A STUDY ON THE CLINICAL PRESENTATION OF HIV-TB COINFECTION AND ITS CORRELATION WITH CD4 COUNT

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CERTIFICATE

This is to certify that **A STUDY ON THE CLINICAL PRESENTATION OF HIV-TB COINFECTION AND ITS CORRELATION WITH CD4 COUNT** by **S. MALATHI** post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-600010, under my guidance and supervision in fulfillment of regulations of the **TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY** for the award of **M.D.DEGREE BRANCH I, PART II, (GENERAL MEDICINE)** during the academic period from May 2005 to March 2008.

DR.M.DHANAPAL M.D., D.M.
The Dean,
Kilpauk Medical College
Chennai-600010.

Prof.**G.RAJENDRAN M.D.**
Professor and Head
Kilpauk Medical College
Chennai-600010

Prof.**M.D. SELVAM M.D.**
Professor.
Kilpauk Medical College
Chennai-600010.

Prof.**P.CHINNAIYAN M.D**
Professor.
Kilpauk Medical College
Chennai-600010

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CONTENTS

INTRODUCTION

The burden of TB and HIV /AIDS poses unprecedented challenges on the public health system in India. TB and HIV are overlapping epidemics. They are closely interlinked. Untreated HIV infection leads to progressive immuno deficiency and increased susceptibility to infections including TB. TB is the leading cause of HIV related morbidity and mortality.

HIV is the most important factor fuelling the TB epidemic in populations with a high HIV prevalence in many countries especially in sub-Saharan Africa[1] and increasingly in Asia and South America.

Studies have shown that there is close association between HIV and TB. Evidence of this interaction included several observations repeatedly made by WHO[2], National governments and funding partners.

These observations are

- The areas that have been mostly affected by HIV epidemic also report the greatest increase in the incidence and prevalence of the TB.
- The largest increase in TB cases has occurred among people aged 25-40 years. The very same age group mostly affected by HIV/AIDS.
- TB is the most common opportunistic infection among AIDS patients(Between 60-75% of AIDS patients will develop TB)

- HIV prevalence among TB patients is higher than in the general population. (It is estimated a prevalence of 5.2% of HIV in adult TB in India).

GLOBAL SCENERIO OF HIV AND TB

- 2 billion infected with M.Tuberculosis.
- More than 40 million are HIV infected[3].
- 15.0 million affected with HIV/TB co-infection.
- Over 90% of HIV co-infection resides in developing nations.
- 1 out of in 3 persons with HIV positive is infected with TB.

INDIAN SCENERIO OF HIV AND TB

- India accounts for one fifth of global TB burden[4].
- 40 million infected with TB bacilli.
- 1.8 million new cases of TB occurred annually [5].
- 5.22 million are infected with HIV.
- 2 million people co-infected with TB & HIV.

IMPACT OF HIV ON TB[6]

- HIV infection increases the risk of disease reactivation in people with latent TB. It is around 10% per year in HIV infected patients compared to less than 0.1 % annually in those without HIV infection.
- HIV infected patients are more susceptible to new TB infection.
- HIV is the most powerful risk factor for progression of TB infection to TB disease.
- Life time risk of developing TB is 60% in HIV positive as compared to 5-10% risk in HIV negative.
- Increased emergence of drug resistance.
- Cause of death is complication other than TB due to accelerated progression of HIV.

IMPACT OF TB ON HIV[7]

- TB shortens the survival of patients with HIV infection.
- TB accelerates the progression of HIV as observed 6-7 fold increase in HIV viral load in TB patients.
- CD4+ T cell count falls and results in progressive immuno suppression.
- TB is the cause of death in 1 out of 3 people with AIDS Worldwide.

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This study is focused to know about various clinical presentations of tuberculosis in HIV infected patients and the relationship with CD4 count. As HIV-TB co-infection leads to increased morbidity and mortality diagnosis of HIV-TB co-infection should be done at the earliest and thereby proper treatment , adequate care and support to be given all patients with HIV/AIDS.

AIM OF THE STUDY

1. To study the clinical presentation of tuberculosis in HIV positive patients.

2. To study the correlation of CD4 count with the radiological findings of Pulmonary tuberculosis.

REVIEW OF LITERATURE

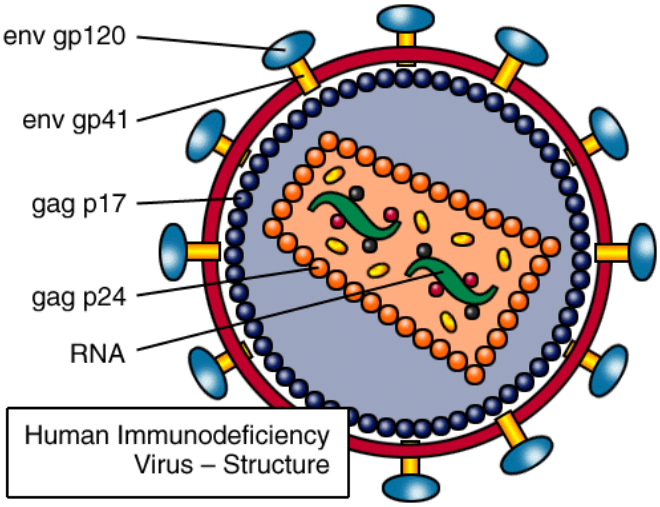
HIV VIRUS

The etiologic agent of AIDS is HIV, which belongs of family of human retro viruses (retro viridea) and the sub family lentiviruses. There are two sub types of HIV namely HIV-1and HIV-2. They are cytopathic viruses. HIV-1 was discovered by Luc Montagnier[8] and his associates at the Institute Pasteur in Paris in 1983. HIV-2 was first identified among patients in Cameroon in 1985. HIV-2 is more similar to SIV (Simian Immunodeficiency Virus) than HIV-1 and it is much less virulent usually not resulting in full blown AIDS, but still fatal.

The HIV variants are divided into three groups: M, for major, N, and O, for other or H, I, J, and K. the B-clade is dominant in US, Europe, Southeast Asia, and South America. Clades E and B are dominant in Asia and A, C, and D are dominant in Africa.

Morphology of HIV

Electron microscopy shows that HIV virus is an isosahedral structure containing numerous external spikes formed by the two major envelope proteins. The external glycoprotein 120 and transmembrane glycoprotein 141.



The core virus particle is composed p24 capsid protein and contains viral RNA and Enzymes. All retro viruses have common 3 coding regions.

- Gag - encode capsid proteins.
- Pol - encode viral enzymes necessary for replication, reverse transcriptase, integrase and protease.
- Env - encode external glycoprotein that protrudes out of the lipid viral envelope and is responsible infectivity of the virus particles by means of attachment to specific cellular receptors.

VIRAL LIFE CYCLE[9]

The unique feature of the virus is that it gains entry to host cells by binding to the CD4 receptor using the viral surface membrane glycoprotein 120. This allows viral attachment and penetration of the host cell. The CD4 receptor is present predominantly on T-helper lymphocytes, which are therefore a major target for the virus. Following penetration of the host cell, the viral RNA is transcribed by the viral enzyme reverse transcriptase into a DNA copy which becomes incorporated into the host cell genomic DNA. This viral DNA may then lie dormant within the cell or undergo replication (particularly if that cell is stimulated) resulting in transcription of RNA copies and translation to viral proteins resulting in new virus formation and assembly. Viruses then bud from the cell surface. New virus is then available to infect other cells and repeat the process.

DEFINITION OF AIDS

AIDS definition has varied widely, the most widely used the centre for Disease Control (CDC) classification of 1993. The USA definition includes individuals with CD4 count below 200/µl or CD4 percentage of total lymphocyte count of <14% in addition to the clinical classification based on the presence of specific indicator diagnosis called as AIDS -defining conditions. In Europe, the definition remains based on the diagnosis of specific clinical conditions with no inclusion of CD4 lymphocyte count.

CLASSIFICATION OF AIDS:

1993 REVISIED CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED AIDS SURVEILLANCE CASE DEFINITION FOR ADULTS[10]

Bacterial infections, multiple or recurrent.

Candidiasis of bronchi, trachea or lungs

Candidiasis, esophageal

Cervical cancer, invasive

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (> 1 month's duration)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV related

Herpes simplex, chronic ulcer (>1 month's duration) or

bronchitis, pneumonitis or Esophagitis

Histoplasmosis, disseminated or extra pulmonary

Isosporiasis, chronic intestinal (>1 month's duration)

Kaposi sarcoma

Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia

Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary of brain

Mycobacterium tuberculosis, any site (pulmonary or extra pulmonary)

Mycobaterium avium-intracellulare complex or Mycobacterium kansasii (disseminated or extrapulmonary)

Pnemocystis jirovecii pneumonia

Pneumonia, recurrent

Progressive multifocal leukoencephalopathy

Salmonella septicemia,recurrent

Toxoplasmosis of brain

Wasting syndrome of HIV infection

CLINICAL CATEGORIES

	A	B	C
$CD4^+$ T Cell Categories	Asymptomatic, acute(primary) HIV, or PGL	Symptomatic, Not A or C Conditions	AIDS Indicator Conditions
1.>500/uL	A1	B1	C1
2.200-499/uL	A2	B2	C2
3.<200/uL AIDS indicator T cell count	A3	B3	C3

Clinical conditions in category C are listed in the 1993 aids Surveillance.

CLASSIFICATION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

(WHO CLINICAL STAGING SYSTEM)

Clinical Stage 1

Asymptomatic

Persistent generalized Lymphadenopathy (PGL)

Performance scale 1; asymptomatic, normal activity

Clinical Stage 2

Weight loss<10% of body weight

Minor mucocutaneous manifestations

Herpes zoster, within the last 5 years

Recurrent upper respiratory tract infections (e.g. bacterial sinusitis) And/or performance scale 2; symptomatic, normal activity

Clinical stage 3

Weight loss,>10% of body weight

Unexplained chronic diarrhea,> 1 month

Unexplained prolonged fever (intermittent or constant),> 1month

Oral candidiasis (thrush)

Oral hairy leukoplakia

Pulmonary tuberculosis, within the past year

Sever bacterial infections (e.g pneumonia, pyomyositis)

And/or performance scale 3; bedridden,>50% of the day during the last Month

Clinical stage 4

HIV wasting syndrome

Pneumocystis jirovecii pneumonia

Toxoplasmosis of the brain

cryptosporidiosis,extrapulmonary

Cryptococcosis,extrapulmonary

Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or Lymph nodes

Herpes simplex virus (HSV) infection,mucocutaneous > 1 month,or visceral any duration

Progressive multifocal leukoencephalopathy (PML)

Any disseminated endemic mycosis (e.g.

Histoplasmosis,coccidioidomycosis)

Candidiasis of the esophagus,trachea,bronchi, or lungs

Nontyphoid Salmonella septicemia

Extrapulmonary tuberculosis

Atypical mycobacteriosis, disseminated

Lymphoma

Kaposi sarcoma (KS)

HIV encephalopathy

And/or performance scale 4: bedridden, >50% of the day during the last month.

WHO CASE DEFINITION FOR AIDS SURVEILLANCE IN ADULT WHERE HIV TESTING FACILITIES NOT AVAILABLE

Case definition for AIDS is fulfilled if atleast two major signs and one minor sign are present.

Major Signs:

- Weight loss > 10 % of body weight
- Chronic diarrhea for more than one month.
- Prolonged fever more than one month.

Minor Signs:

- Persistent cough more than one month
- History of herpes zoster
- Oropharyngeal candidiasis
- Generalised lymphadenopathy
- Chronic progressive herpes simplex infection.

HIV – MODES OF TRANSMISSION

I) Sexual Intercourse -84.5%

It is a major route of transmission. The risk of becoming infected depends on four major factors.

- ❖ Higher the frequencies of act, higher the number of sexual partners.
- ❖ The type of sexual act
  - Anal
  - Vaginal
  - Oral
- ❖ The amount of viral load present in the Blood[11].
- ❖ The presence of other sexually transmitted diseases or genital lesions in either partner.

II) Blood Borne infections 3.27%

III) Mother to child transmission 2.16%

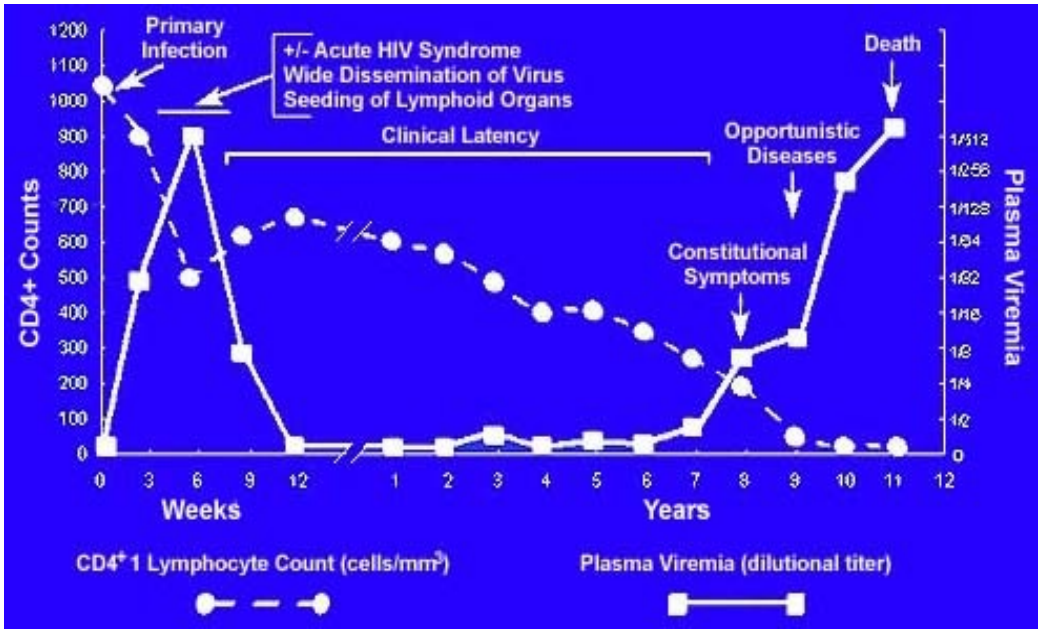
IV) Drug abuse 3.36%

V) Others 6%

HIV contaminated Instrument

- ❖ Organ transplants
- ❖ Occupational exposure

NATURAL HISTORY OF HIV INFECTION



The clinical spectrum of HIV infection includes primary infection **(the acute retroviral syndrome)** asymptomatic infection, early symptomatic infection and advanced immunodeficiency with opportunistic complications.

Viral load or viremia is monitored by measurement of HIV-RNA in plasma, and immunological status is reflected in the absolute number of CD4. Plasma viremia declines precipitously with antibody seroconversion and the development of an anti HIV immune response usually reaching a steady state level within 6 to 12 months[12].

In most asymptomatic pts, the cd4 count declines gradually over several years. The slope of decline is a function of the plasma viral load. Plasma viremia increases, accompanied by a more rapid decline in CD4 cell count before the onset of asymptomatic disease. As the viral load increases and CD4 cell count falls and risk of opportunistic infections, malignancies, wasting, neurologic complications and death increases substantially.

There is considerable variation in the progression of HIV disease with some individuals progressing from infection to AIDS in less than 5 years[13] and so called long term non progressors remaining asymptomatic without treatment or evidence of immunologic decline for many years[14]

A number of laboratory tests have been correlated with progressive immunodeficiency, the development of AIDS and mortality. Taken together, however the CD4 lymphocyte count and plasma viral load are the best prognostic markers of the HIV infection.

The CD4 lymphocyte count a specific test for cellular immuno competence is a sensitive predictor of the development of symptomatic HIV infection and AIDS in the near term as it reflects the current immunologic capacity Conversely, the plasma viral load (HIV-1RNA) is an extremely useful predictor of disease course over a more extended period of time and is strongly associated CD4 cell count decline.

In addition the average annual decline in the CD4 count of HIV infected men varied according to their initial vital load, decreasing by 36 CD4 cells/year among men with baseline HIV-1 RNA less than 500 copies/ml and by 77 CD4 cell/year among men with baseline HIV-1 RNA greater than 30,000 copies/ml[15].

Put in the context of HIV pathogenesis, the viral load measures the replicative rate of the infection and its destructive potential for the cellular immune system, and the CD4 count gauges the extent of immune compromise and present risk of opportunistic infections. The mean survival time after a CD4 count of 200/mm^3 is 40 months[16].

Other markers of HIV disease progression include the HIV p24 antigen, serum b2 microglobulin, neopterin, and labile interferon alfa, antip24 antibody and soluble CD8.

Clinical findings may also predict the disease progression, oral candidiasis and oral hairy leucoplakia are early clinical markers of immunosuppression. Generalized lymphadenopathy is also a clinical marker of HIV infection. Most opportunistic infection increases the risk of death independent of CD4 cell count[17].

IMMUNOPATHOLOGY OF HIV INFECTION

HIV subverts the immune system by infecting CD4+ T cells. It is clear that HIV induces dysfunction of nearly all elements of the immune system and that the pathogenesis of HIV disease is multifactorial[18].

CD4 was identified as the major cellular receptor for HIV fusion and entry in 1984[19]. Transfection of the CD4 gene into CD-4 negative (CD-4) human cells rendered them infectable with HIV[20].

HUMORAL IMMUNE RESPONSES

Antibodies that bind HIV proteins, including the viral surface envelope glycoprotein, can be detected in the plasma within weeks of HIV infection coincident with the decline of plasma viremia[21].

Both the CD4 and co-receptor binding sites are well conserved among known viral isolates and are not glycosylated. For these reasons they are thought to be important targets of neutralizing antibodies.

CELLULAR IMMUNE RESPONSES

Cytotoxic T-Lymphocytes

MHC class I-restricted, HIV-specific $CD8^+$ cytotoxic T-lymphocyte (CTL) responses are found in the peripheral blood within the first few months of HIV infection and are detected during the chronic phase of infection in the majority of HIV infected individuals[22].First the temporal association of the peak of the HIV-specific CTL response with the decline of viremia during acute infections is thought to represent the effect of virus specific CTL in restricting HIV replication in humans[23].HIV specific $CD8^+$ T cells falls due to lack of $CD\text{-}4^+$ T-cell help.

$CD\text{-}4^+$ T-cell Responses

Unlike most other infections of humans, HIV infection is characterized by the absence of HIV specific $CD\text{-}4^+$ T-cell proliferative responses in the vast majority of untreated patients[24].Because HIV infects $CD\text{-}4^+$ T-cell, it was believed that the early loss of HIV specific proliferative responses may be the result of infection and deletion of HIV specific $CD\text{-}4^+$ T-cell in the lymphoid tissues on encountering the virus. Thus, there is now

general agreement that HIV specific $CD4^+$ T cells persist in patients with progressive disease.

MECHANISMS OF CD4+ T CELL DYSFUNCTION AND DEPLETION[25]

Direct Mechanisms

- Loss of plasma membrane integrity due to viral budding
- accumulation of unintegrated viral DNA
- Interference with cellular RNA processing
- Intracellular gp 120-CD4 autofusion events
- Syncytia formation

Indirect Mechanisms

- Aberrant intracellular signalling events.
- Autoimmunity.
- Innocent bystander killing of viral antigen-coated cells.
- Apoptosis.
- Inhibition of lymphopoiesis.
- Activation induced cell death
- Elimination of HIV infected cells by virus-specific immune response.

RESERVOIRS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

RESTING CD4 T CELLS

This resting CD4 cells is established during the earliest stages of HIV infection.

LYMPHOID TISSUE

Lymphoid tissue is a major site of HIV replication and plays a role in the progression of disease throughout all stages of infection.

$CD8^+$ T cells

Dysregulation of $CD8^+$ T cell numbers and function is evident throughout the course of HIV disease. After acute primary infection, $CD8^+$ T cell counts usually rebound to supernormal levels and may remain elevated for prolonged periods. Increase in $CD8^+$ T cells during all but the late stages of disease may in part reflect the expansion of HIV specific $CD8^+$ cytotoxic T lymphocytes. In addition to cytotoxic T lymphocyte activity, other $CD8^+$ T cell functions are impaired during HIV disease progression, including loss of noncytolytic non-MHC restricted $CD8^+$ T cell derived HIV suppression

B-lymphocytes:

Dysregulation of B -cell activation and the decreased ability of these cells to respond to antigen are likely responsible in part for the increase in certain bacterial infections seen in advanced HIV disease in adults.

NATURAL KILLER CELLS

Abnormalities of NK cells are observed throughout the course of HIV disease and these abnormalities increase progression. NK cells, like $CD8^+$ T cells, may inhibit HIV replication by cell-mediated killing, as well as by secretion of soluble HIV inhibitory factors.

NEUTROPHILS

Dysregulation of neutrophil function occurs at all stages of HIV infection. The oxidative capacity of neutrophils after priming with granulocyte macrophage colony-stimulating factor is also increased in HIV infected individuals. The opsonizing activity of neutrophils is significantly impaired in HIV infection and the degree of impairment correlated with disease progression.

MONOCYTE – MACROPHAGES

Cells of the monocyte-macrophage lineage play key roles in the immunopathogenesis of HIV disease. Dysfunction of these cells contributes to $CD4^+$ T cells dysfunction and to impair host defense against intracellular pathogens. These cells are central to the pathogenesis of HIV-induced central nervous system disease.

DENDRITIC CELLS

Dendritic cells are among the first cells to encounter HIV after mucosal[26] exposure and are probably responsible for transporting the virus to lymphoid organs thus facilitating infection of $CD4^+$ T cells and viral dissemination.

TUBERCULOSIS

Magnitude of Tuberculosis in India

- Today 2 of every 5 Indians are infected with TB bacilli. There is a strong chance of that of them atleast 10 % will develop TB disease.
- 1.8 million new TB cases occurred annually
- Among that 0.8 millions have sputum positive.

- 1 sputum positive patient can infect 10 to 15 persons in a year if left untreated.

The etiologic agent of Tuberculosis in human is Mycobacterium tuberculosis. It is a rod shaped, non spore forming thin aerobic bacterium, measuring 0.5 µm to 3 µm. they are often neutral on gram's staining .However, once stained, the bacilli cannot be decolorized by acid alcohol. Acid fastness is due to high content of mycolic acids, long chain cross linked fatty acids, and other cell wall lipids.

Mode of transmission

M.Tuberculosis most commonly transmitted from a patient with infectious pulmonary Tuberculosis to other persons by droplet nuclei, which are aerosolized by coughing, sneezing or speaking. The tiny droplets dry rapidly. The smallest (<10µm in diameter) may remain suspended in the air for several hours and may gain direct access to the terminal air passages when inhaled.

Determinants of transmission of infection from exposure

Depends on

- Intimacy and duration of that contact.
- The degree of infectiousness of the case.
- The shared environment of the contact, such as over crowding in poor

ventilated rooms.

- Cases with sputum AFB positive by microscopy are highly infectious.

Determination of development of disease from infections

Depends on:

- Endogenous factors, such as individual innate susceptibility to disease and level of functions of cell mediated immunity.
- Age is an important determinant of the risk of disease after infectious. Among infected persons, the highest during late adolescence and early adulthood. The incidence of women peaks at 25 to 34 years of age. The risk may increase in elderly, because of waning immunity and co-morbidity.
- The presence of HIV co-morbidity.

Pathogenesis and immunity

About 2 to 4 weeks after infection, two host responses to M.Tuberculosis develop: a tissue damaging response and a macrophage-activating response. The tissue damaging response is the result of a delayed -type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys non-activated macrophages that contain multiplying bacilli. The macrophage-activating response is a cell mediated phenomenon resulting in

the activation of macrophages that are capable of killing and digesting tubercle bacilli.

Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the form of tuberculosis that will develop subsequently. Cell mediated immunity confers partial protection against M.tuberculosis, while humoral immunity has no defined role in protection.

2 types of cells are essential. Macrophages, which directly phagocytize tubercle bacilli and T cells (mainly CD4+ lymphocytes) which induce protection through the production of lymphokines especially interferon γ (IFN- γ) alveolar macrophages secrete a number of cytokines.

- Interleukin 1 (IL-I) contributes to fever
- Interleukin (IL-6) contributes to hyperglobulinimea
- Tumor necrosis factor α (TNF α) contributes to killing of mycobacteria the formation of granulomas. Systemic effects such as fever and weight loss.

Reactive CD4+ lymphocytes produces cytokines of the TH-1 pattern and participate in MHC class II restricted killing of cells infected with M.Tuberculosis. TH I CD4+ produces IFN- γ and IL-2 and promotes cell

mediated immunity. TH-2 cells produce IL-4, IL-5, IL-10 and promote humoral immunity.

CLINICAL MANIFESTATIONS

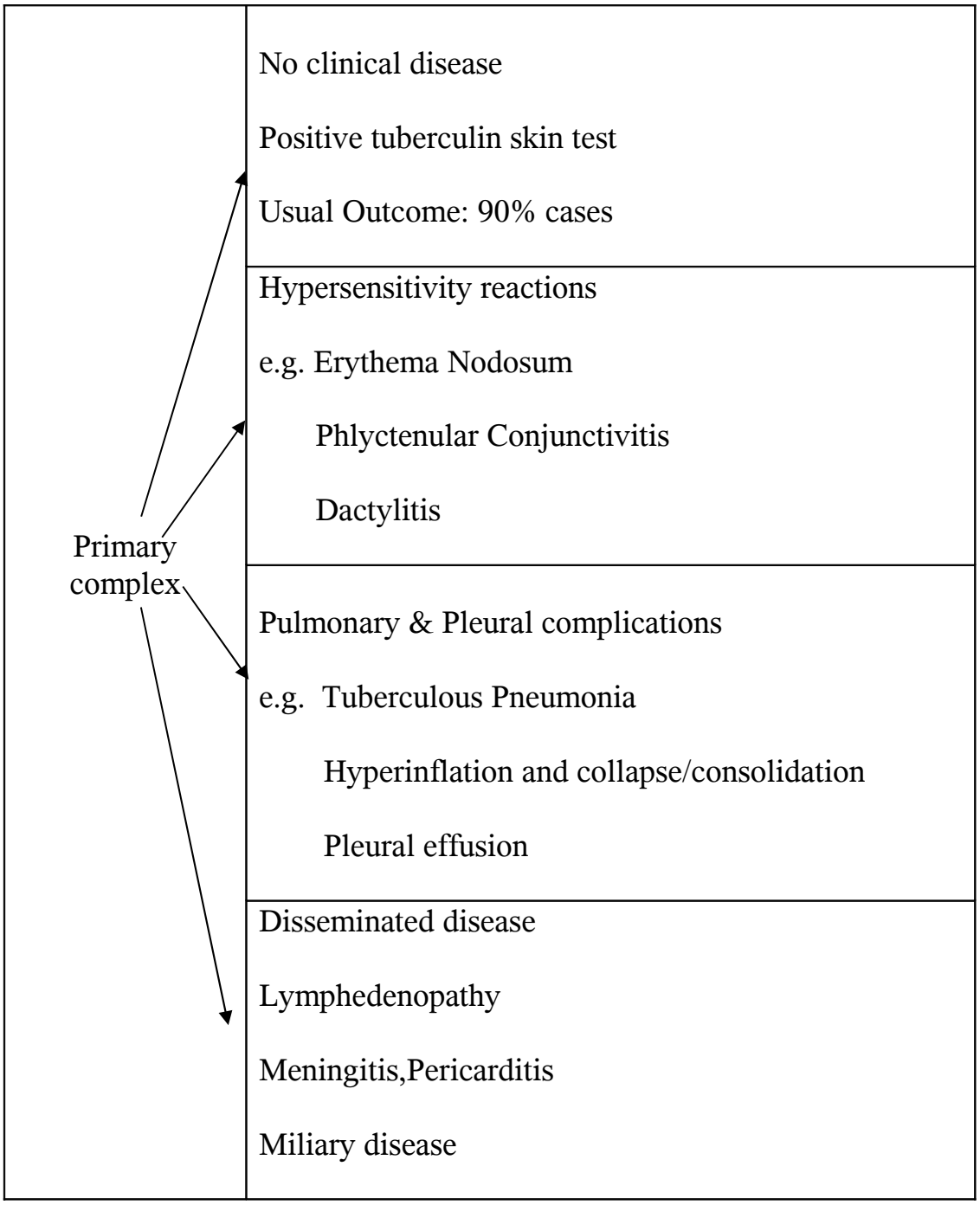
Tuberculosis is classified as pulmonary or extra-pulmonary. Before the recognition of HIV infection,>80% of all cases of tuberculosis were limited to the lungs. However, up to two-thirds of HIV infected patients with tuberculosis may have both pulmonary and extrapulmonary disease and extrapulmonary disease alone. Pulmonary tuberculosis: It can be primary or post primary (secondary).

Primary disease

Droplet nuclei, which are inhaled into the lungs, lodge in the terminal alveoli of the lungs. The resulting lesion is Ghon focus. Lymphatics drain the bacilli to hilar lymphnodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. The immune response develops about 4 to 6 weeks after primary infection.

The size of infecting dose of bacilli and the strength of immune response determine subsequent course. In most cases the immune response stops the multiplication of bacilli. However a few dormant bacilli persist. If the immune response is not strong enough to prevent multiplication bacilli, the disease occurs within a few months.

Outcome of primary infection:



Post primary Tuberculosis

- Post primary also called adult type, reactivation or secondary tuberculosis
- Due to endogenous reactivation of latent infection.
- Usually localized to the apical and posterior segments of upper lobes, where the high oxygen concentration favor myco bacterial growth Superior segments of the lower lobe also frequently affected.
- May present as cavities, upper lobe infiltrates, fibrosis, progressive pneumonia, endobronchial TB.

Symptoms and signs

General symptoms are like fever, night sweats, weight loss, anorexia, malaise and general weakness. Respiratory symptoms are cough, purulent sputum, hemoptysis, dysnoea pleuritic chest pain and wheeze.

Physical findings are of limited value in pulmonary tuberculosis. Crepitations are present and persist during inspiration especially after coughing, rhonchi due to partial obstruction of bronchi, and amphoric breath sounds in cases with large cavities in the lung.

Systemic features include fever (low grade and intermittent) and wasting pallor and clubbing may occur in chronic tuberculosis. Anemea and

leukocytosis can occur. Hyponatremia due to the syndrome of innappropriate anti diuretic hormone (SIADH) can occur.

Extra pulmonary Tuberculosis

In the order of frequency, sites to be involved are lymphnodes, pleura, genitourinary tract, bone and joints, meninges, peritoneum, and pericardium. As a result of heamatogenous spread extrapulmonary TB is seen more commonly today.

Tuberculosis lymphadenitis

It is the most common presentation of extra pulmonary tuberculosis in HIV infected patients. Most commonly cervical and supraclavicular sites are involved. Diagnosed by fine needle aspiration cytology or surgical biopsy. AFB are seen in 50% of cases, cultures are positive in 70 to 80% and histologic examination shows granulomatous lesion. Among HIV infected patients, granulomatous disease is usually not seen.

Miliary or disseminated tuberculosis

- Due to heamatogenous spread of TB bacilli.
- In children it is due to recent primary infections.
- In adults due to the recent infection or reactivation of old dormant foci.
- Lesions are 1-2 mm in diameter resemble millet seeds Physical

findings include hepatosplenomegely, lymphadenopathy, eye-choroid tubercle seen upto 30% case. Meningismus can occur, chest radiography shows miliary reticulonodular pattern, other findings include large interstitial infiltrates and pleural effusion.

DIAGNOSIS

1. AFB Microscopy

Samples are sputum, tissue, urine, gastric lavage.

Sputum microscopy[27] - three specimens are currently recommended by WHO for ruling out pulmonary tuberculosis. The rationale behind this recommendation is that some patients shed mycobacteria irregularly and in small numbers; thus increasing the number of specimens would increase the yield. The chance of missing positive cases on smear is reduced if more than one specimen is examined; the first spot specimen has a case yield of 86 to 90%. The second sputum sample examination takes the yield to over 98%. The overall yield for smears is superior with multiple specimens than with a single specimen[28].

2. Microbacterial culture - Using (Lowenstein-Jensen or Middlebrook 7H10) and incubated at 37 c under 5% co2. Bacilli grow slowlyand requires 4-8 weeks. Rapid diagnosis is possible within 2 to 6 days by Bactec method using radio metric culture system.

3. Chest x-ray

A characteristic feature which favors the diagnosis of TB[29] is

- Opacities mainly the upper zone.
- Patchy or nodular opacities.
- Cavitating lesions.
- Presence of calcification.

Normal chest film, although not completely, not exclude pulmonary tuberculosis.

4. PPD skin testing

It is widely used in screening for M.Tuberculosis. Limited value in active tuberculosis because of low sensitivity and specificity.

5. Nucleic acid amplification (NAA) Test[30, 31]

There are 2 direct amplification tests to detect Mycobacterium tuberculosis from clinical specimens. At this point of time it is important to note that the US FDA has only validated these tests for respiratory specimens. Approval of NAA tests on blood is still awaited.

a) DNA tests

Polymerase Chain reaction. In this test, a segment of the DNA is amplified and the finished products run on a gel to look for bands. This is a qualitative test.

A recent addition to the PCR range is the Real time PCR, which actually gives a quantitative estimation of the number of DNA copies present in the sample.

b) RNA tests

Transcription mediated amplification: It is better than DNA PCR.

These NAA test results should be interpreted with caution because of the possibilities of false positives and false negatives and the reliability of the lab performing the test.

6. Cytokine release assay-QuantiFERON-TB test.

It is useful for the diagnosis of latent tuberculous infection useful particularly in HIV infected patients and children.

Additional diagnostic procedures

- sputum induction by ultrasonic nebulisation of hypertonic saline
- fibreoptic bronchoscopy with bronchial washings or transbronchial biopsy
- Bronchoalveolar lavage
- Invasive procedures for suspected extrapulmonary TB like CSF for TBM,pleural fluid and biopsy for pleural effusion,bone marrow and liver biopsy for miliary TB.

HIV & TB CO-INFECTION

HIV infected patients are at markedly increased risk for reactivation TB and for second episode of Tuberculosis from exogenous reinfection. The suggested mechanism of reactivation or increase in susceptibility of TB infections in HIV positive patients are due to depletion of CD4 lymphocytes and macrophages.

IMMUNE INTERACTION IN HIV AND TUBERCULOSIS[32]

The key components of the immune response in TB include T Lymphocytes and alveolar macrophages.CD4+ T Lymphocytes, especially the T-helper type 1 (Th1) subclass, are the major effector cell in cell-mediated immunity of TB or the 'policeman' responsible for controlling TB. When M. Tuberculosis reaches the lower respiratory tract, the initial defence against infection is alveolar macrophage. The organism is engulfed by the macrophage through phagocytosis. Subsequently, macrophage lymphocyte interaction involves Th-1 and natural killer lymphocytes that secrete IFN-alpha in response to mycobacterial antigens, which activates alveolar macrophage to produce a variety of mediators including reactive oxygen and nitrogen species that are involved in growth inhibition and killing of mycobacteria. These cellular interactions are mediated by Th-1 cytokines.

Macrophages can also secrete interleukin (IL)-12,another Th-1 cytokine, in a positive feedback loop to amplify this process.

In HIV, CD4+ T cell depletion removes policeman of TB control in the lung resulting in dissemination of Mycobacterium tuberculosis. Consequently, disseminated tuberculosis (DTB) and extrapulmonary tuberculosis (EPTB) are more common. On the other hand, the activated macrophages also release proinflammatory cytokines, such as tumor necrosis factor- alfa, IL-1 and IL -6 which enhance HIV replication and thus HIV load.

The risk of death in HIV infected patients with TB was reported to be twice that in HIV infected patients without TB independently of the CD4 cell count. The higher mortality rate among patients with TB appeared to be due to progressive HIV infection rather than TB.

PATHOLOGY

A wide spectrum of histopathological changes[33] is seen in HIV infected patients with TB. However, there are three identifiable histological stages of cellular immune responses which may also correlate with the stage of HIV infection.

A. Granulomatous response

- Relatively intact cellular immune response and have typical granulomatous response.
- Epitheloid macrophage and langerhan's giant cell abundantly present.
- Number of myco bactria in lesion are reduced.
- Cluster of CD4+ T-cell around epitheloid macrophage.

B. HYPOREACTIVE RESPONSE

With progressive immune suppresion and decrease in CD4+ T-cell count,

- loss of Epitheloid macrophage and langhans giant cell.
- number of myco bactria in lesion are increased.
- necrosis in mixed suppurative and caseous lesions.

C. ANERGIC RESPONSE

In late stage of AIDS, no relative decrease in no of macrophages

- langhans giant cell are absent.
- granuloma formation absent.
- caseous necrosis is replaced suppuration, coagulative necrosis and apoptotic debris seen.
- Large no of myco bacteria are present with in macrophages.

CLINICAL PRESENTATON OF HIV –TB COINFECTION[34, 35,36]

The clinical features of Tuberculosis in HIV patients depends on whether TB occurs in early or late in the course of HIV .The presentation depends on the degree of immunosuppression. Weight loss and fever are more common in HIV positive with TB. Patients than in those who are HIV negative. Conversely, cough and hemoptysis are less common in HIV positive pulmonary TB, because there is less cavitation / inflammation and endobronchial irritation in HIV positive patients. When TB tends to occur earlier in the course HIV infection, the clinical, radiological, bacteriological findings do not defer substantially from those HIV negative patients. Thus there is predominantly pulmonary lesions located at the upper lobe and cavitation results. Tuberculin test are positive and sputum smear positivity is not reduced.

When TB occurs late in the course of HIV infection or in patients with AIDS, the features are more atypical. Pulmonary disease may occur in atypical sites such as lower zone or diffuse consolidation. Mediastinal adenopathy is more common and involvement of extra pulmonary sites such as lymphnodes, brain, pleura, pericardium, bone, GIT. In chest X-ray diffuse lower lobe reticulo nodular infiltrates and mediastinal/hilar

adenopathy are more common. Tuberculin positivity is less common.Sputum smear negative is more common.

Feature of PTB	Stage of HIV infection	
	Early	Late
Clinical picture	Often resembles,post primary PTB	Often resembles,primary PTB
Sputum smear	positive	Often negative
Chest x-ray	Often cavitating	Often infltrating,intrathoracic adenopathy,no cavitation

Diagnosis of TB in HIV infection

The diagnosis of tuberculosis in HIV infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of

- atypical radiographic findings
- a lack of classic granuloma formation in the late stages
- negative results in PPD skin tests.

Diagnostic difficulties

Patients with HIV have frequent pulmonary infection .Each time such as infection occurs , the patient must be evaluated for TB .The causes of respiratory infection in HIV which gives confusion with pulmonary TB include bacterial pnenumonia , pneumocystitis carinii , suppurative lung disease, myco bacterium avium complex, cytomegalovirus virus, fungal infections. Myco bacterium TB infection develops when the CD4+ count falls below 400/ml as compare to other infection which develop when the CD4+ falls much below 250/ml. In general, Tuberculosis develops under any CD4+ value but, if the count go below 200/ml a more atypical presentation of pulmonary TB often occurs.

MANAGEMENT OF HIV-TB CO INFECTION[36, 37]

The treatment tuberculosis and HIV Co infection presents with significant challenges due to concerns of drug-drug interactions, toxicities, added pill burden and adherence issues.

The management of TB/HIV infection should follow the same principles as for persons without HIV infection except for the use of Thiacetazone. (Thiacetazone causes severe cutaneous reactions, exfoliative dermatitis and even Steven Johnson Syndrome. Ethambutol may be used instead of thiacetazone). The regimen should consist of the standard 4 drug therapy, as per TB treatment guidelines, that is, INH, Rifampin, pyrazinamide, ethambutol or streptomycin given for 2 months followed by INH and RIF for 4 months when the organisms are sensitive to first line agents. In the event of a slow or suboptimal response, prolongation of the continuation phase to 7 months should be considered. Intermittent therapy should be avoided.

CHEMOPROPHYLAXIS

HIV infected patients, are at high risk for progressive TB and therefore after active TB, has been ruled out, it is important to give prophylaxis to patients with a PPD induration of. 5mm, previous positive PPD or those who have been in close contact with a case of pulmonary TB. This can be given as 6-12 months of daily or twice weekly INH + either rifampicin or rifabutin with comparable efficacy.

RECOMMENDATIONS[38]

- Treatment principles + for HIV +ve and HIV –ve individuals remain the same.
- Patients of active TB require immediate treatment.
- In ART naïve patients, wait for 4-8 weeks after starting AKT and then begin antiretroviral treatment. This aids the clinician in better judgment of side effects and paradoxical reactions.
- EFV based regimens should be preferred.
- Directly observed therapy is better for HIV-TB coinfected patients.
- Though the potential for drug interaction between Rifamycins and antiretroviral agents is high, rifampin should be included in the regimens with dose adjustments.
- Rifamycins may become resistant with intermittent therapy.
- There may be paradoxical reactions or immune reconstitution syndrome (IRS) during treatment with ATT the may be interpreted as clinical worsening. These will mimic worsening of the tuberculosis and are characterized by fever, new infiltrates, or increasing pleural effusion. such patients should be continued with the ATT and Antiretrovial treatment
- (ATT) along with NSAIDS and high dose Prednisone (1mg/kg * 1-2 weeks, followed by tapering doses) in severe cases.

Situation	Recommendations
Pulmonary TB and CD4+<50/cumm or extra pulmonary TB	Start Tb therapy followed by ATT soon as the patient tolerates ATT drugs. Watch for development of IRS
Pulmonary TB and CD4 50-200/cumm or total lymphocytic count<1000-1200/cumm	Start Tb therapy. Start one of these regimens as soon as patient is able to tolerate ATT and is clinically stable. Delay in starting ART may increase risk to other OIs.
PTB and CD4>200cumm or total lymphocytic count >1000-1200/cumm.	Treat TB. Monitor CD4 counts. Start ART after completion of ATT.

MATERIALS AND METHODS

Place of Study	:	Department of Medicine, KMCH
Type of Study	:	Cross sectional Study
Collaborating Department	:	Chest Clinic, ART Clinic
Duration of Study	:	January 2006 to July 2007

CASE SELECTION

INCLUSION CRITERIA

- Patients who have been diagnosed as HIV positive either by Rapid Test or ELISA and who have clinical and investigatory evidence of pulmonary TB or Extra pulmonary TB are enrolled in the study. These patients are picked up from ART Clinic.

- Those patients who sought medical attention for any form of Tuberculosis at chest clinic OP, who are HIV negative, are chosen as controls.

- Patients between the age group of 15 to 55 are enrolled in the study.

EXCLUSION CRITERIA

- Patients below the age of 15 and above the age of 55 are excluded in the study.
- HIV positive individuals who did not have clinical or investigatory evidence of any form of TB were excluded.

- Patients who had other causes of immuno suppression such as Diabetes, Lymphoma, Leukemea, visceral malignancy, malnutrition, on immuno suppressive drugs were excluded.

METHODOLOGY

CLINICAL EXAMINATION

All HIV positive patients were meticulously examined for the presence of Pulmonary and Extra pulmonary Tuberculosis. Their symptoms were analyzed in a detailed manner. Complete general examinations for presence of opportunistic infection and respiratory system and other system examination were done.

All of them were subjected to the following investigations. Basic blood investigation, sputum smear for AFB, chest x-ray PA view, PPD reactivity by mantaoux test and CD4 count. Special investigations were done in patients with extra pulmonary TB like FNAC of lymphnode, biopsy, and CSF analysis.

1. SPUTUM SMEAR FOR AFB

Done by using Ziehl Neelsen technique:

- Fix the smear on the slide
- Cover the fixed smear with carbol fuchsin for 3 minutes
- Heat, rinse with tap water and decolorize with acid alcholol for 3 -5 seconds.
- Counterstain with methylene blue for 3 – 5 seconds.
- Rinse again with tap water.
- Observe under microscope by using the oil immersion lens.

The bacilli appears as red, beeded rods, 2- 5 µm long and 0.25 – 0.5 µm wide.

Minimum of three sputum samples (2 spot + 1 early morning sample) should be examined.

Results are read as follows.

If the slide has	Results	Positive (grading)
More than 10 AFB per oil immersion field	Pos	3+
1-10 AFB per oil immersion field	Pos	2+
10-99 AFB per 100 oil immersion fields	Pos	1+
1-9 AFB per 100 oil immersion fields	scanty	Record exact figure
NO AFB in 100 oil immersion fields	Neg	-

In cases of TB Lymphadenitis, FNAC of the lymphnode was done.

2. Chest Skiagram

All patients were taken x-ray chest PA views and if necessary lateral view. Infiltrations are carefully looked and also looked for cavitation, lymphnode enlargement either in the mediastinum and/or hilar region.

3. PPD Reactivity by Mantaux

0.1 ml of purified protein derivative – 5TU injected intra dermally into the left forearm of the patients. The results are read at 48-72 hours later. In duration in the transverse axis is measured. Positive reactions indicate that the patients had been exposed to TB bacilli. In duration of more than 5 mm is indicative of TB infection in HIV infected patients.

4. CSF ANALYSIS

In patients who had presented with signs of meningeal irritation or altered sensorium lumbar puncture was performed under aseptic precautions. CSF was subjected to cytology and bio chemical analysis. CSF analysis favoured TB meningitis

5. CD4 count assay

Blood was collected in heparinized bottles for flow cytometry analysis. Blood was drawn in the morning and heparinized and was sent to Chennai Medical College for analysis of CD3, CD4 and CD8 counts by flow

cytometry. Flow cytometry is used in the phenotyping of T cell subsets for monitoring of HIV pts[39].

PROCEDURE

The Heparinized blood of about 100 µl of whole blood is simultaneously stained and analyzed for CD3, CD4 AND CD8 by FACS Count Cytometry using LASER[40].

RESULTS AND OBSERVATION

A total number of 60 patients of HIV +ve TB and 30 patients HIV-ve TB were enrolled in this study. All the data were fed into a computer and the results were collected using an epidemiology incorporated software.

The following test statistics were used

1) two sample t test
2) wilcoxon Rank Sum test/Mann -Whitney test
3) Chi-square test
4) Fisher -exact

DISCUSSION

TB is the most common opportunistic infection in HIV/AIDS patients [41,42,43] TB and HIV fuel each other, hence untreated HIV - TB co infection further increases the morbidity and mortality in HIV/AIDS patients. So early diagnosis is very necessary to prevent the morbidity and mortality.

This study documents the various clinical presentations of TB among HIV and non HIV patients. The x-ray presentation,sputum AFB,mantoux reactivity were analysed in both these groups . CD4 count was analysed in HIV patients and compared with radiological presentations.

The observations made in these studies that males were commonly infected when compared to females .The mean age group for male 35.95 and female 28.84 in the HIV group and mean age group for male is 33.78 and female is 27.71 in non HIV TB group.

Out of 60 cases of HIV - TB, 45 cases are pulmonary TB,15 cases are extra pulmonary TB and among 30 cases of non HIV-TB , 26 cases are pulmonary TB, 4 cases are extra pulmonary TB . There is no significant correlation. But various studies show that even in HIV/AIDS pulmonary TB

is the most common. It basically depends on the level of patients immuno suppression. When TB occurs in the earlier period of HIV infection,pulmonary TB is more common. When TB occurs late in the period HIV infection, i.e after a significantly depressed CD4 count, extra pulmonary TB is more common. Sometimes both pulmonary and extra pulmonary TB may co-exist in the same patient.

On analyzing the extra pulmonary TB ,out of 15 cases, 7 cases are TB Lymphadenitis , 5 cases are pleural effusuion, 1 is TBM,1 is GIT, 1 is bone. The various studies[44,45] also document the site of EPTB are in the same order of occurence like lymphnode, pleura ,pericardium, meninges, GIT, GUT, bone and others. Dr. Fitz Gerald, Dr. Stan et al University of Coloumbia[46] have noted these points.

On analyzing symptomatology of pulmonary TB, almost all the cardinal symptoms are present in both the groups, but fever and weight loss are the commonest presenting symptoms of HIV-TB i.e about 88% and 91 % respectively. Whereas, cough with expectoration and hemoptysis are more common in non HIV - TB group i.e about 80%. and 46%. Hemoptysis is present only in 6% present in HIV group. This symptom analysis has

significant ‘p’ value Dyspnoea, chest pain have no significant differences in presentation in both groups .The reason being cough and hemoptysis are less common in HIV group is due to less cavitation and less bronchial irritation. One study conducted by Dr. Sowmya Swaminathan, Dr. Rajasekaran, Dr. S. Sangeetha et al, TRC, Chennai also stated the same point.[47,48]

There are interesting observations on made in the x-ray chest. In HIV TB the most common x-ray presentation are mediastinal adenopathy, lower zone infiltration, combined, bilateral extensive infiltration, and millary mottling . Out of 45 cases, 16 cases are found to be mediastinal adenopathy whereas no cases of mediastinal adenopathy was found in non HIV group. The ‘P’ value is 0.00020 which is significant.

Lower zone infiltraion was 10 out of 45 patients in HIV - TB group whereas 1 case was found in non HIV-TB .The ‘P’ value is 0.03636 which is significant. Various other studies also shown this atypical presentation in high percentage. This is very much consistent with observation made by Zumla Malon and Henderson et al[49]. They have found 50 % of case are

having mediastinal adenopathy similar observation also documented by Dianev Havlir, Peter F. Branes M.D. et al.

Another interesting finding in these studies are absence of cavitaiton in HIV TB whereas 58 % are cavitating in non HIV group. The 'P' value is 0.00 which is significant. This finding was consistent with observation made by Decker CF and Lazarus A et al. mentioned in that post graduate medical journal 2000.Upper lobe cavitating lesion is not common is noted by several other authors also and including Zumla Malon and Henderson et al. [49]

There is 1 case of miliary mottling in HIV whereas no millary mottling in non HIV. The 'p' value is 0.6338 which is not significant. Dr. Sowmya Swaminathan et al TRC has noted 11 cases out of 78 HIV-TB. This incidence is quite higher than made in the study.

3 cases are normal chest x-ray in spite of sputum AFB positivity in HIV/TB group.This normal ches x-ray in HIV patient is also noted by Dianev Havlir, Peter F.Branes M.D. et al [50]. Ideally all HIV patient with normal chest x-ray should be subjected to HRCT thorax because the finding

of low density lymphnode with peripheral enhancement on a contrast CT is highly predictive of tuberclosis.

On analyzing the radiographic pattern with CD4 count, it is very well noted when the count >200 upper zone infiltration is common. When the count is <200 atypical presentation like mediastinal adenopathy, lower zone infiltration are common. This has significant 'P' value. Various studies also proved this statement.[51,52,53]

Regarding sputum AFB analysis, 13 out of 60 cases in HIV-TB, 20 out of 30 in non HIV-TB are smear positive for AFB. The 'P' value 0.00001 which is quite significant .This is consistent with observation made out by Zumla Malon and Henderson et al .The reason being less sputum smear positivity in HIV/TB is due to less cavity formation. Sputum smear negativity alone does not indicate absence of tuberculous infection. Ideally[54] these patients should be subjected to sputum culture and sensitivity. Even more this bronchoscopy, BAL, Transbronchial biopsy may be needed to prove semar positivity.

Regarding PPD reactivity by mantoux test the mean Induration in HIV-TB patients are 2.9 mm whereas non HIV-TB, mean induration are

12.8 mm. The ‘p’ value 0.00 which is quite significant . Zumla Malon and Henderson et al also insisted negative TB are more common in HIV positive individuals. Mark FitzGerald, MD and Stan Houston, MD et al observed in his study and stated the false negative tuberculosis test are more likely in a HIV infected patients and is increasingly more common with increasing immuno suppression. Kothari et al[55] stated that on induration 5mm following injection of tuberculin is taken as positive test for TB in HIV infected individuals.

On analysing CD4 count the mean CD4 count of 45 out of 60 cases of pulmonary HIV-TB is 174.2 whereas the mean CD4 15 out of 60 cases of extra pulmonary HIV-TB 114.6 .The ‘p’ value is 0.0285 which is significant. This is consistent with the observation made out of Post FA,Wood R ,Pillay GP et al[56]. in South Africa and various other authors also.

Infact Tuberculosis can develop at any CD4 count. If the CD4 count is moderately low pulmonary Tuberculosis is common. But when the CD4 count is very much lowered extra pulmonary tuberculosis is more common than pulmonary TB. Moreover atypical myco bacterial lesions and opportunistic infections are common.

CONCLUSION

1. 1.As TB is the most common opportunistic infection in all HIV positive individuals, hence all HIV patients should be screened for TB and all TB patients should be screened for HIV status.

2. Tuberculosis has multiple clinical presentations in patients with HIV infection.
3. Atypical chest x-ray findings are common in HIV-TB co infection.
4. The most common atypical presentations are mediastinal adenopathy, lower zone infiltration and miliary mottling.
5. Cavitation is rare in HIV-TB co infection.
6. When the CD4 count is more than 200, upper zone infiltration is more common. When the CD4 count less than 200 atypical x-ray findings are common.
7. Sputum smear negativity is more common,hence sputum culture is essential as a screening procedure .
8. Mantoux test often is false negative in HIV-TB co infection.
9. Lymphnodes, meninges and pleura are the common sites of extra pulmonary TB involvement.

10. Tuberculosis can occur at any level of depletions of CD4 count but when the CD4 count level is grossly low extra pulmonary TB is more common.

Since TB-HIV fuel each other, early diagnosis and proper effective management are essential to reduce the morbidity and mortality.

A STUDY ON THE CLINICAL PRESENTATION OF

PROFORMA

Name

Socioeconomic Status

Age

Height

Sex

Weight

Address

Hospital No

HISTORY

	Yes	No
Constitutional Symptoms		
Cough with Expectoration		
Fever		
Loss of Weight		
Hemoptysis		
Chest Pain		
Breathlessness		
Others (if any)		

Past History of Tuberculosis	Yes	No

Family History of Tuberculosis	Yes	No

General Examination

Examination of Respiratory System

Inspection	Palpation	Percussion	Auscultation

Clinical Diagnosis:

INVESTIGATIONS

Sputum AFB

Positive	Negative

Chest X-Ray

Upper Zone	Mid zone	Lower Zone	Extensive

Unilateral	Bilateral

Nodular	Fluffy

Mantoux Test

0-5 mm	5-10 mm	> 10 mm

A

CD 4 count

< 200	> 200

Others (if any),

ABBREVIATIONS

1. AIDS	Acquired Immuno deficiency Syndrome.
2. HIV	Human immuno deficiency Virus.
3. PTB	Pulmonary Tuberculosis.
4. EPTB	Extra Pulmonary Tuberculosis
5. CD4	Cluster of differentiation
6. DNA	Deoxy Ribonucleic Acid
7. RNA	Ribonucleic Acid
8. PPD	Purified Protein Derivative
9. IL	Interleukin
10. IFN	Interferon
11. PCR	Polymerase chain reaction
12. ART	Anti Retroviral treatment
13. OI	Opportunistic infection
14. IRS	Immune Reconstitution Syndrome.
15. HRCT	High Resoultion computerized Tomogram.
16. BAL	Bronchoalveolar Lavage.
17. AFB	Acid Fast Bacilli
18. FNAC	Fine needle aspiration cytology
19. MHC	Major histo compatability complex

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