HAEMATOLOGICAL PROFILE IN

PULMONARY TUBERCULOSIS PATIENTS

WITH AND WITHOUT HIV

DISSERTATION SUBMITTED FOR

M.D DEGREE (BRANCH I) GENERAL MEDICINE

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CERTIFICATE

This is to certify that this dissertation "HAEMATOLOGICAL PROFILE OF PULMONARY TUBERCULOSIS PATIENTS WITH AND WITHOUT HIV "submitted by **DR. C.VIJAY BABU** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of MD degree Branch I (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

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I, **Dr.C.Vijay Babu** solemnly declare that the dissertation titled **"HAEMATOLOGICAL PROFILE OF PULMONARY TUBERCULOSIS PATIENTS WITH AND WITHOUT HIV ''**has been prepared by me.

This is submitted to the Tamil Nadu, Dr. M.G.R. Medical University Chennai, in partial fulfilment of the regulations for the award of MD degree Branch I (General Medicine).

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CONTENTS

INTRODUCTION

Tuberculosis, caused by mycobacterium tuberculosis is characterized by the presence of granulomas in the infected tissues. Tuberculosis is a disease of great antiquity.

Tuberculosis lesions were seen in vertebrae of Neolithic man in Europe and in Egyptian mummies as early as 3700 B.C. although the lungs are commonly involved, it can involve any organ system in our body. Tuberculosis still continues to be a significant problem in the developing world and is on the rise in developed countries coinciding with increased incidence of HIV infection.

It is estimated that the 3 million people die from tuberculosis each year , the majority in developing countries.the annual incidence of new cases of all forms of tuberculosis (pulmonary and extrapulmonary) world wide is estimated approximately 8 million, of which 95% occur in developing countries. Consequently , the estimated prevalence worldwide is 16 to 20 millions of whom 8-10 million are sputum smear positive and highly infectious.

The number of persons infected with TB bacillus is estimated to be 6-7 billion , of which 1.3 billion live in developing countries. In India , more than 40% of adults are infected with TB and approximately 1.5 million cases are put on treatment every year.

An estimated 5 lakh death from TB occur every year. The greatest burden of TB incidence and mortality in developing countries is in adults aged between 15 to 60 years.

Though haematological abnormalities associated with TB have been well recognised for nearly a century , not many comprehensive studies exist which describe the prevelance and relationship with the severity of the disease .Haematological changes have been observed with pulmonary, extrapulmonary and disseminated TB and usually reversible with ATT.

Anemia is common in TB. The extent of anemia depands on the extent of the disease; when TB is localized to only one organ eg. Lung. The Hb level is usually normal until the disease has made considerable progress , when a mild to moderate normochromic normocytic or slightly hypochromic anemia may develop. Severe anemia is rare in the absence of complications of TB like disseminated TB, ulceration of bowel etc.

Hb level is generally in the range of 1-3 gm/dl below the lower limit and normal for the age and sex of the patient.MCH is usually 22-26 pg. and MCV is usually 77-80 microlitre.slight to moderate anisocytosis and poikilocytosis may be present. Reticulocyte is not decreased . WBC count is usually not affected . rare associated with monoctosis and lymphocytosis. Platelets are usually normal or increased, but thrombocytopenia is per se very rare in pulmonary tuberculosis patients.

AIDS is a chronic, life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging or destroying the cells of immune system, HIV interferes with body's ability to effectively fight off viruses, bacteria and fungi that cause disease. This makes the people more susceptible to certain types of cancers and to opportunistic infections. The virus and the infection itself are known as HIV.

The term acquired immunodeficiency syndrome (AIDS) is used to mean the later stages of an HIV infection.

HIV infection is associated with numerous abnormalities of hematopoiesis, affecting both the myeloid and lymphoid lineages derived from the hematopoietic stem cell. Thus, as many as 70% to 80% of HIV-infected patients develop anemia during the course of infection, while neutropenia may be seen in more than 50% of individuals with more advanced HIV-related immunodeficiency. Thrombocytopenia is also common, occurring in approximately 40% of patients, and serving as the first symptom or sign of infection in approximately 10% of HIV-infected patients.

HIV infection increases the risk of tuberculosis. The HIV epidemic is also likely to have an indirect effect on the incidence of tuberculosis because of the increased number of infectious individuals in the population.

HIV infection has dramatically increased the incidence of tuberculosis. There was a direct increase in those who were HIV infected, but also a doubling in tuberculosis incidence in those remaining HIV negative, implying considerable

ongoing Mycobacterium tuberculosis transmission. This has occurred despite active case finding and directly observed therapy, which exceeds WHO targets for cure rates.

In considering above facts , a comparative study was conducted in Government Rajaji Hospital , Madurai , to compare the haematological profile in patients with pulmonary tuberculosis per se and patients with pulmonary tuberculosis with HIV.

REVIEW OF LITERATURE

Background:

Tuberculosis (TB) is the number one infectious disease killer worldwide. The World Health Organization estimates that 2 billion people have latent TB, while another 3 million people worldwide die each year due to TB.

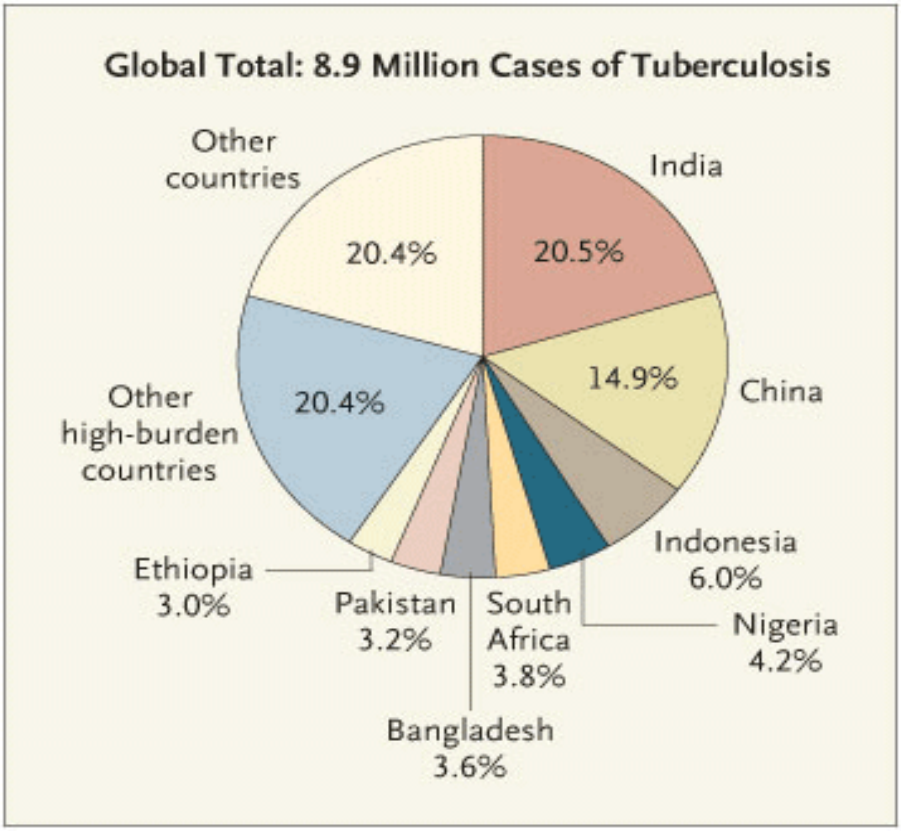
ETIOLOGY:

Pulmonary tuberculosis is caused by *Mycobacterium tuberculosis*. TB is transmitted by airborne droplet nuclei, which may contain fewer than 10 bacilli. Exposure to TB occurs by sharing common airspace with a patient who is infectious. When inhaled, droplet nuclei are deposited within the terminal airspaces of the lung. Upon encountering the bacilli, macrophages ingest and transport the bacteria to regional lymph nodes.

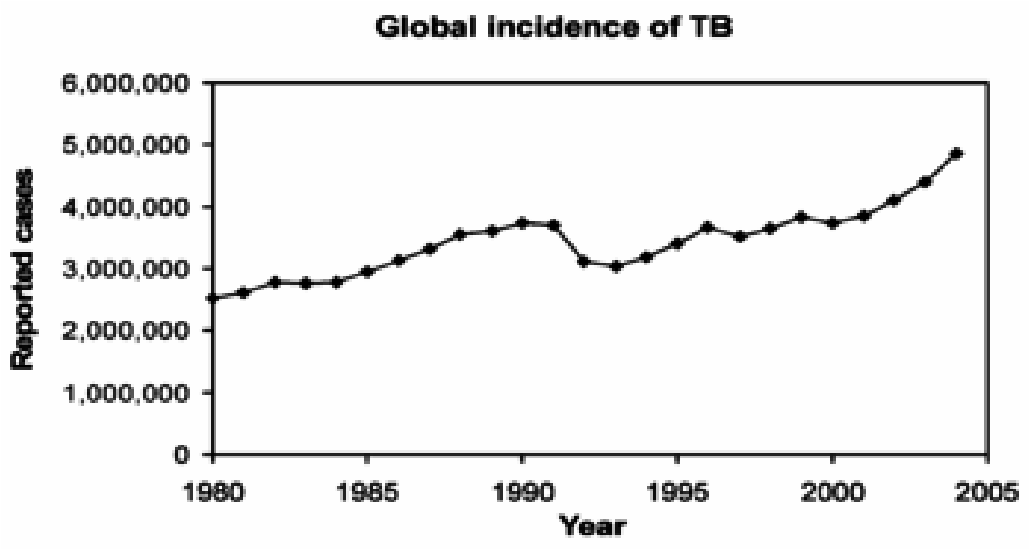
The bacilli have 4 potential fates: (1) they may be killed by the immune system, (2) they may multiply and cause primary TB, (3) they may become dormant and remain asymptomatic, or (4) they may proliferate after a latency period (reactivation disease). Reactivation disease may occur following either (2) or (3) above.

BURDEN OF PULMONARY TUBERCULOSIS IN INDIA

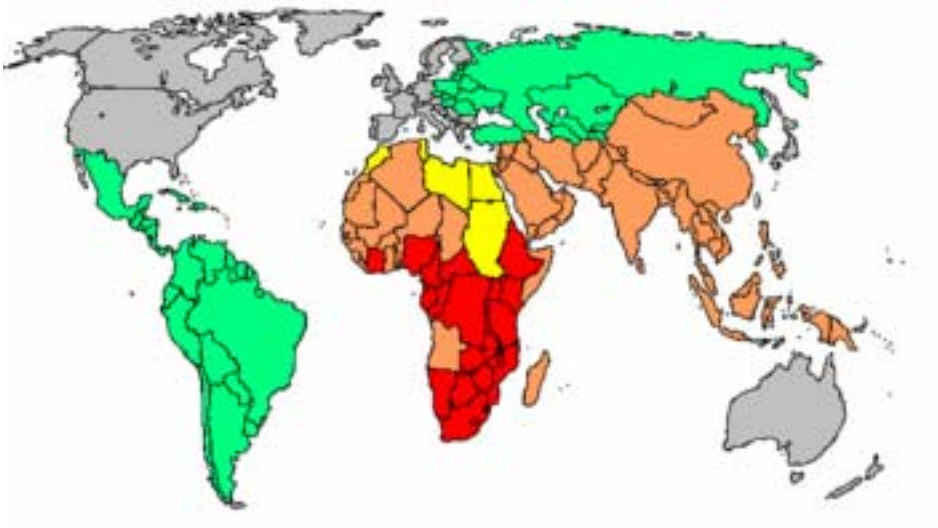
INDIA is in a unique position with respect to the global tuberculosis epidemic. Tuberculosis remains the leading infectious cause of death in India, killing close to 500,000 people a year. India has far more cases of tuberculosis than any other country in the world.-about 2 million new cases each year and accounts for nearly one third of prevalent cases globally.



(REF 2 : Source WHO TB manual 2006)



(REF 4: Global incidence of tuberculosis between 1980-2005)



World TB incidence. Cases per 100,000; Red = >300, orange = 200–300; yellow = 100–200; green 50–100 and grey <50. Data from WHO, 2006.

Race: Tuberculosis is a worldwide infection. Endemic areas include India, Southeast Asia, and sub-Saharan Africa.

Sex: No sex predilection exists for tuberculosis.

Age: Infection may occur at any age and is most significant at the extremes of age. Primary tuberculosis is usually seen in young children in endemic regions. The incidence is increasing in individuals in nonendemic regions who are immunocompromised.

PATHOLOGY AND PATHOGENESIS:

About 90% of those infected with *Mycobacterium tuberculosis* have asymptomatic latent TB infection (sometimes called LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease. However, if untreated, the death rate for these active TB cases is more than 50%.

TB infection begins when the mycobacteria reach the pulmonary alveoli , where they invade and replicate within alveolar macrophages. The primary site of infection in the lungs is called the Ghon focus . Bacteria are picked up by dendritic cells , which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes . Further spread is through the bloodstream to the more distant tissues and organs where secondary TB lesions can develop in lung apices, peripheral lymph nodes, kidneys, brain, and bone.All parts of the body can be affected by the disease, though it rarely affects the heart, skeletal muscles , pancreas and thyroid.

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma with lymphocytes surrounding the infected macrophages.

The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes (CD4+) secrete cytokines such as interferon gamma which activates macrophages to destroy the bacteria with which they are infected. T lymphocytes (CD8+) can also directly kill infected cells.

Importantly, bacteria are not always eliminated within the granuloma, but can become dormant, resulting in a latent infection. Another feature of the granulomas of human tuberculosis is the development of cell death, also called necrosis, in the center of tubercles To the naked eye this has the texture of soft white cheese and was termed caseous necrosis.

If TB bacteria gain entry to the bloodstream from an area of damaged tissue they spread through the body and set up many foci of infection, all appearing as tiny white tubercles in the tissues. This severe form of TB disease is most common in infants and the elderly and is called miliary tuberculosis. Patients with this

disseminated TB have a fatality rate of approximately 20%, even with intensive treatment.

In many patients the infection waxes and wanes. Tissue destruction and necrosis are balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria and can therefore pass on infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue.

CLINICAL FEATURE OF TUBERCULOSIS :

- Pulmonary tuberculosis (TB): Typical symptoms of pulmonary TB include a productive cough, fever, and weight loss. Occasionally, patients may present with hemoptysis or chest pain. Other systemic symptoms include anorexia, fatigue, or night sweats.

- Tuberculous meningitis: Patients may present with a headache that is either intermittent or persistent for 2-3 weeks. Subtle mental status changes may progress to coma over a period of days to weeks. Fever may be low-grade or absent.

- Skeletal TB: The most common site of involvement is the spine (Pott disease). Symptoms include back pain or stiffness. Lower extremity paralysis occurs in

as many as half the patients with undiagnosed Pott disease. Tuberculous arthritis usually involves only 1 joint. Although any joint may be involved, the hip or the knee is affected most commonly, followed by the ankle, elbow, wrist, and shoulder. Pain may precede radiographic changes by weeks to months.

- Genitourinary TB: Reported symptoms include flank pain, dysuria, or frequency. In men, genital TB may manifest as epididymitis or a scrotal mass. In women, genital TB may mimic pelvic inflammatory disease. TB causes approximately 10% of sterility in women worldwide and approximately 1% in industrialized countries.

- Gastrointestinal TB: Any site along the gastrointestinal tract may become infected. Symptoms are referable to the site infected, including the following: nonhealing ulcers of the mouth or anus; difficulty swallowing with esophageal disease; abdominal pain mimicking peptic ulcer disease with stomach or duodenal infection; malabsorption with infection of the small intestine; and pain, diarrhea, or hematochezia with infection of the colon.

- Tuberculous lymphadenitis (scrofula): The most common site is in the neck along the sternocleidomastoid muscle. It usually is unilateral, with little or no pain. Advanced disease may suppurate and form a draining sinus.

- Cutaneous TB: Direct inoculation may result in an ulcer or wartlike lesion. Contiguous spread from an infected lymph node typically results in a draining sinus. Hematogenous spread may result in a reddish brown plaque on the face or extremities (lupus vulgaris) or tender nodules or abscesses.

DIAGNOSIS OF TUBERCULOSIS :

Microbiological studies

A definitive diagnosis of tuberculosis can only be made by culturing *Mycobacterium tuberculosis* organisms from a specimen taken from the patient (most often sputum , but may also include pus, CSF biopsied tissue, etc.).

Sputum smears and cultures should be done for acid-fast bacilli if the patient is producing sputum. The preferred method for this is fluorescence microscopy (auramine-rhodamine staining), which is more sensitive than conventional Ziehl-Neelsen staining.

If no sputum is being produced, specimens can be obtained by inducing sputum, genital warts, a laryngeal swab, bronchoscopy with bronchoalveolar lavage, or fine needle aspiration of a collection.

Traditionally, cultures have used the Löwenstein-Jensen (LJ), Kirchner, or Middlebrook media (7H9, 7H10, and 7H11).

Chest X-ray

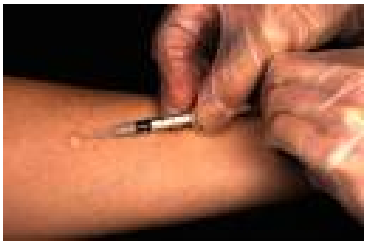
In active pulmonary TB, infiltrates or consolidations and/or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy or

pleural effusions (tuberculous pleurisy). However, lesions may appear anywhere in the lungs. In disseminated TB a pattern of many tiny nodules throughout the lung fields is common – the so called milliary TB. In HIV and other immunosuppressed persons, any abnormality may indicate TB or the chest X-ray may even appear entirely normal.

TUBERCULIN SKIN TEST

Two tests are available: the Mantoux and Heaf tests.

Mantoux skin test



Injecting a Mantoux skin test

Reading mantoux after 48-72 hrs

The Mantoux test for TB involves intradermally injecting PPD tuberculin and measuring the size of induration 48-72 hours later.

CDC classification of tuberculin reaction

An induration (palpable raised hardened area of skin) of more than 5-15 mm (depending upon the person's risk factors) to 10 Mantoux units is considered a positive result, indicating TB infection.

5 mm or more is positive in

1. HIV-positive person
2. Recent contacts of TB case
3. Persons with nodular or fibrotic changes on CXR consistent with old healed TB
4. Patients with organ transplants and other immunosuppressed patients

10 mm or more is positive in

1. 1.Recent arrivals (less than 5 years) from high-prevalent countries
2. Injection drug users
3. Residents and employees of high-risk congregate settings (e.g., prisons, nursing homes, hospitals, homeless shelters, etc.)
4. Mycobacteriology lab personnel
5. Persons with clinical conditions that place them at high risk (e.g., diabetes , prolonged corticosteroid therapy, leukemia , end-stage renal disease , chronic malabsorption syndromes, low body weight, etc)
6. Children less than 4 years of age, or children and adolescents exposed to adults in high-risk categories

15 mm or more is positive in

1.Persons with no known risk factors for TB

A tuberculin test conversion is defined as an increase of 10 mm or more within a 2-year period, regardless of age.

RECENT TEST TO DETECT PULMONARY TB

Adenosine deaminase

In 2007, a systematic review of adenosine deaminase by the NHS Health Technology Assessment Programme concluded "There is no evidence to support the use of ADA tests for the diagnosis of pulmonary TB. However, there is considerable evidence to support their use in pleural fluid samples for diagnosis of pleural TB, where sensitivity was very high, and to a slightly lesser extent for TB meningitis. In both pleural TB and TB meningitis, ADA tests had higher sensitivity than any other tests."

Nucleic acid amplification tests (NAAT)

This is a heterogeneous group of tests that use polymerase chain reaction (PCR) to detect mycobacterial nucleic acid. These test vary in which nucleic acid sequence they detect and vary in their accuracy. The two most common commercially available tests are the amplified mycobacterium tuberculosis direct test (MTD, Gen-Probe) and Amplicor Interferon-γ release assays Interferon-γ (interferon-gamma) release assays (IGRAs) are based on the ability of the *mycobacterium tuberculosis*

antigens for early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) to stimulate host production of interferon-gamma.

Because these antigens are not present in non-tuberculous mycobacteria or in BCG vaccine, these tests can distinguish latent tuberculosis infection (LTBI).

The blood tests QuantiFERON-TB Gold and T-SPOT.TB use these antigens to detect people with tuberculosis. Lymphocytes from the patient's blood are cultured with the antigens. These tests are called interferon γ tests and are not equivalent.If the patient has been exposed to tuberculosis before, T lymphocytes produce interferon γ in response.

Both tests use ELISA to detect the interferon γ with great sensitivity. The distinction between the tests is that QuantiFERON-TB Gold quantifies the total amount of interferon γ when whole blood is exposed to the antigens, whereas T-SPOT.TB , a type of ELISPOT assay, counts the number of activated T lymphocytes that secrete interferon γ.

AIDS

Acquired immune deficiency syndrome or **acquired immunodeficiency syndrome** (**AIDS** or **Aids**) is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus(HIV) in humans, and similar viruses in other species (SIV, FIV, etc.). The late stage of the condition leaves individuals susceptible to opportunistic infections and tumors. Although treatments for AIDS and HIV exist to decelerate the virus progression, there is currently no known cure.

HIV, et al., are transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid, and breast milk. This transmission can come in the form of anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, or breastfeeding, or other exposure to one of the above bodily fluids .

HIV BURDEN IN INDIA :

Estimated number of people living with HIV/AIDS, 2006[3]

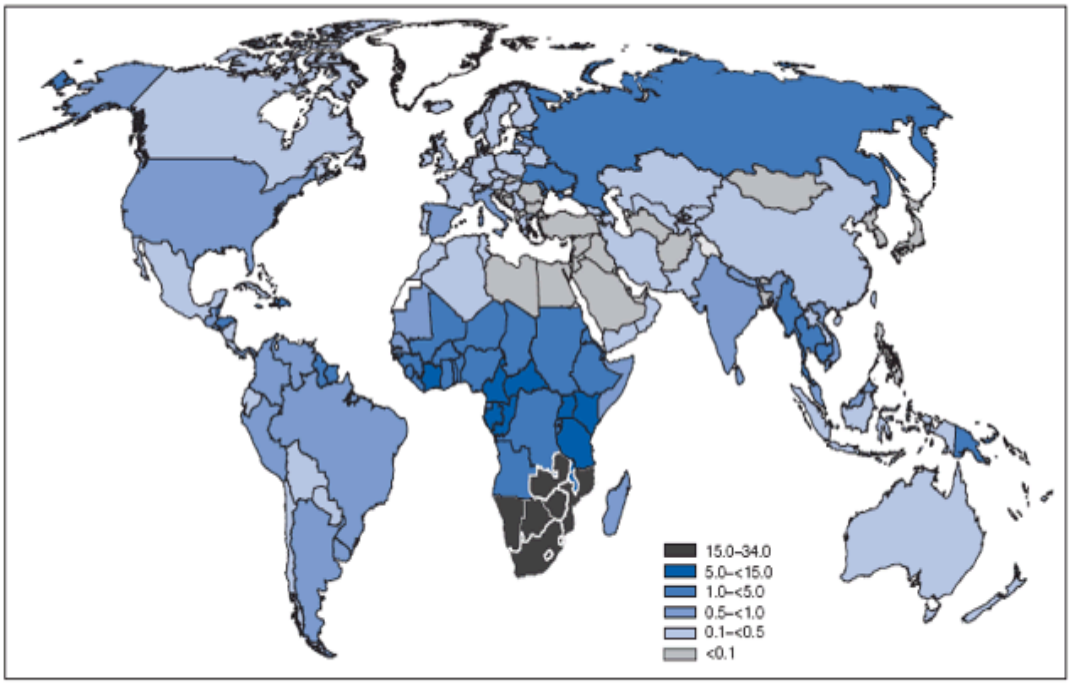
People living with HIV/AIDS	2 million - 3.1 million
Adult (15 years or above) HIV prevalence	0.36%

NACO (India 2006)

Previously it was thought that around 5 million people were living with HIV in India - more than in any other country. Better data, including the results of a national household survey, led to a major revision of the prevalence estimate in July 2007. It is now thought that around 2.5 million people in India are living with HIV.

EPIDEMOLOGY OF HIV BURDEN :

FIGURE. Estimated percentage of adult population* living with human immunodeficiency virus (HIV) infection, by country — worldwide, 2005†



SOURCE: Joint United Nations Programme on HIV/AIDS (UNAIDS). 2006 report on the global AIDS epidemic. Geneva, Switzerland: UNAIDS; 2006. Available at http://www.unaids.org/en/hiv_data/2006globalreport/default.asp.
*Aged 15–49 years.
†The worldwide estimate of the number of persons living with HIV is 38.6 million.

Prevalence of HIV among adults per country at the end of 2005.

Age distribution of HIV infected patients in INDIA (2007)

Age group	HIV prevalence (%)		
	Male	Female	Total
15-19	0.01	0.07	0.04
20-24	0.19	0.17	0.18
25-29	0.43	0.28	0.35
30-34	0.64	0.45	0.54
35-39	0.53	0.23	0.37
40-44	0.41	0.19	0.30
45-49	0.48	0.17	0.33
Total age 15-49	0.36	0.22	0.28

The National Family Health Survey, which tested more than 100,000 people for HIV, also found prevalence to be higher in urban areas (0.35%) than in rural areas (0.25%).

Sex distribution of HIV patients in INDIA (2007)

Gender	Cumulative AIDS cases
Male	88,245
Female	36,750
Total	124,995

HIV BURDEN IN TAMIL NADU :

When surveillance systems in the southern Indian state of Tamil Nadu, home to some 62 million people, showed that HIV infection rates among pregnant women were rising - tripling to 1.25% between 1995 and 1997 - the State Government acted decisively. Funding for the Tamil Nadu State AIDS Control Society (TANSACS), which had been set up in 1994, was significantly increased. Along with non-governmental organisations and other partners, TANSACS developed an active AIDS prevention campaign. This included hiring a leading international advertising agency to promote condom use for risky sex in a humorous way, without offending the many people who do not engage in risky behaviour. The campaign also attacked the ignorance and stigma associated with HIV infection.

The HIV prevalence at antenatal clinics in Tamil Nadu was 0.88% in 2002 and 0.5% in 2005, though several districts still have rates above 1%. The general population survey of 2005-2006 found a rate of 0.34% across the state. Prevalence among injecting drug users was 18% in 2005. Tamil Nadu had reported 52,036 AIDS cases to NACO by July 2005, which is by far the highest number of any state.

PATHOGENESIS OF HIV INFECTION :

AIDS is the most severe acceleration of infection with HIV. HIV is a retrovirus that primarily infects vital organs of the human immune system such as $CD4^+$ T cells (a subset of T cells , macrophages and dendritic cells. It directly and indirectly

destroys $CD4^+$ T cells. $CD4^+$ T cells are required for the proper functioning of the immune system.

When HIV kills $CD4^+$ T cells so that there are fewer than 200 $CD4^+$ T cells per microliter (μL) of blood , cellular immunity is lost, leading to the condition known as AIDS. Acute HIV infection progresses over time to clinical latent HIV infection and then to early symptomatic HIV infection and later to AIDS, which is identified on the basis of the amount of $CD4^+$ T cells in the blood and the presence of certain infections.

In the absence of antiretroviral therapy , the median time of progression from HIV infection to AIDS is nine to ten years, and the median survival time after developing AIDS is only 9.2 months. However, the rate of clinical disease progression varies widely between individuals, from two weeks up to 20 years. Many factors affect the rate of progression. These include factors that influence the body's ability to defend against HIV such as the infected person's general immune function. Older people have weaker immune systems, and therefore have a greater risk of rapid disease progression than younger people. Poor access to health care and the existence of coexisting infections such as tuberculosis also may predispose people to faster disease progression. The infected person's genetic inheritance plays an important role and some people are resistant to certain strains of HIV. An example of this is people with the CCR5-Δ32 mutation are resistant to infection with certain strains of HIV.HIV is genetically variable and exists as different strains, which cause different rates of clinical disease progression.

The use of highly active antiretroviral therapy prolongs both the median time of progression to AIDS and the median survival time.

DIAGNOSIS :

WHO disease staging system for HIV infection and disease

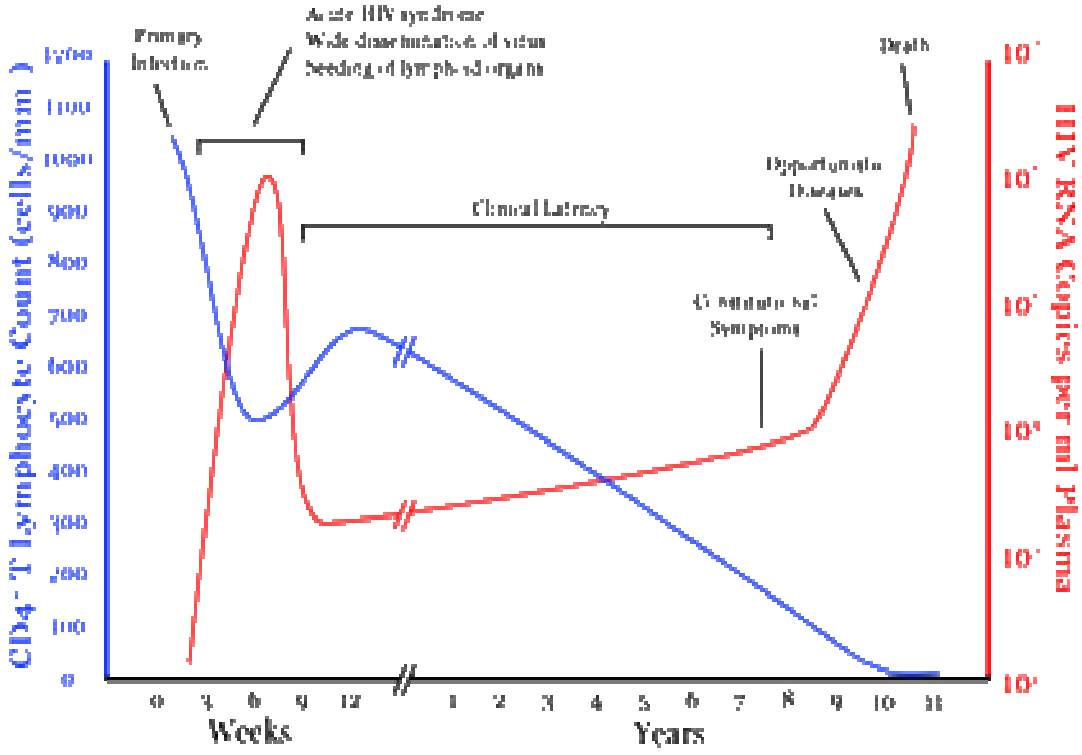
In 1990, the World Health Organization (WHO) grouped these infections and conditions together by introducing a staging system for patients infected with HIV-1. An update took place in September 2005. Most of these conditions are opportunistic infections that are easily treatable in healthy people.

Stage I: HIV infection is asymptomatic and not categorized as AIDS

Stage II: includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections

Stage III: includes unexplained chronic diarrhea for longer than a month, severe bacterial infections and pulmonary tuberculosis

Stage IV: includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma, these diseases are indicators of AIDS.



A generalized graph of the relationship between HIV copies (viral load) and CD4 counts over the average course of untreated HIV infection.

(Blue line)$CD4^+$ T Lymphocyte count (cells/mm^3)

(Black line) HIV RNA copies.

HIV AND TB

Tuberculosis and HIV around the world

Tuberculosis is the most common HIV-related opportunistic infection in India, and caring for patients with both diseases is a major public health challenge. India has about 1.8 million new cases of tuberculosis annually, accounting for a fifth of new cases in the world — a greater number than in any other country . Patients with latent Mycobacterium tuberculosis infection are at higher risk for progression if they are coinfected with HIV. Patients with HIV infection have a similar bacteriologic response to tuberculosis treatment as those who are not infected but have higher risks of recurrence and death. The influence of tuberculosis coinfection on the progression of HIV disease is controversial.

In 2004, about 330,000 people in India died from tuberculosis.[1] Two of every five persons — more than 400 million — have latent tuberculosis infection.[3] Tuberculosis can be expected to develop in more than half of those who are also infected with HIV. At present, however, only about 5% of new tuberculosis cases in India occur in people with HIV coinfection. The situation differs from that in sub-Saharan Africa, where the incidence of tuberculosis in many countries is higher than in India and as many as 80% of patients with tuberculosis are coinfected with HIV. In Africa, HIV has reversed gains in tuberculosis control that were achieved a quarter-century ago.Such a reversal is unlikely to occur in India.

People with latent TB are increasingly becoming infected with HIV, and many more are developing active TB because HIV is weakening their immune system. People who are co-infected with both HIV and latent TB have an up to 800 times greater risk of developing active TB disease and becoming infectious compared to people not infected with HIV.

People with advanced HIV infection are vulnerable to a wide range of infections and malignancies that are called 'opportunistic infections because they take advantage of the opportunity offered by a weakened immune system. Tuberculosis is an HIV related opportunistic infection. A person that has both HIV and active TB has an AIDS-defining illness.

The HIV/AIDS epidemic is reviving an old problem in well resourced countries and greatly worsening an existing problem in resource poor countries. The are several important associations between epidemics of HIV and tuberculosis:

1. Tuberculosis is harder to diagnose in HIV positive people
2. Tuberculosis progresses faster in HIV-infected people
3. Tuberculosis in HIV positive people is more likely to be fatal if undiagnosed or left untreated
4. Tuberculosis occurs earlier in the course of HIV infection than other opportunistic infections
5. Tuberculosis is the only major AIDS-related opportunistic infection that poses a risk to HIV-negative people.

PATHOGENESIS OF HIV & TB COINFECTION

CD4 cell-mediated immunity and macrophage function are essential in the control of *M tuberculosis* infection. During primary infection of an immunocompetent host, cell-mediated immunity usually develops and arrests progression of disease. About 5% of patients whose primary infection is controlled have reactivation years to decades later. In another 5% of patients, infection is not contained, and primary pulmonary, extrapulmonary, or disseminated TB can occur.

The hallmark of HIV infection is progressive deterioration and depletion of CD4 cells, coupled with defects in macrophage and monocyte function. There is evidence that the immune response in patients with TB might enhance HIV viral replication and accelerate the natural progression of HIV infection. The risk of TB developing in an HIV-infected patient who is latently coinfected with *M tuberculosis* approaches 10% per year, as opposed to a 10% lifetime risk in an immunocompetent host. Patients with more advanced HIV infection (CD4 count, <200 cells/mm^3) who are newly infected with *M.tuberculosis* may lack the ability to contain the primary infection, which can progress rapidly and is fatal if not treated.

HAEMATOLOGICAL MANIFESTATIONS OF TUBERCULOSIS

Anaemia is a common complication of pulmonary tuberculosis. The precise mechanism of anaemia in pulmonary tuberculosis is not clearly known, but anaemia of inflammation as well as of Fe deficiency has been implicated. Both are common in developing countries. It is extremely difficult to distinguish anaemia of Fe deficiency from anaemia of inflammation with the haematological indices used routinely. Adult male patients 15-60 years of age with pulmonary tuberculosis and a blood haemoglobin concentration 80-110 g/l were included in the study; healthy adult males matched for age and socio-economic status were taken as controls. Blood haemoglobin concentration, total erythrocyte count (TEC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscul ar haemoglobin and serum Fe, total Fe-binding capacity and ferritin were estimated before treatment and 1, 2 and 6 months after treatment. **(REF 7)**

Reactive thrombocytosis in pulmonary tuberculosis (ref 12)

The incidence of reactive thrombocytosis in active pulmonary tuberculosis was studied in 122 patients. Thrombocytosis was common, platelet counts often exceeding 1 X 10(12)/1.

A significant inverse correlation was noted between the mean platelet volume and the platelet count (r = -0.54, p less than 0.0001). Interval estimation suggested that this relation was non-linear. Further studies were done in a small group of six patients.

Platelet survival was considerably shortened, the platelets aggregated excessively in vitro, serum concentrations of thrombopoiesis stimulating activity were raised, and serotonin uptake and release were within normal limits. The degree of thrombocytosis correlated significantly with the degree of inflammation measured by the erythrocyte sedimentation rate (r = 0.40, p less than 0.003) and serum C-reactive protein concentration (r = 0.35, p less than 0.008).

HAEMATOLOGICAL MANIFESTATION IN HIV PATIENTS

HIV infection is associated with numerous abnormalities of hematopoiesis, affecting both the myeloid and lymphoid lineages derived from the hematopoietic stem cell. Thus, as many as 70% to 80% of HIV-infected patients develop anemia during the course of infection, while neutropenia may be seen in more than 50% of individuals with more advanced HIV-related immunodeficiency. Thrombocytopenia is also common, occurring in approximately 40% of patients, and serving as the first symptom or sign of infection in approximately 10% of HIV-infected patients. **(ref 13)**

Anemia is very common in HIV-infected individuals, occurring in approximately 30% during the initial asymptomatic years of infection and found in 80% to 90% of patients over the course of disease. In an attempt to ascertain the

precise incidence of anemia in the setting of HIV infection prior to the availability of HAART, Sullivan and colleagues evaluated data derived from the case records of 32,867 HIV-infected persons who received medical care from January 1990 through August 1996.. Using a definition of anemia as a hemoglobin level < 10 g/dL or a physician's diagnosis of anemia, the authors calculated the 1-year incidence of anemia as a function of the stage of HIV disease. The 1-year incidence of anemia was 37% among patients with clinical AIDS, 12% among patients with immunologic AIDS, as defined by a CD4+ cell count < 200 cells/mm^3 in the absence of an AIDS-defining clinical condition; and 3% among HIV-infected individuals with neither clinical nor immunologic AIDS. **(REF 14)**

Neutropenia is reported in approximately 10% of patients with early, asymptomatic HIV infection, and in more than 50% of those individuals with more advanced HIV-related immunodeficiency. As with other peripheral blood cytopenias in the setting of HIV infection, multiple etiologies for neutropenia may be present, either singly or in combination. Thus, decreased colony growth of the committed progenitor cell, CFU-GM, may lead to decreased production of both granulocytes and monocytes. Soluble inhibitory substances, produced by HIV-infected cells, have been noted to suppress neutrophil production in vitro. Decreased serum levels of G-CSF have been described in HIV-seropositive subjects with afebrile neutropenia (< 1000 neutrophils/dL), indicating that a relative deficiency of this specific hematopoietic growth factor may also contribute to persistent neutropenia.

Finally, myelosuppression and neutropenia may result from any one of several medications commonly used in HIV-infected patients. **(ref 15)**

Thrombocytopenia is relatively common during the course of HIV infection, occurring in approximately 40% of patients and serving as the first symptom or sign of infection in approximately 10%. Sullivan and colleagues recently evaluated the 1-year incidence of thrombocytopenia (< 50,000/mm^3) in a group of 30,214 HIV-infected patients as part of the retrospective 10-city Adult and Adolescent Spectrum of Disease Project, sponsored by the CDC. The incidence of thrombocytopenia during 1 year was 8.7% in patients with clinical AIDS, 3.1% in patients with immunologic AIDS (CD4+ cell count < 200 cells/mm^3), and 1.7% in patients with neither condition. Over time, development of thrombocytopenia was associated with clinical or immunologic AIDS, history of injection drug use, history of anemia or lymphoma, and African American race. After controlling for multiple factors (AIDS, CD4+ cell count, anemia, neutropenia, antiviral therapy, receipt of prophylaxis against P carinii), thrombocytopenia was significantly associated with shorter survival (risk ratio, 1.7: 95% confidence interval = 1.6-1.8).

The major cause of thrombocytopenia in HIV disease is idiopathic thrombocytopenic purpura (ITP), in which antibody-coated platelets are removed from the circulation by the macrophages in the spleen. The resulting thrombocytopenia may result in bleeding or bruising, predominantly from the mucous membranes or skin. However, the majority of patients with HIV-related ITP do not actually experience bleeding or have had only minor bleeding manifestations. Furthermore, the likelihood

of clinical bleeding is very low until the platelet count drops below 10,000/mm^3. Nonetheless, the potential risk of life-threatening bleeding into the central nervous system does exist in the setting of ITP, serving to render this a condition of some concern. **(ref 15)**

HAEMATOLOGICAL MANIFESTATIONS IN HIV – TB INFECTED PATIENTS

- Isolated thrombocytopenia commonly seen in these patients.
- Severe degree of anemia , leucopenia , pancytopenia seen in advanced disease .
- Severe cytopenia is also secondary to myelosuppressive drug therapy or hypersplenism.
- Leucocytosis is more common in patients with extra-pulmonary tuberculosis with out HIV than patient with HIV infection. (ref 16)

According to this study absolute lymphocyte count of less than 1x 10 – 9 / litre in 80% of HIV – TB patients and in only 40 % of HIV NEGATIVE - TB POSITIVE patients. **(ref 17)**.

AIM OF THE STUDY

1. To study selected Haematological parameters namely haemoglobin, Total RBC count, WBC count, ESR, and platelets in pulmonary tuberculosis patients.

2. To find out variations among HIV positive and negative patients.

MATERIALS AND METHOD

Setting : All TB patients who were attending Thoracic medicine department , GRH, Madurai. And patients refered from Anti retroviral therpy centre, with sputum positivity for AFB (acid fast bacillius)

Collaborating Departments :		**Department of thoracic medicine &** **A**nti retroviral therapy centre (ART) Madurai Medical College Madurai.
Design of the study	**:**	**ANALYTICAL STUDY**
Period of study	**:**	01.09.2006 – 31.10.2007
Sample size	**:**	**60** **(TB with HIV : 30 / TB without HIV : 30)**
Ethical committee approval :		Obtained
Consent	**:**	Informed consent was obtained
Financial support	**:**	Nil
Conflict of interest	**:**	Nil

A total of sixty cases were taken for the study. They were divided in to two groups. The first group was sputum smear positive pulmonary tuberculosis ,which consist of thirty patients and they were HIV ELISA negative . the second group was

sputum smear positive pulmonary tuberculosis , which consist of thirty and they were HIV ELISA positive.

BASELINE INVESTIGATIONS :

A baseline blood glucose (random blood sample) ,renal function test (blood urea and serum creatinine), liver function test (total / direct / indirect bilirubin , SGOT, SGPT , ALP) , total protein , albumin , globulin. was done in all sixty patients.

SELECTION CRITERIA:

In the pulmonary tuberculosis group, only sputum positive for acid fast bacilli were selected for this study . Then according to the ELISA positivity they were divided in to TB + VE HIV negative and TB + VE HIV positive.

A total of sixty patients were taken for this study. The patients selected were more than 15 years of age group. Among HIV negative and TB positive : twenty three were males and seven were females. Among HIV positive and TB positive : twenty four were males and six were females.

All patients taken the study had active disease. In HIV + ve patients CD4+ cells count in range between 200-350 cells/microlitre and HIV RNA copies less than 50,000/ml were selected for this study.

EXCLUSION CRITERIA :

1. old healed pulmonary tuberculosis lesion.
2. diabetes and other metabolic disorder.
3. malignancy

4. collagen vascular disorder
5. gross organ disorder.
6. patients on steroid, iron therpy ,or vitamin therpy.
7. patients with bleeding disorder.
8. Tobacco and alcoholics.
9. pregnancy
10. past and current intake of ATT (anti tuberculosis therapy)
11. patients on ART (anti retroviral therapy) .
12. CD4+ < 200 cells / microlitre and HIV RNA copies > 1,00,000 / ml.

Tuberculosis patients were diagnosed by clinical examination, X-ray chest (PA view) and sputum smear examination. The sputum smear examination was done by Ziehl- Neelson technique. Sputum specimen was collected on the spot when a patient is suspected to of having tuberculosis. This is called a spot specimen. The patient is then given a sputum container to collect an early morning specimen before his second meeting . this is called early morning specimen. When the patient returns with the early morning specimen, a second spot specimen is also collected.

The **ZIEHL – NEELSON** staining :

1. spread the sputum on a slide using a broom-stick.
2. Allow the slide to air dry for 15 – 30 minutes.
3. Fix the slide by passing it over a flame 3 – 5 times for 3 – 4 seconds each time.
4. Pour filtered Carbol-fuschin to cover the entire slide.
5. Gently heat the the slide until vapour rise . do not boil.

6. Leave it for 5 minutes.
7. Gently rinse the slide with tap water until all the carbol fuschin stain is washed away.
8. Pour 25% sulphuric acid on to the slide .
9. Wait for 2 – 4 minutes.
10. Rinse gently with tap water and allow it to drain off.
11. If the slide is still red , re apply sulphuric acid for 1-3 minutes and rinse with tap water.
12. Pour 0.1 % methylene blue on to the slide and wait for 30 seconds.
13. Rinse with tap water and allow it to dry.
14. Examine the slide under microscope using X 40 lens to select the suitable area and then examine , under X 100 lens using a drop of immersion oil.

Confirmation of HIV infection is by ELISA antibody testing. It was reconfirmed using **WESTERN BLOT** technique. The method of ELISA used in this technique is **INDIRECT ELISA TECHNIQUE**.

Patients height was measured in metre and weight was measured in kilograms . then by using the formula Height /$(\text{Weight})^2$ the BMI was calculated .

A full blood blood count was carried out in a 5ml anticoagulated blood sample. A thick and thin stained blood film was prepared for examination of morphology of the different cells and by specific stains red blood cell , white blood cell and platelet count was determined.

The examination of stained blood film is most important and by this the red cells are examined to access their degree of haemoglobinisation and their shape. If both are normal , they are called as normochromic and normocytic . pale staining which suggests under haemoglobinisation is called as hypochromia and reduction in the size of RBC is called as microcytosis.

One ml of blood is introduced in to automated cell counter. Specific values like Haemoglobin, RBC count , WBC (total) count , Differential count (D.C) , Platelet count , are obtained which are the basic parameters to be studied.

Cell counters

Automated cell counters sample the blood, and quantify, classify, and describe cell populations using both electrical and optical techniques. Electrical analysis involves passing a dilute solution of the blood through an aperture across which an electrical current is flowing. The passage of cells through the current changes the impedance between the terminals (the Coulter principle.A lytic reagent is added to the blood solution to selectively lyse the red cells (RBCs), leaving only white cells (WBCs), and platelets intact. Then the solution is passed through a second detector. This allows the counts of RBCs, WBCs, and platelets to be obtained. The platelet count is easily separated from the WBC count by the smaller impedance spikes they produce in the detector due to their lower cell volumes.

Optical detection may be utilised to gain a differential count of the populations of white cell types. A dilute suspension of cells is passed through a flow cell, which passes cells one at a time through a capillary tube past a laser beam. The reflectance,

transmission and scattering of light from each cell is analysed by sophisticated software giving a numerical representation of the likely overall distribution of cell populations.

ESR :

ESR is calculated in both HIV +VE TB NEGATIVE and HIV +VE TB POSITIVE patients. To perform the test, anticoagulated blood is placed in an upright tube, known as a Westergren tube and the rate at which the red blood cells fall is measured and reported in mm/h.

The normal values are ;

MEN

< 50 years - <15mm/hr and

> 50 years - <20 mm/hr.

WOMEN

< 50 years - < 20 mm/hr and

> 50 years - < 30 mm/hr.

RESULTS

The collected data was analysed using Epidemiological information package 2002 developed by Centre for Disease Control (CDC) Atlanta in Collaboration with WHO. CHI square test was used for test of significance. These data was compared with published literature.

In our there were 60 patients and they were divided in to two broad categories , namely TB with HIV patients and TB without HIV.

CHARECTERISTICS OF CASES INCLUDED IN THE STUDY :

STATUS OF THE PATIENTS	NUMBER OF PATIENTS
TB with HIV	30
TB without HIV	30

AGE AND SEX DISTRIBUTION ;

TABLE: 1

Status	MALES	%	FEMALES	%
TB with HIV	**25**	**83.3**	**5**	**16.6**
TB without HIV	**23**	**76.6**	**7**	**23.3**

Regarding distribution of sex , there is a male predominance in the study. Around 83.3% are males among TB with HIV group and females are only 16.6% in this group. In case of TB without HIV also male dominated this study around 76.6% and only 23.3% females.[table 1]

TABLE: 2

	< 25 yrs	%	25 – 45 yrs	%	> 45 yrs	%
TB with HIV	1	3.3	21	70	8	26.6
TB without HIV	0	0	26	86.6	4	13.3

TABLE: 3

	<25 years		25 – 45 years		> 45 years	
	males	**females**	**males**	**females**	**males**	**females**
TB with HIV	**0**	**1**	**17**	**4**	**8**	**0**
TB without HIV	**0**	**0**	**21**	**5**	**2**	**2**

Both TB and HIV affects mainly the adult age group. In our study around 70% of patients belonging to TB with HIV were in age group of 25 – 45 years. Among patients belonging to TB without HIV also predominantly belong to this age group which constitute around 86.6%.

Among 70% of patients belonging to TB with HIV , 56.6% were males and 13.3% were females. Likewise , among 86.6% of patients belonging to TB without HIV group , 70% were males and 16.6% were females.**[table 2,3]**

BODY MASS INDEX :

Since both TB and HIV are chronic wasting disease , the co-infection of TB with HIV further worsen this scenario. From this study, 90% of patients belonging TB with HIV were underweight with BMI less than 18.5.

Among the patients belonging to TB without HIV 73.3 % were under the category of underweight with their BMI less than 18.5. only 2 patients belonging to TB without HIV were under the category of overweight with their BMI more than 24.9.

There were no patients under TB with HIV with BMI more than 24.9%. **[table 4]**

TABLE: 4

	< 18.5		18.5 – 24.9		> 24.9	
	n	**%**	**n**	**%**	**n**	**%**
TB with HIV	**27**	**90**	**3**	**10**	**0**	**0**
TB without HIV	**22**	**73.3**	**6**	**20**	**2**	**6.6**

BMI

<18.5→underweight

18.5-24.9→normal

>24.9→overweight

CORELATION OF HAEMATOLOGICAL PARAMETERS WITH THE STUDY GROUPS :

HAEMOGLOBIN

TABLE: 5

	< 11 gm / dl		> 11 gm / dl	
	n	**%**	**n**	**%**
TB with HIV	24	80	6	20
TB without HIV	20	66.6	10	33.3

From the table 5 , Anemia is common in both and 80% of anemic patients in TB with HIV , 70% were males and 10 % were females. Among 66.6% of anemic patients in TB without HIV group, 50% were males and 16.6% were females.

Association of HIV with TB further worsens the anemia, as evidenced by 33.3% of TB without HIV were not anemic , whereas only 20% of the patients in TB with HIV were not anemic.

With respect to sex distribution among anemic patients in both groups , males were more affected, with 70% in TB with HIV and 50% in TB with out HIV.**[table 6]**

TABLE: 6

	< 11 gm / dl				> 11 gm / dl			
	males		females		males		females	
TB with HIV	21	70%	3	10 %	4	13.3 %	2	6.6%
TB without HIV	15	50%	5	16.6%	8	26.6%	2	6.6%

TABLE: 7

	RANGE	MEDIAN	MEAN
TB WITH HIV	6.4 – 12.6 Gm	9.1 Gm	9.2 Gm
TB WITHOUT HIV	6.0 – 12.8 GM	9.9 Gm	9.74 Gm

RED BLOOD CELLS :

In correlation with haemoglobin, total RBC counts were reduced in both the study groups, 80% of the patients belonging to TB with HIV had counts less than 3.5 million cell/cumm.

Whereas 83.3% of patients in TB without HIV group had counts less than the reference range. **[table 8, 9]**

REFERENCE RANGE FOR TOTAL RBC COUNT : 3.8 – 5.8 million cells/cumm.

TABLE: 8

RBC	RANGE (millions/cumm)	MEDIAN (millions/cumm)	MEAN (millions/cumm)
TB with HIV	2.3 – 4.2	3.3	3.3
TB without HIV	2.2 - 4.2	3.0	3.1

TABLE: 9

	< 3.8 million RBC / cumm				3.8-5.8 million RBC / cumm			
	males		females		males		females	
TB with HIV	21	70%	3	10%	4	13.3%	2	6.6%
TB without HIV	20	66.6%	5	16.6%	3	10%	2	6.6%

WHITE BLOOD CELL (WBC) COUNT / TOTAL COUNT :

There is no much difference in total WBC count among two study groups. From tables 10 and 11 , we can infer that 28 patients in TB with HIV and 28 patients in TB without HIV have their total counts with in the normal range of 3,500 – 10 ,000 cells / cumm.

Only 2 patients in TB with HIV had lecopenia and none had leucocytosis.

Whereas 2 patients in TB without HIV had leucocytosis and none had leucopenia.

TABLE: 10

WBC (in cells /cu mm)	RANGE	MEDIAN	MEAN
TB WITH HIV	3400 - 10000	6500	6538
TB WITHOUT HIV	3600 - 10950	6500	6696

TABLEL 11

	< 3,500 cells / cumm		3,500-10,000 cells / cumm		> 10,000 cells / cumm	
	males	**females**	**males**	**females**	**males**	**females**
TB with HIV	2	0	23	5	0	0
TB without HIV	0	0	22	6	1	1

DIFFERENTIAL COUNT (D.C)

There was no much difference in neutrophil and lymphocyte counts among these two study groups. Among the 30 patients in TB with HIV 76.6% of males and 16.6% of females had normal range of neutrophil counts (**NORMAL RANGE: 43 – 76 %**),

Whereas 70% were males and 23.3% were females among TB without HIV.

PLATELETS:

TABLE: 12

PLATELETS (in cells / cu mm)	RANGE	MEDIAN	MEAN
TB WITH HIV	40,000 – 3,00,000	1,60,000	1,54,333
TB WITHOUT HIV	1,00,000 – 5,60,000	3,05,000	3,31,666

From tables 12 and 13, we can infer that thrombocytopenia is major finding among TB with HIV patients. Around 63.3% patients have thrombocytopenia and 36.6% patients had normal platelet count among TB with HIV group.

Whereas thrombocytopenia was only 10% among TB without HIV patients. Instead 53.3% patients had normal platelet counts and around 36.6% patients had thrombocytosis.

TABLE: 13

	<1,50,000 cells/cumm		1,50,000-3,90,000 cells/cumm		>3,90,000 cells/cumm	
	n	%	n	%	n	%
TB with HIV	19	63.3	11	36.6	0	0
TB without HIV	3	10	16	53.3	11	36.6

.

TABLE: 14

	<1.5 lacs/cu mm				1.5-3.9 lacs/cu mm				>3.9 lacs / cu mm			
	males		females		males		females		males		females	
TB with HIV	16	53.3%	3	10%	9	30%	2	6.6%	0	0	0	0
TB without HIV	3	10%	0	0	12	40%	4	13.3%	8	26.6%	3	10%

From table 14 we can infer that , among the thrombocytopenic patients in TB with HIV , 53.3% were males and 10% were females. And among the patients with thrombopoesis in TB without HIV , 26.6% were males and 10% were females.

The p value is 0.0001, hence this correlation of platelet count among these two study group is significant.

ERYTHROCYTE SEDIMENTATION RATE:

TABLE: 15

ESR (IN MM / HR)	RANGE	MEDIAN	MEAN
TB WITH HIV	20 - 120	98	102
TB WITHOUT HIV	60 - 120	30	38

From table 15 , we can infer that, the range of ESR among patients with TB and HIV was 20 – 102 , whereas it was between 60 – 120 among TB patients without HIV .

Similarly the mean ESR was 38 mm / hr among TB with HIV patients, whereas it is 102 mm /hr among TB patients without HIV.

TABLE: 16

	0 – 30 mm / hr		31 – 60 mm / hr		61 – 90 mm / hr		91 – 120 mm / hr	
	n	%	n	%	n	%	n	%
TB with HIV	16	53.3	9	30	2	6.6	3	10
TB without HIV	0	0	1	3.3	16	53.3	13	43.3

TABLE: 17

	0-30mm/hr				31-60mm/hr				61-90mm/hr				91-120mm/hr			
	males		females		males		females		males		females		males		females	
H+	13	43%	2	10%	7	23%	2	7%	2	7%	0	0	3	10%	0	0
H-	0	0	0	0	1	3%	0	0	13	43%	3	10%	9	30%	4	13%

From tables 16 and 17 , we can infer that , most patients have their ESR < 60 mm / hr i.e around 83.3% patients among TB with HIV study group. Whereas around 96.6 % patients have their ESR around 60 – 120 mm / hr among TB without HIV.

The P value is 0.002, which is significant.

DISCUSSION & COMPARATIVE ANALYSIS

This study comprises two sets of study groups. First group of patients consist of pulmonary tuberculosis patients with asymptomatic HIV infection. Second group of patients consist of pulmonary tuberculosis per se.

Thirty patients were chosen randomly in each group to avoid selection bias. Patients less than 15 years and more than 60 years were excluded . After excluding the patients coming under exclusion criteria **(REF table 2 page :)** , thirty patients were chosen in each category.

Among tuberculosis patients, only pulmonary tuberculosis patients were included in this study , excluding extra – pulmonary tuberculosis , Multi – Drug resistant TB (MDR TB) , disseminated TB.

The diagnosis of pulmonary TB was made after routine clinical examination, which include cough with expectoration for more than three weeks , evening rise of temperature , anorexia , loss of weight. Such patients were subjected to three days sputum analysis. Patients with sputum AFB positivity were alone chosen for this study.

These sputum positivity patients were further subjected to clinical examination.

Those patients who gave sexual promiscuity and high risk group for sexually transmitted diseases were further subjected to HIV screening test after written consent.

The high risk group patients belong to commercial sex workers , lorry / truck drivers , multiple sex partners , child abuse , ex – prisoners , etc.

Those patients with HIV ELISA test positivity were isolated , and HIV was further confirmed using the gold standard test namely **WESTERN BLOT**.

These TB patients with HIV positivity were subjected to CD 4 + cells count assay and HIV RNA copies were measured. Those patients with CD 4 + cell count between 200 – 350 and HIV RNA copies between <1,00,000 were only chosen for this study.

Hence the HIV patients chosen for this study were mostly asymptomatic or in the early stage of HIV infection.

Clinically some of these patients had oral candidasis in our study group 14 patients had oral candidasis. But for that, they had only symptoms and signs of pulmonary tuberculosis as mentioned before.

Routine baseline investigations were done in these patients , which include renal function test, liver function test , random blood glucose. A chest X- Ray PA view was taken in all these patients.

5 ml of anti-coagulated blood was taken after venipuncture. This blood was subjected to automated analyzer counting and peripheral smear examination.

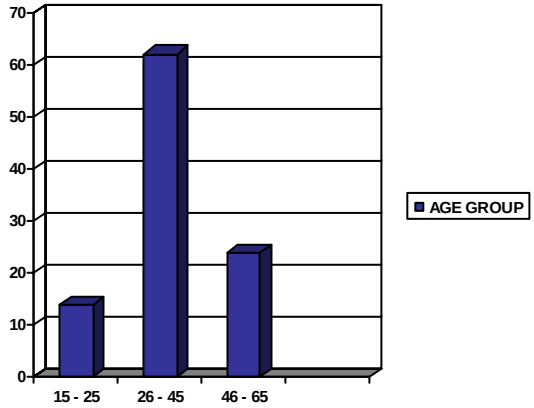
From results obtained from complete haemogram , these two sets of patients namely TB with HIV and TB without HIV were compared with respect to haematological profile.

Our study clearly shows that both HIV and TB affects the adult age group.

Among patients belonging to TB with HIV 70 % were in the age group of 25 – 45 years, whereas it is 86.6% in patients belonging to TB without HIV.

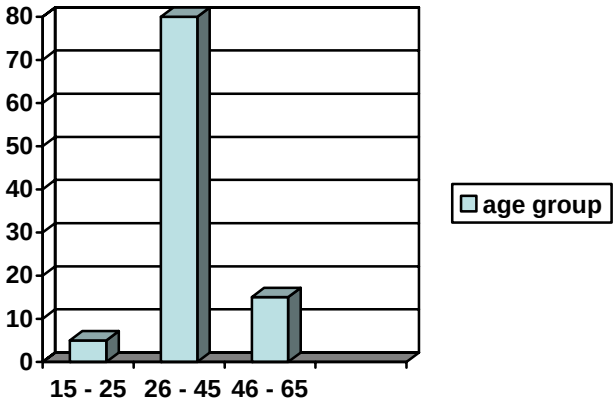
This is further confirmed by study conducted by Olaniyi J . A , et al **(ref 3)**, in Tanzania, in which 74% of patients belong to age group of 25 – 45 years. Hence both TB and HIV have great impact in patients of adult age group.

FIGURE 1 : age wise distribution (in percentage) of TB with HIV patients



X axis – Age group of the patients; Y axis – percentage of patients in each group

FIGURE 2 : Age wise distribution (in percentage) of TB without HIV patients



Regarding the sex distribution between these two sets of patients , both HIV and TB is more common in male sex . In our study, 83% were males and 16.6% were females in patients with TB with HIV , whereas it is 76.6% males and 23.3% females in TB without HIV.

This finding can not be taken as fool proof , as the female patients attending the thoracic medicine OP is very less, due to social stigma and taboos.

Regarding BMI, majority of patients in both the group belong to underweight i.e, BMI < 18.5. around 90 % of patients in TB with HIV group and 73.3% of patients in TB with out HIV were under weight.

According to study by Morris , Bird and et.al..the basic pathogenesis for cachexia in HIV and TB patients was due to cytokines IL-1 , IL-6 , and TNF – alpha.

Among the various haematological abnormality noted in these patients , anemia , thrombocytopenia , and variation in ESR were very significant,

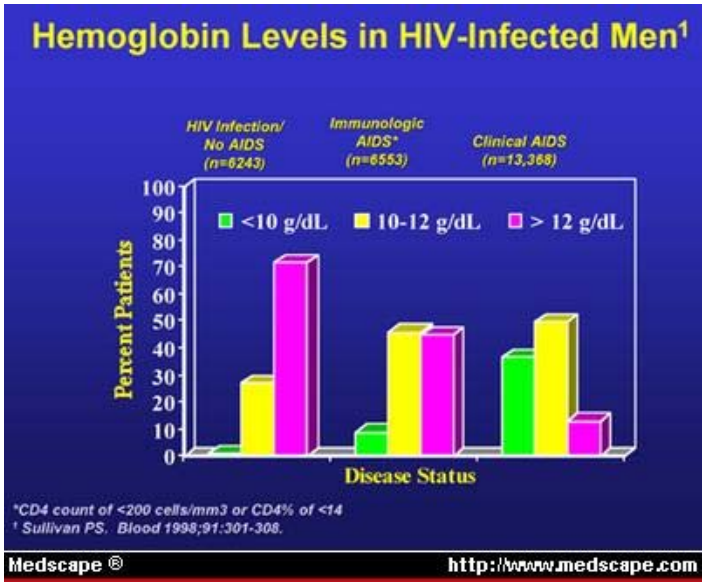
ANEMIA :

In our study anemia was found in both groups. In case of patients of TB with HIV 80% had haemoglobin less than 11gm / dl and 66.6% of TB without HIV patients had Hb less than 11 gm/dl. Among the anemic patients belonging to TB with HIV 87.5% were males and 12.5 % were females.

In case of anemic patients belonging to TB without HIV , 75% were males and 25 % were females.

Our study is well comparable to the study done by Morris, sharma et.al, in which anemia was seen in 80% of patients with TB and HIV coinfection.

FIGURE ; 3 : Hemoglobin levels in HIV infection/ Immunological AIDS.



Our study coincide with that study conducted by SULLIVAN PS in HIV infected males, i.e, around 70% of male patients are anemic in the category of TB with HIV. Mostly these patients belong to HIV infection or immunological AIDS, which are cases chosen particularly for this study.

Since the HIV patients chosen for this study belong to early stage of HIV infection, there is no remarkable changes in WBC counts. According to Murphy M, Metcalfe et.al **(ref 8)**., neutropenia occur in late stage of CLINICAL AIDS, whereas lymphocytopenia may occur before neutropenia as HIV infection mostly attacks lymphocytes.

In our study also both the group of patients i.e TB with HIV and TB without HIV had normal WBC count in 93%.

In case of differential count, 23% of TB with HIV patients had lymphocytopenia.

In patients with tuberculosis, there was no significant alteration in terms of total WBC counts, and differential counts.12% of patients with Tuberculosis per se had lymphocytosis.

PLATELETS:

According to a study conducted in 350 pulmonary TB patients, thrombopoeisis is seen 33% of patients, 3 % had thrombocytopenia and 64 % had normal to low normal level of platelets (Dr.Sharma MD AIIMS, JIMA, 2006)

In HIV positive patients, according to Sullivan PS, Hanson DL et al **(ref 7)**, isolated thrombocytopenia may be early consequences of HIV infection and if CD 4 count is less than 250, this may increase upto 40 % due to direct toxic effects of HIV on the megakaryocytes.

According to Adrian Mindel et al HIV and haematological problems, thrombocytopenia is common in HIV disease and only if persistent, cause bleeding.

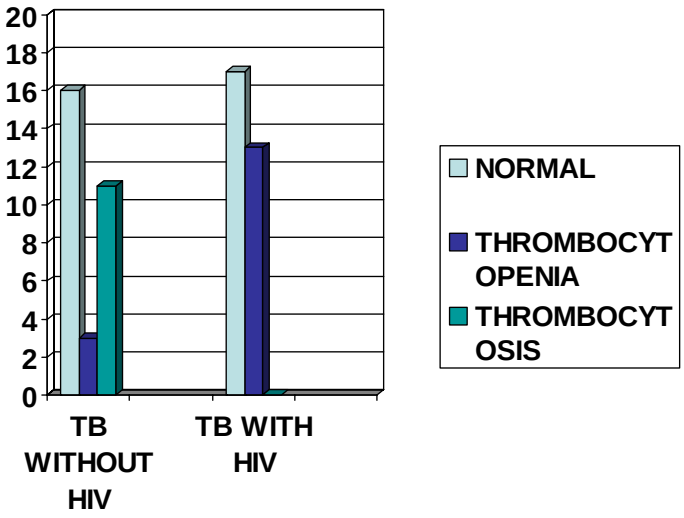
In our study, 63.3% of patients belonging to TB with HIV positive status had thrombocytopenia, whereas only 10% of patients had thrombocytopenia among TB without HIV status.

In the contrary, 53.3% of patients had normal platelet counts and 36.6% had thrombocytosis in patients with TB per se.

Among the patients with thrombocytopenia I TB with HIV study group , 84.2% were males and 15.7% were females.

Among patients with thrombocytosis in TB with HIV negative status, 72.7% were males and 27.2% were females.

VARIATION IN PLATELET COUNTS AMONG TUBERCULOSIS PATIENTS WITH AND WITHOUT HIV



Y axis – No. of patients in the study group

ERYTHROCYTE SEDIMENTATION RATE

ESR is a marker of ongoing inflammatory reaction. It may be elevated in gross situations. The tuberculosis patients had high ESR value compared HIV positive TB patients.

According to the study of KAMALESH SARKAR and co workers, ESR may be an indicator for screening of tuberculosis patients for underlying HIV infection, particularly in poor resource settings.

They had taken 34 patients with TB positive and HIV positive in one group and 25 patients with TB without HIV in another group. They have done routine investigation which included Total count (TC), Differential count DC), haemoglobin (Hb), ESR for both group of patients.

The data were compared between the two groups. According to the study, there was not much difference in basic investigations between these two groups except in ESR values. Most tuberculous patients with HIV infection had a much lower ESR value compared to the control group.

TB with HIV	Mean value of ESR 38.5 mm/hr
	Median value of ESR 30 mm/hr
TB without HIV	Mean value of ESR 142 mm/hr
	Median value of ESR 108mm/hr.

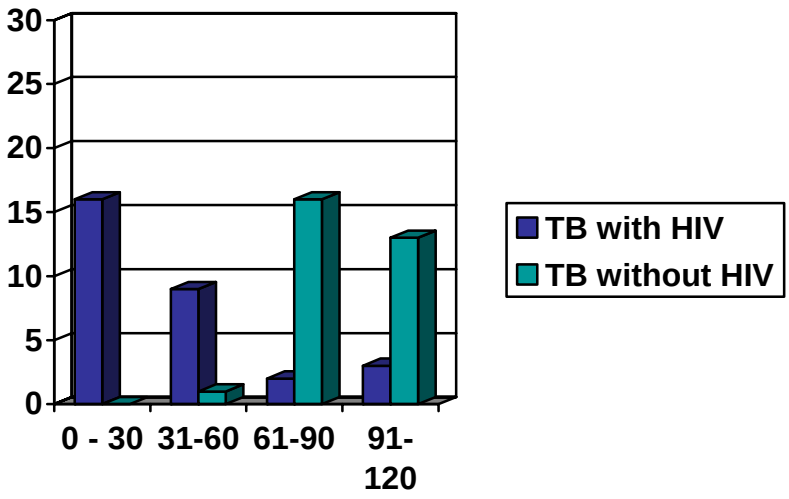
In our study, 96.6% of patients belonging to TB without HIV negative status had ESR more than 60 mm / hr., in which 73.3% were males and 26.3% were females. Only 3.3% of patients in TB with out HIV had ESR less than 60 mm / hr.

In our study , 83.3% of patients belong to TB with HIV had ESR in the range of 0-60 mm/hr. and only 16.6% of patients in this group had ESR in range of 61 – 120 mm / hr.

Among these 66.6% of males had ESR less than 60 mm / hr and 16.6% of females had ESR less than 6omm / hr.

Hence **p value is 0.001,** which is significant, we can conclude that ESR is drastically reduced in patents with TB- HIV co-infection rather TB alone.

FIGURE 3 : Correlation of ESR with study groups



X axis – ESR ; Y axis – No. of patients

SUMMARY OF HAEMATOLOGICAL CHANGES

Haematological parameter	HIV status	range	median	mean	'p' value
Haemoglobin (in gm / dl)	Positive	6.4-12.6	9.1	9.2	0.201 In significant
	Negative	6-12.8	9.9	9.76	0.231 In significant
RBC (in mill /cumm)	Positive	2.2-4.2	3.0	3.1	0.121 In significant
	Negative	2.3-4.2	3.3	3.3	0.212 In significant
WBC (in cells/cumm)	Positive	3400-10000	6500	6538	0.112 In significant
	Negative	3600-10950	6500	6696	0.211 In significant
ESR (in mm/hr)	Positive	20-120	30	38	0.001 Significant
	Negative	60-120	108	102	0.002 Significant
Platelets (in mill/cumm)	Positive	0.4-3.0	1.60	1.54	0.001 Significant
	Negative	1.0-5.6	3.05	3.31	0.002 Significant

SUMMARY

The study **"HAEMATOLOGICAL PROFILE OF PULMONARY TUBERCULOSIS PATIENTS WITH AND WITHOUT HIV**" was done in 60 patients, with 30 patients in TB with HIV and 30 patients in TB without HIV, who attended the department of thoracic medicine and anti retroviral therapy centre, GRH, Madurai.

Pulmonary tuberculosis patients were detected by clinical examination and by sputum positivity for AFB, using Ziehl-Nielson technique. Among pulmonary tuberculosis patients, HIV was confirmed by both ELISA and WESTERN BLOT assay.

After a baseline investigations, complete haemogram was done on these patients using automated analyzer and peripheral smear examination.

In our study, 83.3% were males and 16.6 % were females in the TB with HIV group. Whereas 76.6% were males and 23.3% were females in the TB without HIV group. Hence males dominated in both groups.

In our study, 70% of patients were in the age group of 25 – 45 years in the TB with HIV group, whereas 86.6% 0f patients were in age group of 25 – 45 years in the TB without HIV. Hence, both the disease predominantly affect adults.

In our study, 90 % of patients were underweight with BMI less than 18.5, in TB with HIV group, and 73.3% of patients were underweight in TB without HIV group. Since both disease causes chronic wasting, co-infection of TB with HIV may have deleterious effect in BMI.

In our study, 80 % were anemic in the TB with HIV and 66.6% were anemic in TB without HIV group. Among those anemic patients, male patients were more (70 % vs 34%) anemic.

In our study, WBC count was not much altered in both the study groups, in which more than 65% of patients had normal WBC count in the TB with HIV groups and 70% of patients had normal WBC counts in TB without HIV. Since HIV was in early stages, the WBC count has not drastically reduced.

In our study, 63.3% of patients with TB and HIV had thrombocytopenia, whereas only 10% of patients had thrombocytopenia in TB without HIV group. Instead, 36.6% of patients had thrombocytosis in the TB without HIV group.

Since isolated thrombocytopenia is a well documented feature in HIV patients, and either normal platelet counts or thrombopoeisis occur in pulmonary tuberculosis patient per se, the co-infection TB and HIV has drastically reduced the platelet count in these patients.

In our study, yet another finding is that, patients with tuberculosis per se have increased ESR count, whereas TB-HIV coinfection has drastically reduced the ESR

count. Among patients with TB and HIV 83.3% of patients had ESR less than 60 mm/hr., whereas 96.6% of TB without HIV patients had ESR greater than 60 mm/hr. since, ESR is a marker of chronic inflammatory states like TB and HIV is a immunosuppressive state, the co-infection of TB with HIV has drastically reduced ESR values in these patients.

CONCLUSION

I. Both the diseases predominantly affect the male sex.

II. Both the diseases affect the economically productive age group of the nation, namely adults belonging to 25 – 45 years.

III. Anemia is common in both diseases, but the combination further worsens this scenario.

IV. There is not much reduction in WBC count, as the patients chosen for this study belong to either asymptomatic AIDS or immunological AIDS.

V. The platelet counts are drastically reduced even in asymptomatic AIDS patients, hence this parameter can be used as marker of early HIV infection among the pulmonary tuberculosis patients.

VI. ESR values are drastically reduced in TB patients with HIV, rather TB patients per se. hence, an ESR less than 60 mm / hr in pulmonary tuberculosis patients should arouse a suspicion of underlying immunocompromised state.

LIMITATIONS OF THE STUDY

Since the study group contained 60 patients, selection bias have been confounded, with respect to sex distribution, Hence a large study group is needed to overcome this bias.

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GLOSSARY

1. BMI	:	body mass index
2. Hb	:	haemoglobin
3. TC	:	total count
4. P	:	polymorphs
5. L	:	lymphocyte
6. E	:	eosinophil
7. M	:	monocyte
8. ESR	:	Erythrocyte sedimentation rate
9. HIV	:	Human Immunodeficiency Virus
10. AIDS	:	Acquired ImmunoDeficiency Disease
11. TB	:	tuberculosis
12. RNTCP	:	revised national tuberculosis control program
13. NACO	:	national AIDS control society
14. ELISA	:	enzyme linked immunosorbent assay.

PROFORMA

Name: Age: Sex :

IP/OP No : Occupation :

Marital status: WHO stage :

Educational status :

Clinical status :

Cough with expectoration for > 3 weeks : Y/N

Evening rise of temperature : Y /N

Loss of appetite (anorexia) : Y/N

Significant loss of weight : Y/N

Past History :

Diabetes : Y/N Hypertension : Y/N

IHD : Y/N Pulmonary TB: Y/N

Drug History : Y/N Anti retroviral drugs (For HIV)

Anti Tuberculosis Drugs (for Pulmonary TB)

Personal History :

Smoking: Y/N Duration: Packs/ Day

Alcohol : Y/N Duration:

Diet : Veg/ Non veg

Family History ;

Diabetes : Y/N

PERSONAL HISTORY :

Exposure to STD : Y/N

H/o sexual promiscuity : Y/N

Examination :

Height : in meters Weight : in Kilogram BMI ;

Vital signs

(a) Pulse rate (b) Respiratory rate

(c) Blood pressure

Systems :

Cardio vascular status

Respiratory status

Neurological status

Investigations:

Urine albumin :

Sugar :

Deposit :

Blood Urea :

Ser Creatinine :

Liver Function Test:

Complete haemogram (incl.peripheral smear study);

CD4 Count / ul :

Percentage :

HIV RNA copies:

Chest X-ray (PA view):

MASTER CHART - TB with HIV

S.NO	IP NO	AGE	SEX	WEIGHT	HEIGHT	BMI	Hb	RBC	TC	P	L	E	M	ESR	PLATLET
		in years		in kg	in cm		in gm	in million						in mm/hr	cells/cmm
1	29837	55	M	35	154	14.76	9	3	9200	56	42	2	0	42	1,60,000
2	23234	55	M	36	159	14.28	7.2	2.5	7600	52	40	8	0	24	80,000
3	28365	65	M	50	172	16.9	12.6	4.2	6550	52	44	4	0	26	1,80,000
4	23432	45	M	37	166	13.5	11.2	4	7300	60	36	4	0	28	2,50,000
5	29832	47	M	40	161	16.4	5.5	2	3400	79	20	1	0	36	70,000
6	23273	19	F	49	168	17.4	11.4	3.8	6000	58	39	3	0	48	2,00,000
7	26734	52	M	41	158	16.4	6.4	2.2	5850	57	43	0	0	58	60,000
8	28934	46	M	51	170	17.6	7	2.4	3600	70	26	4	0	60	1,00,000
9	23273	26	M	37	166	13.6	7.2	2.5	5900	52	46	2	0	24	90,000
10	29387	35	M	34	155	14.2	9.6	3.2	6300	60	33	7	0	30	1,00,000
11	32232	30	F	35	155	14.6	10.6	3.5	7400	67	26	2	5	32	1,80,000
12	23463	65	M	41	158	16.5	12.6	4.2	6550	52	44	4	0	22	2,80,000
13	30893	25	M	51	170	17.6	7.2	2.5	3600	63	36	1	0	62	50,000
14	30897	40	M	59	160	23	8	2.7	8000	62	36	0	0	74	50,000
15	30987	45	F	36	165	14	8.6	2.9	7050	62	36	2	2	22	2,00,000

S.NO	IP NO	AGE	SEX	WEIGHT	HEIGHT	BMI	Hb	RBC	TC	P	L	E	M	ESR	PLATLET
16	31898	32	M	36	156	14.8	8.9	2.9	7600	62	33	3	0	20	3,00,000
17	26343	25	F	42	160	16.4	7.6	2.6	6400	62	33	5	2	28	1,00,000
18	27354	25	M	46	167	16.54	10.2	3.4	3400	56	42	2	0	52	1,20,000
19	27365	33	F	44	163	16.6	12.8	4.3	7400	60	40	0	0	30	1,60,000
20	28376	36	M	55	158	22	8.8	3	5750	56	40	2	2	44	3,00,000
21	29833	32	M	40	167	14.4	8.4	2.9	6350	56	40	2	2	28	40,000
22	25436	35	M	44	162	16.7	9.4	3.1	6400	64	34	2	0	102	2,80,000
23	28734	21	M	28	145	13.4	10.2	3.4	7400	64	34	2	0	26	1,60,000
24	28372	33	M	54	164	20.14	9	3	6450	46	50	2	2	30	2,40,000
25	29374	55	M	42	162	16.03	9.8	3.3	7200	56	42	2	0	106	1,60,000
26	22323	29	M	31	151	13.59	10.7	3.7	8600	60	40	0	0	48	2,20,000
27	29323	35	M	45	160	17.5	12.6	4.2	10000	56	40	0	4	28	1,70,000
28	24383	32	M	31	154	13	8.2	2.8	7400	42	56	0	2	22	90,000
29	21928	29	M	45	160	17.5	7.9	2.7	5300	56	36	6	2	28	1,00,000
30	30918	33	M	32	157	13	7.1	2.4	6800	46	52	2	0	120	80,000

MASTER CHART - TB without HIV

S.NO	I.P NO	AGE	SEX	WEIGHT	HEIGHT	BMI	Hb	RBC	TC	P	L	E	M	ESR	PLATELET
		in years		in kg	in cm		in gm/dl	mill/cumm	cells/cmm						mill/cumm
1	29834	33	M	43	156	17.6	8.9	3.1	8350	80	18	2	0	88	4.9
2	24394	30	F	41	170	14.2	12.2	4.2	6100	62	36	2	0	80	5.6
3	29387	35	M	47	168	16.6	11.8	4.1	7200	62	36	2	0	68	4.7
4	23453	27	M	40	159	15.8	11.8	4	6300	60	34	3	3	76	2
5	28374	30	F	41	170	14.2	10.9	3.6	6750	56	41	3	0	116	2.7
6	24355	38	M	35	155	14.6	8.8	3	8500	68	30	2	0	96	4.9
7	39887	40	M	44	153	18.8	8.6	3	8000	62	36	0	2	120	3.5
8	32433	35	M	41	158	16.5	9.4	2.6	10950	60	38	2	0	116	3.6
9	32662	50	M	44	157	14.9	11.6	3.8	5000	65	35	0	0	108	3.4
10	37726	42	M	59	147	27.3	10.4	3.4	5200	63	34	0	3	92	2.2
11	38463	30	F	35	155	14.6	10.6	3.5	7400	67	26	2	5	106	2.7
12	42234	47	F	47	168	16.7	12.6	4.2	6800	58	38	4	0	78	3.1
13	36253	35	F	58	157	23.6	7.4	2.6	10950	60	38	2	0	106	4.8
14	23432	45	F	41	156	16.5	7.2	2.6	3600	63	36	1	0	120	2
15	27873	42	M	41	151	16.3	12.6	4.2	6000	52	46	2	0	96	4.8

16	28837	29	M	36	170	12.5	12.8	2.6	8100	52	46	2	0	92	5.1
17	37726	33	M	39	161	15	11.2	3.7	7650	48	45	2	0	116	1.6
18	37776	30	M	34	151	14.9	10	3.3	7450	48	50	2	0	98	1.7
19	34283	31	M	43	150	19.1	10.6	3.5	5400	57	40	3	0	60	5.4
20	32493	42	M	39	158	15.6	8.8	3	6400	40	56	1	3	104	2.8
21	34263	52	F	38	160	14.8	9.8	3.3	6700	56	44	0	0	98	4.8
22	39263	35	M	49	168	18.4	7.6	2.7	3700	46	52	2	0	86	2
23	24363	38	M	29	151	14.1	11.6	3.8	6400	55	41	4	0	84	2.2
24	29387	32	M	35	165	14.3	9.8	3.4	3700	48	50	2	0	92	2.8
25	26372	30	M	43	158	17.2	7.2	2.6	6500	62	35	3	0	80	1
26	26632	50	M	58	149	26.1	6	2.3	6400	52	44	2	0	96	1.2
27	28763	37	M	64	167	23	9.6	3.2	5600	51	48	1	0	75	3
28	25435	38	M	45	154	18.9	11.4	3.8	8500	52	48	0	0	108	4.8
29	25377	45	M	67	163	17.7	9.2	3.1	6500	46	52	2	0	112	5.2
30	27366	36	M	52	154	21.9	6	2.3	4500	48	52	0	0	114	1