SPECTRUM OF TUBERCULOSIS IN HIV PATIENTS AND ITS CO-RELATION TO CD4 COUNT

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CHENNAI

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CERTIFICATE

This is to certify that the dissertation titled **"SPECTRUM OF TUBERCULOSIS IN HIV PATIENTS AND ITS CO-RELATION TO CD4 COUNT"** is the bonafide original work of **Dr. BHARATH RAJ KIDAMBI** in partial fulfillment of the requirements for M.D. Branch-I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in APRIL 2016. The Period of study was from April 2015 to September 2015.

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DECLARATION

I, **Dr. BHARATH RAJ KIDAMBI** solemnly declare that dissertation titled **"SPECTRUM OF TUBERCULOSIS IN HIV PATIENTS AND ITS CO-RELATION TO CD4 COUNT"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during April 2015 to September 2015 under the guidance and supervision of my unit chief Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – APRIL 2016.**

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CONTENT

INTRODUCTION

INTRODUCTION

Tuberculosis infection is rampant in a country like India. Tuberculosis prevalence is stable, but there has been increased incidence due to increasing incidence of Human immunodeficiency virus infection. In 2004, there was an estimated 5.134 million people living with HIV/AIDS in India. The tuberculosis incidence was 1.8 million per year. In recent years, human immunodeficiency virus infection has turned out to be the most important risk factor for active tuberculosis in patients with mycobacterial tuberculosis infection.

Retroviral diseases pose a great problem to both the control programmes of both Human immunodeficiency control programmes as well as for pulmonary tuberculosis programmes. In controlling tuberculosis and HIV co infection, controlling HIV by highly active anti-retroviral therapy (HAART) will control the new incidence of tuberculosis. WHO started a campaign 3 by 5 in 2004 to make HAART available to resource limited areas.

In patients with retroviral disease and Koch's disease, the risk of developing tuberculosis is 10% per year. There is a synergistic relationship between Tuberculosis and Retroviral disease HIV.

Human immunodeficiency virus infection accelerates the progression of tuberculosis and makes it more resistant to treatment. Mycobacterium tuberculosis infection accelerates the retroviral disease progression. We shall discuss the pathogenesis of co-infection of retroviral disease with Koch's disease, its epidemiology, and clinical aspects emphasizing on the spectrum of tuberculosis with relation to degree of immunosuppression.

AIMS AND OBJECTIVES

AIMS and OBJECTIVES

I. To describe the various clinical manifestations of TB in people living with HIV and AIDS (PLHA) and to correlate it with the degree of immunosuppression.

II. To Correlate CD4 cell count and TB spread.

REVIEW OF LITERATURE

A. REVIEW OF LITERATURE

A.1 SOURCE OF LITERATURE

The literature source for review of our study was taken from published studies describing the pattern of disease spread, treatment protocols and its occurrence. Priority was given to more recent studies and older studies were used when no other data is available. Articles published in English were only used. WHO site and Medline were the main electronic data used for the review of literature.

Indian studies were given priority and global scenario was used for comparison. Studies about co-infection and drug treatment strategies employed were appraised from few articles. The aim of selecting the literature review was to fill the gaps in knowledge regarding co-infection. The main limitations were the lack of convincing studies from India regarding the present status of the coinfection with retroviral disease and pulmonary tuberculosis.

A.2 AETIOLOGY OF TUBERCULOSIS

TABLE 1
Classification of Mycobacteria That Often Cause Infections in Humans (Runyon, 1959)*

M tuberculosis complex
M tuberculosis
M bovis
M africanum
M leprae
Slow growing mycobacteria (more than 7 days)
M kansasii (photochromogens, Runyon Group I)
M marinum
M gordonae (scotochromogens, Runyon Group II)
M scrofulaceum
M avium complex (nonchromogens, Runyon Group III)
M avium
M intracellulare
M scrofulaceum
M terrae complex
M ulcerans
M xenopi
Rapidly growing mycobacteria (Runyon Group IV)
M fortuitum
M chelonae
M abscessus

**M* indicates *Mycobacterium.*
Runyon EH. Anonymous mycobacteria in pulmonary disease. Med Clin North Am. 1959;43:273-90. Taken from Griffith y Wallace.[7]

Tuberculosis was discovered by Robert Koch in the year 1895. He submitted his paper Etiology of tuberculosis to the physiological society of Berlin. Discovery of the bacilli, its acid fast nature and the

experiments with inoculation led to rapid advancements in understanding the pathogenesis of Tuberculosis[1].

Tuberculosis is caused by Mycobacterium tuberculosis complex. The complex includes M.tuberculosis, M.bovis, M.microti, M.canetti and M.africanum. M.canetti was recently discovered and it can also cause infection in human beings.

Opportunistic mycobacteria or the atypical mycobacteria includes M.avium and M.intracellulare. Atypical mycobacteria are particularly important in immunocompromised patients.

Mycobacterium tuberculosis complex are distinguished using microbiological tests. It is a slow growing organism, needs optimal temperature for its growth and it is a facultative anaerobe.

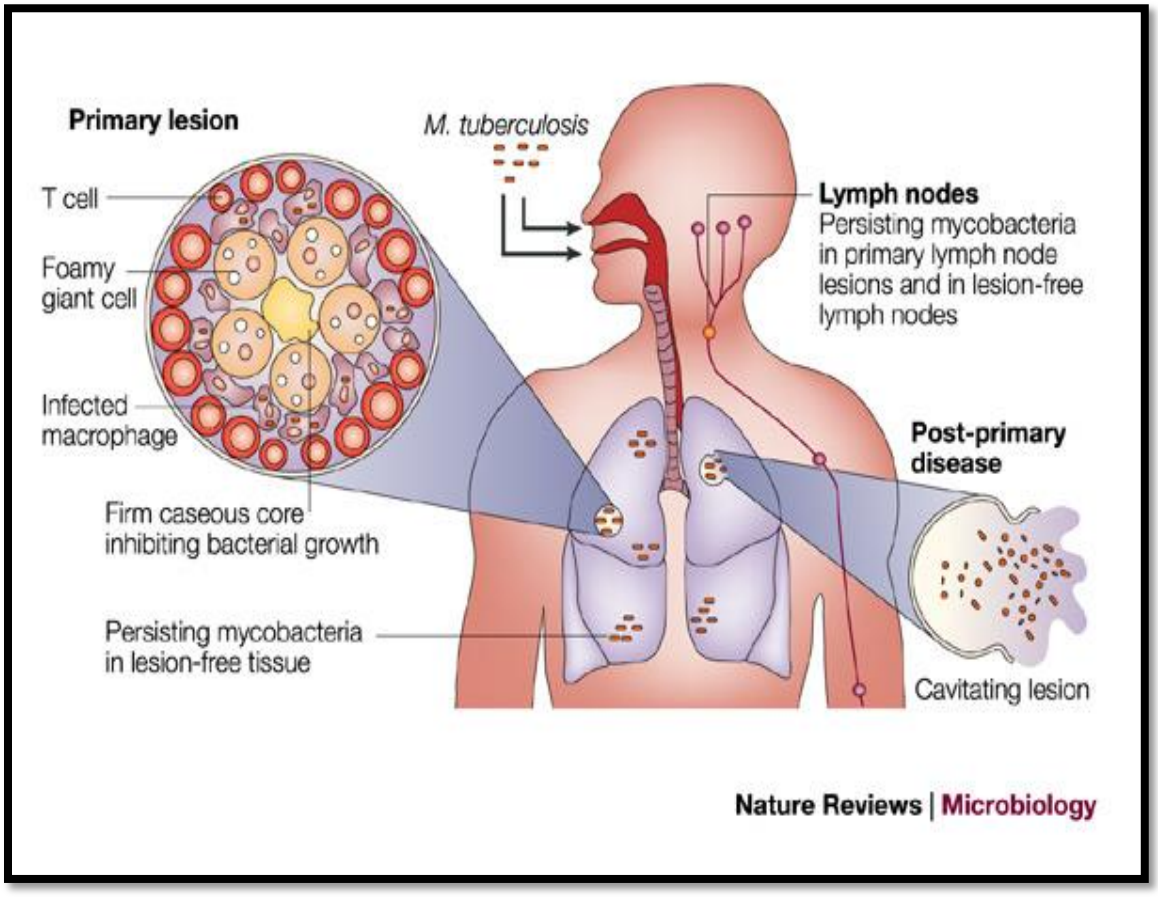
A.3 TUBERCULOSIS - PATHOGENESIS

Risk factors for acquiring tuberculosis are people from low socioeconomic status, living in crowded places, Human immunodeficiency virus infection. The sites usually involved by tuberculosis is Pulmonary and extra-pulmonary sites. The common extra-pulmonary Lymph node, bone, joints, genito-urinary, meninges and gastrointestinal system.

It is transmitted from person to person by inhalation of aerosol and droplet. The other methods of transmission are by consumption of unpasteurized milk (M.bovis) and by inoculation. Trans-placental route of transmission has been reported[2].

A.4 PRIMARY TUBERCULOSIS

The progression of clinical disease depends on the immune status of the individual.



Patient with pulmonary tuberculosis are the main source of infection to the public. The particle size of the droplet is 1-5 micrometers containing the bacilli. Usually patients who are secreting active bacilli in sputum are said to have active e pulmonary tuberculosis. The droplet size being as small as one to five micrometer can stay in the atmosphere for a longer time approximately for few hours.

In immunocompetent individual the disease pathogenesis depends on 3 factors

a) Number of M.tuberculosis organisms involved.

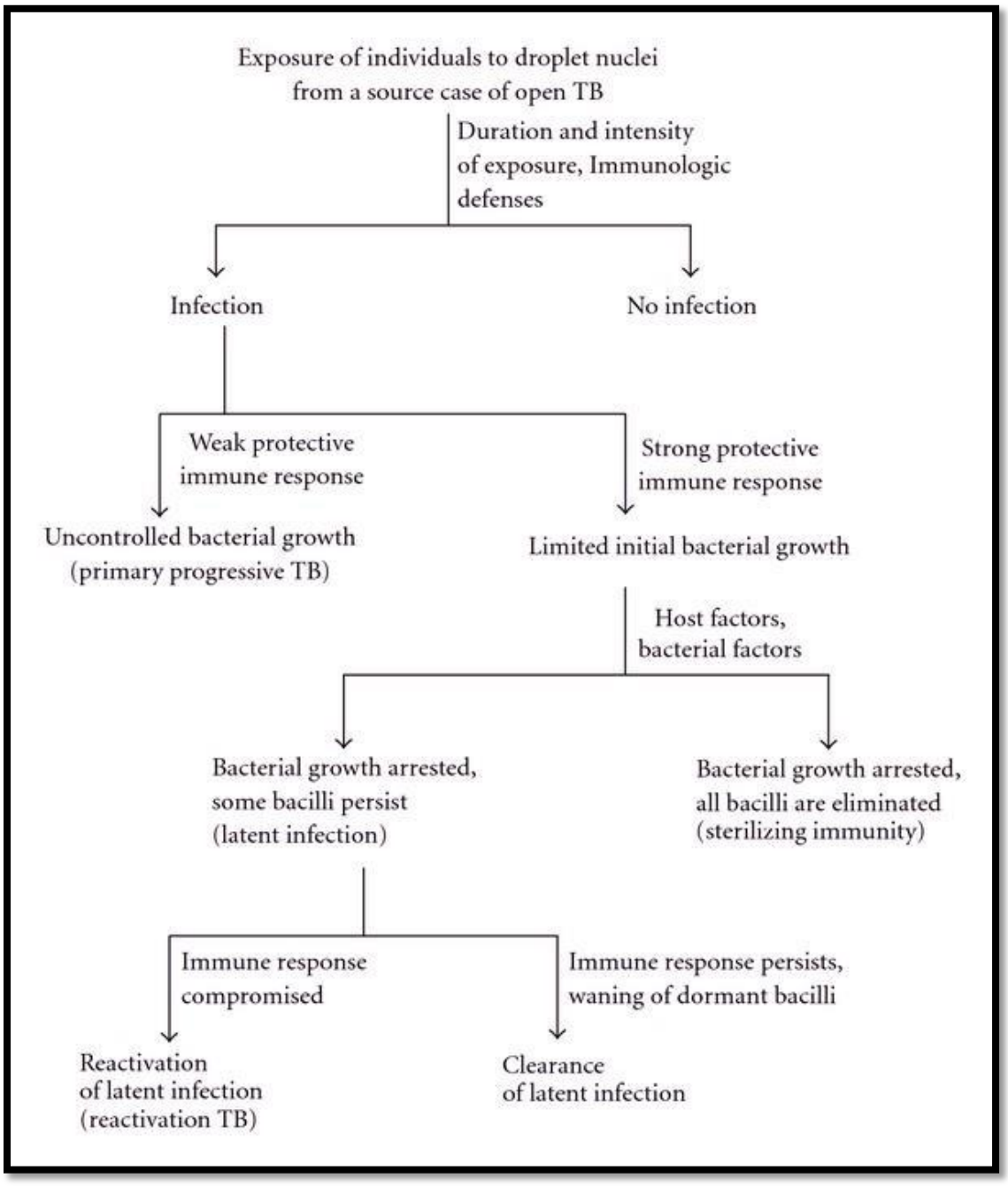
b) Infecting dose and the virulence of the organism

c) The development of cell mediated immunity

Th1 cell is the primary cell which is involved in cell mediated immunity.

Disease in immunocompetent disease naïve individual almost always begins in the lungs. Inhaled bacilli usually gets deposited in the distal airspaces in lower part of upper lobe and upper part of lower lobe .The mycobacterium bacilli is then internalized by the pulmonary alveolar macrophages. Other cell groups are also affected namely the pneumocytes. These are the epithelial cells in the alveoli. The

mycobacterium which is taken up by the phagocytes start replicating within the macrophage itself. After replication, it starts spreading to the lymph nodes. Initial lesion is called Gohn focus where there is a 1 to 1.5cm consolidation which often caesates[3].



In patients who are infected with mycobacterium tuberculosis bacilli, it usually takes few weeks for the immune response to start the response. The activated T- lymphocyte stimulates macrophages, and other immune cells which start forming granuloma's in an attempt to wall of the infection. The bacilli is not destroyed, rather contained within the granulomas. This is the proof for the existence of the term Latent Tuberculosis infection, where in the bacilli in the caeseating granulomas are not destroyed rather are dormant. They can be activated at a later stage in the event of a defect in the cell mediated immunity.

Getting into more detail, the Antigen presenting cells recognize the pathogen associated molecular patterns (PAMP) by specific pathogen recognition receptors (PRR). The host cell identifies the bacilli through different antigens[4].

1. Toll like receptors (TLR)
2. Nucleotide binding oligomerization domain like receptors (NLR)
3. C-type lectins

There are few specific molecules which are included as C-type lectins. These include mannose receptor, DC-SIGN cells (Dendritic cell- specific intercellular adhesion molecule grabbing nonintegrin and dectin-1. The non-immune cells namely, fibroblast and epithelial cell also express Toll like receptors (TLR).

The interaction between toll like receptor and the bacilli have a variety of consequences and may end up either being beneficial to the host or the pathogen.

The Toll like receptors play a very important role in the microbial host interaction. The toll like receptor 2 and 4 are key components in the internalization of mycobacterium tuberculosis. The different gene polymorphisms of the TLR are the reason for the varied response of the individual to the bacilli.

The tubercular bacilli contain few unique mixture of lipids and glycoproteins which contain very high levels of mycolic acid in its cell walls. The notable few are

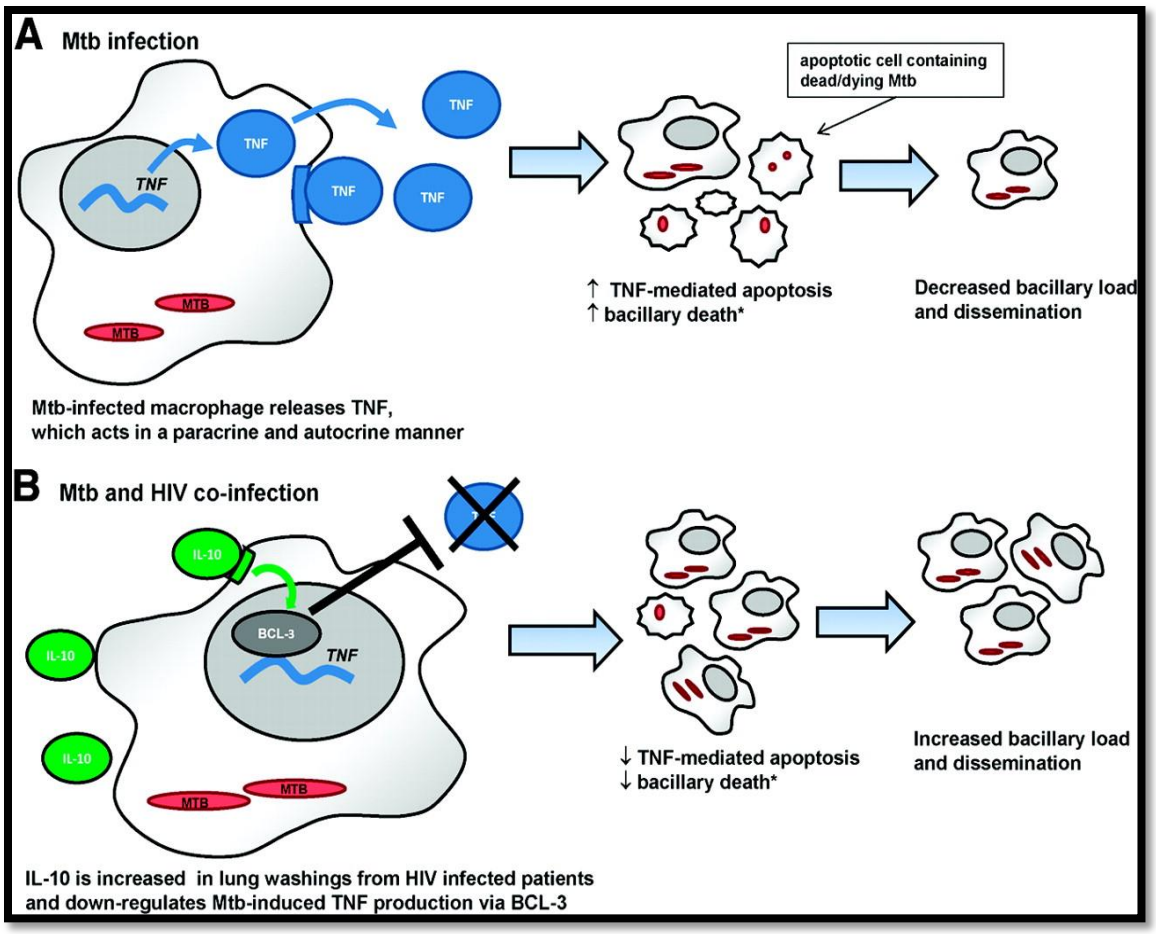
1. 19 and 27 kilo Dalton lipoproteins.
2. 38 kilo Dalton glycoprotein
3. Lipomannan

4. Mannose capped lipoarabinomannan

These result in interaction with the TLR which causes transcription and release of various cytokines which are responsible for pro inflammatory reaction[5].

The normal anti-inflammatory response mounted by the body in response to this pro inflammatory cascade is by tyrosine kinase receptor family called Tyro3/Axl/Mer (TAM).This is a TLR mediated negative feedback mechanism. Mycobacterium tuberculosis uses this to its advantage. The 19 kilo Dalton lipoprotein acts similar to TLR 2 and modulates its function. It downregulates the activation of the infected macrophage and hence evades immunity. There is insufficient presentation of antigen to the effector CD4 cells which leads to decrease in inflammatory cytokines.

On a similar note, the mannose receptor lipoarabinomannan inhibits phagolysosome formation within the macrophage hence, prevents the destruction of the bacilli within the macrophage.



All these events are taking place within the pulmonary alveolar macrophages. The bacilli trying to escape and evade the immunity and the host trying to control the infection. The Dendritic cell with the antigen travel to the lymph node and activate the CD4 and CD8 lymphocytes and prime them, the CD4 and CD8 cells then travel to the infected site, attracted by the chemokines released by the infected macrophages. There they attract macrophages and

fibroblasts, epithelial cells etc. in an attempt to control the infection by the formation of the granuloma.

Within the granuloma the CD4+ t cells secrete Gamma interferon (Y-IFN). This helps the host to wall off the infection. The bacilli are facultative anaerobes, so cannot survive with low oxygen tensions within the granuloma. However some bacilli do stay dormant within the granuloma. The central zone of the granuloma typically consists of casseous material which is made up by dead macrophage and the bacilli. The wall of the granuloma is made up by epithelial cells, macrophages and fibroblasts. The walls of the latent tuberculosis is made up of more of fibroblasts than macrophages[6].

The granuloma microenvironment is very complex. The low oxygen

Tension, increased levels of nitric oxide and carbon monoxide are involved transcription of various factors within the tubercle bacilli that help in sporulation and dormancy. The granuloma walling off effect can be clinically utilized by the delayed type hypersensitivity reaction for purified protein derivative test. This is called the tuberculin skin test.

The cells which play an active part in controlling the infection is

1. Macrophages
2. Dendritic cells
3. αβ-T cells (both CD4+ and CD8+)
4. CD1 restricted T cells
5. Natural killer cells

These cells especially CD4 cells elaborate the central key cytokine gamma interferon which activates macrophages. There has been reports of gamma interferon independent pathway also. Thus depletion of CD4 plays an important role in reactivation of tuberculosis.

The CD4 helper T cell orchestrates these immune functions through

1. Fas-FasL interaction which causes apoptosis of the infected macrophage.
2. Production of inflammatory cytokines namely IL2 and TNF alpha.
3. Helps CD8 helper cell enhancing its cytotoxic ability by increasing IL-15 levels.
4. Produces nitric oxide, whose exact role in control of TB is yet to be established.

The CD8 helper T cell plays its part during the control of infection in the latent Tuberculosis and the reactivation of tuberculosis. Its role in primary Tuberculosis is not convincingly studied. It kills the M.tuberculosis bacilli directly by releasing granulysin.

CD1 T cells and T αβ-T cells play a small role in presenting the lipids and lipopeptides to the CD4 helper T cells.

The gamma interferon produced by CD4 cells, NK cells and macrophages help in augmenting the antigen presentation to the Helper CD4 cells. It does this by transcription of more than over 200 genes which upregulate MHC class 2 expression. TNF alpha and nitric oxide production is also very important as they produce reactive nitrogen intermediates which help in killing the bacilli. They also play a role in preventing the apoptosis of memory T cells.

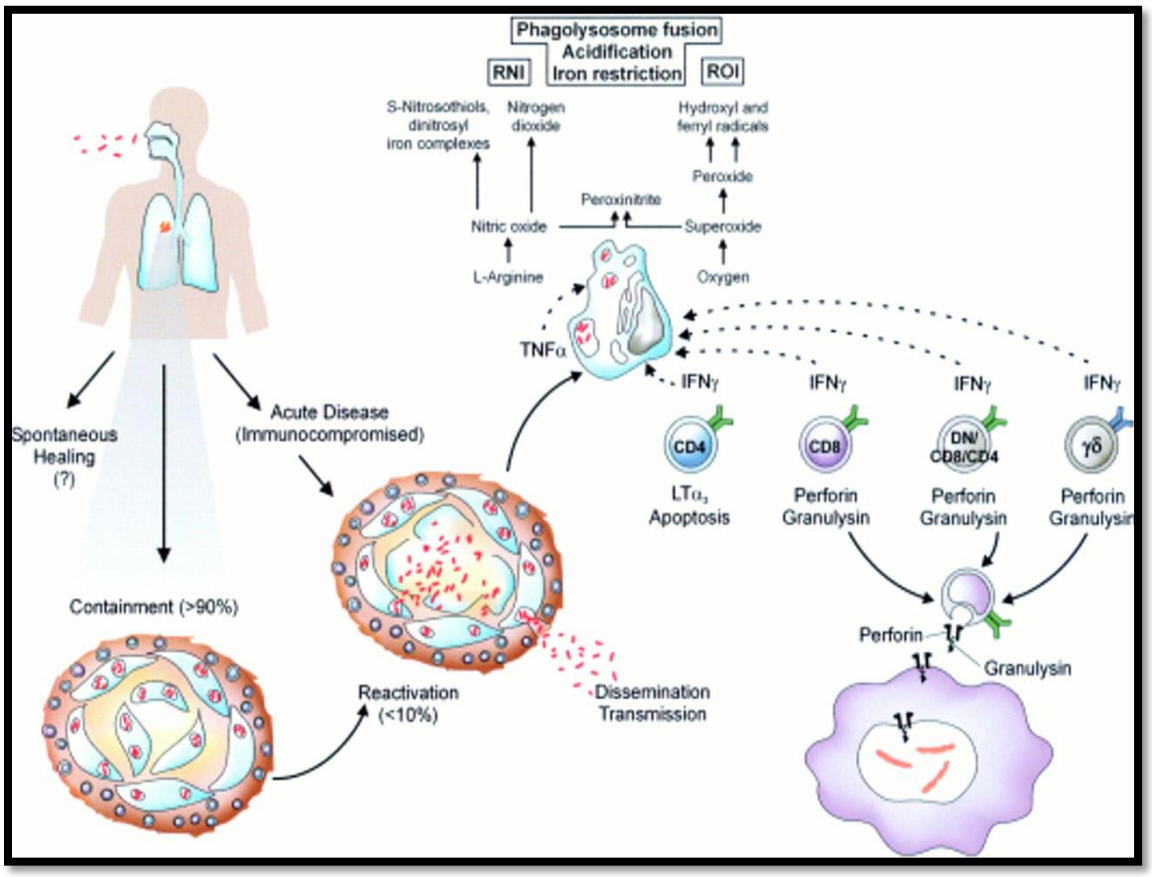
TNF or the tumour necrosis factor alpha secreted by the activated CD4 t helper cell is a cytokine which acts synergistically with gamma interferon in augmenting the response against the mycobacterium bacilli. It is an important immunomodulation. Studies show that mice deficient in tumour necrosis factor alpha or gamma interferon or IL2 do not mount satisfactory response against the mycobacterium. The

TNF alpha stimulates the secretion of cytokines like MCP and RANTES[7].

Mycobacterium counteracts these host reactions by its main method of evading immunity. It does so by inhibiting the antigen presentation to the macrophages. The mannose Lipo arabino mannan and the 19 kilo Dalton lipoprotein downregulate the gamma interferon induced genes. It also plays a role in inhibiting MHC class 1 antigen processing via Toll like receptor (TLR).By chronically downregulating the antigen processing, it makes time for itself to multiply, as it is a slow growing bacilli.

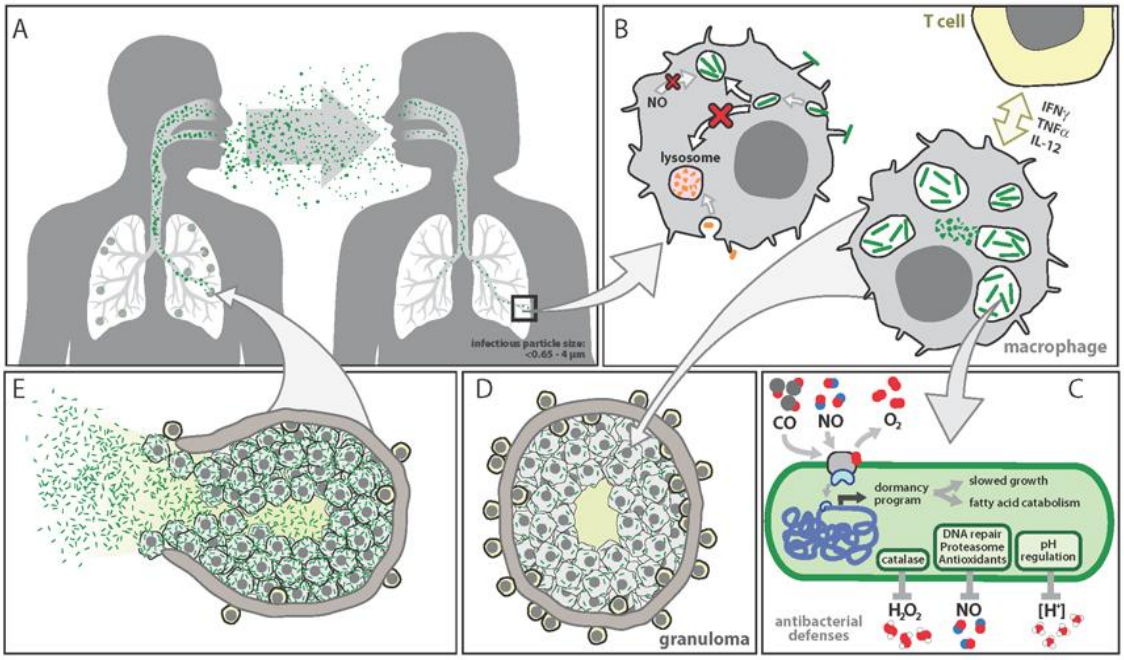
The mycobacterium bacilli counteracts the antimicrobial action of nitric oxide and reactive nitrogen intermediates by having an enzyme alkyl peroxide reductase. The T-cells and the macrophages elaborate the Nitric oxide inside granuloma's using the enzyme iNOS (Nitric oxide synthetase) this results in formation of nitrotyrosine and peroxynitrite which are toxic to the bacilli. This is all proved in studies where knockout mice for iNOS were susceptible for the reactivation of latent TB. This also proves that though Reactive nitrogen intermediates are important in controlling tuberculosis, it is not sufficient by itself.

There are exists a protein in the tubercle bacilli, a protein akin to our hemoglobin called glbN and glbO. Bacilli which lack these genes are highly susceptible to attack from RNI or the reactive nitrogen intermediates.



The formation of phagolysosome within the macrophage is essential step in the host defense for killing the bacilli. It takes place by a fission fusion event that remodels the membrane and recruitment of vacuolar proton transporting ATPase. This lowers the internal ph. which helps in killing the bacilli. Calcium plays a role in signaling

cascade. The rise in intracytosolic calcium, cascade leads to the culmination of activation of PI-3K and leads to fusion of lysosomal membrane to endosome which forms the phagolysosome.



The Mycobacterium secrete

1. Mannose lipoarabinomannan Man LAM
2. SecA2 protein
3. NADH dehydrogenase
4. Two proteins – Rv3654c and Rv3655c

These help the Mycobacterium bacilli in evading immunity, by preventing apoptosis of the infected macrophage. If not for these proteins, the infected macrophage would have been destroyed,

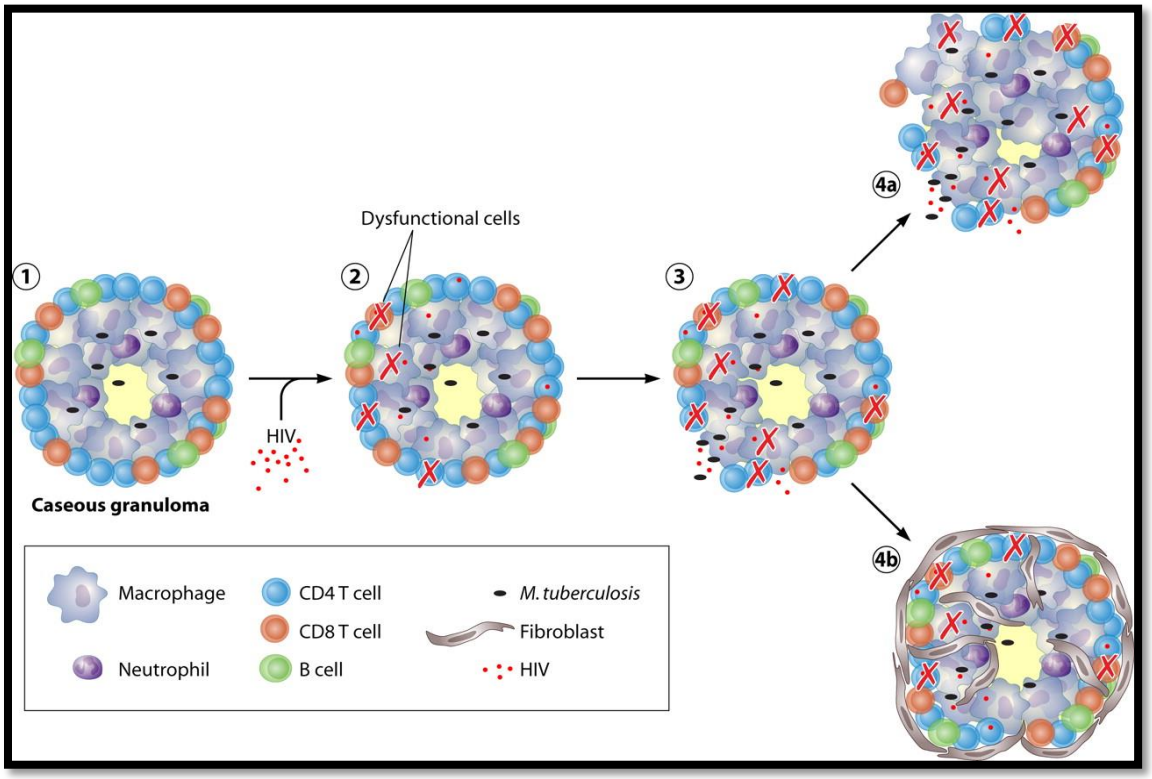
because it would have been activated to undergo apoptosis by the CD8 T Cell[8].

From the above discussions it is evident that the mycobacterium bacilli have enough tricks in its arsenal to evade the host immunity. These have been extensively studied in experiments, where either they have injected these genes from a pathogenic mycobacteria into a non-pathogenic strain or by injection knockout mice with these strains. Now after evading the immunity, it stays within the granuloma only to be reactivated at a later stage.

The process of reactivation is complex. The most important risk factor as it is already elaborated is the depletion of CD4 t cells and CD8 T cells by the HIV virus. After this is done, there are several factors which trigger the dormant TB bacilli to get reactivated once again.

The Mycobacterium produces a lot of proteins and made sure that lots of gene are there for one purpose, to ensure the survival of the bacilli within the macrophage. Weakening immune system typically due to HIV, but can also occur in other conditions namely debility, elderly individual, Post-transplant patients on immune suppression, immunomodulatory drugs, and diabetic patients.

The reactivation typically involves the upper lobes where there is a higher ventilation compared to perfusion. This supports good bacillary growth. The bacilli contain certain enzymes which are lytic transglycolases and resuscitation promoting factors and endopeptidases. These help the bacilli to get reactivated.



Latent Tuberculosis is the non-replicating bacilli within the granuloma which becomes activated under favorable conditions. They cause active tuberculosis. During the dormant phase, the bacilli stop replicating inside the granuloma due to the low pH and the hypoxic environment, much before the immune system action could start. This

is similar to the bacteriostatic culture in which mycobacterium is grown exogenously. These non-replicating bacilli are resistant to killing.

The non-replicating bacilli are taken up by the foam laden macrophages which travel along with the macrophage and enter various parts of the lung. In this process re-infection of the upper lobes fare a better chance of reactivation of the resistant bacilli because of the higher oxygen tension. The subsequent reactivation in an immunocompetent individual leads to an array of inflammatory cascade that leads to liquefaction, caseation and cavitation of the upper lobes.

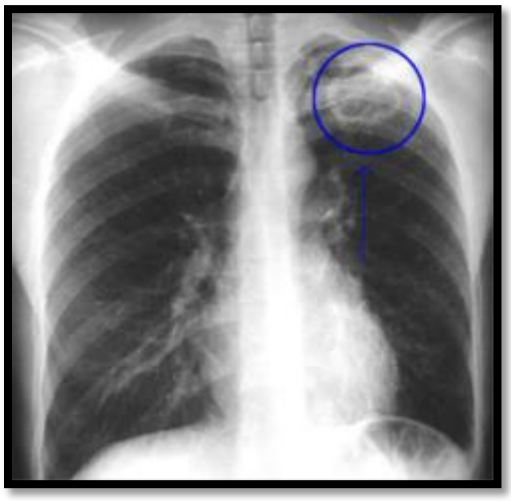
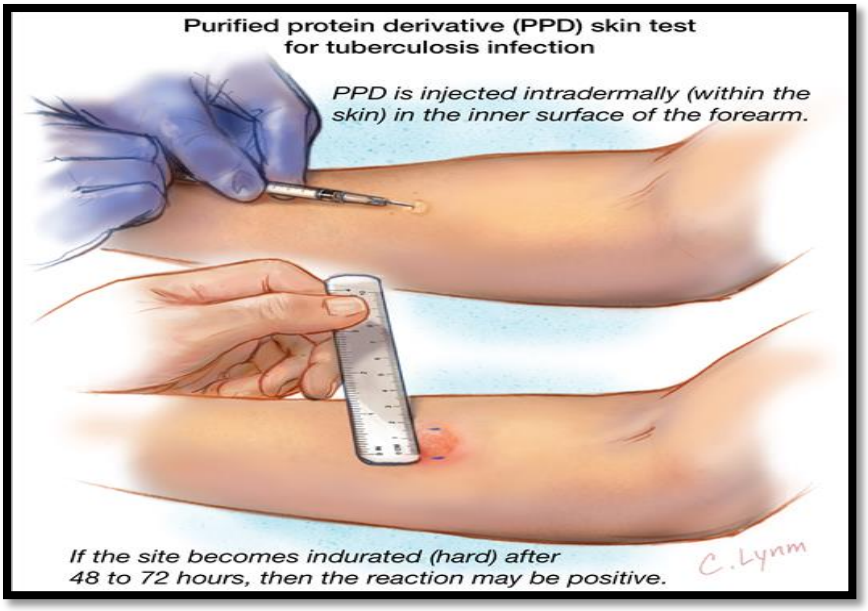


Figure: - cavitation Left Upper lobe

This is similar to the phenomenon of IRIS or the immune reconstitution inflammatory syndrome, wherein in HIV patients, the

initiation of treatment suddenly boosts the CD4 cell count and the individual is suddenly able to mount a good immune response to the previously tolerated bacillary replication which went unchecked. This is supported by the cohort analysis of the national study of tuberculosis[9].

The diagnosis of the latent tubercular bacilli is done by delayed type hypersensitivity. We inject a cocktail of antigens from the tubercle bacilli. This is known as purified protein derivative (PPD). When rechecked after 48 hours, if the induration is more than 5 mm is considered positive in HIV positive individuals. Since in Asia there are many people who are exposed to atypical mycobacteria, the induration more than 10 mm is considered positive.



More than 20 mm in duration is considered to be as having active disease. Negative test that is less than 5 mm when checked after 48-72 hours it could be due to anergy also. It might be in conditions where the CD4 helper cells are defective. BCG vaccination can cause false positive reactions.

There are better tests to diagnose latent infections. The next one which was developed was gamma interferon assay. This targeted early secreted antigenic target -6 and culture filtrate protein 10.The next technology which was developed are the flow cytometry. It requires less than one milliliter of blood for the analysis.

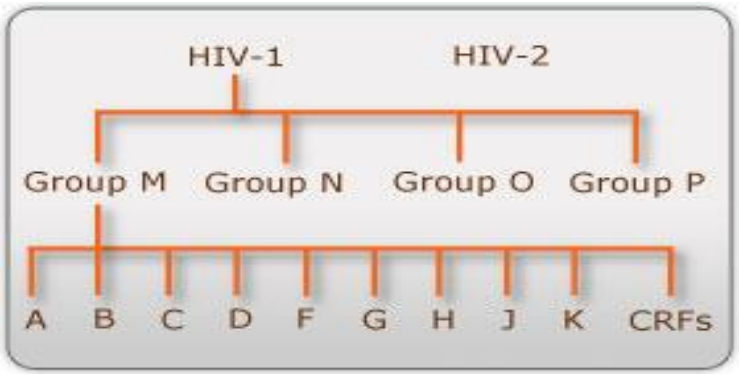
Quantiferon GOLD and SPOT TB are the two commercially based samples. They utilize the above mentioned target antigens namely ESAT6 and T cell themselves. The recent advancement in these were the Quantiferon GOLD in tube. IT also utilizes the TB 7.7 also.

Although few of these tests cannot distinguish between the active TB and the Latent TB, they are very helpful in detecting active TB in immunosuppressed individuals. They are also of more benefit to countries where Mycobacterium tuberculosis incidence is low. In countries with high endemicity, it is only of moderate value.

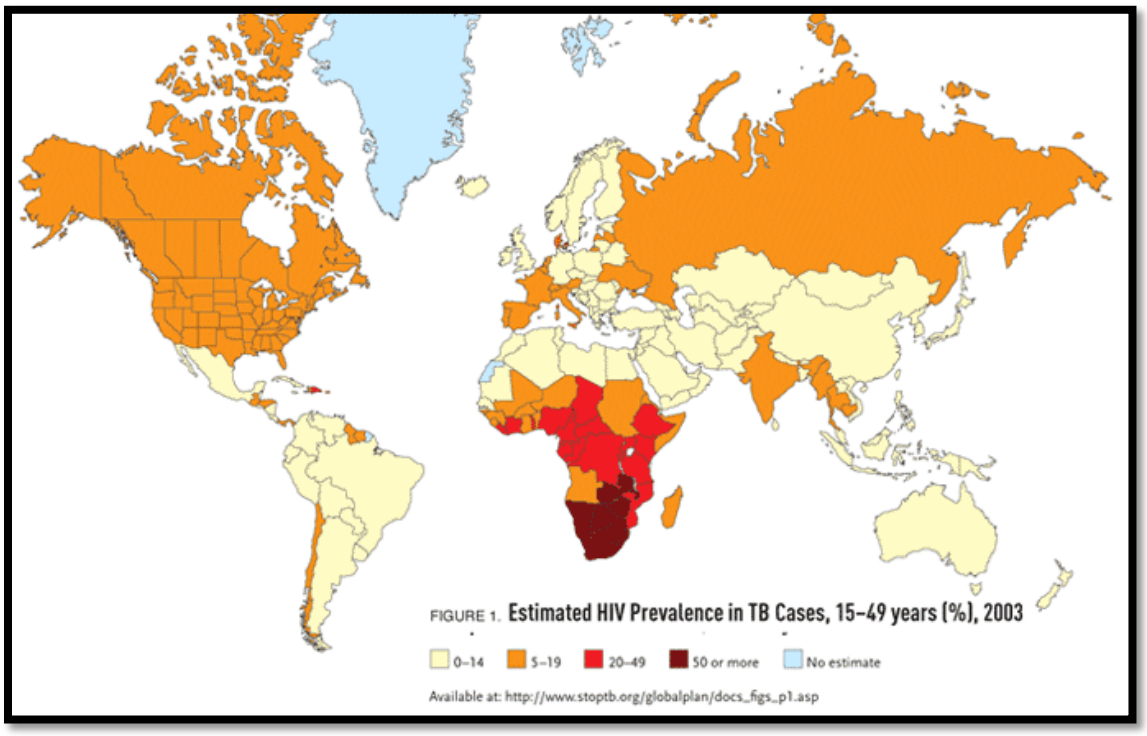
B. HIV- HUMAN IMMUNODEFICIENCY VIRUS

B.1 EPIDEMIOLOGY AND AETIOLOGY

HIV or the human immunodeficiency virus belongs to lentivirus group of retroviruses. It was discovered in early 1980's. Two types of viruses were identified and the HIV 2 was only seen in West Africa, although a spread has been reported in recent years. Around 1980 patients who had lymphadenopathy were evaluated and for the first time in Pasteur institute the T cells were cultured and the HIV infection was discovered. Phylogenetic analysis of certain earlier isolates show that HIV 1 was prevalent even before the AIDS pandemic. HIV 1 the common infectious agent is further sub classified into M, N and O. M type causes the global burden of HIV. It is further subdivided into A-D, F-H and K subgroups. HIV 2 is less virulent than HIV 1.



HIV was initially a zoonotic infection. It is very similar to simian immunodeficiency virus which should have first infected the bushman hunters. HIV type C is the commonest subtype in West Africa and India. Subtype B is common in America and Western Europe.



All these are due to the spontaneous mutation of the reverse transcriptase enzymes .Transmission of HIV 2 is very slow and attenuated. In around 2012 the global estimate of HIV was 35.3 million. Most of the prevalence comes from Sub Saharan Africa. The recently introduced HAART the highly active anti-retroviral therapy has reduced the incidence the HIV. After WHO campaign around 10

million people from low income and middle income countries had started having availability to anti-retroviral therapy .Reduction in homosexual transmission, through awareness and decrease in injection needles, recycling of injection needles saw a declining trend of HIV both in developing and developed countries. In western countries, the main transmission was through Men who have sex with men (MSM) [10].

They were given awareness of the high risk behavior, receptive anal intercourse recipients were given HAART, and the stigmata to receive care was taken care of. The number of children suffering from HIV and AIDS is huge, around 38 %. This is due to mother to child transmission, and the lower availability of HAART to children who do not seek treatment.

B.2 HIV-1 TRANSMISSION

HIV transmission occurs through

1. Sexual transmission
2. Blood and blood products
3. Vertical transmission from mother to child

TABLE 1

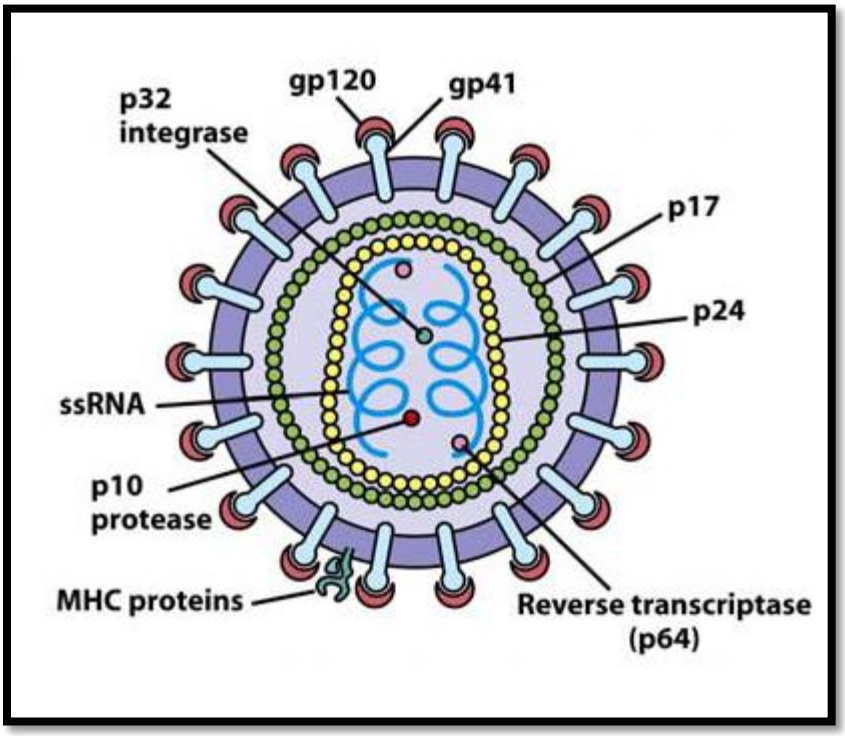
Summary of HIV transmission risk by type of non-occupational exposure

Type of exposure (from a source known to be HIV positive)	Risk of HIV transmission per exposure	Ref.
Accidental needlestick injury	0.2%-0.4%	[15]
Mucosal membrane exposure	0.1%	[26]
Receptive oral sex	From 0 to 0.04%	[27,28]
Insertive vaginal sex	≤ 0.1%	[29-32]
Insertive anal sex	≤ 0.1%	[29-32]
Receptive vaginal sex	0.01%-0.15 %	[29,31,33,34]
Receptive anal sex	≤ 3%	[28,32,34]
IDUs sharing needle	0.7%	[35]
Transfusion	90-100%	[36]

The most important determinant in risk of sexual transmission is the number of viral copies in the fluid. Risk can be minimized if the amount of viral copies can be decreased logarithmically. Acute HIV infection have very high viral loads which propagate HIV epidemic .The other problem which increase the risk of transmission is the presence of other sexually transmitted diseases. Male circumcision seems to provide effective protection against STD.

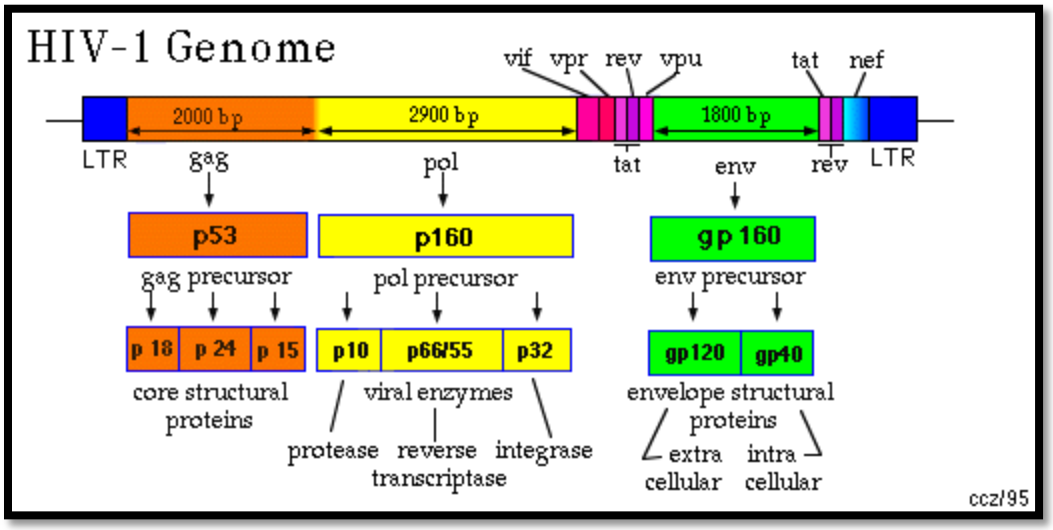
Behavioral factors like having many sexual partners also seemed to increase the risk of acquiring HIV infection. A simple measure of wearing protective contraceptives like condom can decrease the risk of transmission of HIV. Women represent 57 % of the population

living with HV. Increasing high risk behavior among women, increasing alcoholism smoking and IV drug use and the stigma to search treatment cause problems in women with HIV.



The virus has a diameter of 100-120 nanometer with a spherical morphology. It has a truncated core with a lipid core. The core contains 2 copies of single stranded RNA, along with the enzymes protease, integrase and reverse transcriptase. The viral genome is 9.2 kilo base pairs long and contains 3 structural, 2 envelope and 3 genes for enzymes. It is a single stranded positive sense RNA. Their ends are covered by polyadenylated caps which prevents it from

enzyme degradation. There is an element called tyrosine RNA which acts as a primer of viral RNA[11].



The Human immunodeficiency virus contains the genes called the regulatory genes. These help the virus to produce proteins and help the virus from infection and replication.

TAT gene – Tran's activator of transcription is a regulatory gene which is encoded by 2 different exons. It codes for a protein which is 102 Amino acid long. IT acts through TAT –receptor binding which activates viral transcription. When it is shed into circulation, there is a chance of development of antibody to this protein. It however induces apoptosis of both CD4 cells which are infected and those which are not infected. It can act as a neurotoxin, which is shown in vitro experiments.

REV gene– It is another regulatory gene which forms an essential accessory protein whose function is to transport mRNA. Rev dependent RNA transport is important for early and late phases of viral replication.

VIF gene – viral infectivity factor

It produces a 23 kilo Dalton protein found I the cytoplasm. It helps the virus to infect cells which contain CD4 receptors. The mechanism of action is less clear. The viruses with no Vif gene infect other cells at least 25 times slower than other viruses.

NEF gene – negative factor, produces a 27 kilo Dalton protein. It helps in downregulation of the receptor expression and enhances infectivity of the virus. Nef Phenotypes of the viruses are present but not understood to a large extent.

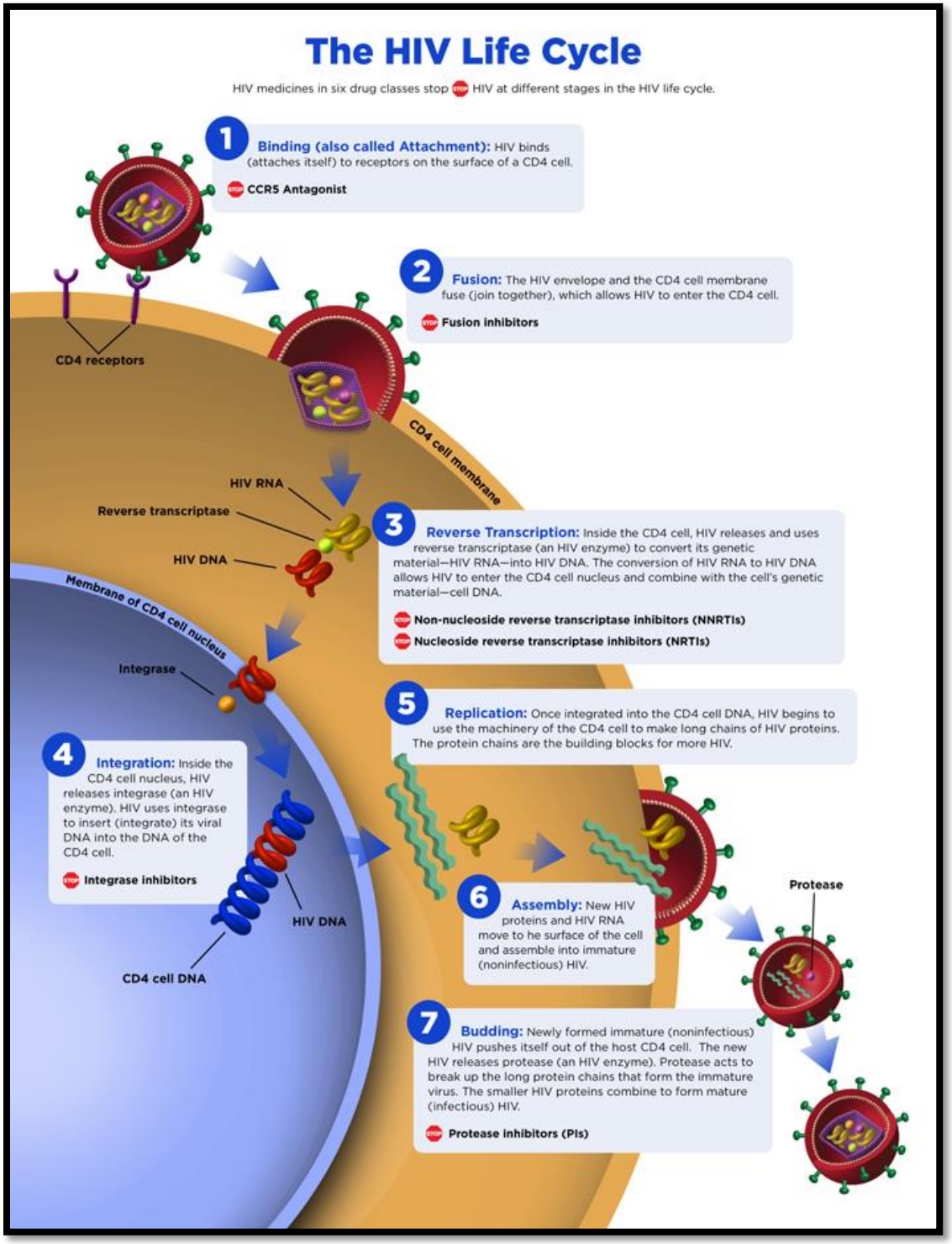
VPU gene – viral protein U, It produces a protein which is 81 amino acids long. It is a membrane protein which also encodes envelope and regulated by Rev. It helps in release of viral particles from plasma membrane of infected cell and degrades CD4 in the endoplasmic reticulum.

VPR gene – viral protein R, produces a protein which is 96 amino acids long one more protein 14 kDa responsible for G2 cell cycle arrest thought to indirectly enhance viral replication by increasing transcription from LTR. Vpr expression causes breaks in the nuclear lamin structure, which weakens nuclear envelope and interferes with DNA synthesis thus cycle arrest prior to mitosis. It is also implicated in facilitating infection of non-dividing cells, mostly macrophages. Vpr also functions to connect the pre-integration complex to the cellular nuclear import machinery[12].

B.3 PATHOGENESIS

THE NATURAL CYCLE OF HUMAN IMMUNODEFICIENCY VIRUS

HIV targets CD4 T lymphocytes, the virus entry is complex. The entry requires the CD4 cells to interact along with a chemokine receptors. There are 2 receptors CCR5 and CXCR4. Monocytes, macrophages and dendritic cells also contain these receptors. HIV entry into the astrocytes and the renal epithelial are the only cells that are HIV independent. There are 2 phases of the cycle. The first phase is the entry into the host cell. The second phase is the integration of the virus into the genome.



There are two phases in latency of the virus.

1. Pre integration latency

2. Post integration latency

Pre integration latency – there is generation of viral DNA before the integration to the host.

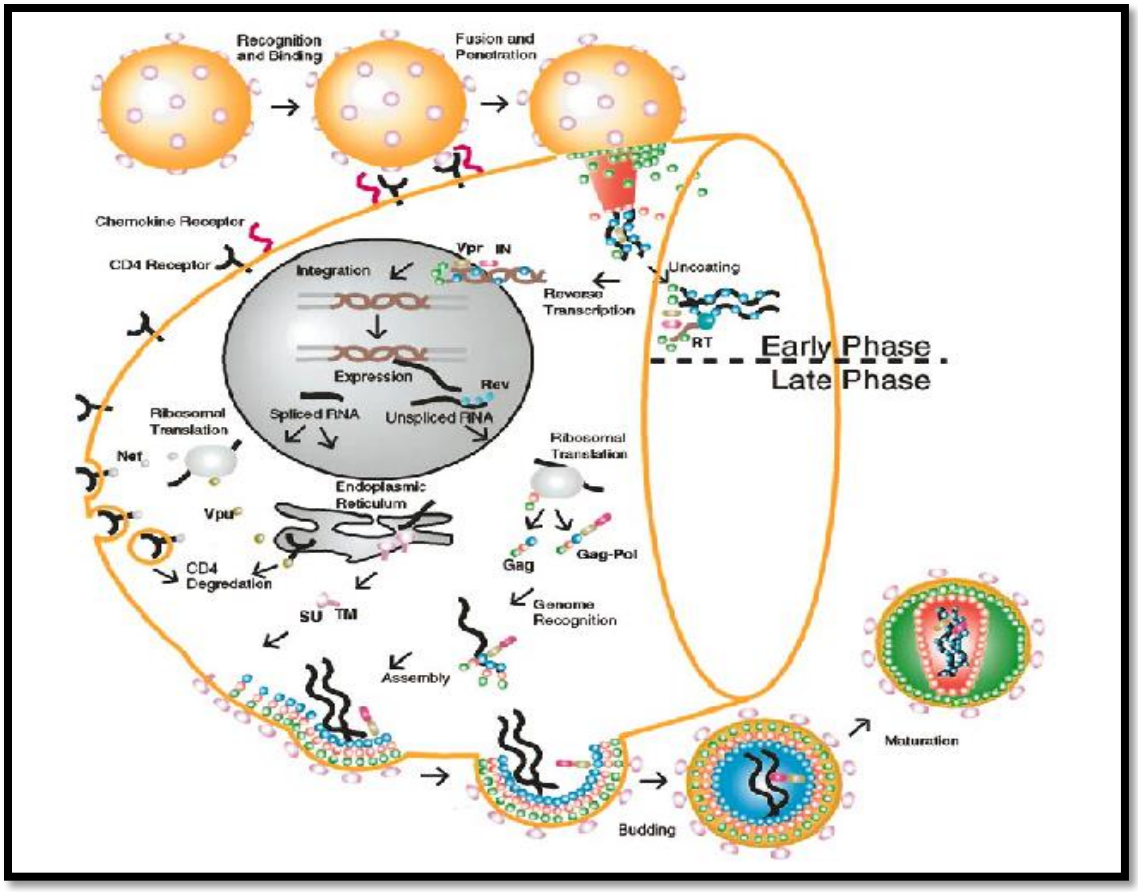
Post integration latency – refers to the lack of viral replication after the viral DNA into host genome.

Virus enters the host through the CD4 and CXCR4 and CCR5 chemokine receptors. As a result the contents of the core are released, the enzyme reverse transcriptase and integrase. Viral protein R help the virus to integrate the viral DNA into host genome by aiding the transport into the nucleus.

During the early phase of replication only the mRNA encoding the TAT REV and NEF genes are transcribed, and their proteins are sent out into the cytoplasm. The amount REV gene function translates into the amount of spliced mRNA.

The viral RNA REV complex is then transported across the nuclear membrane back and forth where it utilizes Guanosine triphosphate for its energy.

The late phase of replication involves both rev dependent and rev independent pathways. Ribosomal frameshift mechanism is involved in creating some of the gag pol precursor[13].

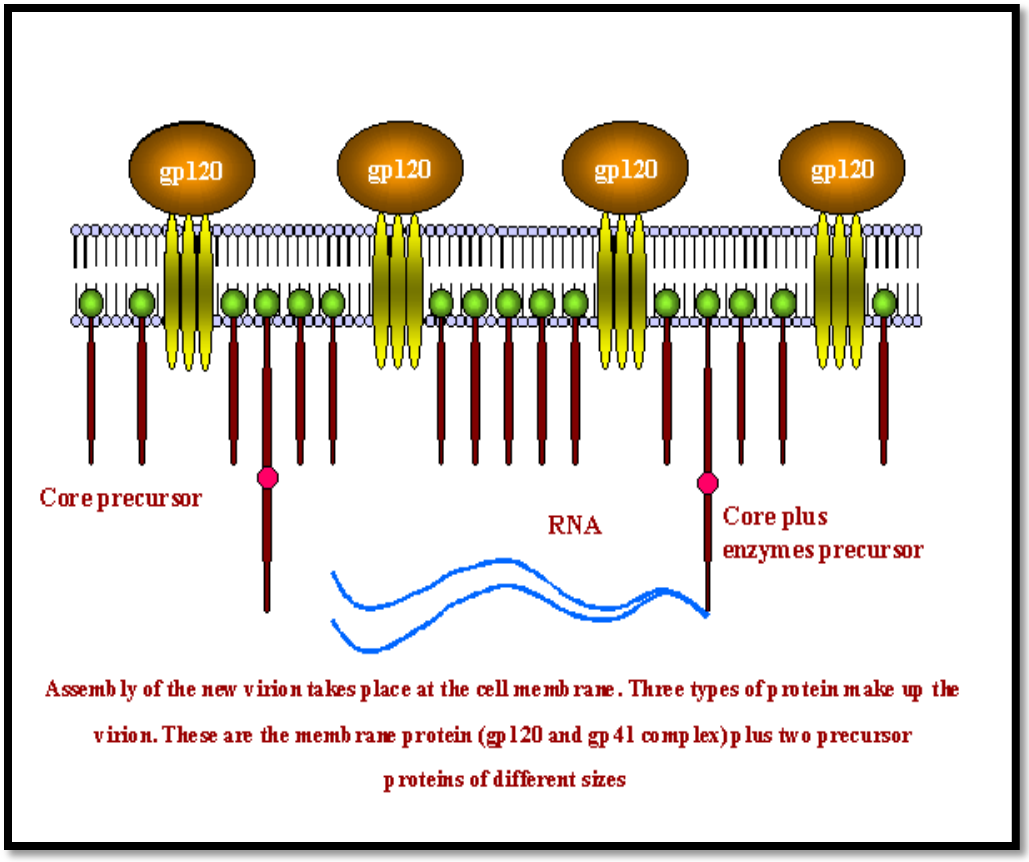


ASSEMBLY AND BUDDING

Inside the macrophages inside the cytoplasm, assembly of the virus particles takes place. The gag gene product is cleaved into matrix, capsid, nucleocapsid which associates into a virion spontaneously.

Cyclosporine inhibits the association of Virions with cyclophilin.

The envelope is formed by the gene product of ENV. Then it is cleaved into gp120 and gp41.GaG products forms the encapsidation.



Assembly of the new virion takes place at the cell membrane. Three types of protein make up the virion. These are the membrane protein (gp120 and gp41 complex) plus two precursor proteins of different sizes

REVERSE TRANSCRIPTASE ENZYME

The enzyme has no proofreading activity and accumulates mutation at a rate of $10^{4-}10^{6}$ and each time it replicates it destroys nearly 2 billion CD4 cells per day. The half-life of a free virus is 6 to 8 hours approximately[14].

B.4 CLINICAL FEATURES

The Human immunodeficiency virus can have protean manifestations, it can range from completely asymptomatic individual to completely debilitated individual. Patients can remain without any

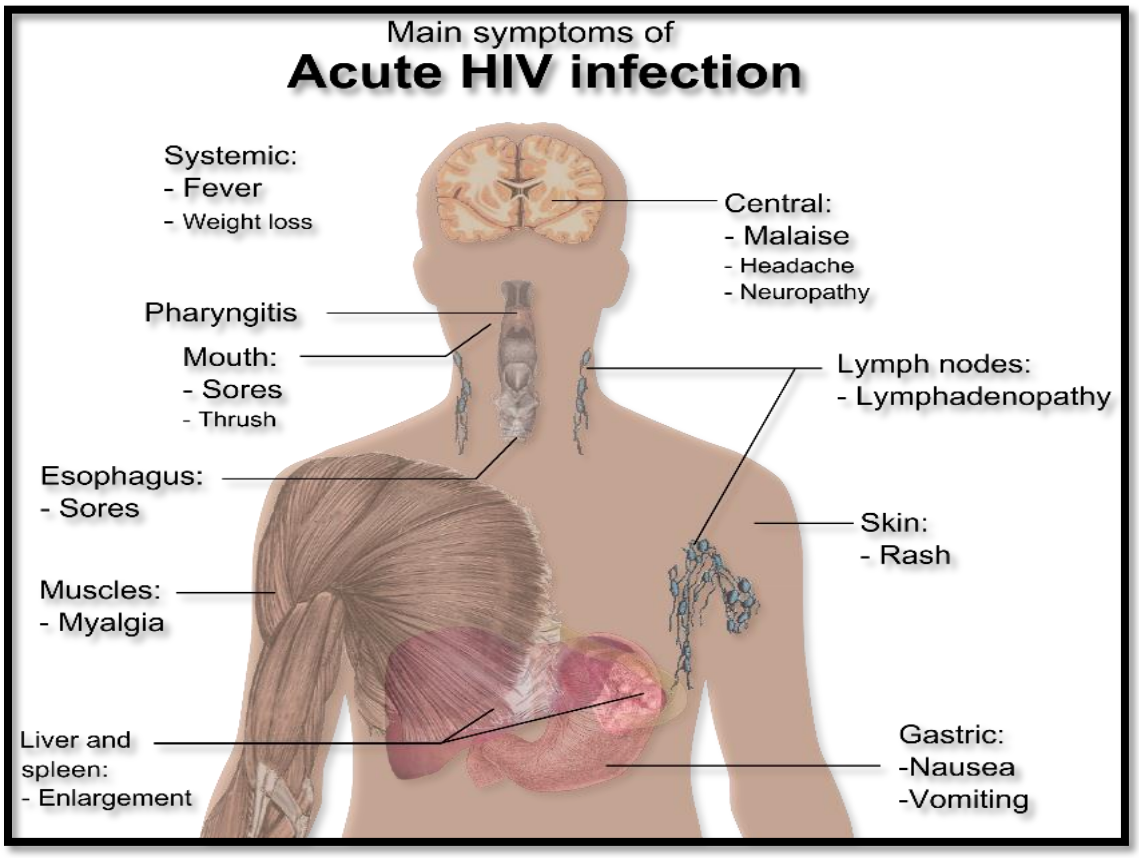
significant symptoms for about 8 to 10 years. This is because of the long incubation period of HIV. As HIV advances depleting the CD4 cells, the first manifestations may be the initial Opportunistic infections. These diseases are very uncommon in any normal or immunocompetent individual. Human immunodeficiency virus per se can cause severe debilitation and death. Opportunistic infections includes both infective and cancerous conditions. The better term to use would be opportunistic conditions. The infections seen in HIV infection are many. They can be classified as bacterial, viral, parasitic and fungal.

The frequency of opportunistic infections are dependent on the geographic conditions. Overall Tuberculosis is the commonest opportunistic infections. Other common infections seen are pneumocystis jirovecii, CNS infections which are common are Tuberculoma, tuberculous meningitis and Primary CNS lymphoma.

Visceral leishmania are common in some areas of Bihar. According to degree of immunosuppression clinical phases can be differentiated into primary, early, intermediate and advanced HIV infection.

PRIMARY HIV INFECTION

The initial presentation of HIV infection is similar to an ordinary viral infection. Fever, skin rash, headache and diarrhea. As soon as viral replication occurs, there is a drastic fall in CD4 cell count. The viral load increases rapidly and forms a set point[15].



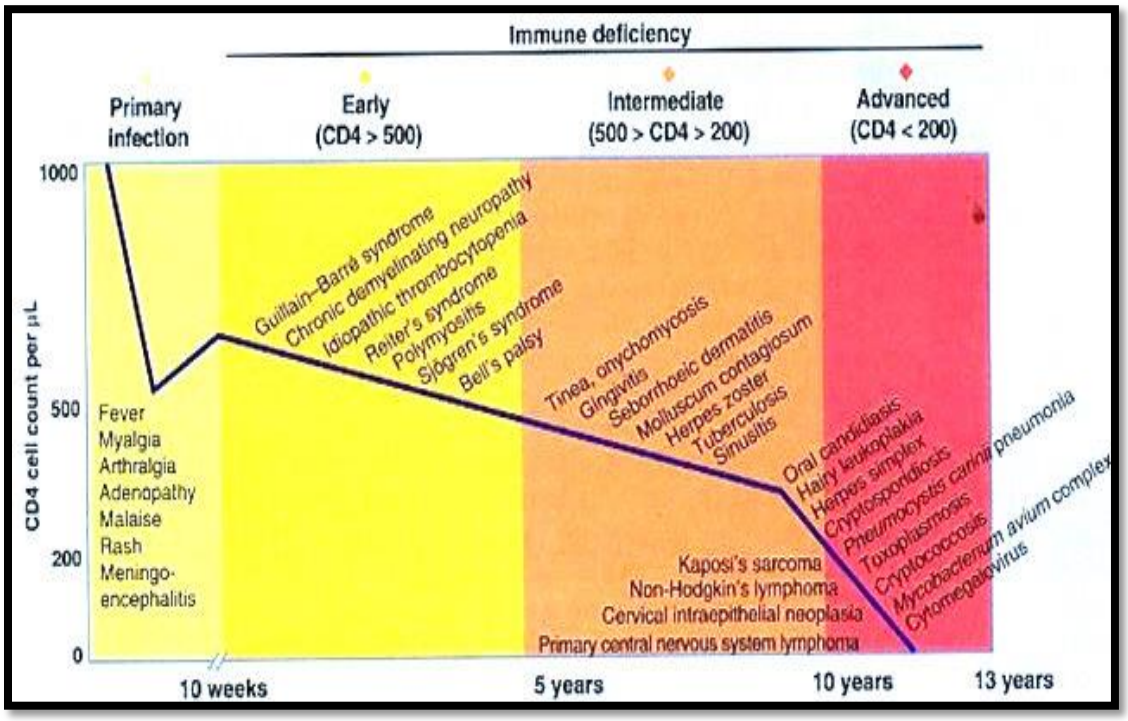
During this phase patients are extremely infectious. This is of no clinical value. Patient usually doesn't come to hospital at this stage as there is no significant clinical deterioration.

PRIMARY HIV INFECTION – COMMON CLINICAL FEATURES

General	Dermatology	CNS	GIT	Lungs
Pyrexia Sore throat Enlarged lymph nodes Joint pain Muscular pain Fatigability Loss of appetite /weight loss	Rash Itching Mucocutaneous ulceration Hair loss	Headache Kernigs sign Peripheral neuropathy Radicular pain GBS Cognitive disorders	Candidiasis Nausea/ vomiting Loose stools	Cough

EARLY IMMUNODEFICIENCY

Patients with CD4 count <500 cells/cubic millimeter are considered to be in this stage. In this stage usually more of autoimmune diseases and neurological illness have seemed to occur. Diseases like Bell's palsy, acute inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy and Bell's palsy have seemed to occur.



CD4 decline and the clinical picture

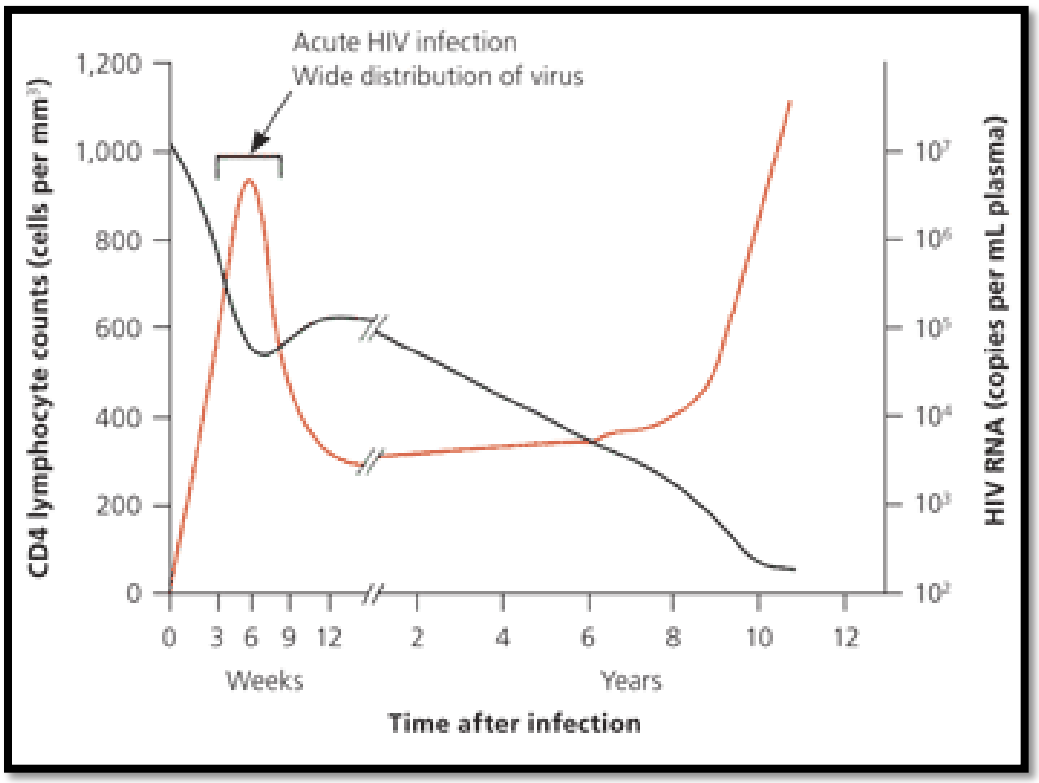
INTERMEDIATE IMMUNODEFICIENCY

Patients with CD4 count between 200 and 500 cells/cubic millimeter are considered to be in this stage. In this stage the commonest infection seen are the seborrheic dermatitis, molluscum contagiosum, herpes zoster, sinusitis, gingivitis[16].

ADVANCED IMMUNODEFICIENCY

Patients with CD4 count less than 200 cells/cubic millimeter are considered to be in this group. This gives rise to very advanced

immunodeficiency which causes some abnormal pathogens to affect the individual. Like Oral hairy leucoplakia, candidiasis, cryptococcosis, Mycobacterium avium complex.



WHO STAGING

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections

Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral condiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

WHO started large number of campaigns once AIDS pandemic started, its famous campaign is 3 by 5 among all the undertakings. The clinical staging was bought on to help the countries where CD4 testing was not available or affordable.

B.5 LABORATORY DIAGNOSIS

The laboratory diagnosis is taken from a source which is meant for the State government. It is offered to all people who approach the

centers counselling called ICTC. The center here in Madras medical college follows the national AIDS program algorithm. The first guidelines were given in 1989 for the diagnosis of HIV by the Centre of disease Control. They also started testing for HIV 2 but was not useful for our country. This was started in the year 1992. The most recent international update regarding this was started in the year 2014. The updates include tests for HIV antigens and newer antibodies. HIV nucleic acid tests are included specially. This is to prevent the people who may be in window period, in an area of high prevalence, this is very important as this percentage might contribute to a huge amount of people[17].

These are the purposes of HIV testing

1. Prophylaxis management and treatment.
2. Safe blood , blood product and organ donation
3. Effectiveness of targeted intervention assessment
4. Sentinel surveillance
5. To identify Asymptomatic individuals
6. To diagnose clinically suspected cases
7. For peace of mind of patients practicing high risk behavior.

RATIONALE

After viral infection, first antigenemia is observed. It is only after 3 to 8 weeks that patient will start developing antibodies. Antibodies of IgM and IgG are produced. The period before the production of antibody where only the antigen persists is called Window period. The first antigens to rise are the protein products of the gene Gag (namely -55 and p24). P24 levels continue to rise along with concomitant progression of the disease to AIDS. Antibodies will however persist throughout infection.

We usually check for the Ig A levels in saliva and other secretions. IgM is invaluable in contributing to the early detection after needle stick injury or during the neonatal period.

Informed consent is very important prior to all those who undergo HIV detection tests.

Similarly confidentiality is of utmost importance[18].

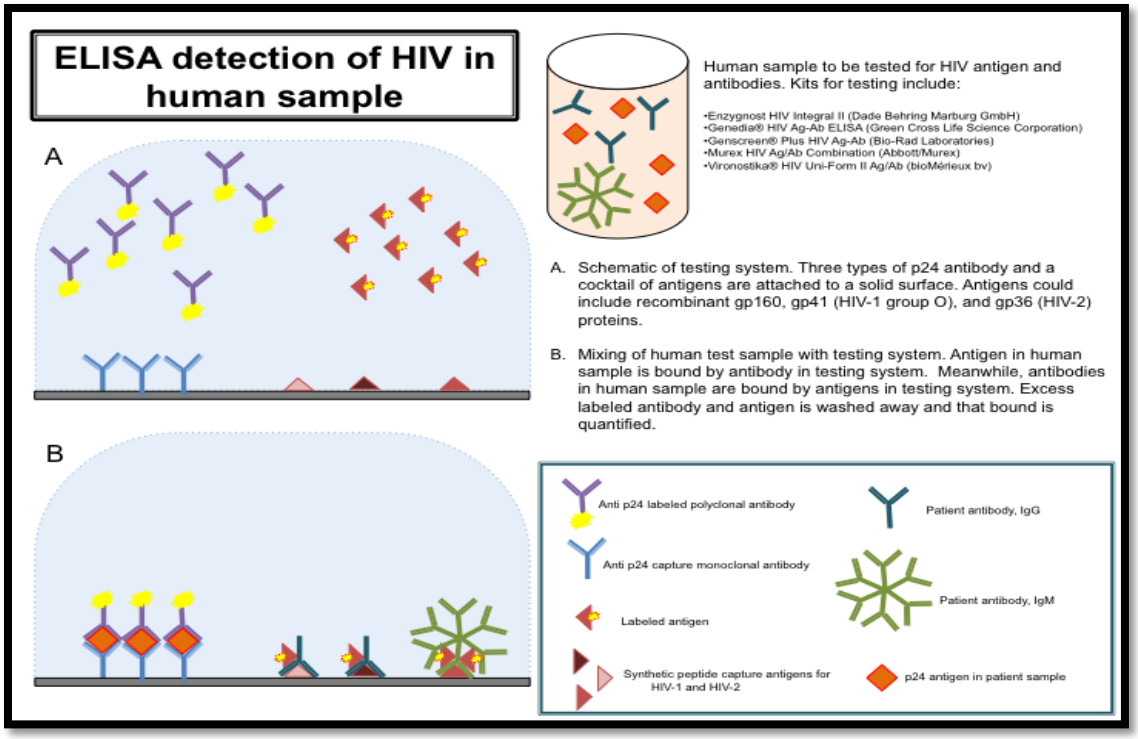
TESTS

There are 2 tests that are routinely done for detection of HIV.

1. Screening test
2. Supplemental test

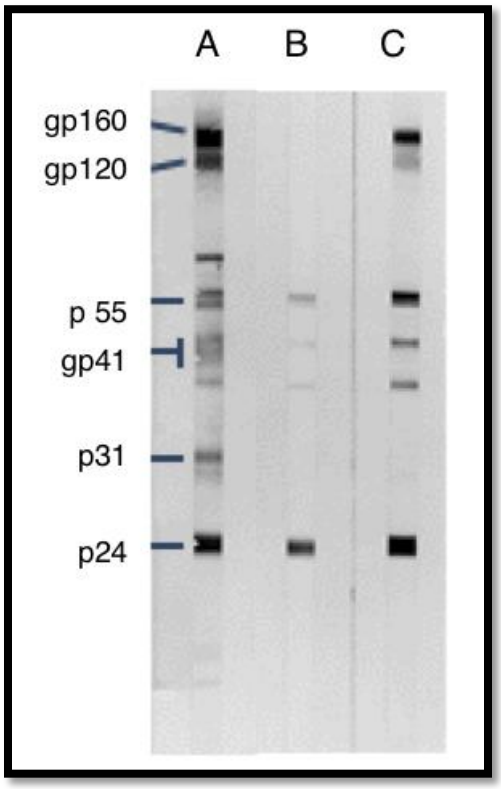
SCREENING TEST

Screening tests are used for the purpose of screening donated blood and blood product. The most commonly employed method is Enzyme linked immunosorbent assay. It is called ELISA. It is a simple screening test. It takes about two to three hours to yield the result. Simple screening test takes lesser time. These are called Rapid ELISA



SUPPLEMENTAL TEST

Supplemental tests are performed on samples which are reactive in screening tests. This is done to confirm the diagnosis of the infection in the individual. The supplementary test commonly used is called the western blot Immunofluorescence test.



The usual protocol which is followed is, if patient's serum is reactive for one screening test, another screening test with a different antigen is used. If that is also reactive, a supplementary test is used. When

choosing the ELISA kit, it has to be ensured they have antibodies against HIV 1 and HIV 2.

SPECIMEN: The usual specimen collected is the patients' blood, serum or plasma. This is the best sample. Other specimens are urine and other secretions.

ELISA TESTS

ELISA tests can be indirect, competitive, sandwich or Capture assay.

Out of these indirect ELISA is the one which has been used. In this the HIV antigen is usually bound by a covalent bond to the solid medium, and the antibodies in the patient's serum is allowed to flow through. If the immunoglobulin binds to specific substrate, it will show as a color reaction.

There are some important technical considerations when interpreting the results.

INTERPRETATION OF RESULTS

While interpreting the positive results one should always keep in mind that screening test reactivity are never used to interpret result as

positive. We should keep in mind the possibility of hemolysis, repeated freezing, thawing, bacterial contamination and temperature of the surrounding.

We should practically remember some causes of false positive results which are autoimmune diseases where there may be multiple antibodies. Multiple pregnancies, multiple transfusions, hyper gamma globulinemia, antipolysterene antibodies and Hepatitis B immunisation.[19]

False negative result that is result being negative when the HIV infection is present can occur, in window period, laboratory error.

B.6 JOINT TREATMENT FOR TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY

Ever since the first case report of HIV infection from Chennai, it has taken a rampant course throughout India. Along with the course of AIDS, there has been a resurgence of Tuberculosis. This has mandated for the two national guidelines to include each other in its program for a better control.

Approximately around 2.31 people suffer from HIV infection in India according to surveillance studies in 2009. This led to an increased risk of more than 8 times in acquiring tuberculosis in a high endemic area like India. With subsequent therapy with HAART or the highly active anti-retroviral therapy, a declining trend of the new tuberculosis case was observed, but never the less an HIV infected patient, remained at a higher risk than HIV negative individual for acquiring tuberculosis.

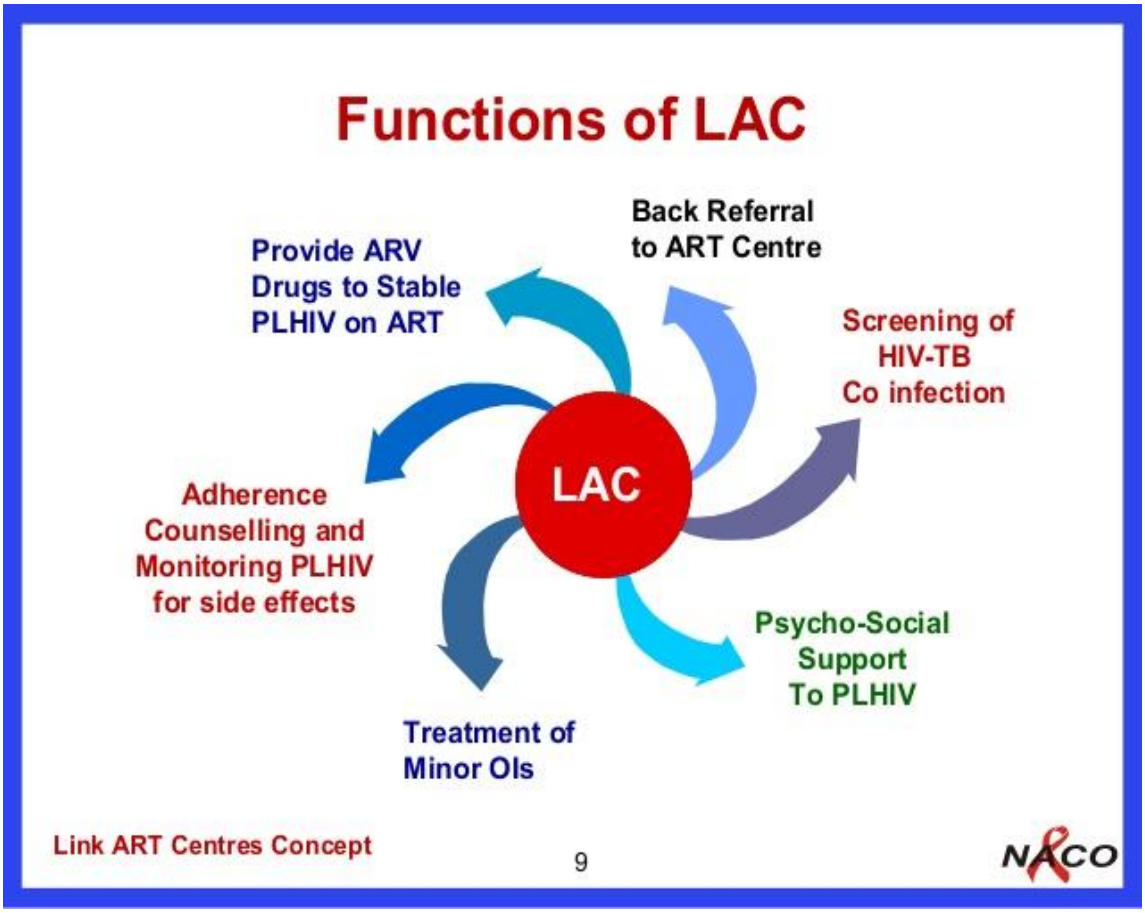
In Indian literature, the incidence of Tuberculosis in HIV is approximately 60 %.The cause of death in many cases has been attributed to a pulmonary tuberculosis sequele in a HIV positive patient. Even after effective Tuberculosis control, the control of HIV worsened and such patients went in for severe T-Cell depletion and opportunistic infections.

The strategies that were employed were, to find and effectively treat active tuberculosis. This will break the transmission cycle between active individuals and HIV positive individuals. Apart from the TB center which gives basic services to identify tuberculosis, it was started in HIV testing centers also. Therefore, Tuberculosis testing

was started in addition in ART centers, Community centers, NGO targeted intervention sites .Counsellors and clinicians were trained to give the best possible care for the HIV – TB coinfected individual.

With HIV – TB co infected individuals to the tune of 60 %, it is imperative that a new method of Tuberculosis case finding is needed. It is called intensified tuberculosis case finding. It is done in ART centers, as once a person gets HIV TB co infection, with his regular visits, he can spread TB to many HIV Positive individuals. The ART center officers are given special training to carefully recognize the TB symptoms in HIV patient and offer him proper diagnosis, treatment before he can become a source of infection and start spreading the bacilli to poor people, who have come to ART center to seek treatment.

Other centers like community based centers and link center also serve the same purpose, hence they must also be trained.



INTENSIFIED TB CASE FINDING – ART

Any HIV positive patients with symptoms of

1. Cough (both acute and chronic)
2. Hemoptysis
3. Pyrexia of unknown origin
4. Unexplained weight loss, night sweats, loss of appetite
5. Pleuritic chest pain
6. Swelling in neck, groin, armpit, and abdomen.

Patients with HIV should be under constant surveillance for TB

All these symptoms must be questioned during

a. Pre ART registration and follow up
b. ART initiation
c. Monthly visits to ART center and follow up.
d. All patient encounters at ART center

All the staff not only the medical officer are responsible for tracking the symptoms of tuberculosis in HIV positive individual. If any suspected patient is found, he is referred immediately to the medical officer for treatment.

On the same day, patient has to be tested for sputum positivity by an institutionally designated microscopy center using RNTCP lab form with an ART stamp. Chest skiagram is mandatory.[20]

The RNTCP technician, then screens the sputum and answers directly to the medical officer of ART. The ART medical officer then takes a decision, to either treat the infection directly, or to take help of the clinicians if required. It is the responsibility of the ART Medical officer to manage the opportunistic infections. If once the patient turns

out to have sputum smear positivity, then the ART medical officer would immediately try and register the patient in DOTS center[24].

SIMPLIFIED CLINICAL FEATURES IN A PATIENT WITH HIV

It is the constitutional symptoms that must first raise the suspicion in a HIV positive individual. This is true for both HIV positive and negative individual.

A HIV positive patient with constitutional symptoms is Tuberculosis unless proved otherwise.

TUBERCULOSIS CASE DEFINITIONS

SPUTUM SMEAR POSITIVE TUBERCULOSIS: - Patient with even one smear positive with radiological signs of TB

SPUTUM SMEAR NEGATIVE TB: - Patients with both the smear negative, and after 14 days antibiotic therapy, shows no response and Chest X-ray shows active Tuberculosis.

EXTRA PULMONARY TUBERCULOSIS: - It is the involvement of organs other than the lung, such as pleura, lymph node, genito urinary tract, bones and joints, and the central nervous system.

Patient with both pulmonary and extra pulmonary features will fall under pulmonary TB but his site of extra pulmonary spread will be noted.

BASIC TREATMENT REGIMENS - TUBERCULOSIS

Treatment category	Type of patients	Treatment regimens***	
		Intensive phase	Continuation phase
Category 1 (new case)	New sputum smear-positive PTB New sputum smear-negative PTB New EPTB	$2(H_3R_3Z_3E_3)$	$4(H_3R_3)$
Category 2 (retreatment)	Sputum smear-positive relapse Sputum smear-positive treatment failure Sputum smear-positive treatment after default	$2(H_3R_3Z_3E_3S_3)+1(H_3R_3Z_3E_3)$	$5(H_3R_3E_3)$
Category 4	All patients with diagnosed Multidrug resistant TB	6 (9) Km levo Eto Cs Z E	18 levoEto Cs E

PTB: Pulmonary tuberculosis, EPTB: Extra pulmonary tuberculosis, H: IsoniazidR: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin, Km: Kanamycin, Levo: Levofloxacin, Eto: Ethionamide, Cs: Cycloserine, TB: Tuberculosis. ***Prefix indicates month and subscript indicates thrice weekly

The Numbers in the chart which precede the letters refer to the months of treatment. The number in subscript which succeeds the letters refer to the doses per week. This is the strength of the ATT drugs.

1. INH referred as H – 600 mg
2. Rifampicin referred as R – 450mg
3. Pyrazinamide referred as Z – 1500mg
4. Ethambutol referred as E – 1200 mg
5. Streptomycin referred as S – 750 mg.

Table 3a: WHO recommended doses of the first-line anti-tuberculosis drugs

Drugs	Daily doses (mg/kg)	Route	Thrice weekly dosage (mg/kg/dose)
Isoniazid (H)	5 (4–6)	Oral	10 (8–12)
Rifampin (R)	10 (8–12)	Oral	10 (8–12)
Ethambutol (E)	15 (15–20)	Oral	30 (25–35)
Pyrazinamide (Z)	25 (25–30)	Oral	35 (30–40)
Streptomycin (S)	15 (12–18)	Oral	15 (12–18)

Table 3b: Recommended doses of second-line anti-TB drugs

Drugs	Daily doses (mg/kg)	Route	Maximum daily dose
Kanamycin (K)	15	IM	Up to 1 g
Amikacin (A)	15	IM	Up to 1 g
Ethionamide (Eto)	10–15	Oral	Up to 1 g
Cycloserine (Cs)	10	Oral	Up to 1 g
Para amino salicylic acid (PAS)	250	Oral	Up to 1 g
Ofloxacin (Ofx)	15–20	Oral	800–10000 mg
Levofloxacin	7.5–10	Oral	750-1000 mg
Moxifloxacin	7.5–10	Oral	400 mg

Patients who weigh less than 30 kg's should receive in pediatric doses.

Steroids are indicated in tuberculosis in cases of tuberculous meningitis, pericarditis, pleuritic, serositis, and adrenalitis.[21]

TREATMENT OF TB IN HIV PATIENTS

DOTS STRATEGY

Directly observed treatment in short course, at least during the intensive phase is the cornerstone in treatment of HIV. First of all after categorizing the HIV patient with TB into category 1 and 2, next step is to ensure DOTS. A health worker, or a trained observer

(DOTS provider) encourages, supports and supervises the patient to swallow the tablets. Receiving Anti tuberculous therapy at the right dose, at the right time and right dosage is of paramount importance. Failure to utilize DOTS, in an HIV positive individual has shown to increase case fatality rate.

PROVISION OF ATT

ATT is being provided free of cost, in color coded and patient wise boxes. There are two boxes, one for intensive phase, and one for continuation phase. If a patient is diagnosed as TB in ART center, ATT can be initiated in ART center itself. Patient will be provided the minimum weekly dose, before he can get shifted to a nearby DOTS center.

PATIENTS WHO ARE ON SECOND LINE ART

The protease inhibitors interact with rifampicin. Hence patient who are taking protease inhibitor based regimen need to be changed on a different regimen.

Rifampicin will increase the need for stepping up the dosage of protease inhibitor which will cause increased side effects.

NACO has recommended the use of Rifabutin for patients taking Lopinavir/ritonavir based ART regimens. Dose of rifabutin is 150mg thrice weekly. Side effect profile is very similar to rifampicin[23].

TREATMENT OF HIV IN HIV/ TB COHORT

The goals of therapy are

1. Prolongation of life, and improvement of QOL
2. To decrease viral load to undetectable levels
3. To increase or normalize the CD4 counts.
4. To limit drug toxicity
5. Reduce HIV transmission

BENEFITS OF ART INITIATION

It is well known, that ART initiation decreases TB incidence. HIV positive patients with CD4 counts less than 350 cells/cubic millimeter are at great risk of AIDS related death. Without ART, ATT treatment alone would not suffice. The use of HAART is essential for the decrease in viral load.[22]

Usually TB treatment with ATT is initiated as it already represents WHO clinical stage 3 or 4.

Strategy for initiation of treatment for both TB and HIV infection

CRITERIA	TB TREATMENT	ART
Extrapulmonary TB (regardless of CD4 count)	Start immediately	Start ART as soon as TB treatment is tolerated (between two weeks and two months).
Pulmonary TB (CD4 <200 cells/mm3)	Start immediately	Start ART as soon as TB treatment is tolerated (between two weeks and two months).
Pulmonary TB CD4 = 200–350 cells/mm3	Start immediately	Start ART after completion of initial TB treatment phase (start earlier if severely compromised).
Pulmonary TB CD4 >350 cells/mm3	Start immediately	Monitor CD4 count. Consider ART if CD4 cell count drops below 350 cells/mm3.

The decision to start ART should also be based on clinical evaluation of other signs of immunodeficiency.

ART treatment is guided on CD4 cell count and the category of pulmonary tuberculosis .All patients are started on ATT, then if the CD4 count is less than 350 cell/cu mm of blood, then ART is initiated as soon as ATT is tolerated. Preferably it is started after 2 weeks, before 2 months. The commonly used ART drugs can be divided into

NRTI	NNRTI	PI
Zidovudine (AZT)		Lopinavir/r (Aluvia/Kaletra)
Lamuvudine (3TC)		Saquinavir (SQV)
Didanosine (ddl)		Ritonavir (RTV)
Stavudine (d4T)	Nevirapine (NVP)	Atazanavir (ATV)
Abacavir (ABC)	Efavirenz (EFV)	Darunavir (DRV)
Tenofovir (TDF)		Nelfinavir (NFV)
Emtricitabine (FTC)		Indinavir (INV)

First Line regimen of ART in HIV TB co infected individual.

1. AZT + 3TC + (EFV) (for patients with Hemoglobin >9g/dl)

Second line alternative regimen

2. D4T + 3TC + (EFV)

In special situations TDF or tenofovir is substituted in the regimen.

Commonly used 1st line ART regimens in India

NAME OF DRUG	TRADE NAME
Zidovudine + Lamivudine + Nevirapine	Duovir-N/Zidolam N/Virocomb N
Stavudine+ Lamivudine + Nevirapine	Triomune-30/Emtri 30/Virolans 30
Zidovudine + Lamivudine + Efavirenz	Duovir + Efavir
Stavudine+ Lamivudine + Efavirenz	Lamivir-S(30)+ Efavir
Tenofovir + Lamivudine + Efavirenz	Tenolam E/Trioday/Dinmek
Tenofovir + Emtricitabine + Efavirenz	Viraday/Trustiva/Vonavir

A special note on IRIS

IRIS

This is known as immune reconstitution inflammatory syndrome. IRIS typically occurs in individuals started on ART, anywhere between 5 days to months after initiation. It usually presents as

1. Fever
2. Worsening of pre-existing lymphadenopathy
3. Rarely, tracheal compression

Therapy for serious IRIS reactions are corticosteroids.

Now we move on to the actual study.

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTINGS

The study was conducted in the Institute of Internal medicine and ART centre at Madras Medical College and Rajiv Gandhi Government General Hospital.

ETHICAL COMMITTEE APPROVAL

OBTAINED

STUDY DURATION

This study was done for a duration for a period of six months.

STUDY POPULATION

Patients admitted in medical wards with HIV TB co infection.

TYPE OF STUDY

Prospective and observational study of 100 patients

SAMPLE SIZE

100 patients recruited from Institute of Internal medicine and antiretroviral center from Rajiv Gandhi Government General Hospital Chennai.

INCLUSION CRITERIA

Patients who are HIV infected as evidenced by ELSIA and western blot Reactivity, and with clinical features and radiological features of tuberculosis.

EXCLUSION CRITERIA

Patients who are

1. HIV negative and TB
2. Patient not willing for follow up
3. Patient not willing for the study
4. Patient who are too sick and moribund
5. Those who have been diagnosed prior and have already started ATT.
6. MDR and XDR Tuberculosis.

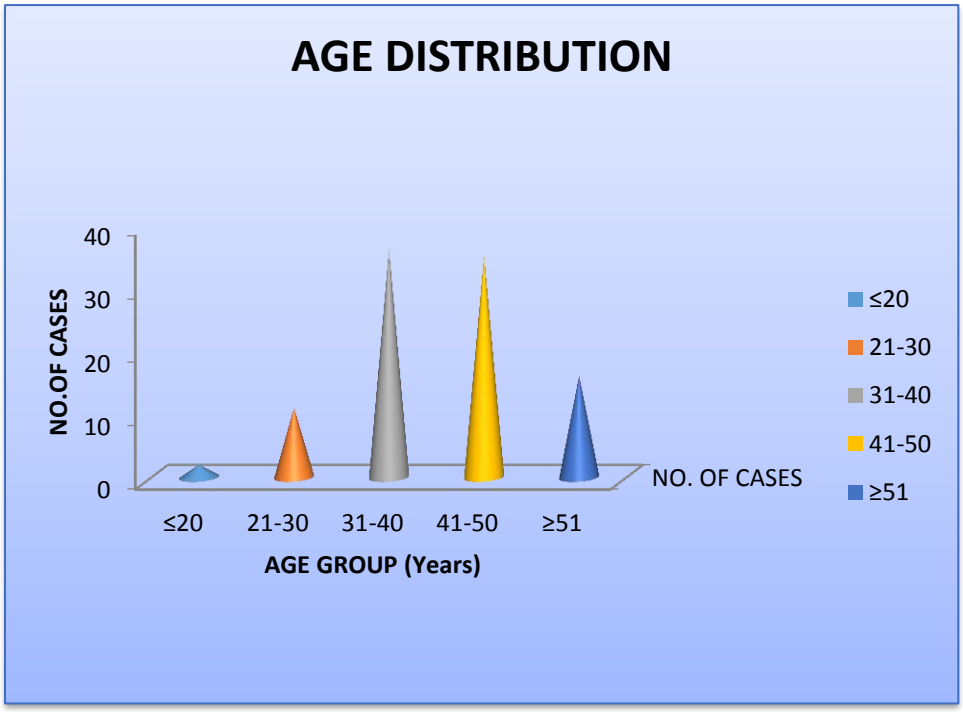
DATA COLLECTION AND METHODS

We examined 100 patients recruited from Institute of Internal Medicine, and Anti-retroviral center. Informed consent was obtained from each patient and relatives in necessary cases. They were given a questionnaire and were subjected to thorough clinical examination. Patients were asked to take routine blood investigations like renal function tests, liver function tests, CD4 cell count and Chest X-ray and sputum examination by Ziehl-Neelson of acid fast bacilli (AFB). Histopathological examination of typical granulomatous reaction was demonstrated in relevant cases. If extra pulmonary tuberculosis was suspected, relevant investigations like ascetic fluid analysis, pleural fluid analysis ultrasound abdomen, CT brain, MRI brain and MR spectroscopy was taken. All the data was entered in the proforma (enclosed). Data was analyzed using Excel data analysis software and p value was calculated using paired T test.

OBSERVATION AND RESULTS

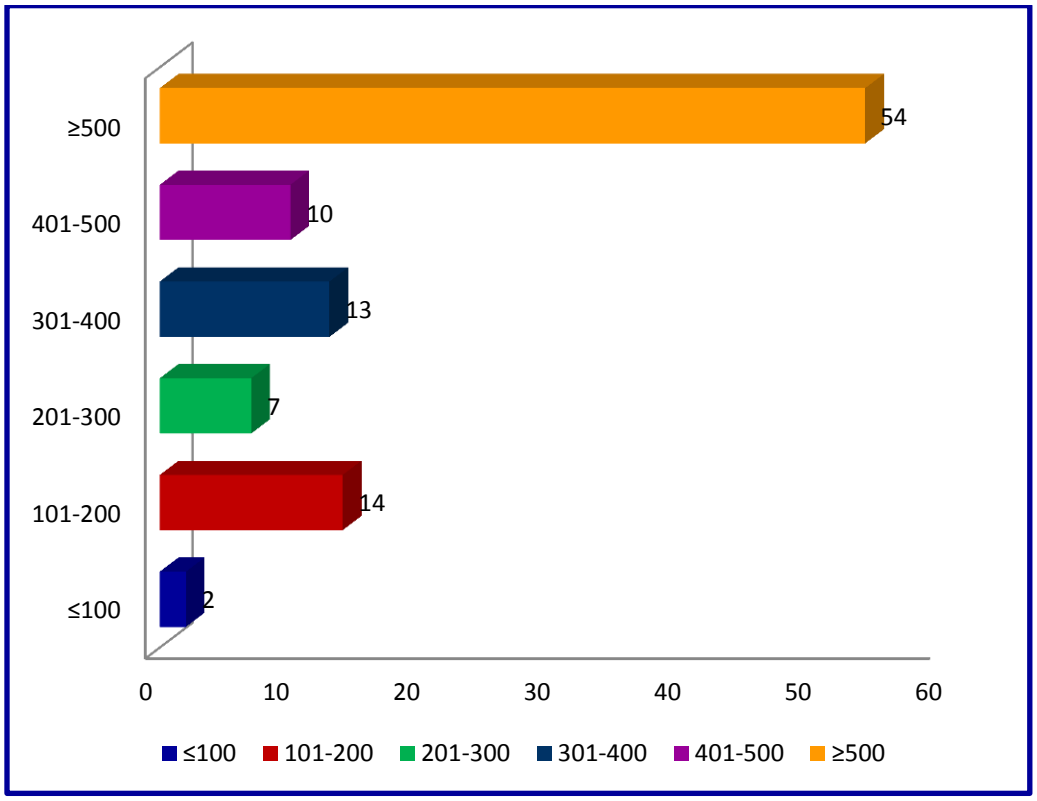
AGE DISTRIBUTION

AGE GROUP (Years)	NO. OF CASES
≤20	2
21-30	11
31-40	36
41-50	35
≥51	16



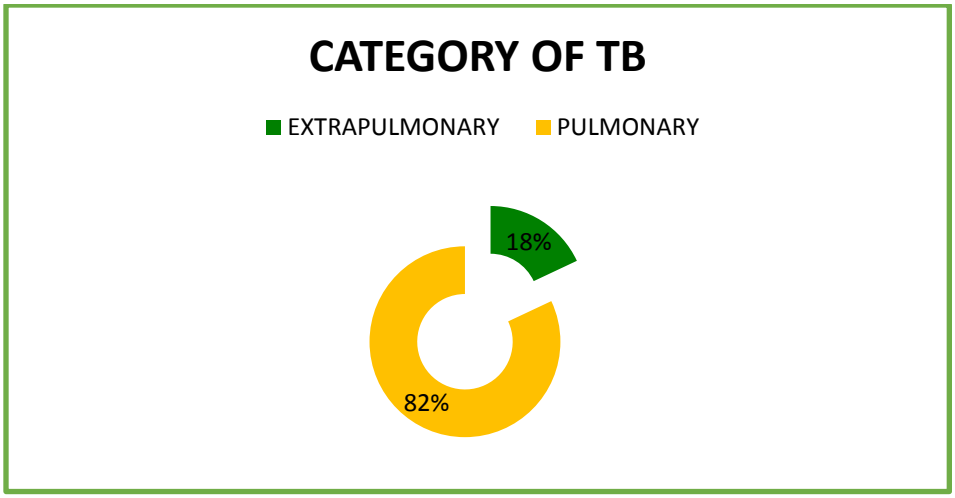
RANGE OF CD4 CELL COUNT

CD4 COUNT (Cells/ cu mm)	NO. OF CASES
≤100	2
101-200	14
201-300	7
301-400	13
401-500	10
≥501	54



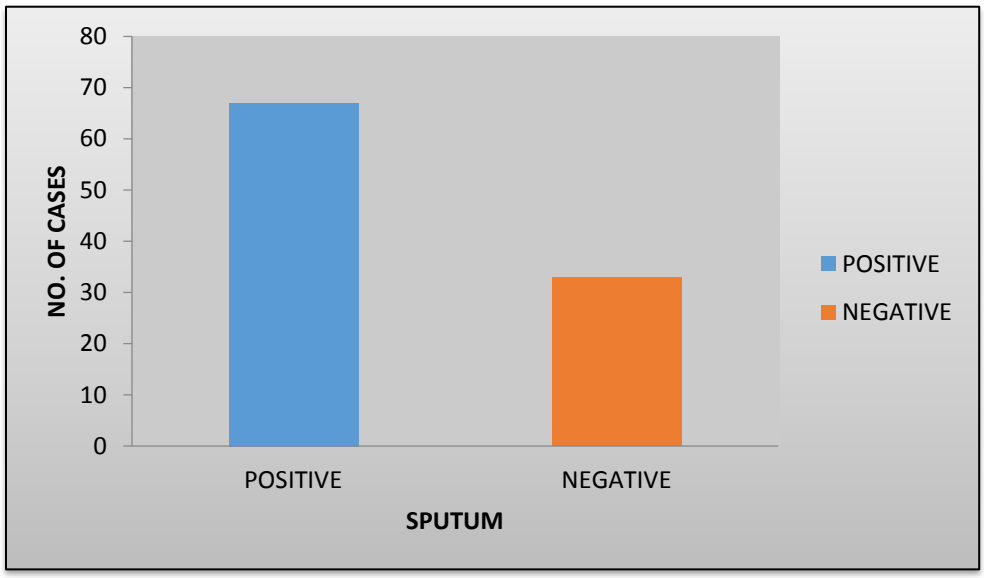
CATEGORY OF TB

TUBERCULOSIS	NO. OF CASES
EXTRAPULMONARY	18
PULMONARY	82



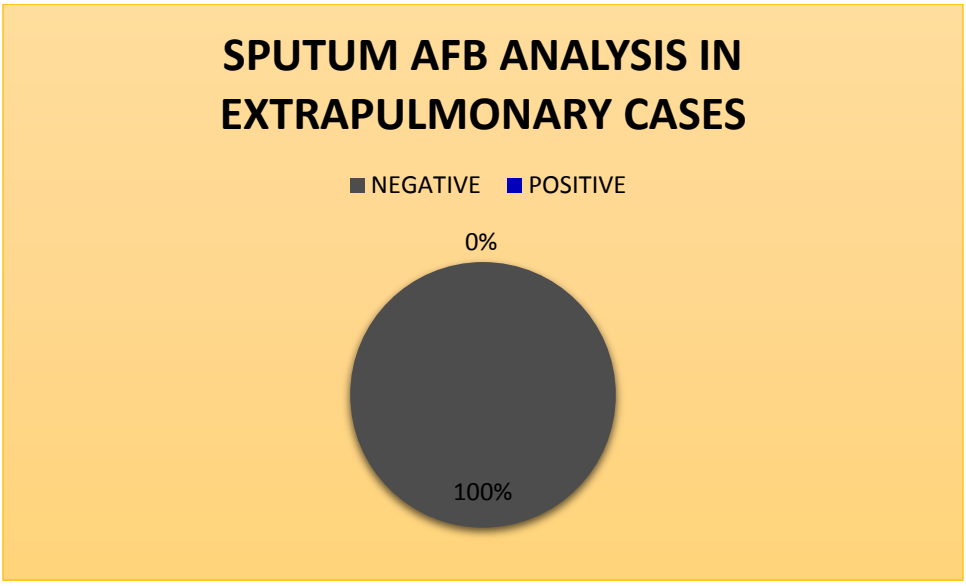
SPUTUM ANALYSIS

SPUTUM	NO. OF CASES
POSITIVE	67
NEGATIVE	33



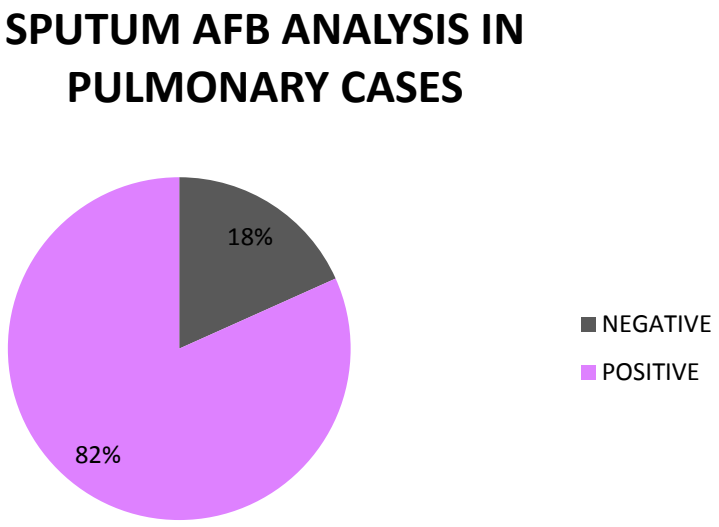
SPUTUM AFB ANALYSIS IN EXTRAPULMONARY CASES

SPUTUM	NO. OF EXTRAPULMONARY CASES
NEGATIVE	18
POSITIVE	0



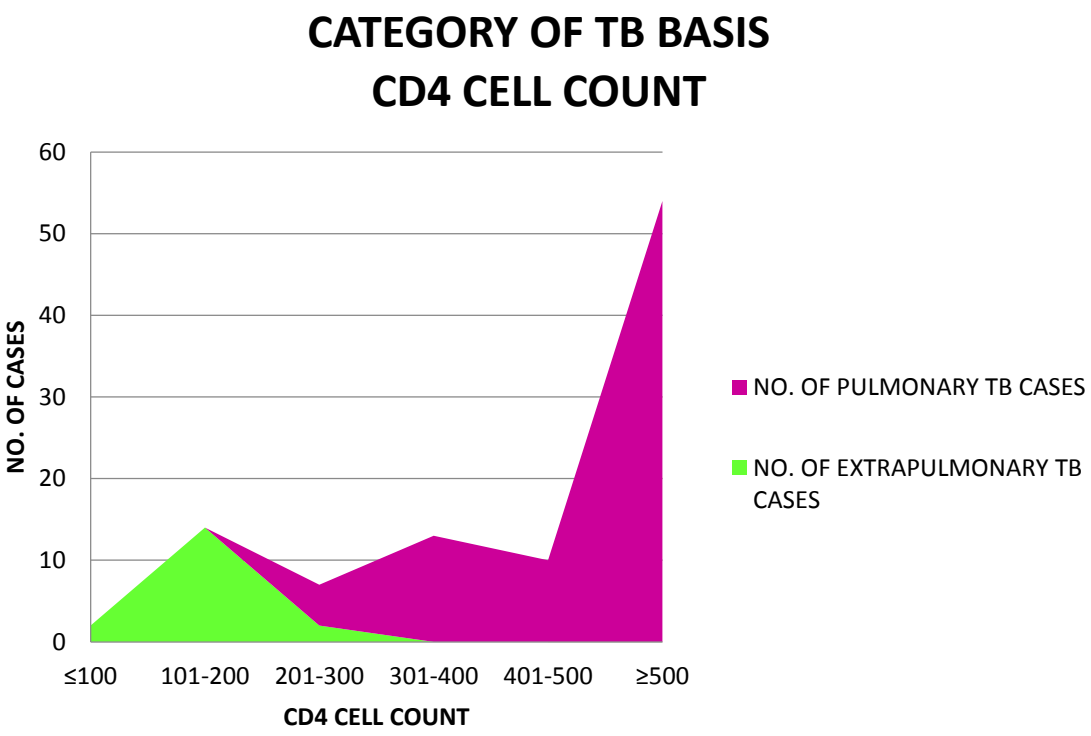
SPUTUM AFB ANALYSIS IN PULMONARY CASES

SPUTUM	NO. OF PULMONARY CASES
NEGATIVE	15
POSITIVE	67



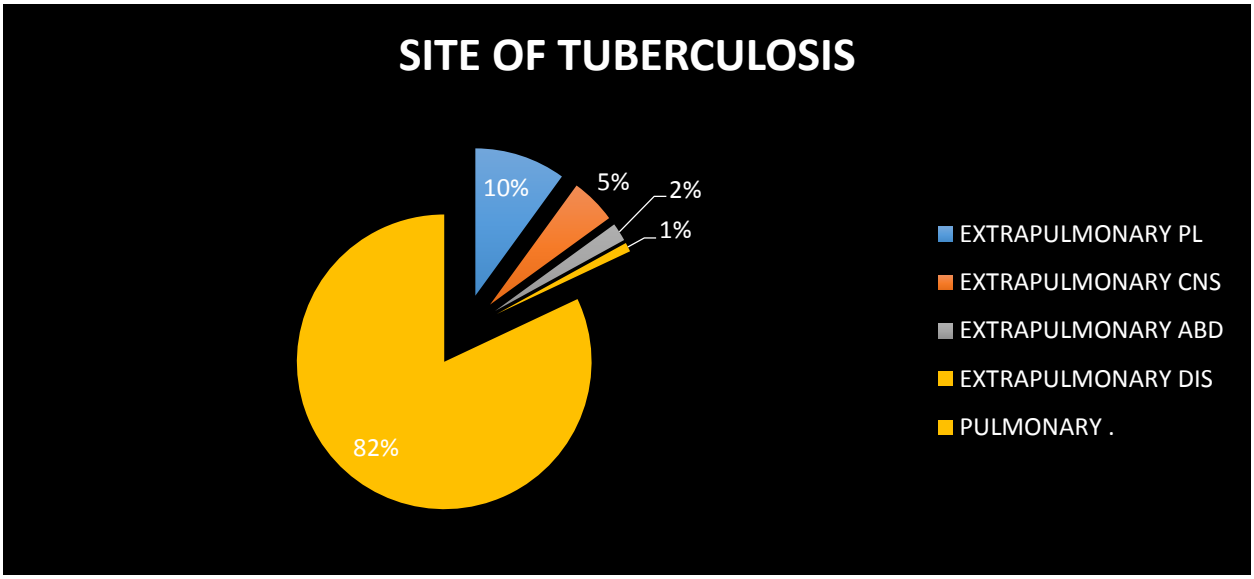
CATEGORY OF TB BASIS CD4 CELL COUNT

CD4 COUNT (Cells/ cu mm)	NO. OF EXTRAPULMONARY TB CASES	NO. OF PULMONARY TB CASES
0-100	2	0
101-200	14	0
201-300	2	5
301-400	0	13
401-500	0	10
≥501	0	54



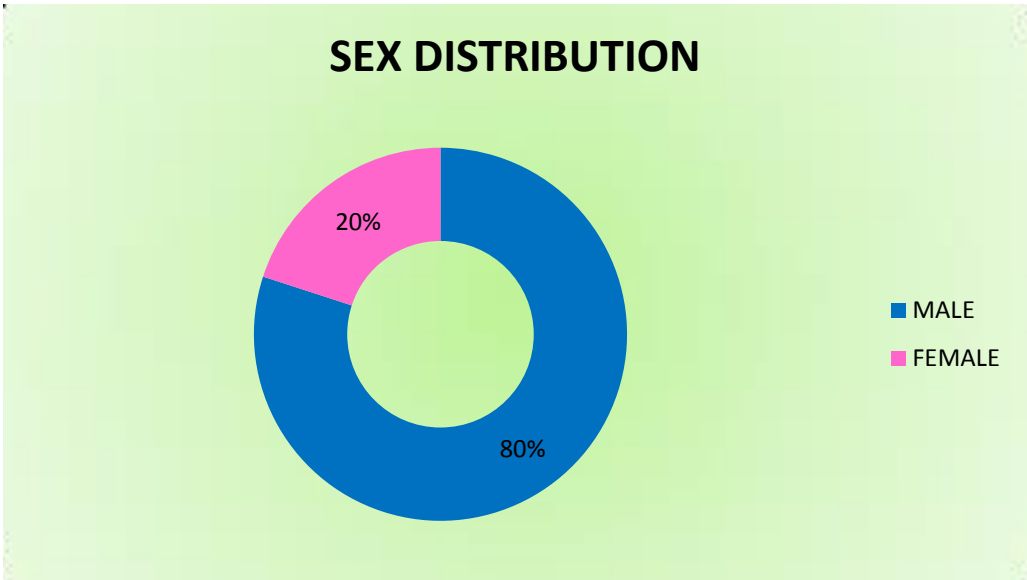
SITE OF TUBERCULOSIS

TUBERCULOSIS	SITE	NO. OF CASES
EXTRAPULMONARY	PL	10
EXTRAPULMONARY	CNS	5
EXTRAPULMONARY	ABD	2
EXTRAPULMONARY	DIS	1
PULMONARY	.	82



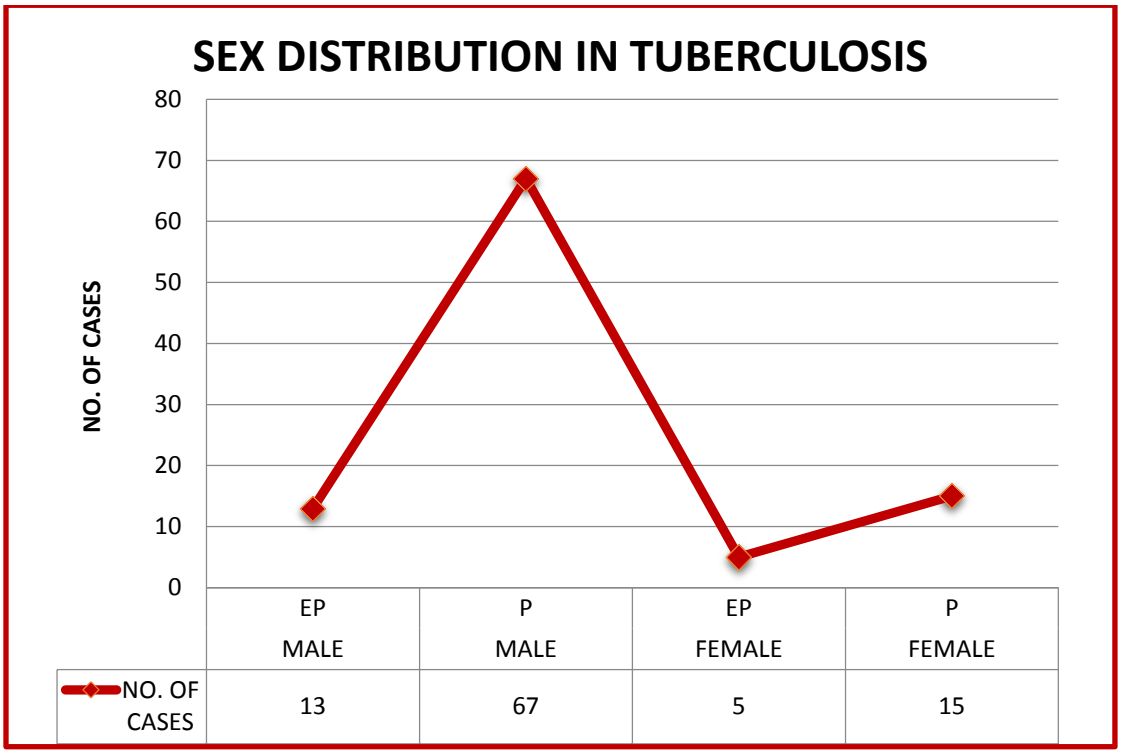
SEX DISTRIBUTION

SEX	NO. OF CASES
MALE	80
FEMALE	20



SEX DISTRIBUTION IN TUBERCULOSIS

SEX	TUBERCULOSIS	NO. OF CASES
MALE	EP	13
MALE	P	67
FEMALE	EP	5
FEMALE	P	15



RESULTS

AGE DISTRIBUTION

In our present study 36 % of patients were in the age group between age 31-40 and 35 % of patients were in age group between 41-50 years. This is in accordance with the long incubation period of HIV. 2 % were below the age of 20 years and 16 % of the patients were above 51.

SEX DISTRIBUTION

80 % of the study population were males and 20 % were females. 67 patients among the male population had pulmonary Tb whereas only 15 patients among the female population were pulmonary tuberculosis. Likewise, extra pulmonary TB was seen in 13 male patients and 5 female patients.

.CD4 CELL COUNT RANGE

The CD4 cell count ranged from 59 (lowest) to 711 cells /cu mm. The values were arbitrarily arranged with a difference of 100 cells/cu mm. 54 % of the patient had a CD4 cell count more than 500 cells /cu mm. 16 % of patients had CD4 count less than 200 cell/cu mm.

SPUTUM ANALYSIS

67 % of the patients in our present study proved to be sputum positive for acid fast stain. All the patients with extra pulmonary tuberculosis were sputum negative. This goes in accordance with many other studies, sputum analysis is not a sensitive investigation for extra pulmonary tuberculosis. For pulmonary tuberculosis, with CD4 cell count above 200 cells/cu mm of blood, sputum AFB is still a sensitive investigation to detect pulmonary tuberculosis.

TB CD4 RELATIONSHIP

CD4 COUNT (Cells/ cu mm)	FOR NO. OF EXTRAPULMONARY TB CASES	FOR NO. OF PULMONARY TB CASES
Mean	3	13.66666667
SD	5.477225575	20.44178727
P value	0.026	0.052

It tells us that the p-value for a one-tail test would be 0.1564, make the -1 the exponent of the 6.Then you will see the more familiar 0.156x6^-1. This is the number 0.026. Extra pulmonary is Significant which is less than alpha = 0.05.

The majority of the patients having CD4 cell count more than 200 in the present study demonstrated that they had pulmonary

tuberculosis. Patients who had a count between 350 to 500 cells /cu mm, demonstrated atypical sites involved in the lungs for pulmonary tuberculosis. Most of the patients (18 %) who had extra pulmonary tuberculosis had CD4 cell count less than 200 cells/cu mm.2 patients just above 200 cells/ cu mm, had extra pulmonary manifestations.

The threshold level of CD4 count of 200 cells/cu mm for extra pulmonary tuberculosis is statistically proved significant p value by paired t test.

DISCUSSION

DISCUSSION

In India, tuberculosis prevalence was stable and was getting under control till the HIV epidemic started. HIV became a strong risk factor for TB resurgence. Among the opportunistic infections which affected People living with HIV and AIDS, Tuberculosis was the commonest of them all. Tuberculosis could affect HIV positive individual with any degree of immunosuppression. As explained above the in the review of literature, tuberculosis accelerates Human immunodeficiency virus infection and HIV accelerates TB progression. The degree of immunosuppression is evidenced by CD4 cell count. In our study, 100 patients were enrolled from medical wards and antiretroviral center who satisfied the inclusion criteria for the study. Majority of them, 80% were male patients and (20 %) were female patients. Most of the males, were drivers by profession and the females were home makers. The commonest mode of transmission was by Sexual transmission. This is in concordance with the other studies suggesting that HIV in India spreads more by heterosexual transmission than by homosexual transmission. CD4 cell count for these patients ranged from 59 to 711 cells per cubic millimeter. The patients above 500 cells per cubic millimeter of blood, showed

predominantly tuberculosis very similar to patients who had tuberculosis and were HIV negative. Predominantly upper lobe was involved in post primary stage. In patients who had CD4 cell count between 350 and 500 cells per cubic millimeter of blood, most of the patients had atypical locations of the post primary Tb, having predominant involvement of the lower lobe. In patients whose CD4 count was less than 200 cells per cubic millimeter of blood, all of them had extra pulmonary tuberculosis in our study. Commonest form of extra pulmonary tuberculosis was pleural tuberculosis. All of them presented with pleural effusion, majority was on the right side. The sputum analysis revealed that all extra pulmonary tuberculosis cases were negative for acid fast stain. Among the pulmonary tuberculosis patients, sputum was positive in 82 % patient and negative in 18 %. According to our study, sputum analysis still proves a cost effective method to analyze the tuberculosis in HIV positive individuals who has CD4 cell count more than 200 cells per cubic millimeter of blood. Very closely related study done by Jaryal et al in 2011 showed that extra pulmonary TB were common manifestation in HIV positive individuals, which is not in accordance with our study. In his study, CNS spread of tuberculosis is the most common extra

pulmonary manifestation. In another study Brig S K Sharma et al, the commonest extra pulmonary manifestation was in lymph nodes. CD4 cell count seems to play pivotal role in the variation in clinical manifestations of tuberculosis in HIV infected individuals. CD4 cell count demonstrates the degree of immunosuppression. A threshold value of 200 cells per cubic millimeter was identified as the value below which most of the manifestations of tuberculosis was extra pulmonary. This demonstrates that CD4 count should be used as a branch point while treating HIV TB coinfection. A value below 200 cells per cubic millimeter of should prompt us to search for extra pulmonary tuberculosis.

LIMITATIONS OF THE STUDY

1. The data was collected from a single center.
2. The sample size is small for HIV TB coinfected population.
3. Potential for Bias and hence inaccuracy.

Large multi-centric studies in future prospective studies are needed to fully ascertain the accuracy of the above findings.

CONCLUSION

CONCLUSION

Tuberculosis is the commonest opportunistic infection among people living with HIV and AIDS (PLHA).

Among the spectrum of Tuberculosis possible in HIV infected individuals, Pulmonary Tuberculosis is more common than extra pulmonary tuberculosis.

The sensitivity of sputum smear in detecting pulmonary tuberculosis in PLHA is decreased as compared to Non HIV infected individuals.

Above CD4 count of 200 cells per cubic millimeter, most of the patients were suffering from pulmonary tuberculosis. Below the CD4 count of 200 cells per cubic millimeter, patients were suffering from extra pulmonary tuberculosis predominantly.

Among the patients in the study suffering from extra pulmonary Tuberculosis, the most common site was Pleura.

CD4 cell count can be a cost effective method in guiding us to identify the organ commonly affected by tuberculosis in HIV positive individuals and in future may help in formulating an algorithm for HIV TB coinfection.

BIBILIOGRAPHY

BIBILIOGRAPHY

1. Dannenberg AM. Immune mechanisms in pathogenesis of pulmonary TB.

2. Long R, Scalcini M, Manfreda L, Baptiste MJ, and Hershfield E. The impact of HIV on the usefulness of sputum smears for the diagnosis of TB.

3. Swaminathan S and Naredran G HIV and Tuberculosis in India. 2008 J. Bioscience

4. Pitchenik AE, Rubinson HA. The radiographic appearance of tuberculosis in patients with AIDS and Pre AIDS. Am rev Resp diseases.

5. Modilevsky T, Sattler Fr, Barnes PF – Myco bacterial disease in patients with HIV infection.

6. Sharma SK, Mohan A, Kadhiravan T 2005 HIV – TB co infection, epidemiology diagnosis and management.

7. de Noronha AL, Bafica A, Nogueira L, Barral A, Barral-netto M, 2008 Lung granulomas from mycobacterium tuberculosis / HIV -1 co infected patients display decreased in situ TNF production.

8. Kumaraswamy N, Vallabheni S, Flanigan TP, Mayer KH, Solomon S 2005 – clinical profile of HIV in India.

9. Vidyanathan P, singh S, 2003, HIV –TB co infection in India.

10. Jain SK, Aggarwal JK, Raj pal S Baveja, 2000 Prevelance of HIV in TB patients in delhi – sentinel surveillance study

11. Sharma SK, Kadhiravan T, Banga A, Goyal T, Bhatia I, Saha PK. Spectrum of clinical disease in a series of 135 hospitalised HIV-infected patients from north India. BMC Infect Dis 2004; 4:52.

12. TB India. RNTCP status report. Available from: http://www.tbcindia.org/pdfs/TB%20India%202010. [Last accessed on 2010 Apr 24].

13. World Health Organization. A Clinical Manual for Southeast Asia. WHO/TB/96.200 (SEA). Geneva: World Health Organization; 1996.

14. Dermont M, Anthony H, Haileyesus G. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implication for policies. Trop Med Int Health 2005; 8:734.

15. Deivanayagam CN, Rajasekaran S, Senthilnathan V, Krishnarajsekhar R, Raja K, Chandrasekar C, et al. Clinico-

radiological spectrum of tuberculosis among HIV seropositive: A Tambram study. Indian J Tuberc 2001; 48:123.

16. Bhagyabati DS, Naorem S, Singh TJ, Singh KB, Prasad L, Shantidevi T. HIV and TB Co-infection. Journal, Indian Academy of Clinical Medicine 2005; 6:220.

17. Swaminathan S, Sangeetha M, Arunkumar N, Menon PA, Thomas B, Shibi K, et al. Pulmonary Tuberculosis in HIV positive individuals: Preliminary report on clinical features and response to treatment. Indian J Tuberc 2002; 49:18.

18. Mohanty KC, Sundrani RM, Nair S. HIV infection in patients with respiratory disease. Indian J Tuberc 1993; 40:5.

19. Rajasekaran R, Lima A, Kamakshi S, Jeyaganesh D, Senthamizhchelvan A, Savithri S et al Trend of HIV infection in patients with tuberculosis in rural south India. Indian J Tuberc 2000;47:223

20. Gutierrez EB, Zanetta DM, Saldiva PH, Capelozzi VL. Autopsy-proven determinants of death in HIV-infected patients treated for pulmonary tuberculosis in Sao Paulo, Brazil. Pathol Res Pract 2002; 198: 339-46.

21. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. Clin Infect Dis 2003; 36: 79-85.

22. Morgan D, Malamba SS, Orem J, Mayanja B, Okongo M, Whitworth JA. Survival by AIDS defining condition in rural Uganda. Sex Transm Infect 2000; 76: 193-7.

23. Perneger TV, Sudre P, Lundgren JD, Hirschel B. Does the onset of tuberculosis in AIDS predict shorter survival? Results of a cohort study in 17 European countries over 13 years. AIDS in Europe Study Group.BMJ 1995; 311 1468-71.

24. Wilkinson D, Squire SB, and Garner P. Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo controlled trials. BMJ 1998; 317 625-9

ANNEXURES

ABBREVIATIONS

HIV	-	Human Immunodeficiency Virus
AIDS	-	Acquired Immunodeficiency Deficiency Syndrome
ART	-	Antiretroviral Therapy
DOTS	-	Direct Observation and Treatment in Short course
WHO	-	World Health Organization
LAM	-	Lipo Arabino Mannan
TLR	-	Toll Like Receptor
CD	-	Cluster of Differentiation
TNF	-	Tumor Necrosis Factor
NK	-	Natural Killer Cells
NOS	-	Nitric Oxide Synthase
ELISA	-	Enzyme Linked Immuno Sorbant Assay
LAC	-	Link ART Center
RNTCP	-	Revised National Tuberculosis Control Programme

PROFORMA

PATIENT DETAILS:

Name: Age: Sex:

IP No.:

ON ADMISSION:

Main Complaints:

H/o cough

H/o sputum

H/o hemoptysis

H/o weight loss

H/o breathlessness

H/o orthopnea/PND

H/o hematemesis

H/o melena

H/o seizures

H/o altered sensorium

H/o altered sleep pattern

H/o chest pain

H/o abdominal pain

H/o fever

H/o constipation

H/o intake of any drugs

Significant Past History: HIV diagnosed on

ART number

TB diagnosed by

CD4 Cell count

CLINICAL EXAMINATION:

Pulse: BP:

RR: Temp:

Pallor: Icterus:

CVS: RS:

P/A:

CNS:

INVESTIGATIONS:

Hemogram:

Renal Function Test:

Liver Function Test:

BT/CT/PT/INR:

Blood Grouping:

CD4 Cell Count:

ECG:

Imaging:

CXR:

USG Abdomen:

CT Chest:

CT Abdomen:

CT Brain:

CERTIFICATE OF APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Bharth Raj Kidambi
Post Graduate M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.Bharath Raj Kidambi,

The Institutional Ethics Committee has considered your request and approved your study titled **"Spectrum of tuberculosis in HIV patients and its co-relation to CD4 cell count" No.01062015.**

The following members of Ethics Committee were present in the meeting held on 09.06.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.P.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Raghumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., DM., Prof. & HOD of MGE, MMC	: Member
7. Prof.Baby Vasumathi, Director, Inst.of O&G, Ch-8	: Member
8. Prof.Ramadevi, Director, Inst.of Bio-chemistry, MMC	: Member
9. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
10. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
11. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
12. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
13. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

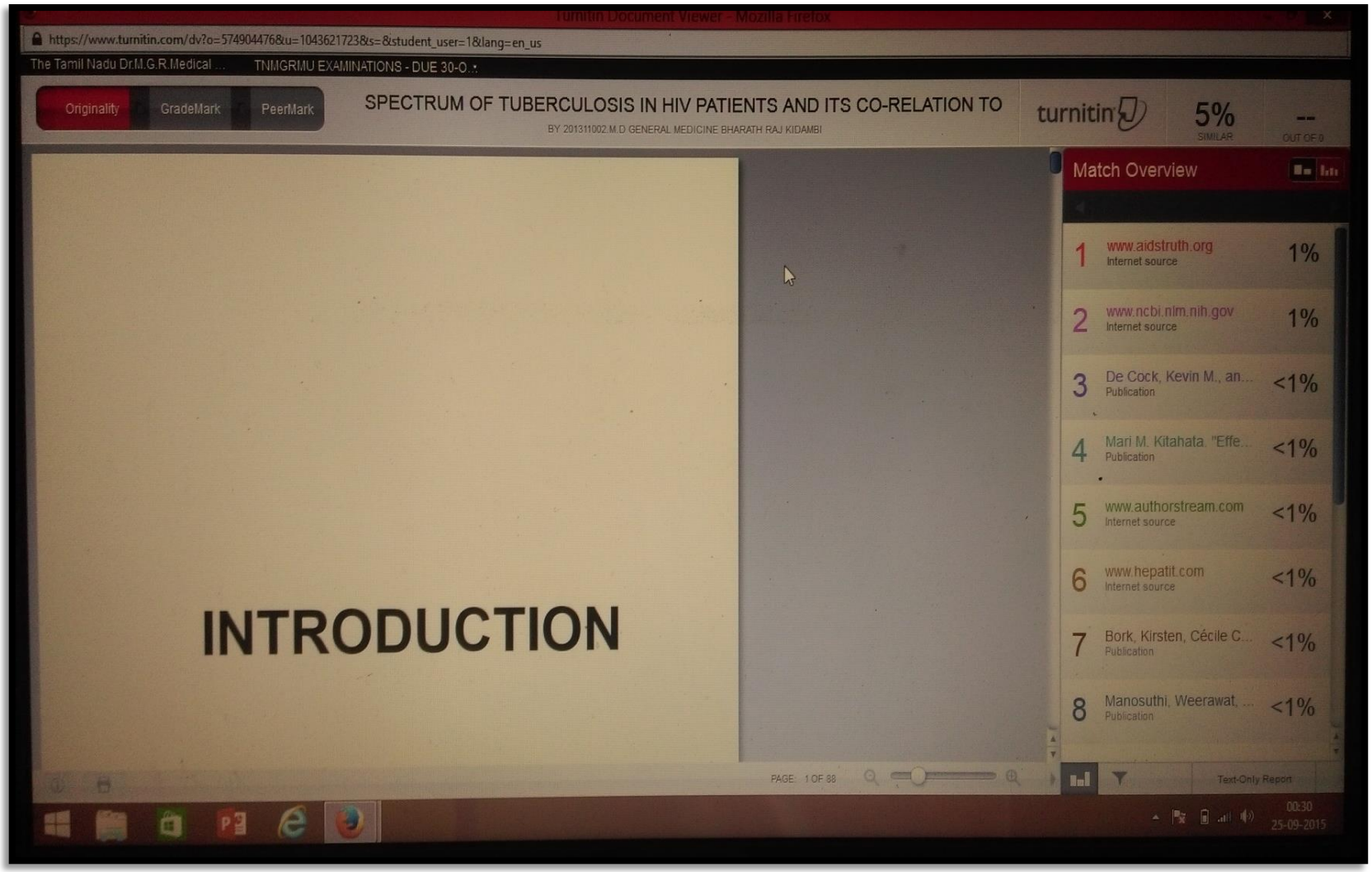
We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

TURNITIN PLAGIARISM SCREEN SHOT



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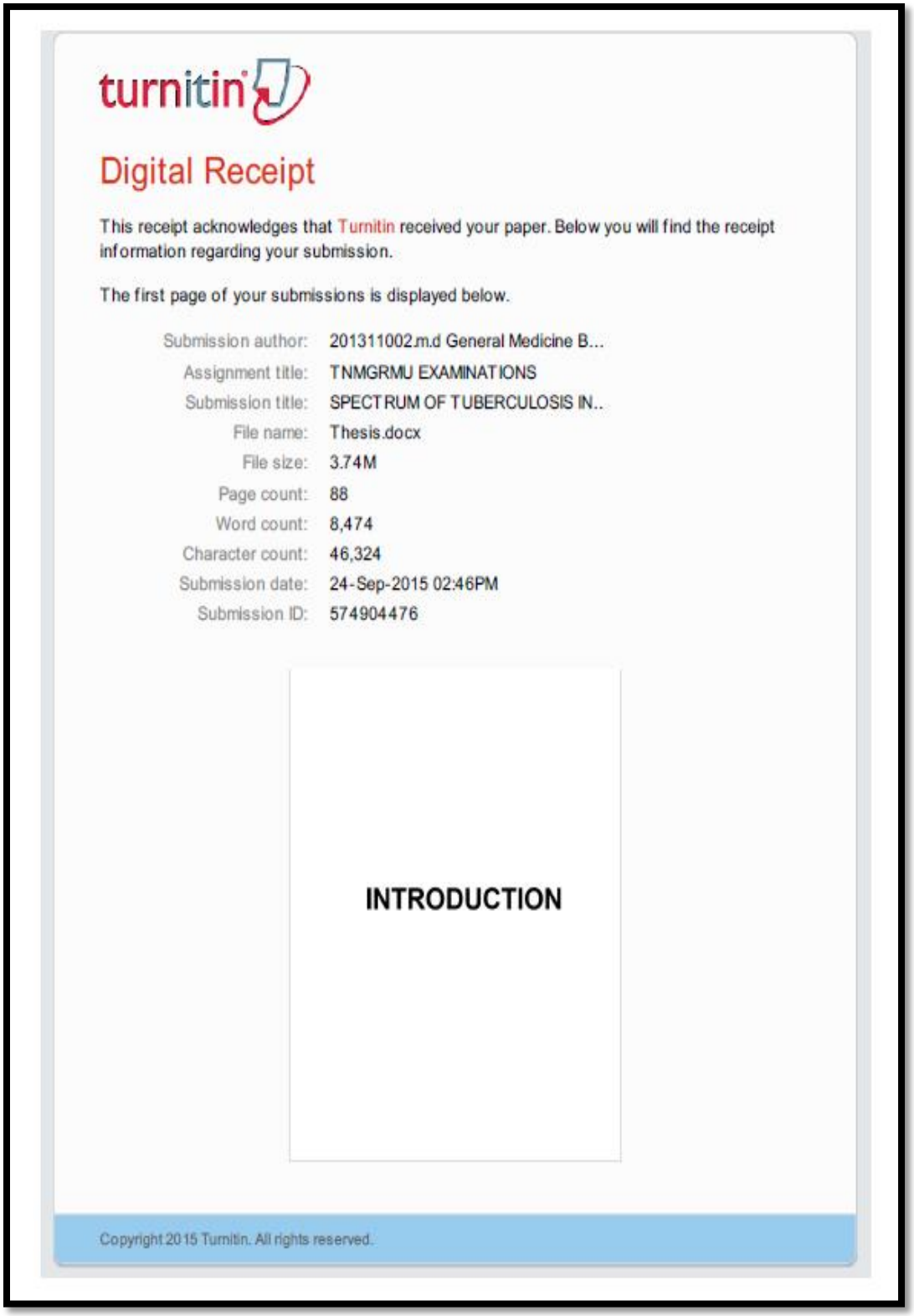

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INTRODUCTION

ஆராய்ச்சிதகவல்தாள்

சென்னை இராஜிவ் காந்தி அரசு பொது மருத்துவ மனையில் "**எச்.ஐ.வி நோயாளிகள் காச நோய் வெளிப்பாடுகளும் மற்றும் CD4 எண்ணிக்கையும் அதன் தொடர்பும்**" பற்றிய ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

.

நீங்கள் இந்த ஆய்விற்கு தகுதியானவர்களாக இருக்கும் பட்சத்தில் தங்களின் மருத்துவ சுயவிவரத்தையும், ஆய்வக பரிசோதனை அறிக்கையும் மற்றும் கதிரியக்க அறிக்கையும் ஆய்வு நோக்கங்களுக்காக பயன்படுத்தபடும். இது உங்களுடைய இறுதி அறிக்கை அல்லது மேலாண்மையை பாதிக்காது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருத்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனை களின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர்கையொப்பம் பங்கேற்பாளர்கையொப்பம்

தேதி:

INFORMATION SHEET

We are conducting a study on “SPECTRUM OF TUBERCULOSIS IN HIV PATIENTS AND ITS CO-RELATION TO CD4 COUNT” among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is

1. To analyze the different manifestations of TB in HIV positive patients.

2. To analyze if the manifestations have a co-relation to the degree of immunosuppression.

We are selecting certain cases and if you are found eligible, we may be using your information which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally

Information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator	Signature of Participant
Date :	
Place:	

ஆராய்ச்சிஒப்புதல்கடிதம்

ஆராய்ச்சிதலைப்பு:

“எச்.ஐ.விநோயாளிகள்காசநோய்வெளிப்பாடுகளும்மற்றும் CD4 எண்ணிக்கையும்அதன்தொடர்பும்”.

ஆய்வுநிலையம் :பொதுநலமருத்துவத்துறை

சென்னைமருத்துவக்கல்லூரி

சென்னை - 600003

பெயர்: தேதி:

வயது: உள்நோயாளிஎண்:

பால்: ஆராய்ச்சிசேர்க்கைஎண்:

ஆய்வு விவரங்களை எனது சொந்த மொழியில் எனக்கு விளக்கினார். எனக்கு சந்தேகம் கேட்க ஒரு வாய்ப்பும், அதற்கு தகுந்த பதில்களும் வழங்கப்பட்டது. ☐

நான் இந்த ஆய்வில் தன்னிச்சையாகதான் பங்ககேற்கிறேன். எந்த காரணத்திலோ எந்த கட்டத்திலும் எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்பதற்க்கு என் அனுமதி தேவை இல்லை என அறிந்து

கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.

☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்கள்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் நான் முழுமனதுடன் ஆய்வில் பங்கேற்க ஒப்புக்கொள்கிறேன். நான் மருத்துவரிடம் உண்மையாக இருப்பேன் என உறுதியளிகிறேன்.

☐

ஆய்வாளரின்கையொப்பம் பங்கேற்பாளர்கையொப்பம்

ஆய்வாளரின்பெயர்: பங்கேற்பாளர்பெயர்/முகவரி

டாக்டர். பரத்ராஜ்கிடாம்பி

PATIENT CONSENT FORM

Study Detail : “SPECTRUM OF TUBERCULOSIS IN HIV PATIENTS AND ITS CO-RELATION TO CD4 COUNT”

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient’s Name :

Patient’s Age :

In Patient Number :

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. □

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that I will not be eligible for any compensation . □

I understand that sponsor of the clinical study, others working on the sponsor’s behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records,

both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. □

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. □

I hereby consent to participate in this study □

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. □

Signature/thumb impression	Signature of Investigator
Patient's Name and Address:	Study Investigator's Name Dr.BHARATH RAJ KIDAMBI

MASTER CHART

S.NO	AGE	SEX	CD4 COUNT	TUBERCULOSIS	SPUTUM
1	29	F	159	EP	-
2	18	M	143	EP	-
3	45	M	504	P	+
4	47	M	159	EP	-
5	54	M	163	EP	-
6	43	M	601	P	+
7	26	F	112	EP	-
8	39	M	523	P	+
9	51	M	298	P	-
10	25	M	178	EP	-
11	38	M	179	EP	-
12	34	M	631	P	+
13	51	M	111	EP	-
14	34	F	710	P	+
15	52	M	145	EP	-
16	33	M	109	EP	-
17	53	M	303	P	-
18	51	M	401	P	+
19	39	M	351	P	-
20	52	M	495	P	+
21	45	M	583	P	+
22	46	M	572	P	+
23	29	F	198	EP	-
24	48	M	521	P	+
25	38	M	359	P	-
26	44	M	411	P	+
27	53	M	378	P	+
28	43	M	598	P	+
29	37	M	632	P	+
30	49	M	471	P	+
31	41	M	711	P	+
32	52	M	359	P	-
33	36	M	391	P	+
34	46	M	377	P	+
35	45	F	653	P	+
36	49	F	548	P	+
37	47	M	298	P	-
38	53	M	257	P	-
39	44	M	501	P	-
40	54	M	365	P	-
41	38	M	609	P	+
42	24	M	59	EP	-
43	31	M	410	P	+
44	28	F	423	P	+
45	35	F	627	P	+

46	47	F	710	P	+
47	39	M	301	P	-
48	19	M	156	EP	-
49	45	M	589	P	+
50	37	M	278	P	-
51	24	M	178	EP	-
52	35	M	672	P	+
53	29	F	375	P	+
54	34	M	647	P	+
55	39	M	491	P	+
56	37	M	490	P	+
57	31	F	221	EP	-
58	49	M	616	P	+
59	52	M	201	EP	-
60	51	M	311	P	-
61	44	M	517	P	+
62	41	M	406	P	+
63	33	F	539	P	+
64	38	M	572	P	+
65	46	M	628	P	+
66	31	M	617	P	+
67	43	M	602	P	+
68	48	F	622	P	+
69	39	M	642	P	+
70	32	M	662	P	+
71	47	M	682	P	+
72	49	M	702	P	+
73	36	M	722	P	+
74	27	F	97	EP	-
75	39	F	556	P	+
76	51	M	270	P	-
77	47	M	578	P	+
78	30	F	611	P	+
79	44	M	667	P	+
80	40	F	656	P	+
81	31	M	641	P	+
82	53	M	327	P	-
83	26	M	139	EP	-
84	36	M	701	P	+
85	45	M	721	P	+
86	41	F	741	P	+
87	41	M	761	P	+
88	48	M	560	P	-
89	34	M	593	P	+
90	38	M	649	P	+
91	52	M	478	P	+
92	47	F	623	P	+
93	34	M	643	P	+

94	38	M	391	P	+
95	46	F	683	P	+
96	44	M	703	P	+
97	41	M	723	P	+
98	37	M	743	P	+
99	32	M	521	P	+
100	35	M	577	P	+

S.NO	AGE	SEX	CD4 COUNT	TUBERCULOSIS	SPUTUM	SITE
1	29	F	159	EP	-	PL
2	18	M	143	EP	-	ABD
3	47	M	159	EP	-	PL
4	54	M	163	EP	-	CNS
5	26	F	112	EP	-	CNS
6	25	M	178	EP	-	PL
7	38	M	179	EP	-	PL
8	51	M	111	EP	-	PL
9	52	M	145	EP	-	ABD
10	33	M	109	EP	-	PL
11	29	F	198	EP	-	CNS
12	24	M	59	EP	-	DIS
13	19	M	156	EP	-	PL
14	24	M	178	EP	-	CNS
15	31	F	221	EP	-	PL
16	52	M	201	EP	-	PL
17	27	F	97	EP	-	CNS
18	26	M	139	EP	-	PL

KEY TO MASTER CHART

M	-	Male
F	-	Female
P	-	Pulmonary tuberculosis
EP	-	Extra pulmonary Tuberculosis
PL	-	Pleura
CNS	-	Central Nervous System
ABD	-	Abdomen
DIS	-	Disseminated
“+”	-	Positive for acid fast bacilli
“-“	-	Negative for acid fast bacilli