hierarchical groups of first-line and second-line drugs (WHO, 2011). Such therapy is associated with a high risk of intolerance and serious toxic effects. Regimens may be chosen on a standardized or empirical basis and then switched to individualized therapy after data regarding drug susceptibility testing become available. However, reliable drug-susceptibility testing is not widely available in regions in

which tuberculosis is endemic, particularly for second-line drugs. Treatment guidelines for multi drug-resistant tuberculosis recommend that the intensive phase of therapy be administered for at least 8 months (WHO, 2011).

Van Deun (2004) a fluoroquinolone and an injectable agent should routinely be included to provide a regimen with at least four second-line drugs that will have certain or nearly certain effectiveness, as well as pyrazinamide. Such therapy should be administered for at least 20 months in patients who have not received previous treatment for multidrug-resistant tuberculosis and for up to 30 months in those who have received previous treatment. An observational study showed that a shorter regimen, with treatment givenfor 9 to 12 months had acceptableefficacy with fewer adverse reactions in a population with no previous exposure to second line drugs. Since most of the recommended drugs have serious side effects that render treatment particularly difficult, expert consultation is always advised for the treatment of multidrug-resistant.

Extensively drug-resistant tuberculosis is extremely difficult to diagnose and treat in countries in which the disease is endemic. The condition has been associated with death rates as high as 98% among HIV-infected persons (Jacobson, 2010).

2.7.4 TB/HIV Co-infection Treatment

TB patients with HIV infection or HIV/AIDS may experience a temporary worsening of symptoms and signs after beginning TB treatment. In TB patients infected with HIV, treatment withantiretroviral (ARV) may interact with treatment of TB, reducing the efficacy of antiretroviral and of anti-TB drugs and increasing the risk of drug toxicity. In patients with HIVrelatedTB, the priority is to treat TB. Options are to defer antiretroviral treatment until TB treatment is completed; defer until completing the initial phase and use H +E in the continuation phase; or use antiretroviral that are less likely to interact with anti-TB drugs (Federal Ministry of HealthEthiopia,2008).

Tuberculosis leads to an increase in HIV replication and accelerates progression of HIV infection, with attendant high mortality. Early initiation of antiretroviral therapy results in a reduction in mortality; among patients with tuberculosis who do not receive antiretroviral therapy, those with very low numbers of CD4+ cells have a high short-term risk of death

(Abdoolkarim, 2011). WHO recommends that antiretroviral therapy be started within the first 8 weeks after the initiation of tuberculosis treatment and that patients with a CD4+ cell count of less than 50 per cubic millimeter receive antiretroviral therapy within the first 2 weeks (WHO, 2012).

The immune reconstitution inflammatory syndrome (IRIS) occurs in at least 10% of HIVinfected patients who start antiretroviral therapy during tuberculosis treatment. The most common manifestations of IRIS are new-onset or worsening respiratory symptoms and increased lymphadenopathy. IRIS is more common in patients who have a reduced number of CD4+ cells and those in whom antiretroviral therapy was initiated early in the course of tuberculosis treatment. For antiretroviral therapy in patients with active tuberculosis, regimens with non-nucleoside reverse transcriptase inhibitors are preferred, and efavirenz is the drug of first choice (WHO, 2012).

The use of rifampicin significantly reduces serum concentrations of protease inhibitors. Studies of the substitution of rifabutin for rifampicin and increased doses of boosted protease inhibitors to avoid this reduction are under way. Patients with HIV-associated tuberculosis should also receive prophylaxis with trimethoprim–sulfamethoxazole.

2.7.5 Follow-up during treatment

According to federal ministry of health (2008) the organization of TB clinics must facilitate the implementation of directly observed treatment (DOT) at least during the initial phase and the adherence of patients to their treatment until cure.Tuberculosis can be cured only if the anti-TB drugs are taken regularly. The choice of the place of treatment depends on two factors: the state of the patient**,** and the ability of the health staff to provide treatment to patients**.**

During the initial phase of treatment, which always contains rifampicin, the patient must take the drugs in front of the health worker who is responsible for verifying that the patient swallowsall of the prescribed drugs every day (WHO, 2003).

The continuation phase of the treatment of TB can be "selfadministered": in that case a supply of drugs in fixed-dose combination is given to the patient at fixed regular intervals, and the patient is given the responsibility to take the drugs correctly every day. The recommended interval between visits for drug supply is not more than one month, and must be set jointly by the health worker and the patient, depending on the ease of access to the health center and the adherence requirements (WHO, 2004).

2.8 Prevention of Tuberculosis

Among the various methods of preventing tuberculosis, the most effective is the identification and effective treatment of patients with infectious pulmonary tuberculosis.Tuberculosis prevention and control efforts also rely on the vaccination of infants. The only available vaccine is Bacillus Calmette-Guerin (BCG). In children, it decreases the risk of getting the infection by 20%. (WHO, 2011)

It is important to pay careful attention to adequate ventilation in institutions where TB patients may be encountered, in order to prevent infection of those in contact with them. Isolation of infectious TB patients (especially where there is an increased possibility that the patient may have multidrug-resistant TB) is important to prevent infection.

Treatment of latent TB infection with Isoniazid (IPT) has limited, individual indications, and applies above all to children aged under 5 years living in close contact with smear positive TB patient and to people living with HIV in whom active TB is ruled out (Federal Ministry of Health,2008).

2.9 Drug resistant tuberculosis

Although its causes are microbial, clinical and programmatic, drug-resistant TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB. (WHO, 2003)

Resistance to TB drug(s) usually occurs as aconsequence of an inadequate treatment, be it irregular, too shortor too weak. It develops because a patient is treated incorrectly oris not able to adhere to the treatment regimen. In both cases, thepatient has not been receiving a

strong enough dosage of the drugover a long enough period of time to kill the bacilli, so the organism is given time to develop resistance to anti-TB drugs (WHO, 2003). Once it is created, resistant TB can be transmitted like any otherTB in a population. It is estimated that the average MDR-TB patient infects up to20 other people in her/his life time, so Some people who have neverbeen previously treated for TB may get resistant bacilli.(Federal Ministry of Health 2008).

Drug resistance was strongly associated with previous treatment. In previously treated patients, the probability of any resistance was over 4-fold higher, and of MDR-TB over 10-fold higher, than for untreated patients. The overall prevalence of drug resistance was often related to the number of previously treated cases in the country. Among countries with a high burden of TB, previously treated cases ranged from 4.4% to 26.9% of all patients registered in DOTS program (WHO, 2004). Agood TB control program–especially with regard to patient followup and adherence- will not generate much resistance.

In Ethiopia, according to a national survey (2003-2006), it is estimated that MDR-TB represents about 1.6% of new TB cases (never treated previously) and 11.8% of re-treatment cases.

Treatment of MDR-TB is more complicated and longer than treatment of TB with no resistance. It is important to treat MDRTB patients both to prevent their death and to limit the dissemination of drug-resistant TB in the community. The prevention of MDR can only be achieved through proper TB case detection, rational diagnosis, standard treatment and, most of all, successful follow up and high adherence of patients. Clearly an efficient DOTS program is the best weapon against MDR (WHO, 2004).

3. RESEARCH METHODS

3.1 Study Area

The study was conducted at DebreMarkos Referral Hospital in DebreMarkos located at North West Ethiopia, which is 300 km away from Addis Ababa. The hospital provides health service to more than 3.5 million populations in its catchments. In the hospital, DOTS clinic was opened in 2012 under the NationalTuberculosis and Leprosy Program of Ethiopia.

3.2 Study population and Sampling Technique

The study was descriptive cross sectional which was quantitative, where retrospective secondary data were collected from the documents of TB patients registered in DOTS Clinic. The subject of the study was PTB outpatients registered from January 2011- December 2015 in the DOTS clinic of DebreMarkos referral Hospital. These patients visited the hospital while they were seeking health care at their own times.In determining the sample size, the study included all 2886 PTB patients with full socio demographic characteristics registered in the DOTS clinic of DebreMarkos referral Hospital.

3.3 Data Collection Technique

The socio demographic data such as sex, age, residence (urban/rural), HIV status (HIV positive/HIV negative), TB category (pulmonary positive/pulmonary negative), resistance (susceptible/MDR)and occurrence of MDR (new/after treatment) were collected from the DOTS registration book.

3.4 Data Analysis

The collected data was first checked manually and it was then transferred into SPSS version 20 statistical software. It was summarized and the proportion of PTB cases screened was determined for each year first and then for the five years period to indicate the overall prevalence rate and the trends (changes) of PTB across 2011-2015.Data were summarized using frequency tabular and graphical expression form through percentage.

Descriptive statistics and regression were used for analysis. Chi square was used to identify the association between independent factors (socio-demographic factors) and dependent factors (TB, drug resistance and TB/HIV co infection). Variables significantly associated in pearson's chi square were included in multivariate logistic regression at 95% confidence interval(CI) to quantify adjusted odds ratio(AOR) or the degree of association between factors. Significance level of $p<0.05$ was considered statistically significant.

4. RESULTS AND DISCUSSION

4.1 Prevalence of Pulmonary Tuberculosis (PTB)

4.1.1 Characteristics and Prevalence of PTB

From a total of 2886 PTB patients who were registered in the DOTS clinic of DebreMarkos referral hospital 1722 (59.7%) were males and 1164(40.3%) were females. The most affected age group was 16-30 (young) 1278(44.3%) followed by 31-45 age group (adult) 745(28.8%) and the least was the old age group with 141(4.9%). 2447 (84.8%) of the patients were registered from rural area, whereas 439(15.2%) were patients from urban area. The data also showed that 2068(71.7%) and 2344(81.2%) of the sputum samples were smear negative and HIV negative PTB patients respectively (Table 1). The prevalence of pulmonary tuberculosis in the study site was 17/100,000 whereas in Ethiopia 79/100,000 (FMHE, 2008). In addition according to the WHO (2014) report the prevalence of all forms of TB was 211/100,000 population in Ethiopia.

Table1characteristics and prevalence of PTB cases

Character		Frequency	Percentage
Sex	Male	1722	**59.7**
	Female	1164	40.3
Age	0-15	338	11.7
	16-30	1278	**44.3**
	31-45	745	25.8
	46-60	384	13.3
	>60	141	4.9
Residence	Urban	439	15.2
	Rural	2447	**84.8**
PTB category (Type)	Smear positive	818	28.3
	Smear negative	2068	**71.7**
Total		2886	100

4.1.2 The prevalence of PTB between male and female patients in each year

The prevalence of PTB patients was higher in males than female outpatients with slight increase along the years (Fig 1). Accordingly, the highest prevalence of 63.1% of PTB male patients was recorded in 2015; whereas the lowest prevalence of 55.9% was recorded in 2014 (Figure 1). The prevalence of females with PTB also increased from 2012-2014. In all cases, the majority of the TB patients were males (59.7%) and this was in agreement with previous findings that 55% of TB patients in northeastern Ethiopia (Daniel, 2015) and 56.8% of TB patients from YirgaCheffe, Southern Ethiopia (Fekadu, 2015) were males. According to WHO (1999), in most developing countries two third of the reported TB patients were men.

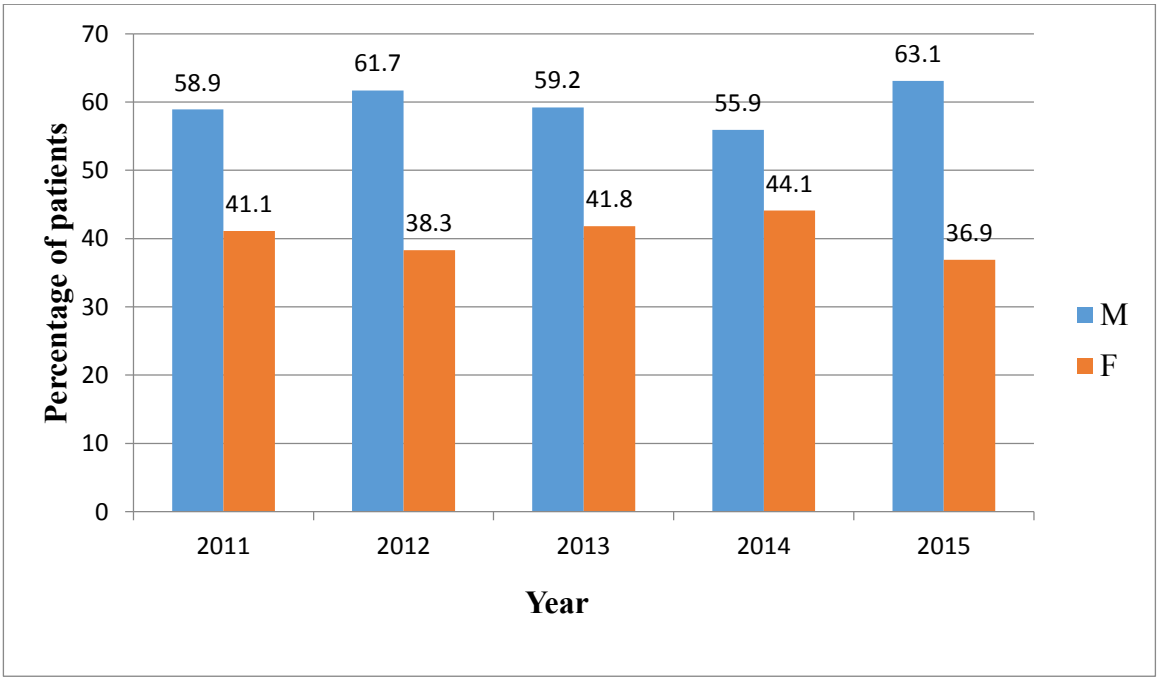

Figure 1: Prevalence of PTB between male and female patients in each year

4.1.3 The prevalence of PTB patients among different age groups

The highest number of PTB patients diagnosed was observed among 16-30 age groups followed by 31-45 and 46-60 age groups with total percentage of 44.3%, 25.8%, and 13.5%, respectively (Figure 2). According to WHO (2009), TB is affecting all age groups. The report also indicated that 15 to 34 age groups were found to be the most affected ones with TB;

accounting for 62% of TB patients. A previous study by FMH of Ethiopia (2008) showed that 75% of people affected by TB are within economically productive age group of 15-54 years indicating that tuberculosis is an obstacle to socioeconomic development. Similarly, Daniel (2015) showed that most TB patients were in the productive age group of 25-45(46.3%).The percentage of PTB distribution in children (0-15 age) in this study was 11.7% (Figure 2). This agrees with the report FMH of Ethiopia (2008), where 1 million (11%) of the total TB cases are children less than 15 years of age. Least pulmonary TB patient were recorded in the age group of >60 (4.9%).

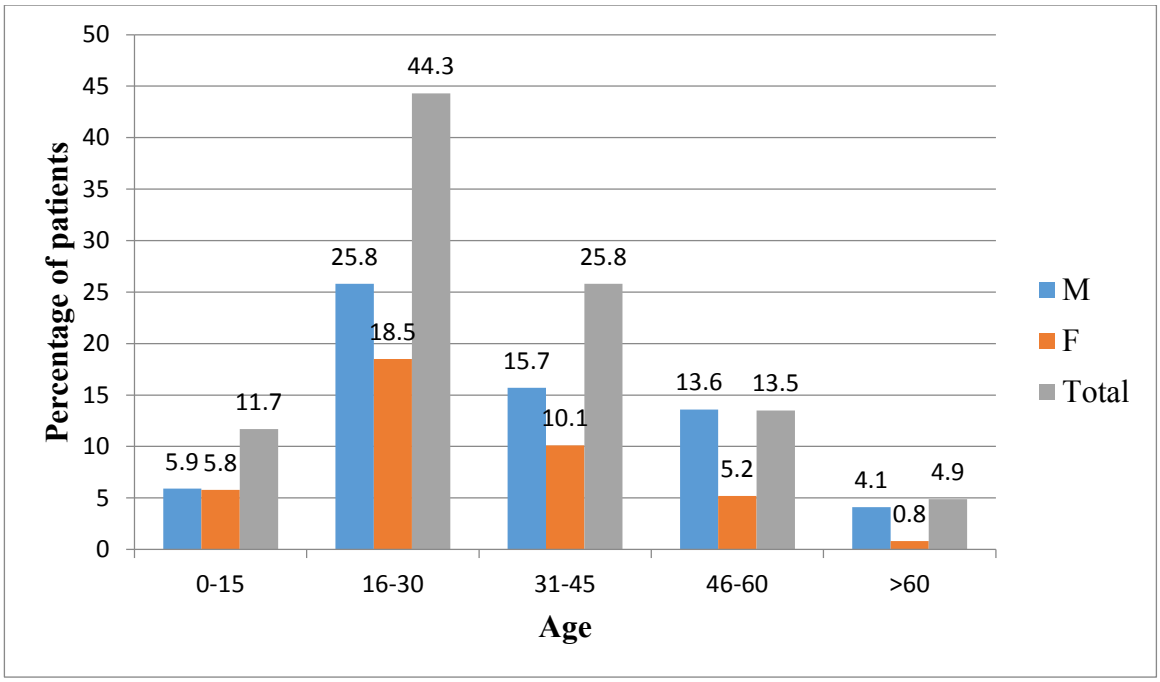

Figure 2: Prevalence of PTB patients among different age groups

4.1.4 The prevalence of PTB patients among age groups at different years

Table 2 prevalence of PTB patients among age groups at different years

Age group	Patients in percent (%)											
	2011		2012		2013		2014		2015		Total	
	M	F	M	F	M	F	M	F	M	F	M	F
0-15	12.1	11.8	14.8	11.2	10.4	8.9	7.7	**10.4**	5.9	**6.8**	**50.9**	49.1
16-30	14.9	11.0	13.7	9.7	8.6	7.0	10.3	8.4	10.7	5.8	**58.2**	41.8
31-45	14.0	9.4	15.7	9.8	11.9	7.0	9.4	5.9	9.9	7.0	**60.9**	39.1
46-60	14.6	8.3	15.9	9.1	9.4	7.3	9.6	7.3	11.5	7.0	**61.0**	39.0
>60	12.8	2.8	29.8	4.3	7.1	1.4	12.1	5.7	22	2.1	**83..8**	16.2

❖ The prevalence of PTB patients among 0-15 age group

In this age group, there was no significant difference between the percentage of male and female patients in each year. Of all children 50.9% were males and 49.1were females but there was Slight increase amongst females in 2014, and 2015.The prevalence of PTB with the age group of 0-15 increased from 2011-2012 and then consecutively decreased since 2013 (Table 2). The highest prevalence of 26.0%was observed in 2012 and the lowest was 12.7% recorded in 2015. This is in contrast to the assessment result by Fekadu (2015) that showed the prevalence of children <14 years increased from (2009) 11.7% to 2013 (26.7%). Previously, the report of Tuberculosis and Leprosy control program of Ethiopia (2002) showed that the incidence of tuberculosis was increasing .The incidence of TB in children is less compared to adults, but they are likely to suffer from more serious forms of TB and may die if not treated properly (FMH of Ethiopia, 2008).

❖ The prevalence of PTB patients among 16-30 age groups

The highest prevalence of PTB patients in both males and females in the 16-30 age groups was observed at 2011 and 2012. The prevalence was again increasing from 2013 - 2015. In addition the prevalence of male patients was relatively higher than the prevalence of females across the year 2011-2015 as indicated in the Table 2. The disproportionately large number of TB in this age group, which comprises a large part of the total working force in the country, could be contributing to poverty (WHO, 2009).

❖ The prevalence of PTB patients among 31-45 age groups

In this age group, the percentage of PTB patients increased from 2011-2012 and the highest was observed in 2012(25.5%). The prevalence decreased from 18.9% in 2013 to 16.9% in 2015. In addition the percentages of males were relatively higher than females across the year from 2011 to 2015 as indicated in Table 2. The number of PTB patients registered in this age group was25.8% which is the second highest prevalence group next from the 16 to30 age groups (44.3%).

❖ The prevalence of PTB patients among 46-60 age groups

The highest percentage of PTB patients among both sexes in this age group was 25.0% registered in 2012 and the lowest was 16.7% registered in 2013. The percentage of patients was slightly increasing from 2013(16.7%) to 2015 (18.5%).The percentage of male patients was relatively higher than that of female patients across the year from 2011-2015 (Table 2).

❖ The prevalence of PTB patients among >60age group

The highest percentage of PTB patients among this age group was 34.0% registered in 2012 and the lowest was 8.5% observed in 2013. The percentage of male patients was relatively higher than females across the years from 2011-2015. In general, the prevalence of both males and females decreased from 24.85% (2011 and 2012) to 16.8% (2013, 2014 and 2015) (Table 2).

4.1.5 Trends of PTB patients from 2011-2015

The total number of PTB patients were 696(24.1%) and 721(25.0) in 2011 and 2012 respectively. This was higher compared to the number of patients in the recent years 481(16.7%), 503(17.4%), and 485(16.8%) in 2013, 2014 and 2015 respectively (Table 3). PTB decreased by 7.58% in the recent three years compared to previous years (2011 and 2012). This was in agreement with the work of Awoke et al (2015) PTB patients were decreased across the year 2008-2013(18.74-13.44) by 5.3%. This might be due to the establishment of DOTS clinic, improvement of diagnosis and treatment of TB patients, but according to the FMHE (2008) pulmonary tuberculosis patients increased from 9.93% (1999/2000) to 14.25 (2006/7). As indicated in Miller and Schieffelbein (1998), about 8.4 million people develop active tuberculosis every year and 2.3 million die of it. It is estimated that 200 million additional people are at risk of developing the disease in the next 20 years, if the current trends are conserved.

The percentages of smear positives decrease in 2013, 2014 and 2015 than in 2011 and 2012 by about 1.78%. It agreed with the work of Hassen et al (2012) the percentage of smear positive pulmonary tuberculosis cases showed gradual decrease from 19.5% in 2006 to 5.8% in 2010. Out of the total TB patients, 28.3% were smear positives and 71.7% were smear negatives (Table 3).This was slightly higher than 6.8% smear positives and 93.2% smear negatives recorded in North-west Ethiopia (Awoke, 2015). This assessment result was inconsistent with the report of FMHE (2008) Smear-positive PTB comprises 75 – 80% of PTBcases, worldwide and 50.13% in Ethiopia. This might be due to the establishment of DOTS and improvement of TB diagnosis and treatment. Among the total smear positive TB cases in this study, 56.7 % were males and 43.3 % were females similar to the previous report of FMHE (2010) 55.5% were male and 44.5% were female smear positive TB cases. Smear positive was also high in 16-30 age group, rural area and HIV negative patients.

Table 3 Trends of PTB patients from 2011-2015

			year					Total
			2011	2012	2013	2014	2015	
category	Smear positive	Count	193	196	132	141	156	818
		% of total	**6.7**	**6.8**	**4.6**	**4.9**	**5.4**	**28.3**
	Smear negative	count	503	525	349	362	329	2068
		% of total	17.4	18.2	12.1	12.5	11.4	71.7
Total		Count	696	721	481	503	485	2886
		% of total	24.1	25.0	16.7	17.4	16.8	100

In descriptive statistics of Pearson's chi-square $p<0.05$was statistically significant but the p-value of residence was 0.153. This means residence was not significantly associated with smear test (smear positive/smear negative) but sex, age, and HIV were significantly associated with smear test (Table 4). In multivariable logistic regression being 0-15,16-30,31-45 and 46-60 age group were found to be 1.874(AOR), 4.050(AOR) , 2.125(AOR) and 1.317(AOR) time more likely to develop smear positive PTB respectively but being male 0.867(AOR) and being HIV positive 0.599(AOR) times less likely to develop smear positive PTB respectively comparing to their counterpart(Table 4).

Table 4 Characteristics and status of smear positive infection inPTB patients

Character		Smear Positive (%)	Smear Negative (%)	Pearson's X^2	p-value	AOR(95%CI)
sex	male	464(16.0)	1258(43.6)	4.110	0.043	0.867(0.732-1.026)
	female	354(12.3)	810(28.1)			1
age	0-15	78(2.7)	260(9.0)			1.874(1.08-3.246)
	16-30	483(16.7)	795(27.5)			4.050(2.457-6.67)
	31-45	174(6.0)	571(19.8)	111.060	0.000	2.125(1.268-3.56)
	46-60	64(2.2)	320(11.1)			1.3170.755-2.295)
	>60	19(0.7)	122(4.2)			1
residence	Urban	112(3.9)	327(11.3)	2.043	0.153	
	Rural	706(24.5)	1741(60.3)			
HIV	Positive	115(4.0)	427(14.8)	16.685	0.000	0.599(0.469-0.76)
	negative	703(24.3)	1641(56.9)			1
Total		818(28.3)	2068(71.7)			

4.2 The prevalence of PTB-HIV co infection and associated factors

The prevalence of PTB-HIV co infection among PTB patients visiting Debremarkos referral hospital was 18.8% (542/2886) (Table 5). The result coincides with the overall report of WHO (2013) where 1.1 million (13%) of the 8.6 million people who develop TB in 2012 were HIV positive. The report of WHO (2014) also showed 11% of co infections in Ethiopia. In addition the overall prevalence of co infection in the present study (18.8%) was consistent with the recent national survey 20% (EFMOH, 2013) and the study done in Western Ethiopia

(17.9%) by EyasuEjeta (2014). However, the result was higher than the study done at Dabat (11.4%) by SebsibeTadesse,TakeleTadesse(2013).

In this study, co-infection was slightly higher in males (10.9%) than females (7.9%) but in some studies, the co-infection rate was slightly higher among female TB patients (9.4%) than males (8.5%) (EyasuEjeta, 2014) and co-infection 25.7% and 22.3% among female and male patients respectively (Daniel, 2015). However, Sebsibe et al, (2013) showed the gap in co-infections between males (37.1%) and females (61.9%) .This calls for further research to explore factors increasing the rate of TB-HIV co infection between each gender group.

The prevalence of co infection was higher between 16-45 age groups (82%) than the other age groups (18%) (Table 5).This agree with the work of Eyasu (2015) where most of co infected patients are found in the age group of 15-44 (76.7%). The development of co infection in 16-30 age groups was the highest (8.1%) which was 7.707 times the development of co infection in above 60 age groups (Table 5). High prevalence of co infection in 16-45 age groups might be due to high HIV transmission in sexually active groups (FMHE, 2008). Tessema et al (2009) also showed that both TB and HIV prevail most in sexually active age groups.
In urban area out of 439 PTB patients 226(51.5) were co infected with HIV but in rural area out of 2447 PTB patients only 316(12.9%) were co infected with HIV. This indicates that co infection was associated with residence. PTB patients in urban area developed co infection 7.059 times than patients in rural area (Table 5). This was consistent with Sebsbe et al (2013) co infection was 53.6% in urban and 46.4% in rural area. Possibly this might be due to the presence of high prevalence of HIV infection among urban dweller (EFMOH, 2007).

In this study the prevalence of smear positive PTB-HIV co infection was 4.0% out of total PTB patients and that of smear negative PTB-HIV co infection was 14.8% (Table 5). This indicates that type of PTB (smear positive/smear negative) was statistically associated with HIV. That is, HIVpositive TB was o.620 times less likely to showsmearpositivethan smear negative (Table 5). Out of total co infections, 21.2% and78.8% was smear positive and smear negative respectively. This result was in agreement with the rate estimated by WHO (2013), Daniel (2015) 39.4% smear positive and 60.6 smear negative; Solomon et al (2014) 43.6% smear positive and 56.4% smear negative.

Table 5 Characteristics and HIV status of PTB patients

Character		HIV positive (%)	HIV negative (%)	Pearson's x^2	p-value	AOR (95%CI)
Sex	Male	314(10.9)	1408(48.8)	.834	.361	
	Female	228(7.9)	936(32.4)			
Age	0-15	27(0.9)	311(10.8)			3.302(1.21-8.98)
	16-30	234(8.1)	1044(36.2)			7.707(3.05-19.46)
	31-45	211(7.3)	534(18.5)	92.781	.000	12.73(5.02-32.26)
	46-60	65(2.3)	319(11.1)			7.1292.74-18.55)
	>60	5(0.2)	136(4.7)			1
residence	Urban	226(7.8)	213(7.4)	362.987	.000	7.0595.61-8.88)
	Rural	316(10.9)	2131(73.8)			1
category	Smear positive	115(4.0)	703(24.4)	16.685	.000	0.620(0.48-0.79
	Smear negative	427(14.8)	1641(56.9)			1
Total		542(18.8)	2344(81.2)			

The trends (changes) of PTB-HIV co infection was steadily decreasing in the last five years from 5.9% in 2011 to 2.0% in 2015 as indicated in the table 6 below. This might be due to increasing diagnosing and treating of HIV patients. This finding was in agreement with the 2012 WHO report on the trends of HIV among TB patients from 2004-2011(WHO, 2012).

Table 6: Trends of PTB-HIV co infection from 2011-2015

			year					Total
			2011	2012	2013	2014	2015	
HIV	positive	Count	169	120	86	108	59	542
		% of total	**5.9**	**4.2**	**3.0**	**3.7**	**2.0**	**18.8**
	negative	count	527	601	395	395	426	2344
		% of total	18.3	20.8	13.7	13.7	14.8	81.2
Total		Count	696	721	481	503	485	2886
		% of total	24.1	25.1	16.7	17.4	16.8	100

4.3 The prevalence of MDR -TB cases and associated factors

Table 7: Characteristics and prevalence of MDR-TB cases

Characters		Susceptible (%)	MDR (%)	Pearson's x^2	p-value	AOR(95%CI)
Sex	male	1678(58.1)	44(1.5)	1.375	.241	
	female	1142(39.6)	22(0.8)			
Age	0-15	337(11.7)	1(0.03)	10.229	.037	14.569(1.40-15.68)
	16-30	1242(43.0)	36(1.2)			2.262(0.62-8.25)
	31-45	724(25.1)	21(0.7)			1.346(0.355-5.102)
	46-60	379(13.1)	5(0.2)			2.354(0.503-11.012)
	>60	138(4.8)	3(0.1)			1
Address	Urban	435(15.1)	4(0.1)	4.385	.036	2.494(0.846-7.349)
	Rural	2385(82.6)	62(2.1)			1
category	Smear Positive	754(26.1)	64(2.2)	156.624	.000	0.011(0.003-0.045)
	Smear negative	2066(71.6)	2(0.1)			1
HIV	Positive	536(18.6)	6(0.2)	4.157	.041	1.541(0.622-3.819)
	Negative	2284(79.1)	60(2.1)			1
Total		2820(97.7)	66(2.3)			

The prevalence of MDR-TB in this study was 2.3% of which 0.2% new cases and 2.1%previously treated cases (Table 7). Drug resistance was strongly associated with previous treatment. This agreed with the report of WHO (2004)that showed the probability of any resistance is over 4-fold higher, and of MDR-TB over 10-fold higher than from untreated patients. The overall prevalence of drug resistance was often related to the number of previously treated cases. In different study sites, new MDR-TB cases ranged from 0% to 2.9% and previously treated cases ranged from 0% to 29.0% of all patients registered in DOTS program (Table 8).

Table 8 MDR-TB cases in different study sites

Country	Study site	New cases	Previously treated	Total	Reference
Ethiopia	Debremarkos	0.2%	2.1%	2.3%	This study
"	Ethiopia	1.6%	11.8%	13.4%	WHO,2013
"	Harar	-	-	37.3%	Mitike et al,1997
"	ArsiZone	-	-	19.5%	Mekdes et al,2001
"	Addis Ababa	-	-	12.0%	Demissie et al,1994
"	Arsi Zone	0%	0%	0%	Mekdes et al,2001
"	Amhara region	-	-	1.0%	Yimer et al,2008
"	South-West Ethiopia	-	-	1.5%	Abebe et al,2010-2011
"	Eastern Amhara	-	-	6.5%	Esmaeletal,2010-2011
"	Addis Ababa	-	-	0.6%	Demissie et al,1998
Nigeria	Nigeria	2.9%	14.0%	16.9%	WHO,2013
South Africa	South Africa	1.8%	6.7%	8.7%	WHO,2013
Bangladesh	Bangladesh	1.4%	29.0%	30.4%	WHO,2013
World wide	World wide	3.6%	20.2%	23.8%	WHO,2013

In this study, higher MDR was observed in males (1.5%), 16-30 age group (1.2%), rural area (2.1%), smear positive pulmonary TB (2.2%) and HIV negative (2.1%) compared to other groups. MDR was statistically not associated with sex but associated with age (16-30), residence (rural), category (smear positive) and HIV (Table 7). High MDR in rural area might be due to poor treatment and improper taking of drugs and giving the chance for *M. tuberculosis* to adapt anti TB drugs

The association of 16-30 age groups with MDR might be also due to the presence of more HIV positives than in the other age groups, because HIV was also associated with MDR. This in lined with the report of FMHE (2008) HIV-positive persons are prone to re-infection with new strains of TB from the community and drug resistance may occur more frequently.

Table 9 Trends of MDR-TB in the study area from 2011-2015

			year					Total
			2011	2012	2013	2014	2015	
resistance	susceptible	Count	696	713	465	488	458	2820
		% of total	24.1	24.7	16.1	16.9	15.9	97.7
	MDR	count	0	8	16	15	27	66
		% of total	**0.0**	**0.3**	**0.6**	**0.5**	**0.9**	**2.3**
Total		Count	696	721	481	503	485	2886
		% of total	24.1	25.1	16.7	17.4	16.8	100

The trend of MDR was 0%, 0.3%, 0.6%, 0.5% and 0.9% for 2011, 2012, 2013, 2014, and 2015 respectively (Table 9). The trend of MDR was increasing in the study area from 0.0% in 2011 to 0.9% in 2015. This might be due the spread of HIV, poor treatment of patients and improper taking of drugs. This result agreed with the finding Neville et al (1994) the incidence of MDR-TB has increased both in the developed and developing countries for different reasons. The emergence of MDR-TB in developing countries preceded the HIV epidemic and MDR-TB levels are higher in areas with poor TB control and high retreatment cases. Resistance to TB drug(s) usually occurs as a consequence of an inadequate treatment, be it irregular, too short or too weak. It develops because a patient is treated incorrectly or is not able to adhere to the treatment regimen. In both cases, the patient has not been receiving a strong enough dosage of the drug over a long enough period of time to kill the bacilli, so the organism is given time to develop resistance to anti-TB drugs (WHO, 2003).

5. SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 Summary

Infectious diseases remain a major cause for worsening the living conditions and cause of death for many millions of people in the world. Tuberculosis is a widespread infectious disease caused by *M. tuberculosis* that attack different part of the body typically the lungs. The HIV epidemic worsened the TB situation. In addition, the emergence of MDR-TB is another challenge to control TB in Ethiopia. Despite dramatic progression in their prevention and treatment, PTB remains deadly disease in the study area. Therefore, investigation was required to the prevalence of PTB, PTB/HIV co infection and MDR.

The purposes of the study were:

1 To measure the prevalence ofPTBamong patients attending DebreMarkos referral hospital.

2. To determine the prevalence of PTB-HIV co- infection.

3. To measure the prevalence of MDR among PTB patients.

4. To assess whether the burden of PTB, PTB/HIV co-infection and MDR disease has fallen from 2011-2015 at the study site.

5. To determine the associated factors with PTB, PTB and HIV co-infection and MDR of *M.tuberculosis*.

To achieve these purposes the following leading questions were formulated:

1. What is the prevalence of PTB registered at DOTS clinic of DebreMarkos hospital?

2. What is the prevalence of PTB-HIV co- infection at the study site?

3. What is the prevalence of MDR among PTB patients?

4. Has the burden of PTB, PTB/HIV co-infection and MDR-TB fallen from 2011-2015?

5. What are the associated factors with PTB, PTB and HIV co-infection and MDR of *M.tuberculosis*?

To answer these leading questions, document analysis was the tool employed to gather data for the study. The data were retrospective secondary data registered from 2011-2015 in the DOTS clinic of DebreMarkos referral hospital. Out of the TB patients registered from 2011-2015 in the documents of DOTS clinic of DebreMarkos referral hospital, all the 2886 PTB patients with full information of their socio demographic characteristics were included in the study. Characteristics registered in the document and used for analysis were sex, age, category (smear positive or smear negative), HIV (HIV-positive or HIV-negative), residence (urban or rural), resistance (susceptible or MDR), occurrence of resistance (new or after treatment).

Descriptive cross sectional study was used for assessing the problem. In addition descriptive statistics was used to calculate frequency, percentage and chi-square. Chi-square was used to test the presence of association between dependent and independent factors. In addition logistic regression was used to calculate crude odds ratio (COR) and adjusted odds ratio (AOR) to quantify the degree of association between factors.

From the analyses, the following major findings were obtained:

Out of 2886 PTB patients who were registered in the DOTS clinic of DebreMarkos referral hospital, 1722(59.7%) were males and 1164(40.3%) were females. According to their age groups PTB cases were 0-15(11.7%), 16-30((44.3%), 31-45(25.8%), 46-60(13.3%), and >60 age groups were (4.9%). In addition cases in the rural area were 2447(84.8%) and in urban area 439(15.2%). The prevalence of males greater than that of females in each age group and the highest was observed at age group 16-30 followed by age group 31-45. The trends of PTB patients across the year from 2011-2015 were 696(24.1%), 721(25.0%), 481(16.7%), 503(17.4%) and 485(16.8%) respectively. In general the prevalence of both male and female patients decrease in the recent three years (2013, 2014 and 2015) than the previous two years (2011 and 2012).

Chi-square analysis showed that sex, age and HIV were significantly associated with smear positive pulmonary TB. Being female, 16-30age groups, and HIV negative were more likely to develop smear positive PTB than their corresponding.

The prevalence of PTB-HIV co infection among PTB cases registered was 18.8% (10.9% males and 7.9% females). Co infection was higher in 16-30 age groups (8.1%) than the other age groups. It was also 10.9% in rural area and 14.8% in smear negative pulmonary tuberculosis. The trends of co infection from 2011-2015 was 5.9%, 4.2%, 3.0%, 3.7% and 2.0% respectively. This shows that the trend of co infection was decreasing steadily in the last five years. Pearson's chi-square analysis indicated that age, address and type of PTB were statistically associated with co infection. In addition 16-30 age group, urban dwellers and smear negative PTB were at high risk of co infection.

The prevalence MDR-TB was 0.2% in new cases and 2.1% in previously treated cases. The overall prevalence of MDR-TB was 2.3%. The result shows MDR-TB was strongly associated with previous treatment. Higher prevalence of MDR-TB was observed in males, 16-30 age groups, rural dweller, Smear positive pulmonary TB and HIV positive patients. The trend of MDR-TB from 2011-2015 was 0%, 0.3%, 0.6%, 0.5%, and 0.9% respectively. The result shows that the trend of MDR-TB was increasing in the study area from 2011-2015.

The analysis showed that age, address, category, and HIV were statistically associated with MDR-TB. Being 16-30 age groups, rural dweller, smear positive and HIV positive were more likely to develop MDR-TB than their corresponding parts.

5.2 Conclusion

- The prevalence of PTB across sex, age and address indicated that males, 16-30 age groups and rural dwellers were more affected than their corresponding parts.
- The study revealed that the trends of PTB disease among males and females across the year from 2011-2015 at the study site. PTB cases were higher in the two years (2011& 2012) than the next three years (2013-2015).
- Sex(male), age(16-30), residence(rural) and HIV were significantly associated with PTB
- The prevalence of PTB-HIV co infection in this study was lower than the previous studies in Ethiopia. In addition the rate of PTB-HIV co infection was decreasing across the year from 2011-2015. Nevertheless, people living in the urban area and 16-30 age groups were significantly at high risk of co infection. These groups are sexually

active groups and more exposed for HIV. So, HIV is also significantly associated with the spreading of TB.

The study reveals that the prevalence of MDR-TB was higher in males, 16-30 age groups, rural dwellers, Smear positive PTB and HIV patients. However, significant association was observed between the16-30 age group, smear positive PTB, HIV positive, rural dwellers, and the development of MDR-TB than their corresponding.

The study also revealed that MDR-TB was strongly associated with previous treatment.

The trends of MDR-TB was increasing rapidly across the year from 2011-2015.

5.3 Recommendation

- As the study shows, most of the PTB patients are rural dwellers who are unaware about pulmonary tuberculosis in many aspects i.e transmission, symptoms, diagnosis, treatment, etc. Therefore, the TB awareness program should be initiated in order to aware people about tuberculosis. Government has to educate people through media, seminars, schools etc.
- TB patients should be well oriented how to take the drugs and there should be follow up by health workers
- Age group16-30s are sexually active and most exposed group for HIV. As the statistical result revealed, HIV has a significant association for the development of susceptible TB and MDR-TB. So, HIV prevention program should be strengthened to reduce susceptible TB and the emergence of MDR-TB.
- The introduction of DOTS clinic may have contributed to the low prevalence of PTB in recent three years after it has been established compared to the previous years. Therefore, a wide use of DOTS and strengthening it is recommended to reduce the prevalence of PTB and the emergence of MDR-TB.
- The study indicates that MDR-TB in the study site is a serious public health problem that needs to be addressed urgently. The study also indicates that the previous exposure of anti TB treatment increased the risk of MDR-TB in the study area. Thus strengthening early case detection and proper treatment of drug susceptible TB is essential to limit the emergence of MDR-TB.

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Appendix: A Tables and Figures

Table 10 The prevalence of PTB among each age group and year

age				year					Total
				2011	2012	2013	2014	2015	
0-15	sex	male	Count	41	50	35	26	20	172
			% of Total	12.1%	14.8%	10.4%	7.7%	5.9%	50.9%
		female	Count	40	38	30	35	23	166
			% of Total	11.8%	11.2%	8.9%	10.4%	6.8%	49.1%
	Total		Count	81	88	65	61	43	338
			% of Total	**24.0%**	**26.0%**	**19.2%**	**18.0%**	**12.7%**	**100.0%**
16-30	sex	male	Count	191	175	110	131	137	744
			% of Total	14.9%	13.7%	8.6%	10.3%	10.7%	58.2%
		female	Count	140	124	89	107	74	534
			% of Total	11.0%	9.7%	7.0%	8.4%	5.8%	41.8%
	Total		Count	331	299	199	238	211	1278
			% of Total	**25.9%**	**23.4%**	**15.6%**	**18.6%**	**16.5%**	**100.0%**
31-45	sex	male	Count	104	117	89	70	74	454
			% of Total	14.0%	15.7%	11.9%	9.4%	9.9%	60.9%
		female	Count	70	73	52	44	52	291
			% of Total	9.4%	9.8%	7.0%	5.9%	7.0%	39.1%
	Total		Count	174	190	141	114	126	745
			% of Total	**23.4%**	**25.5%**	**18.9%**	**15.3%**	**16.9%**	**100.0%**
46-60	sex	male	Count	56	61	36	37	44	234
			% of Total	14.6%	15.9%	9.4%	9.6%	11.5%	60.9%
		female	Count	32	35	28	28	27	150
			% of Total	8.3%	9.1%	7.3%	7.3%	7.0%	39.1%
	Total		Count	88	96	64	65	71	384
			% of Total	**22.9%**	**25.0%**	**16.7%**	**16.9%**	**18.5%**	**100.0%**
>60	sex	male	Count	18	42	10	17	31	118
			% of Total	12.8%	29.8%	7.1%	12.1%	22.0%	83.7%
		female	Count	4	6	2	8	3	23
			% of Total	2.8%	4.3%	1.4%	5.7%	2.1%	16.3%
	Total		Count	22	48	12	25	34	141
			% of Total	**15.6%**	**34.0%**	**8.5%**	**17.7%**	**24.1%**	**100.0%**
Total	sex	male	Count	410	445	280	281	306	1722
			% of Total	14.2%	15.4%	9.7%	9.7%	10.6%	59.7%
		female	Count	286	276	201	222	179	1164
			% of Total	9.9%	9.6%	7.0%	7.7%	6.2%	40.3%
	Total		Count	696	721	481	503	485	2886
			% of Total	**24.1%**	**25.0%**	**16.7%**	**17.4%**	**16.8%**	**100%**

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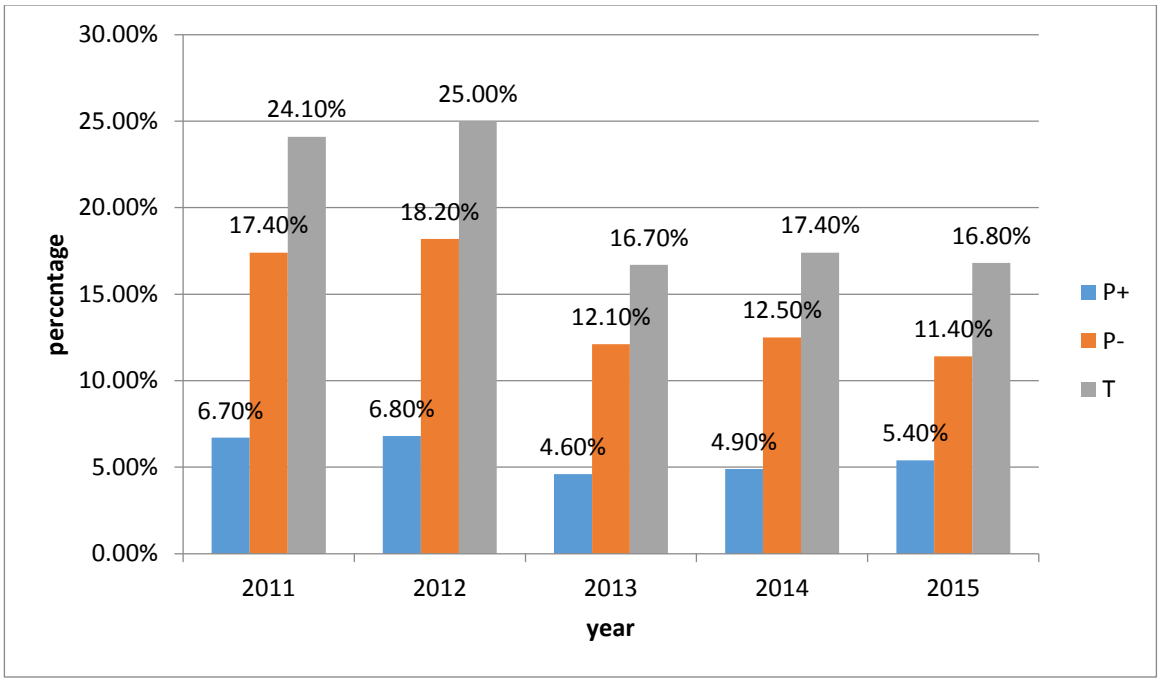

Figure 3 The Trends of PTB from 2011-2015

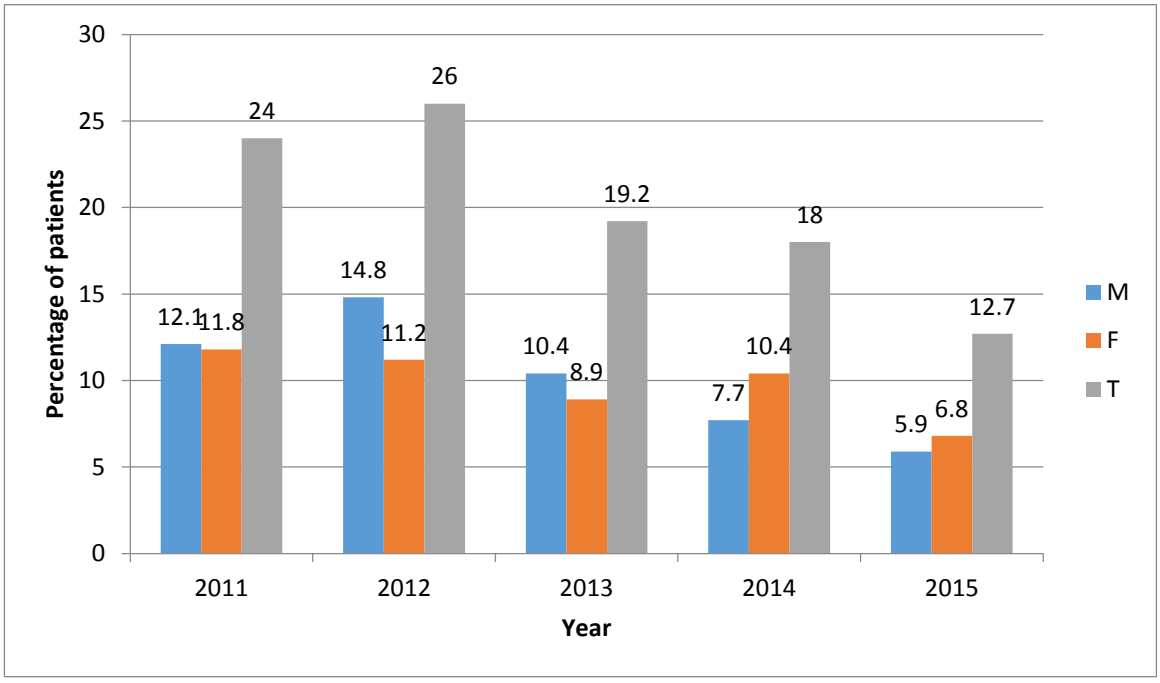

Figure 4 The prevalence ofPTB patients among 0-15 age groups

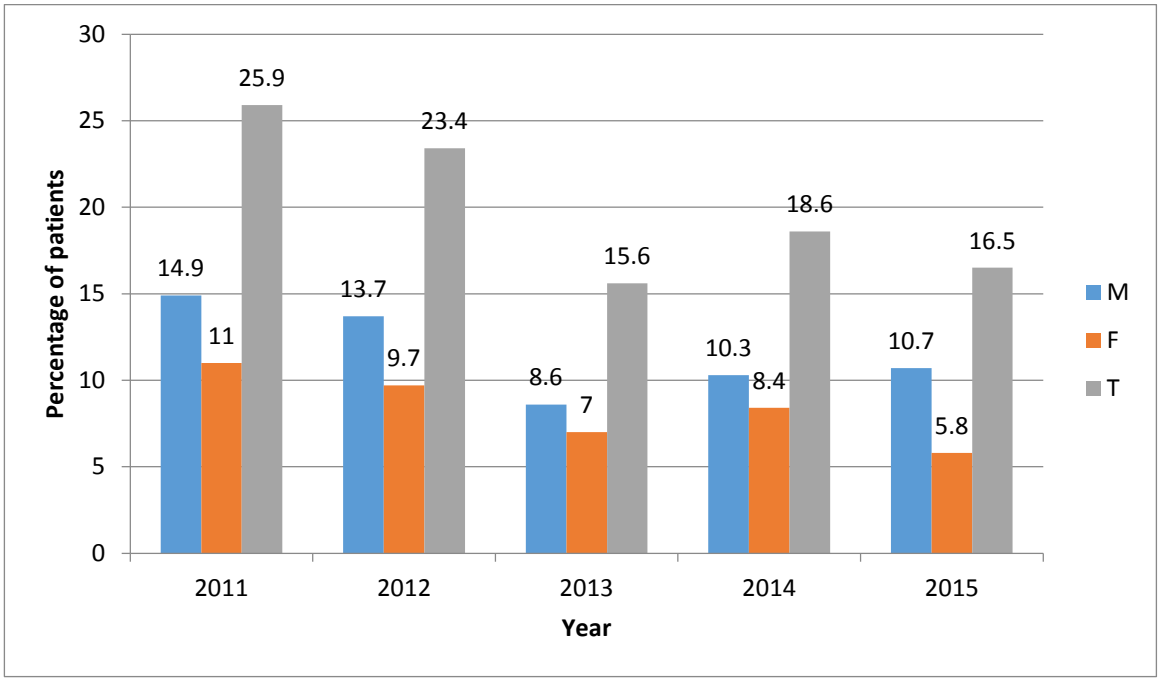

Figure 5: The prevalence of PTB patients among 16-30 age groups

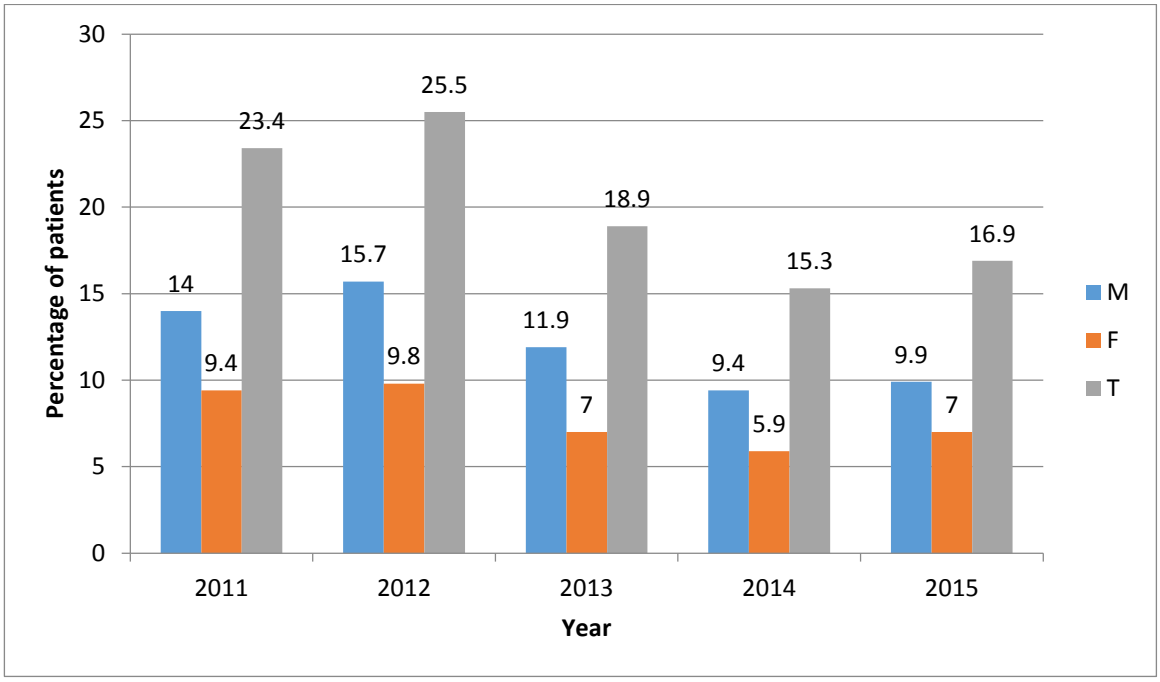

Figure 6: Prevalence of PTB patients among 31-45 age groups

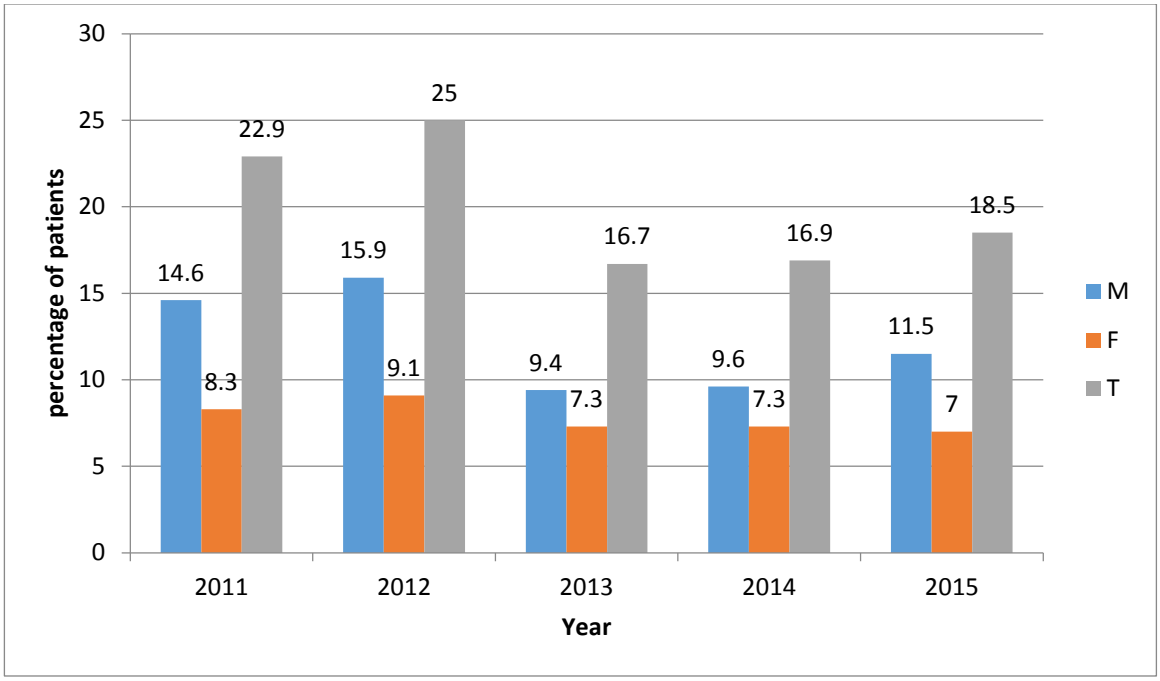

Figure 7 Prevalence of PTB patients among 46-60 age groups

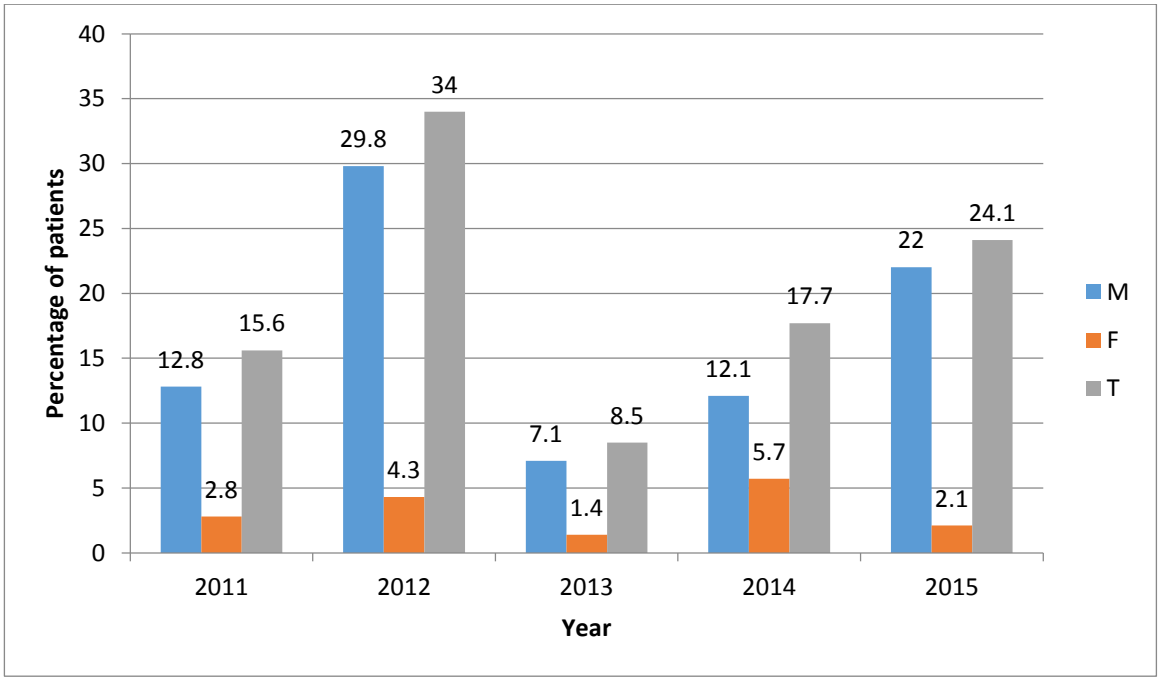

Figure 8 Prevalence of PTB patients among >60 age groups

Table 11 Characteristics of PTB patients and smear positive infection

variable	Category Of variable	Smear Positive (%)	Smear Negative (%)	Pearson's X^2	p-value
sex	male	464(16.0)	1258(43.6)	4.110	0.043
	female	354(12.3)	810(28.1)		
age	0-15	78(2.7)	260(9.0)	111.060	0.000
	16-30	483(16.7)	795(27.5)		
	31-45	174(6.0)	571(19.8)		
	46-60	64(2.2)	320(11.1)		
	>60	19(0.7)	122(4.2)		
address	Urban	112(3.9)	327(11.3)	2.043	0.153
	Rural	706(24.5)	1741(60.3)		
HIV	Positive	115(4.0)	427(14.8)	16.685	0.000
	negative	703(24.36)	1641(56.9)		

Table 12 Multivariable logistic regressions of PTB patients and smear positive infection

variable	Category Of variable	Smear Positive (%)	Smear Negative (%)	COR(95% CI)	P-value	AOR(95% CI)	P-value
sex	male	464(16.1)	1258(43.6)	.844 (.716-994)	0.043	.867 (.732-1.026)	0.098
	female	354(12.3)	810(28.1)	1			
age	0-15	78(2.7)	260(9.0)	1.926 (1.116-3.32)	0.019	1.874 (1.08-3.246)	0.025

	16-30	483(16.7)	795(27.5)	3.901 (2.375-6.41)	0.000	4.050 (2.457-6.67)	0.000
	31-45	174(6.0)	571(19.8)	1.957 (1.172-3.27)	0.10	2.125 (1.268-3.56)	0.004
	46-60	64(2.2)	320(11.1)	1.284 (.739-2.23)	0.375	1.317 (.755-2.295)	0.332
	>60	19(0.7)	122(4.2)	1			
HIV	Positive	115(4.0)	427(14.8)	0.629 (.572-.787)	0.000	0.599 .469-.76)	0.000
	negative	703(24.36)	1641(56.9)	1			

Table 13 Characteristics and HIV status of PTB patients

character		HIV positive (%)	HIV negative (%)	Total(%)	Pearson's x^2	p-value
sex	Male	314(10.9)	1408(48.8)	1722(59.7)	.834	.361
	Female	228(7.90)	936(32.4)	1164(40.3)		
age	0-15	27(0.9)	311(10.8)	338(11.7)	92.781	.000
	16-30	234(8.1)	1044(36.2)	1278(44.3)		
	31-45	211(7.3)	534(18.5)	745(25.8)		
	46-60	65(2.3)	319(11.1)	384(13.3)		
	>60	5(0.2)	136(4.7)	141(4.9)		
address	Urban	226(7.8)	213(7.4)	439(15.2)	362.987	.000
	Rural	316(10.9)	2131(73.8)	2447(84.8)		
Category (smear test)	Smear positive	115(4.0)	703(24.4)	818(28.3	16.685	.000
	Smear negative	427(14.8)	1641(56.9)	2068(71.7)		
Total		542(18.8)	2344(81.2)	2886(100)		

Table 14 Multivariate logistic regression of PTB patients and HIV positive infection

character		HIV Positive (%)	HIV negative(%)	COR (95% CI)	P-value	AOR (95%CI)	p-value
age	0-15	27(.9)	311(10.8)	2.361 (.89-6.26)	.084	3.302 1.21-8.98	.019
	16-30	234(8.1)	1044(36.2)	6.097 (2.47-	.000	7.707 3.05-	.000

				15.05)		19.46	
	31-45	211(7.3)	534(18.5)	10.748 (4.34-26.6)	.000	12.73 5.02-32.26	.000
	46-60	65(2.3)	319(11.1)	5.54 (2.18-14.06)	.000	7.129 2.74-18.55	.000
	>60	5(.2)	136(4.7)	1			
address	Urban	226(7.8)	213(7.4)	7.155 (5.73-8.92)	.000	7.059 5.61-8.88	.000
	Rural	316(10.9)	2131(73.8)	1			
category	Smear positive	115(4.0)	703(24.4)	.629 (.502-.787)	.000	.620 .48-.79	.000
	Smear negative	427(14.8)	1641(56.9)	1			
Total		542(18.8)	2344(81.2)				

Table 15 Characteristics and prevalence of MDR-TB cases

characters		Susceptible (%)	MDR (%)	Total (%)	Pearson's x^2	p-value
sex	male	1678(58.1)	44(1.5)	1722(59.7)	1.375	.241
	female	1142(39.6)	22(.8)	1164(40.3)		
age	0-15	337(11.7)	1(.03)	338(11.73)		
	16-30	1242(43.0)	36(1.2)	1278(44.3)		
	31-45	724(25.1)	21(.7)	745(25.8)	10.229	.037
	46-60	379(13.1)	5(.2)	384(13.3)		
	>60	138(4.8)	3(.1)	141(4.9)		
address	Urban	435(15.1)	4(.1)	439(15.2)	4.385	.036
	Rural	2385(82.6)	62(2.1)	2447(84.8)		
category	Smear Positive	754(26.1)	64(2.2)	818(28.3)	156.624	.000
	Smear negative	2066(71.6)	2(.1)	2068(71.7)		
HIV	Positive	536(18.6)	6(.2)	542(18.8)	4.157	.041
	Negative	2284(79.1)	60(2.1)	2344(81.2)		
Total		2820(97.7)	66(2.3)	2886(100)		

Table 16 Characters and Multivariable logistic regression of MDR-TB cases

characters		Susceptible (%)	MDR (%)	COR	p-value	AOR(95% CI)	p-value
age	0-15	337(11.7)	1(.03)	7.326 (.755-7.052)	.086	14.569 1.40-15.68	.025
	16-30	1242(43.0)	36(1.2)	.75 (.228-2.467)	.636	2.262 .62- 8.25	.662
	31-45	724(25.1)	21(.7)	.749 .221-2.547	.644	1.346 .355-5.102	.662
	46-60	379(13.1)	5(.2)	1.648 .389-6.987	.498	2.354 .503-11.012	.277
	>60	138(4.8)	3(.1)	1			
address	Urban	435(15.1)	4(.1)	2.827 1.023-7.81	.045	2.494 .846-7.349	.099
	Rural	2385(82.6)	62(2.1)	1			
category	Smear Positive	754(26.1)	64(2.2)	0.011 .003-.047	.00	.011 .003-.045	.000
	Smear negative	2066(71.6)	2(.1)	1			
HIV	Positive	536(18.6)	6(.2)	2.347 1.00-5.46	.048	1.541 .622-3.819	.351
	Negative	2284(79.1)	60(2.1)	1			
Total		2820(97.7)	66(2.3)				

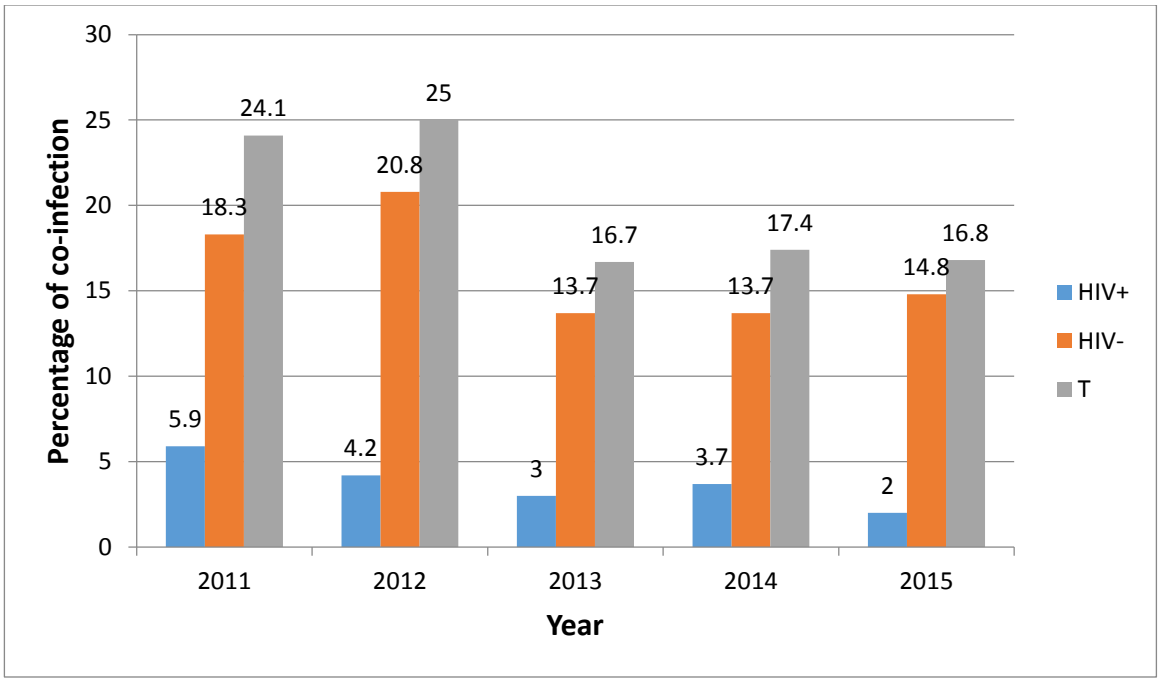

Figure:9 Trends of PTB-HIV co infection from 2011-2015

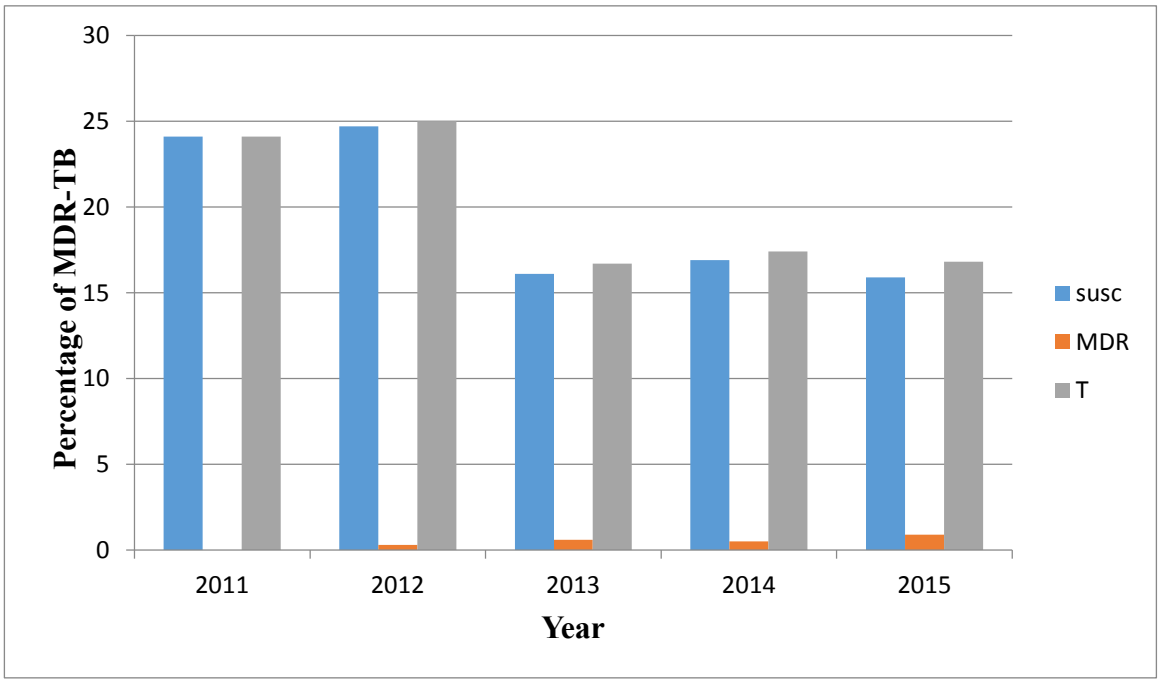

Figure 10 Trends of MDR-TB in the study area from 2011-2015