A DISSERTATION ON

SCREENING FOR TUBERCULOSIS

CO-INFECTION IN HIV INFECTED CHILDREN

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CERTIFICATE

This is to certify that the dissertation entitled **"SCREENING FOR TUBERCULOSIS CO-INFECTION IN HIV INFECTED CHILDREN"** submitted by **Dr. T. ARUN KARTHIK** to the Faculty of Paediatrics, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch VII (Paediatrics) is a bonafied research work carried out by him under our direct supervision and guidance.

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INTRODUCTION

India is one of the largest and most populated countries in the world, with over one billion inhabitants. Of this number, it's estimated that around 2.4 million people are currently living with HIV.

In recent decades, the dramatic spread of the HIV epidemic in sub-Saharan Africa has resulted in notification rates of TB increasing up to 10 times in some countries. The incidence of TB is also increasing in other high HIV prevalence countries, where the population with HIV infection and TB overlap. Even those countries with well organized national tuberculosis programs have seen an increase in TB cases. This is the underlying factor that suggests that TB control will not make much head way in HIV prevalent settings unless HIV control is also achieved. TB is the most common treatable HIV-related disease and a leading killer of people living with HIV/AIDS (PLWHA).

The World Health Organisation (WHO) cites TB treatment as one of the most cost-effective health interventions available – at a cost of only $10 for every year of life gained.

BACKGROUND OF THE STUDY

As HIV progressively destroys the immune system, there is a greater chance of a child infected with HIV developing tuberculosis. The development of active TB accelerates the progression of HIV disease towards full-blown AIDS, because the replication rate of the HIV virus is increased during the active phase of TB.

TB is curable, even in a children who is HIV positive. Curing an HIV positive children of TB not only improves their quality of life, and gives them several more years of life, it also reduces transmission to others in the community. TB is the most common treatable HIV-related disease and a leading killer of children living with HIV/AIDS.

So my study is aimed to screen for TB coinfection in HIV positive children, registered and followed up at ART centre, Madurai . This will help in early initiation of treatment and improve the outcome.

REVIEW OF LITERATURE

HISTORY OF TB[1]

Mycobacterium tuberculosis, the bacteria that causes tuberculosis, has been around for centuries. Recently, fragments of the spinal columns from Egyptian mummies from 2400 B.C.E. were found to have definite signs of the ravages of this terrible disease. Also called consumption, TB was identified as the most widespread disease in ancient Greece, where it was almost always fatal. But it wasn't until centuries later that the first descriptions of the disease began to appear. Starting in the late seventeenth century, physicians began to identify changes in the lungs common in all consumptive, or TB, patients. At the same time, the earliest references to the fact that the disease was infectious began to appear.

In 1720, the English doctor Benjamin Marten was the first to state that TB could be caused by “wonderfully minute living creatures.” He went further to say that it was likely that ongoing contact with a consumptive patient could cause a healthy person to get sick. Although Marten's findings didn't help to cure TB, they did help people to better understand the disease.

The sanitorium, which was introduced in the mid-nineteenth century, was the first positive step to contain TB. Hermann Brehmer, a Silesian botany student who had TB, was told by his doctor to find a healthy climate. He moved to the Himalayas and continued his studies. He survived his bout with the illness, and after he received his doctorate, built an institution in Gorbersdorf, where TB patients could come to recuperate. They received good nutrition and were outside in fresh air most of the day. This became the model for the development of sanitoria around the world. Tuberculosis is spread through the air, so everyone is at some risk.

In 1865, French military doctor Jean-Antoine Villemin demonstrated that TB could be passed from people to cattle and from cattle to rabbits. In 1882, Robert Koch discovered a staining technique that allowed him to see the bacteria that cause TB under a microscope.

CAUSATIVE ORGANISM

Tuberculosis is an infection caused by the rod-shaped, non–spore-forming, aerobic bacterium Mycobacterium tuberculosis. Mycobacteria typically measure 0.5 μm by 3 μm, are classified as acid-fast bacilli, and have a unique cell wall structure crucial to their survival. The well-developed cell wall contains a considerable amount of a fatty acid,

mycolic acid, covalently attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan, providing an extraordinary lipid barrier. This barrier is responsible for many of the medically challenging physiological characteristics of tuberculosis, zincluding resistance to antibiotics and host defense mechanisms. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate. The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cell membrane, another contributor to the permeability barrier of mycobacteria. Another important component of the cell wall is lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macrophages.[2] The cell wall is key to the survival of mycobacteria, and a more complete understanding of the biosynthetic pathways and gene functions and the development of antibiotics to prevent formation of the cell wall are areas of great interest.[3]

TRANSMISSION

Mycobacterium tuberculosis is spread by small airborne droplets, called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis. These minuscule droplets can remain airborne for minutes to

hours after expectoration.[2] The number of bacilli in the droplets, the virulence of the bacilli, exposure of the bacilli to UV light, degree of ventilation, and occasions for aerosolization all influence transmission. Introduction of *M tuberculosis* into the lungs leads to infection of the respiratory system; however, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary tuberculosis.

PATHOPHYSIOLOGY

Once inhaled, the infectious droplets settle throughout the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist. The mucus produced catches foreign substances, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal. This system provides the body with an initial physical defense that prevents infection in most persons exposed to tuberculosis.

Bacteria in droplets that bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages, the most abundant immune effector cells present in alveolar spaces. These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy

the invading mycobacteria and prevent infection.[11] Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens. Several mechanisms and macrophage receptors are involved in uptake of the mycobacteria.The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor.[(4)]The complement system also plays a role in the phagocytosis of the bacteria. The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. Opsonization by C3 is rapid, even in the air spaces of a host with no previous exposure to *M* tuberculosis.[(5)] The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease, called primary progressive tuberculosis. The outcome is essentially determined by the quality of the host defenses and the balance that occurs between host defenses and the invading mycobacteria.

After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours. Regardless of whether the infection becomes controlled or progresses, initial development involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria. Released cytokines attract T lymphocytes to the site, the cells

that constitute cell-mediated immunity. Macrophages then present mycobacterial antigens on their surface to the T cells.[6] This initial immune process continues for 2 to 12 weeks; the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test.

For persons with intact cell-mediated immunity, the next defensive step is formation of granulomas around the *M tuberculosis* organisms. These nodular – type lesions form from an accumulation of activated

T lymphocytes and macrophages, which creates a micro-environment that limits replication and the spread of the mycobacteria. This environment destroys macrophages and produces early solid necrosis at the center of the lesion; however, the bacilli are able to adapt to survive.[7] In fact, *M tuberculosis* organisms can change their phenotypic expression, such as protein regulation, to enhance survival. By 2 or 3 weeks, the necrotic environment resembles soft cheese, often referred to caseous necrosis, and is characterized by low oxygen levels, low pH, and limited nutrients. This condition restricts further growth and establishes latency. Lesions in persons with an adequate immune system generally undergo fibrosis and calcification, successfully controlling the infection so that the bacilli are contained in the dormant, healed

lesions.[7] Lesions in persons with less effective immune systems progress to primary progressive tuberculosis.

PATHOPHYSIOLOGY IN IMMUNOCOMPROMISED

For less immunocompetent persons, granuloma formation is initiated yet ultimately is unsuccessful in containing the bacilli. The necrotic tissue undergoes liquefaction, and the fibrous wall loses structural integrity. The semiliquid necrotic material can then drain into a bronchus or nearby blood vessel, leaving an air-filled cavity at the original site. In patients infected with M tuberculosis, droplets can be coughed up from the bronchus and infect other persons. If discharge into a vessel occurs, occurrence of extrapulmonary tuberculosis is likely. Bacilli can also drain into the lymphatic system and collect in the tracheobronchial lymph nodes of the affected lung, where the organisms can form new caseous granulomas.[7]

CLINICAL MANIFESTATIONS

As the cellular processes occur, tuberculosis may develop differently in each patient, according to the status of the patient's immune system. Stages include latency, primary disease, primary progressive disease, and extrapulmonary disease. Each stage has different clinical manifestations.

LATENT TUBERCULOSIS

Mycobacterium tuberculosis organisms can be enclosed, as previously described, but are difficult to completely eliminate. Persons with latent tuberculosis have no signs or symptoms of the disease, do not feel sick, and are not infectious. However, viable bacilli can persist in the necrotic material for years or even a lifetime, and if the immune system later becomes compromised, as it does in many critically ill patients, the disease can be reactivated. Although coinfection with human immunodeficiency virus is the most notable cause for progression to active disease, other factors, such as sepsis, renal failure, malnutrition also contribute.

PRIMARY DISEASE

Primary pulmonary tuberculosis is often asymptomatic, so that the results of diagnostic tests are the only evidence of the disease. Although primary disease essentially exists subclinically, some self-limiting findings might be noticed in an assessment. Associated paratracheal lymphadenopathy may occur because the bacilli spread from the lungs through the lymphatic system. If the primary lesion enlarges, pleural effusion is a distinguishing finding. This effusion develops because the bacilli infiltrate the pleural space from an adjacent area. The effusion may remain small and resolve spontaneously, or it may become large

enough to induce symptoms such as fever, pleuritic chest pain, and dyspnea.

PRIMARY PROGRESSIVE TUBERCULOSIS

Active tuberculosis develops in only 5% to 10% of persons exposed to *M* tuberculosis. When a patient progresses to active tuberculosis, early signs and symptoms are often nonspecific. Manifestations often include progressive fatigue, malaise, weight loss, and a low-grade fever accompanied by chills and night sweats.[8] Wasting, a classic feature of tuberculosis, is due to the lack of appetite and the altered metabolism associated with the inflammatory and immune responses. Wasting involves the loss of both fat and lean tissue; the decreased muscle mass contributes to the fatigue.[9] Finger clubbing, a late sign of poor oxygenation, may occur; however, it does not indicate the extent of disease.[10] A cough eventually develops in most patients. Although the cough may initially be non productive, it advances to a productive cough of purulent sputum. The sputum may also be streaked with blood. Hemoptysis can be due to destruction of a patent vessel located in the wall of the cavity, the rupture of a dilated vessel in a cavity, or the formation of an aspergilloma in an old cavity. The inflamed parenchyma may cause pleuritic chest pain. Extensive disease may lead to dyspnea or orthopnea because the increased interstitial volume leads to a

decrease in lung diffusion capacity. Although many patients with active disease have few physical findings, rales may be detected over involved areas during inspiration, particularly after a cough. Hematologic studies might reveal anemia, which is the cause of the weakness and fatigue. Leukocytosis may also occur because of the large increase in the number of leukocytes, or white blood cells, in response to the infection.

EXTRA- PULMONARY TUBERCULOSIS

Although the pulmonary system is the most common location for tuberculosis, extrapulmonary disease occurs in more than 20% of immunocompetent patients, and the risk for extrapulmonary disease increases with immunosuppression.[(11)]The most serious location is the central nervous system, where infection may result in meningitis or space-occupying tuberculomas. If not treated, tubercular meningitis is fatal in most cases, making rapid detection of the mycobacteria essential. Headaches and change in mental status after possible exposure to tuberculosis or in high risk groups should prompt consideration of this disease as a differential diagnosis. Another fatal form of extrapulmonary tuberculosis is infection of the bloodstream by mycobacteria; this form of the disease is called disseminated or miliary tuberculosis. The bacilli can then spread throughout the body, leading to multiorgan involvement. Miliary tuberculosis progresses rapidly and can be difficult to

diagnose because of its systemic and nonspecific signs and symptoms, such as fever, weight loss, and weakness. Lymphatic tuberculosis is the most common extrapulmonary tuberculosis, and cervical adenopathy occurs most often. Other possible locations include bones, joints, pleura, and genitourinary system

DEFINITIONS FOR CATEGORIZING FOR TREATMENT OF PEDIATRIC TUBERCULOSIS

IAP along with along with working group on tuberculosis has given the following definitions for childhood tuberculosis[12]

A. Case definitions for site

Pulmonary: Refers to disease involving lung parenchyma.

Extra Pulmonary: Refers to disease involving sites other than lung parenchyma Both pulmonary and Extra pulmonary constitutes Pulmonary.

Extra- Pulmonary involving several sites is defined by most severe site.

B. Case definitions for severity

Less severe Pulmonary TB

- Primary Pulmonary complex (PPC)

Severe Pulmonary TB

All other except PPC e.g.

Progressive primary disease

Fibro-cavitatory disease

Miliary

Extra-Pulmonary TB

Less severe extra-pulmonary TB

Single Lymph node site

Unilateral pleural effusion

Severe Extra-Pulmonary TB

Meningitis Spinal or Bone or Peripheral joints

Bilateral or extensive pleural effusion

Intestinal

Genitourinary

Peritonitis

Pericarditis

Adrenal glands

C. Case definition for bacteriology

Smear positive- Sputum / Gastric aspirate /BAL/any other tissue or fluid

Any sample positive for acid fast bacilli on staining

Smear Negative- None positive

D. Type of patient as per history of previous ATT

New Case A patient who has had no previous ATT or had it for less than 4 weeks.

Relapse: Patient declared cured/completed therapy in past and has evidence of recurrence.

Treatment Failure: Patient who fails to respond/deteriorates after 12 weeks of compliant intensive phase.

Treatment after default: A patient who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months and has active disease.

DIAGNOSIS of TB in CHILDREN

The diagnosis of tuberculosis in childhood continues to be surrounded by considerable uncertainty. Although an elevated erythrocyte sedimentation rate (ESR) may be expected in children with tuberculosis, a recent study found that one-third of children with TB had a normal ESR at the time of diagnosis, suggesting little value in using ESR as a diagnostic test for childhood tuberculosis. The following investigations were routinely done for the diagnosis of TB in children.

BACTERIOLOGY

Demonstration of AFB from any body fluid or tissue is the gold standard of diagnosis of tuberculosis. Such a proof is often lacking in

childhood tuberculosis because of difficulty in collection of sputum and due to paucibacillary primary disease in children. However, studies do report that the yield of a positive test in advanced cases may be as high as in adults. Few studies have reported as high as 33% bacteriological positivity even in primary disease such as hilar adenopathy.[13,14] Therefore, every attempt must be made to bacteriologically prove the diagnosis in every case of suspected tuberculosis.

Early morning gastric aspirate is a preferred specimen for most young children with suspected TB for detecting AFB or isolating *M. tuberculosis*. The child is kept fasting for about 6 hours (at night) and an appropriate size intra-gastric tube is passed in the morning. Initially the aspirate is drawn from the stomach and then a further washing with 15-30 Ml saline is taken.The contents so recovered are then immediately transferred to the laboratory. This specimen can also be collected as an ambulatory procedure after 4-6 hours fasting[15]. Sputum collection is possible in older children with extensive and cavitatory disease, particularly if the patient has a wet cough. Induction of sputum by 3% nebulized hypertonic saline can be tried in older children (after the age of 4 months). The patient is pretreated with nebulized bronchodilators prior to induction. Following saline nebulisation, chest physiotherapy is done to loosen up the secretion and the samples are collected from the throat or

nasopharynx.[16] Whatever method one chooses to use, one needs to collect at least two, preferably three, samples. Where the facilities are limited, these tests may be prioritized and atleast be done in all children with wet cough or children who have definite parenchymal lesion on chest skiagram.

Experience with bronchoscopy and bronchoalveolar lavage (BAL) as a diagnostic tool is limited but it is often needed when evaluating persistent pneumonia. TB remains an important cause of persistent pneumonia in our country. Ziehl-Neelsen stain can reveal AFB only if sample contains >10,000 bacilli per mL. Different culture methods are used, such as LJ medium, Radiometric (Bactec) and Non-radiometric (MGIT) can be used for confirming diagnosis in paucibacillary state. The newer methods are capable of giving faster results and may be used if available. Mycobacterial culture assumes special significance in case of suspected drug resistance.

MANTOUX

The standard tuberculin test recommended for use is the Mantoux's test. Commercially available tuberculin in the country are 1, 2 and 5 Tuberculi Unit (TU) PPD (RT23 equivalent). It is important to raise a wheal of about 6 mm after the intra-dermal injection and the test is read 48-72 hours after an injection. Ballpoint or palpatory methods are

used to read the induration. The width of reaction (induration) in the horizontal plane is noted for interpretation .Mantoux's test or PPD skin test is considered positive if the induration is 10 mm or more. This cut off was recommended using a 1 TU PPD RT23. Currently the laboratories more often use 5 TU PPD (RT23 equivalent), or sometimes even some other higher strengths or types of PPD are used. The standard cut off of 10 mm can actually not be justified for any higher strength of PPD used. The reaction evoked is not only dependent on the amount of antigen given but also does not have a linear relationship with the increasing strengths. Therefore, the current practice may actually lead to an increase in false positive reactions using the 10mm cut off with the higher strength of PPD. The Group recommends that the 10mm cut off may be continued to use for strengths of PPD only up to 5TU. Efforts should be made to use only 1 TU PPD to decrease the false positives[17] and in no case strength higher than 5 TU should be used. Degree of reaction, including necrosis and ulceration, may not necessarily differentiate infected from diseased. Prior BCG vaccine has minimal influence on PPD reaction[18,19]. If the patient returns for reading beyond 72 hours but by 7th day, a positive test can still be read. A repeat test may be needed, if there is no induration and the suspect presents beyond the stipulated time for reading. Repeat tuberculin test when

required should preferably be done on the other arm. The reading of the same should be interpreted as in any other individual.

CHEST RADIOGRAPH

Chest radiograph merely localizes the site of pathology and not etiology. There are no pathognomonic radiological signs of tuberculosis. In relevant clinical setting, certain radiological lesions may strongly suggest tuberculosis and they include miliary, hilar or paratracheal lymphadenopathy with or without parenchymal involvement and fibrocaceous cavitatory lesions. Rarely chest *X*-ray may be normal, such cases should be referred to an appropriate center for further detailed investigations if the clinical suspicion is high. In clinical practice, non-resolving chest shadows despite adequate antibiotic therapy in a symptomatic child raises the possibility of tuberculosis. It is worth mentioning that all persistent radiological lesions are not necessarily due to TB.Asymptomatic patients may have persistent shadows due to parenchymal scarring, pleural thickening, and healed fibroatelectatic changes. On the other hand, a child with bronchiectasis or an interstitial lung disease may have presence of non-resolving shadows with persistent symptoms. Ultrasonography of chest is helpful to assess pleural fluid collection; although decubitus chest *X*– ray film may also reveal similar information. CT scan is rarely necessary and is not cost and radiation

effective. Chest CT scan, however,may offer an opportunity for CT guided biopsy for tissue diagnosis.

HUMAN IMMUNODEFICIENCY VIRUS

AGENT FACTOR

HIV,the causative organism of AIDS is a member of the genus *Lentivirus*, part of the family of Retroviridae.Lentiviruses have many morphologies and biological properties in common. Many species are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors.[20] Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system. Alternatively, the virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.

Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was initially discovered and termed both LAV and HTLV-III. It is more virulent, more infective,[21] and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 compared to HIV-1 implies that fewer of those exposed to HIV-2 will be infected per exposure. Because of its relatively poor capacity for transmission, HIV-2 is largely confined to West Africa.

STRUCTURE AND GENOME

HIV is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120 nm, around 60 times smaller than a red blood cell, yet large for a virus. It is composed of two copies of positive single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24.[22] The single-stranded RNA is tightly bound to nucleocapsid proteins, p7, and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle.[22] This is, in turn, surrounded by the viral envelope that is composed of two layers of fatty molecules called phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral

envelope are proteins from the host cell and about 70 copies of a complex HIV protein that protrudes through the surface of the virus particle.[81] This protein, known as Env, consists of a cap made of three molecules called glycoprotein (gp) 120, and a stem consisting of three gp41 molecules that anchor the structure into the viral envelope. This glycoprotein complex enables the virus to attach to and fuse with target cells to initiate the infectious cycle. Both these surface proteins, especially gp120, have been considered as targets of future treatments or vaccines against HIV.

The RNA genome consists of at least seven structural landmarks (LTR, TAR, RRE, PE, SLIP, CRS, and INS), and nine genes (*gag*, *pol*, and *env*, *tat*, *rev*, *nef*, *vif*, *vpr*, *vpu*, and sometimes a tenth *tev*, which is a fusion of tat env and rev), encoding 19 proteins. Three of these genes, *gag*, *pol*, and*env*, contain information needed to make the structural proteins for new virus particles.[22] For example, *env* codes for a protein called gp160 that is broken down by a viral enzyme to form gp120 and gp41.The six remaining genes, *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* (or *vpx* in the case of HIV-2), are regulatory genes for proteins that control the ability of HIV to infect cells, produce new copies of virus (replicate), or cause disease.[22]

The two Tat proteins (p16 and p14) are transcriptional transactivators for the LTR promoter acting by binding the TAR RNA element. The TAR may also be processed into micro RNAs that regulate the apoptosis genes ERCC1 and IER3. The Rev protein (p19) is involved in shuttling RNAs from the nucleus and the cytoplasm by binding to the RRE RNA element. The Vif protein (p23) prevents the action of APOBEC3G (a cell protein that deaminates DNA:RNA hybrids and/or interferes with the Pol protein). The Vpr protein (p14) arrests cell division at G2/M. The Nef protein (p27) down-regulates CD4 (the major viral receptor), as well as the MHC class I and class II molecules.

Nef also interacts with SH3 domains. The Vpu protein (p16) influences the release of new virus particles from infected cells.[22] The ends of each strand of HIV RNA contain an RNA sequence called the long terminal repeat (LTR). Regions in the LTR act as switches to control production of new viruses and can be triggered by proteins from either HIV or the host cell. The Psi element is involved in viral genome packaging and recognized by Gag and Rev proteins. The SLIP element (TTTTTT) is involved in the frameshift in the Gag-Pol reading frame required to make functional Pol.[22]

TROPISM

The term viral tropism refers to which cell types HIV infects. HIV can infect a variety of immune cells such as $CD4^+$ T cells, macrophages, andmicroglial cells. HIV-1 entry to macrophages and $CD4^+$ T cells is mediated through interaction of the virion envelope glycoproteins (gp120) with the CD4 molecule on the target cells and also with chemokine coreceptors.

Macrophage (M-tropic) strains of HIV-1, or non-syncitia-inducing strains (NSI) use the β-chemokine receptor CCR5 for entry and are, thus, able to replicate in macrophages and $CD4^+$ T cells.[23] This CCR5 coreceptor is used by almost all primary HIV-1 isolates regardless of viral genetic subtype. Indeed, macrophages play a key role in several critical aspects of HIV infection. They appear to be the first cells infected by HIV and perhaps the source of HIV production when $CD4^+$ cells become depleted in the patient. Macrophages and microglial cells are the cells infected by HIV in the central nervous system. In tonsils and adenoids of HIV-infected patients, macrophages fuse into multinucleated giant cells that produce huge amounts of virus.

T-tropic isolates, or syncitia-inducing (SI) strains replicate in primary $CD4^+$ T cells as well as in macrophages and use the α-chemokine

receptor, CXCR4, for entry.[23] Dual-tropic HIV-1 strains are thought to be transitional strains of HIV-1 and thus are able to use both CCR5 and CXCR4 as co-receptors for viral entry.

The α-chemokine SDF-1, a ligand for CXCR4, suppresses replication of T-tropic HIV-1 isolates. It does this by down-regulating the expression of CXCR4 on the surface of these cells. HIV that use only the CCR5 receptor are termed R5; those that use only CXCR4 are termed X4, and those that use both, X4R5. However, the use of coreceptor alone does not explain viral tropism, as not all R5 viruses are able to use CCR5 on macrophages for a productive infection[23] and HIV can also infect a subtype of myeloid dendritic cells,[24] which probably constitute a reservoir that maintains infection when $CD4^+$ T cell numbers have declined to extremely low levels.

Some people are resistant to certain strains of HIV. For example, people with the CCR5-Δ32 mutation are resistant to infection with R5 virus, as the mutation stops HIV from binding to this coreceptor, reducing its ability to infect target cells.

TRANSMISSION OF HIV IN CHILDREN

In children, the mode of transmission is predominantly mother to child (vertical transmission) with transmission rate varying

from 25% to 40%. The transmission can occur intrauterine (materno-fetal transfusion, placental inflammation), intrapartum (on exposure to body fluids and cervical secretions at the time of labour) and through breast-feeding. Infact transmission through breast-feeding has been reported to vary from 14% to 29% in various studies. Thus, the ideal way to prevent vertical transmission of HIV would be to avoid intrauterine, intrapartum and postpartum (breast-feeding) transmission of HIV.

Transmission of HIV by transfusion of blood and blood products is seen in patients with Thalessemia and patients with Hemophilia or leukemia who require repeated transfusions.

Sexual transmission of HIV is rare and is seen in patients who have been sexually abused by HIV infected adults.

Transmission of HIV is found to be more during high viremia, recent infection, low CD4 count state and advanced stage of disease and thus regular monitoring for progression of the disease is essential.

PATHOGENESIS

HIV virus when it enters into a susceptible host zooms to the lymphocytes (predominantly CD4 T cells) and infects the cells. After initial infection, there is a state of high replication leading to acute viral

like illness. But the body's immune system subsequently recognizes the virus as foreign and builds an immune response by a complex interplay of various cytokines and proteins and leads to a latent phase whereby a balance is struck between the acute replication and immune response. This is a phase when the infected individual would be asymptomatic and just a laboratory investigation would reveal the infectivity status.

During the latent phase, the HIV virus lives predominantly in the lymphoid tissue and multiplies. Peripheral viremia is less. The person may just present with generalized lymphadenopathy. Once the fine balance between viral replication and immune response is overcome, the virus leads to peripheral blood over-pooling and viremia with destruction of CD4 T cells and immunosuppression. CD4 T cells also called as helper cells are the cells that lead to activation of CD8 T cells for cell mediated immunity and also help in conversion of B cells to plasma cells and generation of humoral immunity. With destruction of CD4 cells, both cell-mediated immunity and humoral immunity is affected and a person becomes susceptible to opportunistic infections including viral, fungal, bacterial and parasitic and also has increased susceptibility to malignancies.

With increased destruction of CD4 T cells, the HIV virus replicates extensively and can also confer damage to the various organs of the body directly. Thus, a patient may have in addition various organ dysfunctions such as encephalopathy, nephropathy, cardiomyopathy, pulmonary disease, gastrointestinal disease, hepatitis and suppression of bone marrow.

In children, the latent phase is usually not seen, as there are several differences as compared to adults.

1. Children usually acquire the infection vertically whereas predominant mode of transmission in adults is sexual.
2. Children have an immature immune system at the time of acquisition of the virus. Thus, with initial exposure to the virus, children have a prolonged viremia phase, the immune system is not able to mount an adequate immune response and thus progression to AIDS is faster.

DIAGNOSIS OF HIV IN CHILDREN

As maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in children born to HIV-infected mothers, the interpretation of positive HIV antibody test results is more difficult in children below this age. Also, children

who are breastfed have ongoing risk for HIV acquisition: therefore HIV infection can only be excluded after breast-feeding is stopped for > 6 weeks. In India, antibody tests and ELISA can be used for infants > 18 months as per adults; and for infants < 18 months, DNA PCR will be done using dried blood spots (DBS).

In any child > 18 months of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay (EIA) and confirmatory test (immunoblot or immunofluoresence assay) establishes the diagnosis of HIV infection. Incorporation rapid HIV testing during delivery or immediately after birth is crucial for the care of HIV-exposed newborns whose HIV status was unknown during pregnancy.

Following diagnostic tests are considerably more useful in young infants, allowing a definitive diagnosis in most infected infants by 1 – 6 months of age.

TEST	COMMENT
HIV DNA PCR	Preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18months of age: highly sensitive and specific by 2wk of age and available; performed on peripheral blood mononuclear cells. False negatives can occur in non- B subtype HIV-1 infections.
HIV p24Ag	Less sensitive; false positive results during 1 mo of life, variable results; not recommended.
ICD p24 Ag	Negative test result does not rule out infection; not recommended.
HIV culture	Expensive , not easily available, requires upto 4 wk to do test ; not recommended
HIV RNA PCR	Not recommended for routine testing of infants and children younger than 18 months of age, because a negative result cannot be used to exclude HIV infection definitely. Preferred test to identify non-B subtype HIV-1 infections.

There are two widely used classification of HIV/ AIDS in children.

1) WHO clinical staging of HIV /AIDS for children with confirmed HIV infection.
2) WHO immunological classification

WHO Clinical Staging of HIV/AIDS and Case Definition

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2006. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count.

This staging system is used in many countries to determine eligibility for antiretroviral therapy. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥15 years.

CLINICAL STAGE 1

Asymptomatic

Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained persistent hepatosplenomegaly

Papular pruritic eruptions

Extensive wart virus infection

Extensive molluscum contagiosum

Fungal nail infections

Recurrent oral ulcerations

Unexplained persistent parotid enlargement

Lineal gingival erythema

Herpes Zoster

Recurrent or chronic upper respiratory infections (otitis media, otorrhoea, sinusitis or tonsillitis)

CLINICAL STAGE 3

Unexplained moderate malnutrition not adequately responding to standard therapy

Unexplained persistent diarrhea (14 days or more)

Unexplained persistent fever (above 37.5° C intermittent or constant, for longer than one month)

Persistent oral candidiasis (after first 6 – 8 weeks of life)

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis or periodontitis

Lymph node tuberculosis

Pulmonary tuberculosis

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pnemonitis

Chronic HIV- associated lung disease including bronchiectasis

Unexplained anaemia (< 8 g /dl), neutropenia ($< 0.5 \times 10^9$ per liter) and/ or chronic thrombocytopenia ($< 50 \times 10^9$ per liter)

CLINICAL STAGE 4b

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections(such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)

Chronic herpes simplex infection(orolabial or cutaneous of more than one month's duration or visceral at any site)

Extrapulmonary tuberculosis

Kaposi sarcoma

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Central nervous system toxoplasmosis (after one month of life)

HIV encephalopathy

Cytomegalovirus infection

Extrapulmonary cryptococcosis (including meningitis)

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated non-tuberculous mycobacterial infection

Cerebral or B-cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy

Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a. – Unexplained refers to where the condition is not explained by other causes.

b. - Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO Region of the Americas, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

WHO IMMUNOLOGICAL CLASSIFICATION

Following is the revised classification of immune suppression in children

HIV-associated immunodeficiency	<11 months (% CD4+)	12 - 35 months (% CD4+)	36 – 59 Months (% CD4+)	> 5 years cells/ cu.mm
Not significant	> 35	> 30	> 25	> 500
Mild	30 - 35	25 - 30	20 – 25	350 – 499
Advanced	25 - 30	20 – 25	15 – 20	200 – 349
Severe	< 25 % or <1500cells/ cu.mm	< 20 or <750cells/ cu.mm	< 15 or <350cells/ cu.mm	< 15 % or <200cells/ cu.mm

In children, the mode of transmission is predominantly mother to child (vertical transmission). Risk factors for perinatal transmission and strategies to prevent vertical transmission have been laid down by the NACO.

RISK FACTORS FOR PERINATAL HIV TRANSMISSION[25]

The following factors are associated with increased risk of vertical transmission.

i)**Viral factors:** High viral load, non-syncytium inducing phenotype, HIV-1

ii)**Maternal factors:** Advanced disease (low CD4 count, symptoms of AIDS), primary infection of mother during pregnancy, first of twins, rupture of membranes more than four hrs, maternal bleeding, mother not on antiretroviral therapy, vaginal delivery, other sexually transmitted diseases, isolated HIV-1 infection

iii)**Fetoplacental factors:** chorioamnionitis, placenta previa, prematurity (increased peripartum transmission)

iv)**Infant factors:** HLA concordance with mother

v)**Postnatal factors:** breast feeding, higher breast milk virus load, mastitis or maternal nipple lesions, maternal seroconversion during breastfeeding, infant having thrush at less than six month age (in breastfeeding infant)

Prevention of perinatal HIV

In the absence of any intervention the risk of perinatal transmission is 15–30% in non-breastfeeding populations[25].

Breastfeeding by an infected mother increases the risk by 5–20% to a total of 20–45% [26].

The risk of MTCT can be reduced to under 2% by interventions that include antiretroviral (ARV) prophylaxis given to women during pregnancy and labour and to the infant in the first 6 weeks of life, obstetrical interventions including elective caesarean delivery (prior to the onset of labour and rupture of membranes), and complete avoidance of breastfeeding [27-29].

1) ARV regimens for treating pregnant women[30]

A) For HIV-infected pregnant women in need of ART for their own health**,** ART should be administered irrespective of gestational age and continue throughout pregnancy, delivery and thereafter (recommended for all HIV-infected pregnant women with CD4 cell count <350 cells/mm3,irrespective of WHO clinical staging; and for WHO clinical stage 3 or 4,irrespective of CD4 cell count)

B) Recommended regimen for pregnant women with indication for ART is combination of zidovudine (AZT), lamivudine (3TC) and

nevirapine (NVP)or efavirenz (EFV) in antepartum, intrapartum and postpartum period;EFV-based regimens should not be newly-initiated during the first trimester of pregnancy.

C) Recommended regimen for pregnant women who are not eligiblefor ART, but for preventing MTCT is to start ART as early as 14 weeks gestation or as soon as possible when women present late in pregnancy, in labour or at delivery. Two options for ART are available:

i)Option A: daily AZT in antepartum period, combination of single dose of NVP at onset of labour and dose of AZT and 3TC during labour followed by combination of AZT and 3TC for 7 days in postpartum period.

ii)Option B: consists of triple ARV drugs starting as early as 14 weeks of gestation until one week after all exposure to breast milk has ended (AZT + 3TC + LPV or AZT + 3TC + ABC or AZT + 3TC + EFV); [ABC= abacavir].

D) Omission of the Single dose-NVP and AZT+3TC intra and postpartum may be considered for women who receive at least four weeks of AZT before delivery.

E) If a woman received a three-drug regimen during pregnancy, a Continued regimen of triple therapy is recommended for mother through the end of the breastfeeding period.

2)ARV regimens for infants born to HIV infected mothers [31]

i)For breastfeeding infants: daily NVP from birth until 6 weeks of age or until one week after all exposure to breast milk has ended. The dose of nevirapine is 10 mg/ d for infants < 2.5 kg; 15 mg/ d for infants more than 2.5 kg

ii)For non-breastfeeding infants: daily AZT or daily NVP from birth until 6 weeks of age. The dose of zidovudine is 4 mg/ kg twice a day.

3)Intrapartum interventions

i) Avoid rupture of membranes unless medically indicated.

ii) Delivery by elective caesarean section at 38 weeks before onset of labour and rupture of membranes.

iii) Avoid procedures increasing risk of exposure of child to maternal blood and secretions like use of scalp electrodes.

4)Breast feeding

Breast-feeding is an important mode of transmission of HIV infection in developing countries. The risk of HIV infection via breast-feeding is highest in the early months of breast-feeding[32] . Exclusive breastfeeding has been reported to carry a lower risk of HIV transmission than mixed feeding.

Factors that increase the likelihood of transmission include Detectable levels of HIV in breast milk, the presence of mastitis and low maternal CD4+ T cell count.

Mothers known to be HIV-infected should only give commercial infant formula milk as a replacement feed when specific conditions are met (referred to as AFASS – affordable, feasible, acceptable, sustainable and safe in the 2006 WHO recommendations on HIV and Infant Feeding)[33]

Mothers known to be HIV-infected may consider expressing and heattreating breast milk as an interim feeding strategy in special circumstances such as:

a)Low birth weight or is otherwise ill in the neonatal period and unable to breastfeed

b)Mother is unwell and temporarily unable to breastfeed

c)Temporary breast health problem such as mastitis

d)To assist mothers to stop breastfeeding

e) If antiretroviral drugs are temporarily not available

Replacement feeding should be given by katori spoon; bottle feeds should be avoided.

If replacement feeding is not feasible, mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status)

should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then stop once a nutritionally adequate and safe diet without breast milk can be provided.

Breastfeeding should stop gradually in one month.

IMPACT OF HIV ON TB

HIV has a pronounced effect on the development of TB disease. About a third of HIV infected individuals worldwide are co-infected with TB infection. In some countries in sub-Saharan Africa, up to 70 percent of patients with smear-positive pulmonary TB are HIV positive [(34)]. HIV fuels the TB epidemic in several ways. HIV promotes the progression.

To active TB disease, both in people with recently acquired TB infection and with latent M.tuberculosis infection. HIV is the most powerful risk factor for reactivation of latent tuberculosis infection to active disease. HIV infected persons are more susceptible to becoming infected with TB when exposed to M. tuberculosis. The annual risk of developing TB disease in a PLWHA who is co-infected with M. tuberculosis is 5 to 15 percent [(35)] HIV increases the rate of recurrent TB disease, which may be due to either endogenous reactivation (true relapse)

or exogenous re-infection[36]. Increase in tuberculosis cases amongst the PLWHA poses an increased risk of TB transmission to the general community.

An HIV infected person co-infected with M. tuberculosis has a 50 percent lifetime risk of developing TB disease, whereas an HIV non-infected person infected with M. tuberculosis has only a 10 percent risk of developing TB[37,38]. This is especially important in India, where it is estimated that 40 percent of the adult population is infected with M. tuberculosis. It is estimated that 50-60 percent of the HIV-infected persons in India will develop TB disease during their life-time[39]

IMPACT OF TB ON HIV

The course of HIV infection is accelerated following the acquisition of TB infection. The development of TB is associated with increased HIV-1 replication and increased viral loads due to increased systemic immune activation as well as altered local cytokine milieu at sites of *M. tuberculosis* infection. Mycobacteria enhance HIV replication in tissues by inducing nuclear factor kappa-β, the cellular factor that binds to the promoter region of HIV. Mononuclear cell activation is a feature of active TB disease. Mononuclear cells that express HLA-DR are the most productive source of HIV replication. Dysregulation in β chemokines and

their receptors has been described during TB; this may contribute to enhanced viral dissemination. Programmed cell death of T cells is increased at the time of diagnosis of pulmonary TB in HIV-infected patients and may be partly responsible for further loss of immune responses directed to HIV-1. TB provides a milieu of continuous cellular activation and changes in cytokine and chemokine circuits that are permissive of viral replication and expansion in situ.

AIM OF THE STUDY

To screen for TB coinfection in HIV positive children registered in ART Centre , Madurai.

MATERIALS AND METHODS

PLACE OF THE STUDY

This study was conducted at ART centre and institute of child health and research centre, Madurai.

DURATION OF THE STUDY

One year (September 2010 - August 2011)

INCLUSION CRITERIA

Children, who are HIV positive in the age group of 18 months to 12 years registered in the ART centre.

EXCLUSION CRITERIA

Children less than 18 months were not included, as the facility for making diagnosis of HIV by PCR was not available at the ART centre, Madurai.

Children who are taking ATT

METHODOLOGY

Informed consent was obtained from the parent/ guardian for registering the required data.

A special proforma was designed to record the following information.

- Demographic data
- Anthropometry
- Parental and sibling status
- Immunisation status
- Developmental milestones
- Contact history
- Clinical staging
- Immunological staging

The children were subjected to the following investigations that include

- Complete blood count
- ESR
- CD4 count
- Chest X-ray
- Gastric juice for AFB
    1. Ziel – Neelson
    2. Fluorescent microscopy

- Mantoux
- Lymph node biopsy / FNAC (if needed)
- LFT
- Other investigations (If necessary)
    1. USG abdomen
    2. CT scan
    3. CSF analysis

All the children were subjected to chest x-ray and tuberculin skin testing to detect tuberculosis. Sputum smear microscopy for acid fast bacilli (AFB) was performed from the sputum specimens obtained from children, who were found or motivated to expectorate themselves. In very young patients, gastric juice aspirates were examined for AFB.

The overall clinical features, radiological findings, enhanced tuberculin indurations (>5 mm to 1 TU of PPD is considered positive) and sputum smear microscopic study were taken into consideration for diagnosing primary and pulmonary tuberculosis.

Clinical presentation, fine needle aspiration cytology (FNAC) of lymph nodes, enhanced tuberculin indurations (>5 mm to 1 TU of PPD), smear microscopy for AFB from all the aspirates and CSF, ultra

sonography of abdomen and/or CT scan brain, wherever needed, helped in diagnosing extra-pulmonary tuberculosis.

Statistical Analysis

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated by One way ANOVA and ‘t’ test. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate’s chi square test for qualitative variables.

A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATIONS AND RESULTS

TABLE 1

STATISTICS OF HIV-INFECTED CHILDREN AT ART CENTRE, MADURAI as on August, 2009.

CHIDREN	MALE	FEMALE	TOTAL
Registered at centre	377	379	756
On ART	139	136	275
Currently on ART at Madurai centre	74	74	148

TABLE 2

NEWLY DIAGNOSED CASES DURING THE STUDY PERIOD

	MALE	FEMALE	TOTAL
SEPTEMBER	0	3	3
OCTOBER	1	1	2
NOVEMBER	1	3	4
DECEMBER	7	1	8
JANUARY	4	3	7
FEBRUARY	1	1	2
MARCH	5	2	7
APRIL	0	1	1
MAY	2	0	2
JUNE	1	3	4
JULY	2	1	3
AUGUST	2	0	2
TOTAL	26	19	45

Table – 3

Sex Distribution

Total number of children screened during the study period - 103

Sex	No.of cases
MALE	64
FEMALE	39

Of the 103 children screened for TB coinfection, 64 were male children and 39 were female children. Male : female ratio is 1.64 : 1

SEX DISTRIBUTION

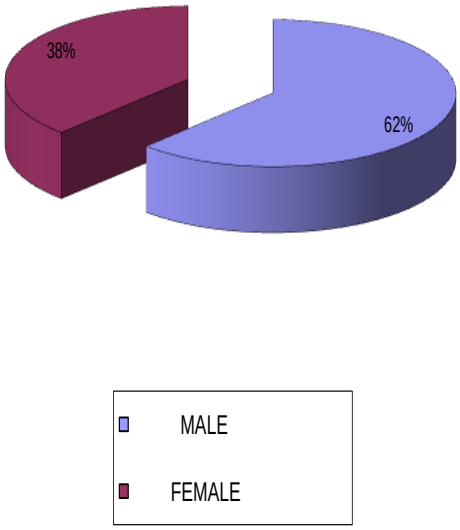

TABLE -4

IMMUNOLOGICAL STAGING

The 103 children were categorized based on WHO immunological system.

The results were as follows

Immunological Staging	No.of cases	Percentage
None or not significant	52	50.48%
Mild	26	25.24%
Advanced	19	18.44%
Severe	06	05.82%

Most of the children(50.48%) in the study group belonged to immunological staging none or not significant

IMMUNOLOGICAL STAGING

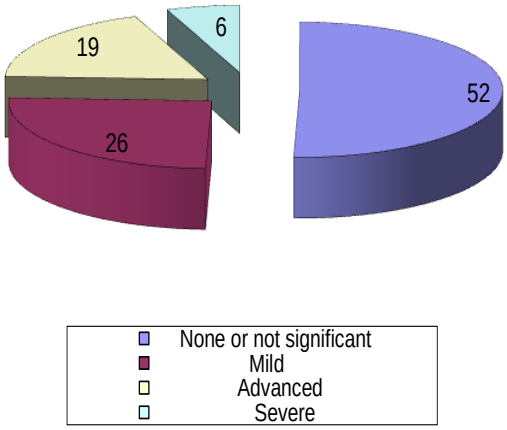

TABLE - 5

POSITIVE CASES

	Screened positive for TB	Negative for TB
Male	8	56
Female	5	34
Total	13	90

No. children screened positive for tuberculosis - 13.

Tuberculosis co-infection in our study was found to be 12.6% (n=13).

SEX DISTRIBUTION IN POSITIVE CASES

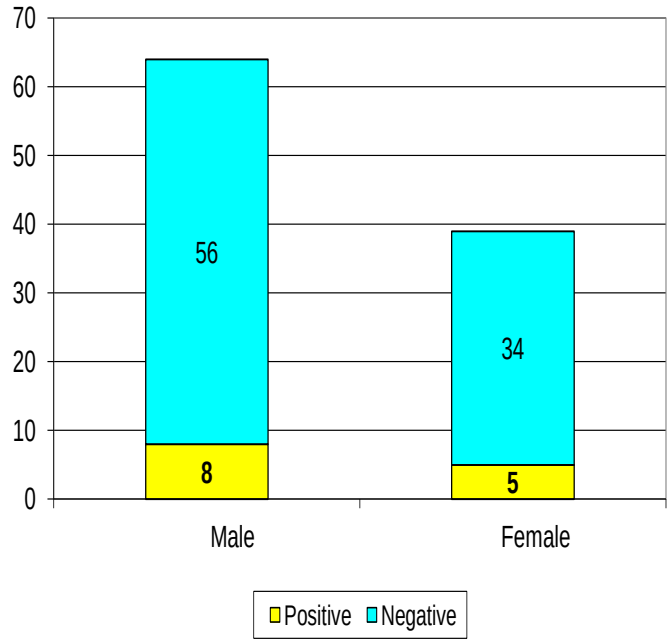

TABLE - 6

CONTACT HISTORY

Contact History	Total No.of cases Screened	Screened positive for tuberculosis	%
Children with contact history	14	10	71.42
Children without contact history	89	3	3.37
Total	103	13	

Out of 13 children screened positive for tuberculosis, 10(76.92%) children had contact with an open case of TB.

CONTACT HISTORY

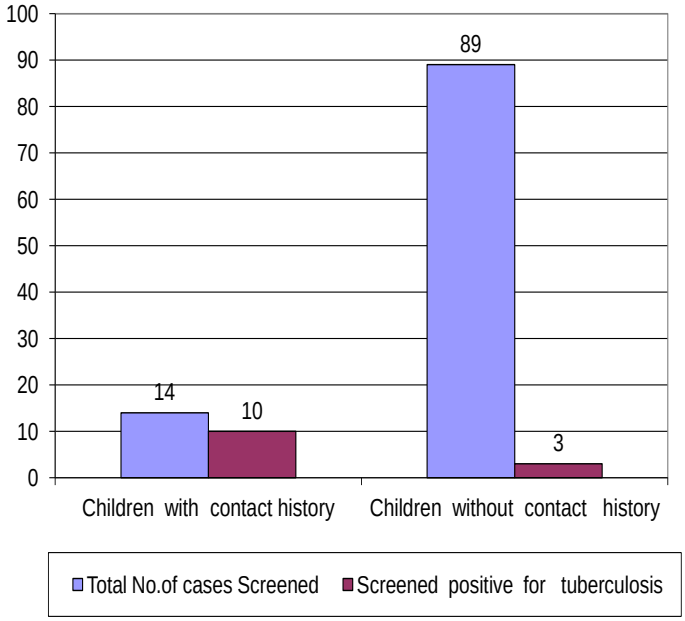

TABLE 7

MANTOUX

Mantoux testing was performed on all the children and the results were as follows:

OBSERVATION	No.of cases
0 mm	70
< 5 mm	22
5 – 9 mm	09
> 10 mm	02

Mantoux positivity was observed in 10.67%(n=11) of screened children.

MANTOUX

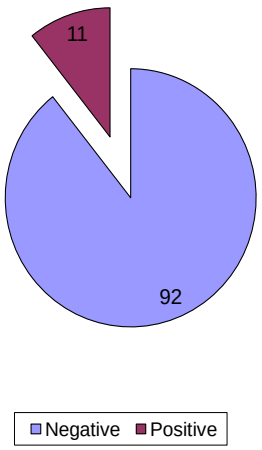

TABLE - 8

CHEST RADIOGRAPHY

CHEST RADIOGRAPHY FINDINGS	No.of cases
HILAR ADENOPATHY	33
PLEURAL EFFUSION	01
LOCALISED PULMONARY INFILTRATES	13
DIFFUSE INFILTRATES	03
MIDDLE LOBE CONSOLIDATION AND COLLAPSE	01
BRONCHOPNEUMONIA	21

Hilar adenopathy was the most common radiological finding, found in 32%(n=33) of screened children.

CHEST RADIOGRAPHY FINDINGS

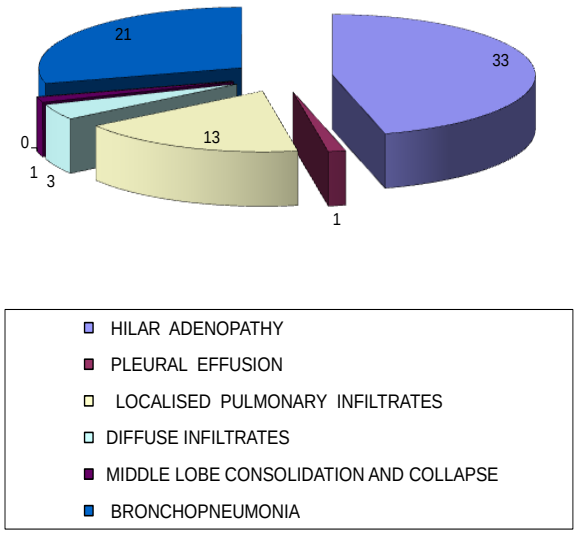

TABLE - 9

GASTRIC JUICE/ SPUTUM MICROSCOPY

POSITIVE	03
NEGATIVE	100

AFB was demonstrable only in 3 cases, out of 103 children screened for.

GASTRIC JUICE/ SPUTUM MICROSCOPY

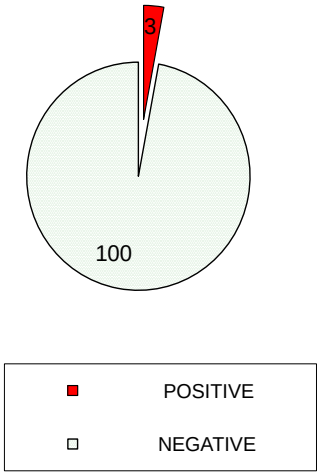

TABLE - 10

LYMPH NODE – FNAC

Of the 103 children screened for TB, 9 (8.7%) children presented with lymphadenopathy.

FNAC was done and the results were as follows:

Caseous Granuloma	2	22.2%
Reactive Lymphadenitis	5	55.55%
Follicular Hyperplasia	2	22.22%

Reactive lymphadenitis (55.5% ; n =5) was the most common finding; followed by caseous granuloma and follicular hyperplasis in 22.22% (n=2).

LYMPH NODE FNAC

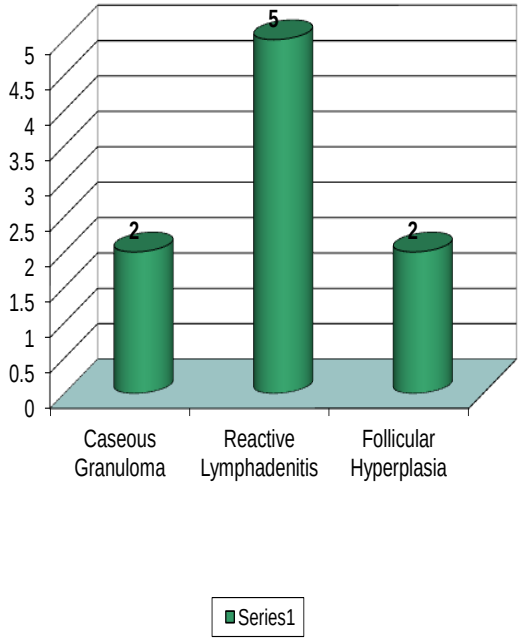

TABLE 11: ANALYSIS OF POSITIVE CASES

CASE No.	Contact History	Mantoux	Chest X-ray	Sputum/Gastric juice Microscopy	Other investigations
01	+	13 mm	Hilar adenopathy	Negative	
02	Nil	8 mm	Normal	Negative	FNAC + ve
03	+	6 mm	Middle lobe consolidation	Positive	
04	Nil	0 mm	Pleural Effusion	Negative	
05	+	9 mm	Hilar adenopathy	Negative	
06	+	10 mm	Hilar adenopathy	Negative	
07	+	8 mm	Normal	Negative	
08	+	2 mm	Hilar adenopathy	Negative	FNAC + ve
09	+	8 mm	Patchy opacity in R upper lobe	Positive	
10	+	7 mm	Hilar adenopathy	Negative	USG-Abd & Ascitic fluid analysis
11	Nil	8 mm	Hilar adenopathy	Negative	
12	+	8 mm	Normal	Negative	
13	+	6 mm	Hilar adenopathy	Positive	

DISCUSSION

SEX DISTRIBUTION IN NEWLY DIAGNOSED CASES

Of the new HIV positive children, 57.7 %(n=26) and 42.2%(n=19) were male and female respectively. This was similar to **S.Rajasekaran et al.,**[40] study at Tambaram in which male & female children constituted 56.9 and 43.1 percent respectively . Male children outnumber female children by a small number.

CONTACT HISTORY

Of the 13 children screened positive for tuberculosis, 10 children (76.92%) had contact with an open case of TB and it was Statistically significant(p value <0.0001)

This was similar to **Ira shah et al**[41] study in which 70.7% had contact with an adult suffering from TB

Young children living in close contact with a source case of smear-positive pulmonary TB are at particular risk for TB infection and disease. The risk of infection is greatest if the contact is close and prolonged, such as that between an infant or toddler and the mother or other caregivers in the household.

INCIDENCE

Tuberculosis co-infection in our study was found to be 12.6% (n=13).

Rajasekaran et al.[40] reported TB coinfection in 63.1 % (n=1115) of HIV infected children. This may be due to high referral and larger population studied and this study was done before initiation of ART.

Following is the incidence of TB in HIV infected children in various Indian studies.

	Daga et al [42] n=28	Dhurat et al. [43] n=55	Lodha et al. [44] n=27	Merchant et al. [45] n=285	Our study n=103
Incidence	8(28.5%)	27(49%)	13(48.1%)	84(29.4%)	13(12.6%)

Andrew Edmonds et al.[46] reported that the TB incidence rate in those receiving ART was 10.2 per 100 person-years [95% confidence interval (CI) 7.4–13.9] compared with 20.4 per 100 person-years (95% CI 14.6–27.8) in those receiving only primary HIV care. TB incidence decreased with time on ART, from 18.9 per 100 person-years in the first 6 months to 5.3 per 100 person-years after 12 months of ART.

MANTOUX

Induration of > 5 mm was considered positive. So 11 children were considered positive and their cathegorization based on WHO immunological staging is as follows:

Immunological Staging	No.of cases	Percentage
None or not significant	0	0
Mild	8	73%
Advanced	3	27%
Severe	0	0

Even in HIV positive children, induration of > 10 mm was observed in two cases.

The following is the number of tuberculin positive cases in various Indian studies:

	Daga et al [42] n=28	Dhurat et al. [43] n=55	Lodha et al. [44] n=27	Merchant et al. [45] n=285	Our study n=103
Tuberculin positivity	04	0	_	_	11

The Mantoux test remains useful in the diagnosis of TB in children and is frequently positive even in HIV-infected children. In a recent study of Malawian children with suspected PTB, 11 out of 31 Mantoux-positive children were HIV-infected.[47] In this study, although less sensitive, the Mantoux was positive in 14 HIV-positive patients, comprising almost one third of the total number of positives.

GASTRIC JUICE/ SPUTUM MICROSCOPY

Only in 3 cases, AFB was demonstrable. The yield of gastric juice/ sputum microscopic studies was low due to paucibacillary nature of TB infection in HIV-infected children.

Berggren Palme et al.,[48] study stated Direct microscopy for acid-fast bacilli was positive for 15% (n=55).

CHEST RADIOGRAPHY

In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. The commonest picture is that of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands.

Of the cases confirmed by Mantoux and Microscopy, hilar adenopathy was observed in 53.8% (n=7); pleural effusion in 7.6 % (n=1) ; local infiltrates in 7.6 % (n=1) ; middle lobe consolidation in 7.6 % (n=1).

Vicci du plessis et al.[49] stated that normal radiographs were reported in 54% of HIV-infected children. Those with radiographic abnormalities had parenchymal disease (34%) ; mediastinal disease (22%) ; and pleural disease(1%). Radiological appearances of TB were seen in 9% of patients

LYMPH NODE FNAC

Of the 103 children screened for TB, 9 (8.7%) presented with lymphadenopathy, FNAC proved to be TB in only 2 cases. Reactive lymphadenitis was the most common FNAC finding.

But **Shobhana et al.**[50] study showed reactive hyperplasia in 55.5%(n=30), and evidence of tuberculous lymphadenitis and NHL in41%(n =22) and 3.7%(n = 2) respectively.

Lakshmi et al.[51]documented 186 cases of tubercular infection out of 643 HIV reactive cases, of which 14%(n=26) had TB lymphadenitis proven by FNAC and ZN stain.

CONCLUSION

- HIV associated TB is a major public health problem. Tuberculosis co-infection in HIV infected children was found to be 12.6% in our study. This may be due to the impact of ART. ART has been shown to reduce the incidence of TB in treated cohorts even in high TB prevalence countries.
- Source of childhood TB is usually an adult, who is in close contact with the children.
- Mantoux is positive even in HIV- infected children. So mantoux is an important diagnostic tool even in HIV-infected children.
- FNAC proved to be TB in only 2 cases . So Lymphnode – FNAC or biopsy is mandatory for children presenting with lymphadenopathy before starting empirical ATT.
- With the conventional sputum positivity and Tuberculin test not providing an adequate diagnostic help, familiarity with clinco radiological spectrum of TB and HIV coinfection will help in early diagnosis.

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PROFORMA

S.No : Date of Interview :

NAME : AGE :

SEX :

ANTHROPOMETRY

HEIGHT -

WEIGHT -

MAC -

AGE AT THE TIME OF DIAGNOSIS -

TEST : ELISA / WESTERN BLOT/ DNA-PCR

HIV STATUS OF PARENTS -

i)Mother (Reactive/Non-Reactive)

(Alive/Dead)

(on ART/ not on ART)

ii)Father(Reactive/Non-Reactive)

(Alive/Dead)

(on ART/ not on ART)

ANTENATAL HISTORY :

i) HIV diagnosed before , during or after pregnancy

ii) Total No. hospital visits

iii) TT injection

iv) IFA intake

v) Anaemia/ PIH / DM /APH

MATERNAL DELIVERY DATA :

i) Mode of delivery

a) Vaginal

b) Assisted

c) Caesarean

ii) Place of delivery

a) Home

b) Institution

iii) Nevirapine prophylaxis

a) Received

b) Not received

c) Status not known

iv) Feeding Practices

a) Breast feed alone

b)Artificial feeds

c)Combined breast & artificial feeds

IMMUNISATION STATUS :

DEVELOPMENTAL MILESTONES :

CONTACT HISTORY :

WHETHER ON COTRIMOXAZOLE PROPHYLASIS OR NOT

GENERAL EXAMINATION :

Pallor -

Jaundice -

Generalised lymphadenopathy-

Clubbing -

Pedal edema -

Oral examination - Candidiasia / Oral hairy Leukoplakia

Cutaneous manifestations – herpes zoster/ Papular pruritic eruptions / Diffuse skin dryness Warts, molluscum Angular cheilits and parotitis

SYSTEMIC EXAMINATION :

CLINICAL STAGING:

IMMUNOLOGICAL STAGING:

INVESTIGATION :

1. Complete blood count
2. Chest X- ray
3. Gastric juice for AFB
    i) Ziel-Neelson
    ii) Fluorescent microscopy
4. Mantoux
5. LFT
6. Other Investigations

FOLLOW UP OF PATIENTS ON ART:

1)New opportunistic infection – yes/no

(If yes, specify)

2) IRIS – yes/no (If yes, specify)

3) ART related toxicity-yes/no (If yes, specify)

4)Treatment failure – yes/no (If yes, specify)

5)Other common childhood infection

Serial No.	AGE(yrs)	SEX	BCG SCAR	CONTACT HISTORY	MANTOUX	MICROSCOPY FOR AFB	CHEST X-RAY	OTHER INVESTIGATIONS
1	4	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
2	11	M	Absent	NIL	0 mm	Negative	Localized Infiltrates	
3	8	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
4	5	F	Absent	NIL	0 mm	Negative	Localized Infiltrates	
5	6	M	Present	NIL	0 mm	Negative	Normal	FNAC – ve
6	3	F	Absent	NIL	0 mm	Negative	Diffuse Infilatrates	
7	11	M	Present	NIL	3 mm	Negative	Normal	
8	7	M	Absent	+	13mm	Negative	Hilar adenopathy	
9	3	F	Present	NIL	2 mm	Negative	Bronchopneumonia	
10	8	M	Absent	NIL	3 mm	Negative	Hilar adenopathy	
11	5	F	Present	NIL	0 mm	Negative	Bronchopneumonia	
12	8	M	Absent	+	0 mm	Negative	Localized Infiltrates	
13	5	M	Absent	NIL	8 mm	Negative	Normal	FNAC + ve
14	7	F	Absent	NIL	4 mm	Negative	Localized Infiltrates	
15	3	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	
16	5	M	Absent	NIL	0 mm	Negative	Normal	
17	8	M	Present	NIL	0 mm	Negative	Hilar adenopathy	
18	11	F	Present	NIL	0 mm	Negative	Localized Infiltrates	
19	10	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
20	4	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	
21	8	F	Present	NIL	0 mm	Negative	Normal	

22	8	F	Absent	+	6 mm	Positive	Consolidation	
23	4	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	
24	8	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
25	11	F	Absent	NIL	0 mm	Negative	Hilar adenopathy	
26	12	M	Absent	NIL	0 mm	Negative	Pleural Effusion	
27	8	M	Present	NIL	0 mm	Negative	Normal	
28	5	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	
29	7	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
30	8	M	Absent	NIL	0 mm	Negative	Normal	
31	4	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
32	9	M	Present	+	2 mm	Negative	Normal	
33	4	F	Present	NIL	0 mm	Negative	Hilar adenopathy	
34	10	M	Absent	NIL	4 mm	Negative	Normal	
35	6	F	Absent	NIL	0 mm	Negative	Hilar adenopathy	FNAC – ve
36	12	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
37	9	F	Absent	NIL	0 mm	Negative	Localized Infiltrates	
38	3	M	Present	NIL	2 mm	Negative	Bronchopneumonia	
39	8	F	Present	NIL	0 mm	Negative	Normal	
40	3	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	
41	4	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	
42	4	F	Absent	+	9 mm	Negative	Hilar adenopathy	
43	5	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	
44	3	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	
45	5	F	Absent	+	10 mm	Negative	Hilar adenopathy	
46	3	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	

47	8	M	Absent	NIL	3 mm	Negative	Normal	FNAC – ve
48	5	F	Present	+	0 mm	Negative	Normal	
49	9	M	Absent	NIL	2 mm	Negative	Hilar adenopathy	
50	11	M	Present	NIL	0 mm	Negative	Normal	
51	5	M	Absent	NIL	3 mm	Negative	Normal	
52	8	F	Present	NIL	0 mm	Negative	Hilar adenopathy	
53	4	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	
54	8	M	Present	NIL	4 mm	Negative	Normal	
55	3	M	Absent	NIL	0 mm	Negative	Diffuse Infilatrates	
56	4	F	Absent	+	8 mm	Negative	Bronchopneumonia	
57	4	M	Absent	NIL	0 mm	Negative	Normal	
58	8	F	Present	NIL	0 mm	Negative	Hilar adenopathy	
59	5	M	Absent	NIL	0 mm	Negative	Normal	
60	4	M	Present	NIL	0 mm	Negative	Bronchopneumonia	
61	8	F	Absent	NIL	2 mm	Negative	Normal	FNAC – ve
62	6	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
63	11	F	Present	NIL	0 mm	Negative	Localized Infiltrates	
64	5	M	Absent	+	2 mm	Negative	Hilar adenopathy	FNAC +ve
65	4	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
66	7	F	Absent	NIL	0 mm	Negative	Localized Infiltrates	
67	7	M	Present	NIL	0 mm	Negative	Normal	
68	5	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
69	9	M	Absent	NIL	0 mm	Negative	Normal	
70	9	M	Present	NIL	3 mm	Negative	Normal	
71	8	M	Absent	+	8 mm	Positive	Localized Infiltrates	

72	4	M	Absent	NIL	2 mm	Negative	Normal	
73	9	F	Present	NIL	0 mm	Negative	Normal	
74	6	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
75	8	F	Absent	NIL	0 mm	Negative	Hilar adenopathy	
76	4	M	Absent	+	3 mm	Negative	Bronchopneumonia	
77	8	M	Present	NIL	0 mm	Negative	Hilar adenopathy	
78	9	F	Absent	NIL	3 mm	Negative	Normal	FNAC – ve
79	4	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	
80	3	M	Present	NIL	0 mm	Negative	Normal	
81	6	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
82	5	F	Absent	NIL	2 mm	Negative	Localized Infiltrates	
83	6	F	Present	NIL	0 mm	Negative	Normal	
84	11	M	Absent	+	7 mm	Negative	Hilar adenopathy	FNAC – ve USG Abd & Ascitic fluid analysis Positive
85	6	F	Present	NIL	0 mm	Negative	Normal	
86	5	M	Absent	NIL	0 mm	Negative	Localized Infiltrates	
87	4	F	Present	NIL	3 mm	Negative	Normal	
88	3	M	Absent	NIL	8 mm	Negative	Hilar adenopathy	
89	4	M	Absent	NIL	0 mm	Negative	Bronchopneumonia	
90	8	M	Present	NIL	2 mm	Negative	Hilar adenopathy	
91	9	M	Absent	NIL	0 mm	Negative	Localized Infiltrates	
92	11	F	Absent	NIL	3 mm	Negative	Normal	
93	2	M	Absent	NIL	0 mm	Negative	Diffuse Infilatrates	
94	6	M	Absent	+	8 mm	Negative	Normal	FNAC – ve
95	5	F	Present	NIL	2 mm	Negative	Bronchopneumonia	

96	9	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
97	4	M	Absent	+	6 mm	Positive	Hilar adenopathy	
98	11	M	Absent	NIL	0 mm	Negative	Localized Infiltrates	
99	4	F	Absent	NIL	0 mm	Negative	Normal	
100	8	M	Absent	NIL	0 mm	Negative	Hilar adenopathy	
101	4	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	
102	3	M	Present	NIL	0 mm	Negative	Hilar adenopathy	
103	4	F	Absent	NIL	0 mm	Negative	Bronchopneumonia	