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4**A Literature Review on Tuberculosis in HIV Reactive Persons: A Co-infection**Priyanka Priyadarshini Pattnaik^{1*}, Manoranjan Pattnaik², Lingaraj Mishra³, Sanghamitra Pati⁴, Rakesh Rosan Kar¹¹S.C.B Medical College & Hospital, Cuttack, Odisha, India.²Dept. of Pulmonary Medicine (Super speciality-DM), S.C.B Medical College & Hospital, Cuttack, Odisha, India.³ICMR-Regional Medical Research Centre (ICMR- RMRC), Nalco Square, Bhubaneswar, Odisha, India⁴Regional Medical Research Centre (ICMR-RMRC), Nalco Square, Bhubaneswar, Odisha, India.

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ABSTRACT: The patient infected with HIV is important for TB. Systemic review synthesis effect estimates of IPT (Isoniazid Prevention Therapy) for TB prevention in adult HIV.MTB (Mycobacterium Tuberculosis) is the most common cause of bacterial infection in human being and globally leading cause of morbidity and mortality, especially in developing countries. HIV is one of the strongest risk factors for TB and over millions of the people over the country are infected with co-infection due to which the coinfection worsens the prognosis of HIV infection by increasing HIV replication and may result in rapid progression of HIV and subsequent immunosuppression and a higher risk of acquiring others, potentially lethal. HIV with TB known as Coinfection is an opportunistic infection. The main objective to assess the effect of IPT on HIV disease progression, all-cause mortality and adverse drug reaction (ADR). Since 2011, WHO has recommended a four-symptom screening rule to exclude active TB in the people living with HIV before starting ATT (Anti-tubercular Treatment) treatment (asymptomatic). We assessed the sensitivity and specificity of the screening rule among people living with HIV based on antiretroviral therapy (ART) status and the added contribution of chest radiography.

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INTRODUCTION:

TB is lung related disease caused by Mycobacterium tuberculosis. It not only affects lungs but also different part of the body like kidney, spine, and brain. TB disease can cause death if it is not treated. TB germs are spread from person to person through the air, when a person with TB disease have throat coughs, sneezes, laughs, or sings. People nearby may breathe in the germs and become infected ^[1-3]. TB is not spread by sharing silverware or cups. Tuberculosis, an ancient disease, continues to remain even today as a major public health problem. The Problem is now complicated by relentless

Keywords: Anti-tubercular Treatment (ATT), antiretroviral therapy (ART), IPT (Isoniazid Prevention Therapy), MTB (Mycobacterium Tuberculosis), adverse drug reaction (ADR).

spread of Human Immunodeficiency virus (HIV) which causes Acquired Immunodeficiency syndrome (AIDS) pandemic and the emergence of multi drug resistant strains. Infection with HIV results in progressive immunodeficiency and renders the infected person become increasingly vulnerable to wide range of pathogens. In many parts of the World, Tuberculosis is the most common opportunistic infection in HIV infected person. The immune defects produced by HIV influence the natural course of TB infection [4]. Thus, the HIV pandemic has altered both the epidemiology of TB and measures for approaches to its control. In populations where the risk of TB and HIV infections are high, the incidence of TB is expected to increase particularly in countries like India [4].

TYPES OF TUBERCULOSIS (TB) [5,6]:

Latent TB:

TB bacteria that stay in body without making you sick, because bacteria remain in rest condition in body. A person with latent tuberculosis infection has no signs of active TB on a chest X-ray, and no TB-causing bacteria can be found in the mucus from the person's lungs (sputum). The only test that can detect latent TB infection in body is a positive by tuberculin skin test (interferon-gamma release assay or IGRA). Person affected with Latent TB does not require any isolation. The infected person shows the symptoms of TB but does not infect other person.

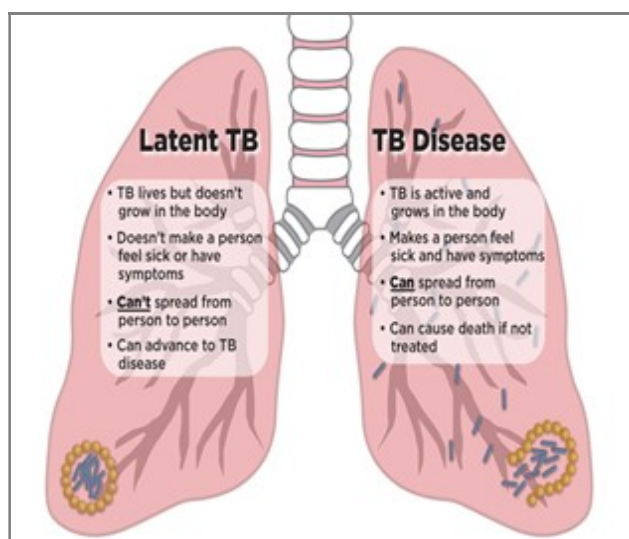


Fig 1. The image shows the difference between latent TB infection and TB disease.

Active TB:

When TB bacteria is alive in body is called active TB. This makes a person fall sick as it can spread from

person to person. It can cause death if not treated. The test done to check TB is active in body.

DIAGNOSIS OF TB [7]:

Mantoux tuberculin skin test:

- The Mantoux tuberculin skin test or tuberculin skin test is performed by injecting a small amount of fluid (called tuberculin) into the skin on the lower part of the arm.
- A person will return within 48 to 72 hours so that trained health care worker look for a reaction on the arm.
- The result depends on the size of the raised, hard area or swelling.

Reading the result of a TB skin test:

Positive skin test:

It means the person's body is infected with TB bacteria. Further Investigation is required to determine if the person has latent TB infection or active.

Negative skin test:

It means the person's body have no TB bacteria & no requirement of further investigation for repeat test.

* The TB skin test is the preferred TB test for children under the age of five.

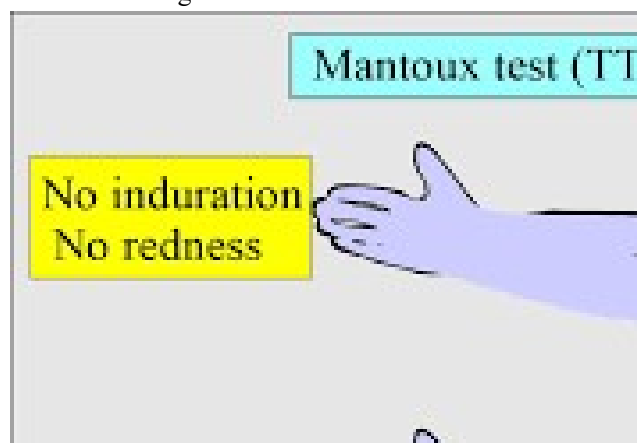


Fig 2. The image depicts the test result of Mycobacterium tuberculosis.

TB Blood Test:

TB blood tests is also known as interferon-gamma release assays or IGRAs. A physician or staff nurse will draw a patient's blood and send it to a laboratory for analysis and results.

Positive TB blood test:

The person's body is infected with TB bacteria. Further Investigation is required to determine if the person has latent TB infection or active.

Negative TB blood test:

The person's body have no TB bacteria & no requirement of further investigation for repeat test.



Fig 3. Image shows Tuberculin Skin Test (Positive TST test) Result.

SYMPTOMS OF TB [8]:

- A persistent cough that may bring up blood or sputum.
- Chest pain.
- Weakness or fatigue.
- Loss of appetite.
- Weight loss.
- Chills.
- Fever.
- Night sweats.

Symptoms of HIV in Men [9]:

- Extreme fatigue.
- Fast weight loss.
- Diarrhea that lasts for more than a week.
- Pneumonia.
- Sores in your mouth, anus, or genitals.
- Fever or severe night sweats that keep coming back.
- Memory loss.
- Red, brown, pink, or purple blotches on or under the skin.

Symptoms of HIV in Women [9]:

- Lack of energy or fatigue.
- Weight loss.
- Frequent low-grade fevers and night sweats.
- Frequent yeast infections (in the mouth).
- Skin rashes or flaky skin that is hard to heal.
- Short-term memory loss.

Worldwide approximately 2 billion people, 2-3 are infected with *Mycobacterium tuberculosis* (*M. tuberculosis*). In most cases, host defences initially limit infection with MTB and the infection remains latent.

However, latent TB infection has the potential to develop into active TB disease at any time. Individuals with active TB become sources and contribute to transmission of the disease and new infections [10]. In 1993, World Health Organization (WHO) declared tuberculosis (TB) as a global emergency. In 2014, the number of new cases of disease was reported to be 9.6 million. Approximately 1.5 million people die from tuberculosis each year. Consequently, active tuberculosis along with other infectious disorders like HIV, gonorrhoea, infectious leprosy, chancroid etc is considered as a communicable disease of public health significance as it is a major public health problem in nearly all resource-constrained countries and has considerably increased in sub-Saharan Africa as a result of the impact of HIV infection [11]. India has the highest burden of TB (due to the huge population size), as per WHO report for 2014 with approximately 2.2 million new cases of TB occurring in India out of the global incidence of 9.6 million [12-14]. It is estimated that about 40 % of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB disease. It is also estimated by the WHO that 220,000 people die from TB each year in India. As per WHO report for 2017, TB was considered as the ninth leading cause of death worldwide. In particular, 6.3 million new cases of TB were reported in 2016. Additionally, 6,00,000 new cases of drug resistant (resistance to rifampicin) were reported, out of which 490,000 cases had multidrug-resistant TB. In an Indian study, the prevalence of LTBI observed according to TST was found to be 42 % [15]. The TB infection is almost exclusively transmitted through air from patients with active pulmonary disease. The risk of transmission to household contacts is greatest when index case is sputum smear positive, close to the contacts, living conditions are overcrowded, bacillary density in respiratory secretions is high, and degree of lung fields involved are more. Therefore, those living within the same household are at higher risk than casual contacts. Further, among the household contacts, younger age and absolute or relative immunodeficiency states increase the risk of acquiring infection from their index case. Several studies from high burden countries have shown that active case finding among household contacts yields significantly more TB cases than passive case detection. In a study carried out in a peri-urban population of South Delhi, India Co-prevalent and Incident TB was found in 4.3 and 2.6 % household contacts of pulmonary TB patients respectively. In

incident cases, the diagnosis was made between 4 to 24 months of follow-up, after index case was diagnosed. The age-wise distribution of incident TB cases was 12.9 % in ≤ 12 years, 48.4 % in 13 to 25 years, 22.6 % in 25 to 40 years and 16.1 % in > 40 years age group. 10 A prospective cohort study carried out in South Africa reported overall TB incidence rate of per 100-person years among household contacts (all age groups) of TB index patients. TB incidence for individuals who were HIV-infected and HIV sero-negative ^[16] at baseline was 5.4 per 100-person years and 0.7 per 100-person years respectively. In a prospective cohort study, 1,206 household contacts of 302 index cases with TB were enrolled in Uganda between 1995 and 1999. All contacts were systematically evaluated for active TB and risk factors for active disease. Among the 1,206 household contacts, 76 secondary cases (6.3 %) of TB were identified. Of these cases, 51 (4.2 % had co-prevalent TB) were recognized in the baseline investigation, and 25 (2.1 % had incident TB) developed during follow-up period. As compared with index cases, secondary cases were present more often with minimal disease. In addition, the risk for secondary TB was greater amongst young children than adults (10 v/s. 1.9 %) and among HIV-seropositive than seronegative contacts (23% v/s. 3.3%). In China, with a similar high-burden of TB in India, the yield for active TB case finding through contact investigation ranged from 0 to 6.9 % in household contacts. A systematic review and meta-analysis of all studies reporting the prevalence of TB and latent TB infection, and the annual incidence of TB among contacts of patients with TB has reported 3.1 % prevalence of TB among household contacts. Incidence of TB in household contacts of index case has been reported to be higher in the first year after exposure. In addition to the above studies, a prospective, observational study investigating adult household contacts for active TB by culture and drug susceptibility testing of index case at the time of diagnosis and again one year later so revealed that incidence rates of multidrug-resistant and extensively drug-resistant tuberculosis among household contacts were extremely high ^[17]. There is an increased risk of exposure to the disease causing organism among the household contacts of TB patients than the general population. A systematic review has shown that among household contacts or other close contact of an index TB case, around 3.5 to 5.5 % are found to have previously undiagnosed and active TB. Despite this potential benefit, routine contact

investigation is performed rarely and inconsistently in resource limited settings probably due to constraints in finance and human resources. TB occurs mainly in people having weaker immune system than healthy immune systems, which is known as opportunistic infection (OI). HIV weakens the immune system, increasing the risk of TB in people with HIV ^[18]. Infection with both HIV and TB is known as HIV-TB coinfection. Untreated latent TB infection is more likely to advance to TB disease in people with HIV than in people without HIV. Treatment with HIV medicines is called antiretroviral therapy (ART). ART protect the immune system and prevent HIV from advancing to acquired immunodeficiency syndrome (AIDS). In people with HIV and latent TB infection, treatment with HIV and TB medicines reduces the chances that latent TB infection will advance to TB disease. It is important to know if you have TB infection because HIV weakens the immune system. When a person's immune system is weak, latent TB infection can quickly progress to TB disease. If you have HIV, it is very important to get a TB test ^[19]. If you have latent TB infection or TB disease, and you do not know your HIV status, you should get an HIV test. This will help physician know way to treat both your TB and HIV infections.

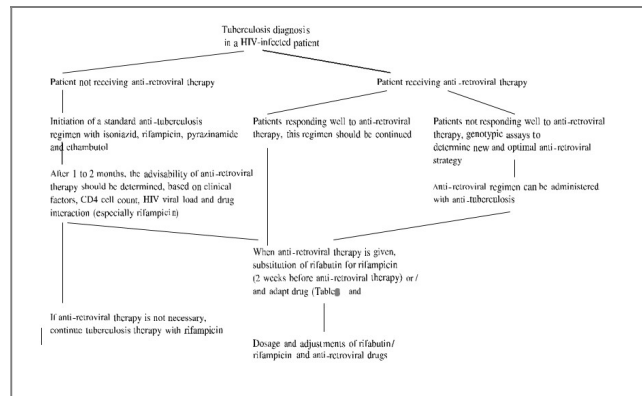


Fig 4. Classification of patient treatment who have diagnosed with TB in HIV patient.

A cohort study was conducted retrospectively at 3 states England, Wales and Northern Ireland and it was observed that PTB patients with HIV (Co-infection) are less effective or transmit infection less than individual having either PTB or HIV ^[1,2]. This is consistent with the results of contact studies across high- and low-burden settings, which have found lower risks of LTBI and TB disease among the contacts of HIV-positive patients than HIV-negative TB patients. This proves that PTB patients and HIV (Co-infection) are less infectious than

individuals without HIV infection^[3,4]. Also, in case of EPTB HIV and TB coinfection are less infectious than individual infection. HIV positive and EPTB are usually first case of cluster as they have more cluster case of HIV than EPTB cases, patients with only EPTB infection are not infectious and transmission of disease by them are less than other infectious diseases. Mainly transmission largely occur from unknown or undiagnosed infectious person than from a known or under treatment infectious person. The Patient diagnosed with latent TB are non-infectious as they have infection in their body but are in resting condition and are non-transmittable. Prevalence of HIV is higher in cluster cases of HIV positive than in HIV negative so it can said that the increased cluster size is because HIV infection is concentrated within some communities, and so the contacts of the HIV-positive infectious case are more likely to be susceptible to infection and progression to active disease^[20-22]. There are other ways of transmission of HIV disease, which may be living conditions, social mixing patterns and health-seeking behaviours, which was not able to account for in the study.

Regardless of whether these HIV-positive cases are the 'true' first case in a cluster or merely the first case in a cluster to develop symptoms or present to care, the first observable patient is still a point at which interventions to diagnose patients earlier or investigate clusters can be targeted. National Institute for Health and Care Excellence guidelines currently suggest contact tracing is unnecessary for EPTB cases, and this is supported by a recent cost-effectiveness study^[7-13].

The observation or findings states that EPTB may not driving criteria for infection transmission but EPTB with HIV coinfection can be the first observable case. It is also investigated that 50 % of the total patient are co-infected of HIV and TB targeting HIV screening and LTBI treatment to the contacts of TB patients with HIV could result in earlier diagnosis of HIV infections, providing the opportunity to initiate anti-retroviral therapy and prevent TB disease from occurring.

In addition, there was negative association between HIV and TB & being a subsequent case in a cluster, compared to being the first case or a non-clustered case. This statement recommends that TB patients wit HIV detected are result of reactivation of remotely acquired Latent Tb infection than newly detected TB infection. These types of TB can be treated if person living with HIV who are born abroad can identified and treat with

Latent TB. This finding contrasts with that of a meta-analysis of the association between HIV and clustering of TB cases in HIV-endemic populations, and more recent studies using Whole Genome Sequencing^[19,20], which concluded that HIV-associated TB was more often the result of recent infection than reactivation of Latent Tuberculosis Infection.

This difference mainly affects higher incidence of TB in general population in countries where TB is endemic and can lead to outspread of TB infection which may differentially affect people living with Human Immunodeficiency Virus (PLHIV) represent a unique cohort due to their underlying immune defects. Human immunodeficiency virus (HIV) is known to invade the immune system thereby decreasing the CD4⁺ T cells count^[5,15].

In the states with low budget settings TB cases are transmitted from outside and the transmission is considered to be at low rate. As there is generally less exposure to TB, HIV contributes more to reactivation of latent TB than to new TB infections.

The study shows culture positive TB cases strain typed at ≥ 23 loci in England, Wales and Northern Ireland over a 5-year period and represents over 80 % of culture-confirmed TB cases and over 50 % of all TB cases in the country during this time.

The data used in the analysis differ in terms of age, sex, ethnicity, place of birth, year of TB diagnosis. Misclassification, which can bias the result and show result greater than normal are not considered in the study^[20].

In the study Clustered TB are classified as first case and others in next group as per their date of identification of TB. TB patients whose who are diagnosed with HIV as the first case in a cluster, when in fact they may just be the first patient in that cluster who developed symptoms or presented to care. So, the misclassification would have occurred. In addition, in the study 50 % of the patient identified with TB are aware of HIV infection detected in them therefore, this would not have influenced the time it took them to present to care, although their disease may have progressed more quickly.

CD4 count of HIV positive individual's data are not included in the study. As the study was, don retrospectively so data was collected routinely, as transmission of TB is not possible to determine. Therefore, CD4 count of HIV positive individuals were not determined and so were unable to explore any

possible association between CD4 count and propensity to transmit TB. Socioeconomic status and diabetes, as these data were not routinely recorded so this was also not included.

Children were also not included in the study as they are less likely to provide sputum samples, to limit the bias we included the children determining TB clustered and whether a case was the first or a subsequent case in a cluster and then excluded patients aged < 15 years from the risk factor analysis. TB/HIV are in minimal risk and are not transmitted therefore, children are not included in the study.

CONCLUSION:

TB is considered opportunistic infection worldwide, which is advanced to HIV infection. It mainly affects the age group of 21 to 40. Most of the patients in advanced stages usually present with more than 3 of the 5 clinical features such as cough with expectoration, dyspnoea, fever, weight loss and haemoptysis. Oral thrush is present in about 35 % patients, which serves as an indicator of severity of disease (HIV infection). Majority of the patients (42 %) were in the CD4+ cell counts range of 100 to 200 Cells / mm³. All children with HIV younger than 5 years of age are considered to have advanced HIV disease.

As per WHO guidelines, HIV remains global issue with ongoing transmission with increasing trends, which declined earlier.

In 2022, 630000 people died from HIV-related disease and 1.3 Million people acquired of HIV. By 2025, 95 % of all people living with HIV (PLHIV) should have a diagnosis, 95 % of those should be taking lifesaving antiretroviral treatment (ART) and 95 % of PLHIV on treatment should achieve a suppressed viral load for the benefit of the person's health and for reducing onward HIV transmission. In 2022, these percentages were 86 (%) [73->98%], 89(%) [75->98%] and 93(%) [79->98%], respectively.

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