



## Recurrence of Tuberculosis can be hurdle for TB Control

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### Introduction

Tuberculosis (TB) is a global disease, found in every country in the world. It is one of the leading infectious causes of death worldwide. The World Health Organization estimates that 1.8 billion people close to one quarter of the world's population are infected with Mycobacterium tuberculosis (M.tb), the bacteria that causes TB. Last year, 10.6 million fell ill from TB and 1.6 million died. TB is an airborne disease that can be spread by coughing or sneezing and is the leading cause of infectious disease worldwide. It is responsible for economic devastation with the cycle of poverty and illness that entraps families, communities and even entire countries. Among the most vulnerable are women, children, and those with HIV/AIDS. There is growing resistance to available drugs, which means the disease is becoming more deadly and difficult to treat. There were more than half a million cases of drug resistant TB last year.<sup>(1)</sup>

The current WHO guidelines for the treatment of drug-susceptible pulmonary TB have recommended a 6-month regimen comprising four first-line anti-TB drugs in the intensive phase (for 2 months) and two drugs in the continuation phase

(for 4 months) i.e. 2 months of Isoniazid/Rifampicin/Pyrazinamide/Ethambutol and 4 months of Isoniazid/Rifampicin (2HRZE/4HR).<sup>(2)</sup>

India and TB: With 28% cases, India was among the eight countries accounting for more than two-third (68.3%) of the total TB patients' count. The other countries were Indonesia (9.2% cases), China (7.4%), the Philippines (7%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and the Democratic Republic of the Congo (2.9%). India accounted for 36% of the global TB related deaths among HIV negative people. India was among the three countries (along with Indonesia and the Philippines) that accounted for most of the reduction in 2020 (67% of the global) and made partial recoveries in 2021.<sup>(1)</sup>

Recurrent TB disease occurs when patients who were previously treated for TB develop a new disease episode, due to either relapse (recurrence of the old infection) or reinfection (infection with a new strain)<sup>[3]</sup>. Recurrent TB disease is associated with poor treatment outcomes and higher mortality rates compared to primary TB infection<sup>[4]</sup>. Clinical, epidemiological, and/or microbiological data cannot be used to differentiate relapse and reinfection.

Distinguishing between the two mechanisms requires evaluating the homology of the MTB strains isolated during the first and subsequent TB episode using molecular DNA fingerprinting technology<sup>[3]</sup>. Recurrence of TB is one important obstacle for End TB strategy in the world and elucidating the triggers of recurrence is important for the current TB control strategy.

Recurrent TB may be seen after completing a full course of anti-tubercular treatment. Compared with the first episodes of TB, patients diagnosed with recurrent TB are less likely to complete treatment and experience higher mortality (Murray et al. 1999). Distinguishing the 2 mechanisms of recurrent TB requires molecular marker analysis of cultures from both episodes, so results are available from only a few studies. These have shown varying proportions of disease due to reinfection<sup>[5-6]</sup>, from <3%<sup>[7]</sup> to >60%<sup>[8,9]</sup>.

**Epidemiology of Recurrent TB:** Recent estimates of recurrent TB across various regions indicate an average of 2290 cases/100000 person-years at 12 months following treatment completion. In high-incidence settings, this rate is as high as 7850 cases/100000 person-years<sup>[8]</sup>. Population-based surveillance reports on the rates of recurrent TB following completion of anti-TB treatment are lacking. An earlier report by Panjabi et al. analyzing 32 studies reported an overall recurrence rate of 3010 and 2290 per 100,000 person-years following 6 and 12 months of treatment, respectively, among controlled trials. They also reported that these rates were higher for observational studies compared to controlled trials. Rates were also reported to be higher in countries with high TB incidence<sup>[54]</sup>. Glynn et al. reported a recurrence rate of 24.4 cases per 100 person-years in HIV-positive individuals and 4.7% per 100 person-years in their HIV-negative counterparts<sup>[10]</sup>. Charalambous et al. reported an overall recurrence rate of 7.89% per 100 person-years in the same setting among a mining population. The recurrence rate was higher in HIV-positive individuals at 8.86 cases per 100 person-years compared to 3.35 cases per 100 person-years in HIV-negative counterparts<sup>[11]</sup>. Narayanan et al. reported a recurrence rate of 14% among an HIV/TB-coinfected cohort of 306

patients from South India. Among the patients with recurrent TB, 88% of recurrent infections were due to reinfection,<sup>[12]</sup>

**Key Words:** Recurrence TB, Reinfection of TB, Relapse of TB, HIV TB

### Material and Methods

The study was carried out in unit 4 OPD of GTB Hospitals Sewri Mumbai in January 2023 and February 2023. GTB Hospitals is a largest hospital in Asia exclusively for tuberculosis with bed strength of 1000 beds for sensitive patients and 200 beds for drug resistance patients, as it is tertiary care hospital, maximum patients are in last stage with lots of complications. Study is a descriptive type and Total Patients in OPD in Jan and Feb was 122 and 141 in unit 4 respectively. Out of which IPD was 45 and 51 for Jan and Feb respectively. Case selection was "Recurrent TB (drug sensitive) who have completed standard treatment of 6 to 8 months and was declared cured and now microbiologically diagnosed as Pulmonary Tuberculosis (PTB) with minimum period between last episode of TB and new episode of TB is 6 months. Study population are adult male or female not less than 14yrs who was adherent to treatment and completed standard treatment course of Anti TB Treatment (ATT). Inclusion Criteria Patient have taken complete ATT without default and now confirmed microbiologically (Sputum microscopy, MGIT Liquid culture, Molecular test recommended by W.H.O. like GenXpert, Line Probe Assay L.P.A.) Patients attending in OPD are more than 80% requires hospitalization having bilateral destroyed lungs on x-ray chest with comorbidity like HIV with low CD4 count, uncontrolled Diabetes, Hemoptysis moderate to severe, Pneumothorax or Hydro pneumothorax, As the disease is chronic, patient develops psychiatric problem also like depression, suicidal ideation which are treated by hospitalization.

### Case Series

**Case 1** – 50 yrs. Male patient, HIV+ on ART, H/o pulmonary Tuberculosis (PTB) 4yrs back, comes with c/o Breathlessness, Cough, and Generalized weakness. Patient is diagnosed as having active

PTB with GenXpert MTB Detected with Resistance to Rifampicin (RMP). Started on oral regimen of 18 months

**Case 2-** 36 yrs. male patient had taken complete ATT standard first line ATT for 6months and now with GenXpert MTB Detected with Resistance to Rifampicin (RMP) started on oral regimen of 18 months

**Case 3** – 53yrs old male patient on ART more than 5yrs, Past H/o PTB 3yrsback taken complete ATT, and restarted on ATT first line one month back, comes with H/o Vomiting 3 days back, admitted symptomatic treatment given, Liver function test shows SGOT and SGPT raised, shifted on hepatosafe drugs. Restarted ATT after LFT becomes normal.

**Case 4-** 47yrs old male patient H/o Diabetes, Recurrent TB, have taken complete ATT, after 3yrs developed PTB with microbiological confirm with GenXpert M.tb Detected and Resistance to RMP. Started on shorter regimen of Bedaquilin.

**Case 5-** 60yrs male H/o PTB 20yrs back, taken complete ATT, H/o Diabetes and Hypertension, Symptomatic since more than 1 month, had H/o of blood streak sputum, GenXpert Mtb detected with no RMP resistance. Started on Fixed dose combination of first line drugs ATT

**Case 6-** 48yrs female on ART more than 10yrs on ART, H/o PTB 5yrs with H/o Cervical lymphadenopathy 10yrs back taken complete ATT, Now she is diagnosed on GenXpert with M.tb detected and Rifampicin resistance. Started all oral longer regimen, patient comes with tingling numbness on both extremities, Linizolid stopped and replacement drug was given with symptomatic treatment.

**Case 7-** 29 yrs. male patient have recurrent TB, He was initially defaulter, Last episode he has taken complete ATT. He comes with Complaint of Fever and Breathlessness. Culture and DST with sensitive only PAS, and Resistance to all drugs, salvage regimen started

**Case 8-** 27yrs old Female patient comes with swelling in the neck since 1month with fever off and on, No other complaint O/E Swelling was on Rt. side of neck in posterior triangle 3cm to 4cm in diameter, soft in the middle, no redness, no pain. H/o Cervical Lymphadenopathy 2yrs, taken

ATT for 8 months. It was advised for FNAC or Excision Biopsy. After biopsy specimen was send for 1. GenXpert, 2. Cytology examination, 3. A.D.A, GenXpert shows MTB Detected with No Rifampicin (RMP) Resistance.

### Discussion

GTB Hospital is a tertiary care hospital for pulmonary TB, Most of patients coming to hospital are having emergency and severe complication due to disease like bilateral extensive disease involving both lungs, or due to anti TB medicine like adverse drug reaction (ADR). Most of patients are defaulter, one of the reason is recurrence of TB, and to minimize the frequency of recurrence, factors associated with this event should be determined. However, the causes of recurrence are unclear. While poor adherence to treatment and sub-standard regimens have been widely documented as risk factors for recurrence of pulmonary TB, other risk factors, including old age, low weight and initial sputum smear status have been less consistently reported with co morbid condition like HIV+ low CD4 count, uncontrolled Diabetes.

Distinguishing between recurrence due to endogenous reactivation or to exogenous reinfection is essential to accurately determine the efficacy of tuberculosis treatment regimens. The contribution of recurrence to the epidemiological profile and pathogenesis of tuberculosis also has important implications for vaccine design, chemoprophylaxis, and design of national tuberculosis control programs. This distinction is particularly important in settings with high tuberculosis prevalence. The successful treatment rate for new patients with TB is only 85%, whereas the rate for MDR-TB (multidrug-resistant tuberculosis)/RR-TB (rifampicin-resistant tuberculosis) is even lower than 57%.

Patients are hospitalized and proper treatment is started, like for drug induced hepatitis are given hepato-safe drugs, HIV+ with ART if drug interaction change of suitable drugs are given. In Diabetes if hyperglycemia, by adding proper drugs like insulin, blood sugar is controlled. We have selected 8patients who fulfill the criteria of recurrent TB, as taken complete treatment with

symptoms of PTB and microbiologically confirmed, Male-5 and Female-3. H/o HIV+ was 2 male and 1 female, most of them are of productive age, due to low blood oxygen level Spo2 less than 90%, Oxygen therapy was given, The risk factors that affect the two types of recurrent TB (reactivation and reinfection) are also complex and diverse. Resistance to anti-tuberculosis drugs, clinical characteristics of patients, genotypes of strains, and HIV or diabetes coinfections are all considered factors that approximately cause differences in the types of TB recurrence. A study has shown that TB and HIV coinfection have bidirectional effects. The main feature of HIV infection, CD4+ T cell depletion, increases the risk of TB reinfection, and the elevation of TNF- $\alpha$  expression on TB increases HIV replication. However, other factors that may affect the types of TB recurrence have not been effectively confirmed.

### Conclusion and Way Forward

HIV+ patients are having higher propensity of recurrent TB and can amplify into drug resistance, which is one of the major threat to TB control program. Current estimates are based on a combination of randomized controlled trials and observational studies, with reliability estimates of the former limited by study follow-up time, and the latter prominently demonstrating higher rates of recurrence. *The report reiterates its call for countries to put in place urgent measures to restore access to essential TB services.*

It further calls for increased investments, multi-sectorial action to address the broader determinants that influence TB epidemics and their socioeconomic impact as well as the need for new diagnostics, drugs and vaccines.

For the TB mitigation strategy to be effective, it is important to increase levels of awareness of people about the disease and ensure that the people affected by TB overcome their social insecurities and access TB care.

### Preventive Measures

Measures can be taken to reduce the recurrent TB, whether it is HIV+ or HIV Neg. Relapse or reinfection lots of evidence based interventions

are available. Ensure the completion of appropriate treatment of all TB patients is extremely important.<sup>(13)</sup> Treatment failure will results into high rates of recurrent TB, mostly in HIV+ patients.<sup>(14,15)</sup> It is also seen in around 5.5% of patients in new TB cases are MDR or XDR TB Patients, only small fraction of these are detected and receive appropriate treatment. Early detection of MDR TB, through rapid molecular test (WHO recommended GenXpert and LPA) will also reduce MDR TB with early effective treatment.<sup>(16)</sup> So doing baseline DST (U-DST) will reduce relapse and evolution of drug resistance. Improving case detection, easier access to care, improving cure rates with community-based interventions, and developing new effective shorter regimens.

In HIV+ patients with TB reinfection is more in high burden settings, another strategy for reducing recurrences is secondary preventive therapy with Isoniazid (INH). Its effectiveness is seen in one small control trial and one observational study for reducing recurrence in HIV- related TB. Risk of recurrence of TB in HIV-infected persons in non-endemic setting was reduced with longer duration of TB treatment than standard duration.

In HIV+ patients low CD4 cell count is a major predictor of recurrent TB both relapse and reinfection, so ART treatment will reduce the recurrence by at least by 50%.<sup>(11,14)</sup> Evidence from clinical trial and observational studies support the role of ART to prevent recurrence of TB. in HIV+ patients. A study in Rio de Janerio, Brazil shows scaling up ART for TB patients also reduce recurrence of TB in HIV+ patients

To reduce reinfection in clinical and community settings, implementation of Infection control measures is critically needed, as the patients with TB and with HIV+ waits in same OPD, waiting area or room, Labs and hospital wards. Ongoing transmission is a significant cause of new disease, especially in Drug Resistance TB.

In resource poor settings HIV and ART clinics have become good source of TB transmission, without bothering the impact of HIV therapies. To reduce the institutional and community transfer, first step is detection of prevalent, undiagnosed cases and initiation of appropriate treatment.

Separate the infectious patients by administrative measures, air flow ventilation by natural or artificial techniques, and in more exposure and intense situations by using Personal Protective equipment (PPE), all above approach are needed to control TB transmission, as nosocomial transmission of TB infection in HIV+ patients is known worldwide.

### Summary

Early and accurate diagnosis with appropriate treatment will prevent recurrence of TB disease. Monitoring of high risk patient like HIV+ and Diabetes will prevent the risk of recurrence. Treatment adherence in TB, and ART in HIV+ patients to prevent low CD4 count, also to control diabetes. Active monitoring of close contacts of TB patients, especially drug resistance patients is also essential.

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