
Introduction

Tuberculosis (TB) is a global health concern.[1] In low- and middle-income countries it is fueled by poverty, population increase and infection with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).[2] South East Asia Region carries about 40% of the global TB burden. India is the highest TB burden country in the world and accounts for more than 25% of the world's incident cases.[3] More than 1000 Indians die of TB every day.

Tuberculosis (TB) is one of the most ancient diseases of mankind and has co-evolved with humans for many thousands of years or perhaps for several million years.[1] The oldest known molecular evidence of TB was detected in a fossil of an extinct bison (Pleistocene bison), which was radiocarbon dated at $17,870 \pm 230$ years[2] ; and in 9000, year old human remains which were recovered from a neolithic settlement in the Eastern Mediterranean.[3] Although as early as 1689, it was established by Dr. Richard Morton that the pulmonary form was associated with “tubercles,” due to the variety of its symptoms, TB was not identified as a single disease until the 1820s and was eventually named “tuberculosis” in 1839 by J.L.Schönlein.[4]

In 1882, the bacillus causing tuberculosis, *Mycobacterium tuberculosis*, was discovered by Robert Koch; and for this discovery, he was awarded Nobel prize in physiology or medicine in 1905.[5] Tuberculosis is caused by a group of closely related bacterial species termed *Mycobacterium tuberculosis* complex. Today the principal cause of human tuberculosis is *Mycobacterium tuberculosis*.

Other members of the *M. tuberculosis* complex that can cause tuberculosis include *M. bovis*, *M. microti* and *M. africanum*. *M. microti* is not known to cause TB in humans; infection with *M. africanum* is very rare, while *M. bovis* has a wider host range and is the main cause of

tuberculosis in other animal species. Humans become infected by *M. bovis*, usually via milk, milk products or meat from an infected animal.[6,7] It is estimated that in the pre-antibiotic era, *M. bovis* was responsible for about 6% of tuberculosis deaths in humans.[8,9]

In spite of newer modalities for diagnosis and treatment of TB, unfortunately, millions of people are still suffering and dying from this disease. TB is one of the top three infectious killing diseases in the world: HIV/AIDS kills 3 million people each year, TB kills 2 million and malaria kills 1 million.[10] Even though tubercle bacilli was identified nearly 130 years ago, a definitive understanding of pathogenesis of this disease is still deficient.[11,12] Although it can affect people of any age, individuals with weakened immune systems, e.g., with HIV infection, are at increased risk. Since the immune system in healthy people walls off the causative bacteria, TB infection in healthy people is often asymptomatic. This bacterium lives and multiplies in the macrophages, thus avoiding the natural defense system in the patient's serum. Infection with TB can result in two stages: asymptomatic latent tuberculosis infection (LTBI) or tuberculosis disease. If left untreated, the mortality rate with this disease is over 50%. For this review article, data available at the official websites of world health organization (WHO); from the Ministry of Health, Government of India; through PubMed central and Google scholar® search engines were extensively consulted.

TB INDIAN SCENARIO

In India, TB has been mentioned in the *Vedas* and the old *Ayurvedic* scriptures. Historically speaking, fight against TB in India can be broadly classified into three periods: early period, before the discoveries of x-ray and chemotherapy; post-independence period, during which nationwide TB control programs were initiated and implemented; and the current period, during which the ongoing WHO-assisted TB control program is in place.

INDIAN SCENARIO

A/C to TIMES OF INDIA SURVEY

Delhi tops the country in prevalence of tuberculosis with 534 cases per 1 lakh population, the TB prevalence survey reveals. **Rajasthan, with 484 cases per 1 lakh people, had the second highest TB prevalence**, followed by Uttar Pradesh (481), Haryana (465) and Chhattisgarh (454).

Kerala had the lowest prevalence with 115 per 1 lakh people.

Findings of the survey also show that childhood TB remains a major problem contributing to around 31% of the global burden.

TB CASES IN INDIA OVER THE YEARS

	India TB Report 2020	2023	2024
Estimated TB cases	26.9 lakh	27.4 lakh	27.8 lakh
Number of cases reported	24.04 lakh	24.2 lakh	25.5 lakh
Reporting from private sector	6.8 lakh	7.3 lakh	8.4 lakh
% cases from private sector	28.20%	30%	32.90%
Estimated mortality	4.36 lakh	3.2 lakh	3.2 lakh

Figure 1 TB CASES IN INDIA OVER THE YEARS

The main reasons for non-adherence in anti-tuberculosis treatment are drug side effects, forgetting to take medication, be away from home, missing date of appointment, lack of transportation cost, lack of social support, poor communication between patient and healthcare providers, and stock out of medicines [11,12,13]. Non-adherence to anti TB treatment results in increased length and severity of illness, death, disease transmission and drug resistance. It has great economic impact in terms of cost to patients as well as the health care system [13, 14].

Adherence to long course TB treatment is complex, dynamic phenomenon with wide range of factors impacting on treatment taking behaviors [15]. Even though there is wide coverage of DOTs program in Ethiopia, there is paucity of evidence on rate, reasons and associated factors of non-adherence on anti TB treatment particularly in the study area. Therefore the present study determines prevalence, reasons and associated factors of non-adherence of anti TB treatment among TB patients

The burden of TB among low and meddle income countries is fuelled due to HIV pandemic, and smoothen by numerous socioeconomic conditions (9). According to research findings, socioeconomic factors such as homelessness, lack of food, financial limitation, lack of transportation cost, low education level, gender, poor health care worker-patient communication, joblessness, social supports etc. are highly associated with TB treatment non-adherence and lost to follow up (9–11). These conditions are related to each other and form a network of causal pathways against TB patient tolerance ability (9). Additionally, overcrowded living condition (9, 12), HIV related immunological weakness (13) and malnutrition (14, 15) are factors that facilitate transmission of bacilli, treatment non-adherence and lost to follow up at economically disadvantaged settings. In general many social determinants of health (SDH) reinforce social stratification in society. Social stratification in turn to an unequal distribution of the social determinants of health, including material living conditions and psychosocial circumstances as well as behavioural and biological risk factors to health problems including TB; finally influence patients' treatment adherence tolerance (16).

Beside, socioeconomic factors, patient's individual behavioural factors, like knowledge about TB disease, duration of treatment, consequences of treatment non-adherence and lost to follow up, feeling better after few weeks of treatment, fear of stigma; attitudes towards treatment and poor communication with health care workers, lack of self-efficacy or motivation to complete treatment are the main behavioural factors that associate with TB treatment non-adherence and lost to follow up ([17-19](#)). Furthermore, alcohol consumption ([19-22](#)) and cigarette smoking ([17, 22](#)) are the two individual behavioural factors that associated with TB treatment non-adherence and lost to follow up that reported so far. TB treatment non-adherence and lost to follow up are continues throughout the nations, and it extended its potential consequences, like initial treatment failure and relapse, which are in turns to prolonging morbidity, mortality, prolonged transmission of bacilli and development of medication resistance types of *M. tuberculosis*)

Despite, implementation of internationally recommended strategy (DOTS) in almost all parts of WHO ([29-31](#)) regions and many national and international efforts exerted against TB prevention and control, still the patients are failing to complete their treatment to declare cure or complete the treatment. Current WHO report shows considerable TB cases are failed after several treatments, many are relapsing (226, 813) after completion of the treatment, many are inter to retreatment (348, 734) after completion of treatment and many cases are developing MDR-TB among retreatment cases (20%) throughout the world ([2](#)). For this, most probability treatment non-adherence and lost to follow up are the main responsible.

Non-adherence to treatment is the patient's inability or refusal to take TB medications according to prescribed by health professional ([32-35](#)). Similarly lost to follow up is a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more ([35](#)). Hence, intensive case notification and observing patients while they are taking the medication only are not sufficient to prevent TB treatment non-adherence and lost to follow up. However, well understanding and

intervening of associated factors which are influencing TB patients' tolerance ability and promote treatment non-adherence and lost to follow up is corner stone to good treatment success. Moreover, well understanding and then intervening of these associated factors at the community, family, individual, health care worker and health care system levels are very important through conducting comprehensive large scale community based interventional study. Therefore, this systematic review was intended to combine the associated factors with TB treatment non-adherence and lost to follow up among TB patients with or without HIV, which previously studied in developing countries since 2008.

A/C TO INDIA TV REPORT 2024

According to the report, the majority of the TB cases are still reported by the government health centres, even as there has been an uptick in notifications by the private sector. Nearly 33% or 8.4 lakh of the 25.5 lakh cases reported in 2023 came from the private sector. To compare, only 1.9 lakh cases were reported by the private sector in 2015, the year considered to be the baseline by the programme that is geared towards the elimination of the disease.

The estimated incidence of TB in 2023 increased slightly to 27.8 lakh from the previous year's estimate of 27.4 lakh. The mortality due to the infection remained the same at 3.2 lakh as per the data. These estimates are based on a new methodology that India developed and has since been accepted by the World Health Organization.

Last year, when the in-country model was used to estimate the number of cases and deaths due to tuberculosis, there was a sudden drop in the mortality figures seen in the global report released by the WHO. India's TB mortality dropped from 4.94 lakhs in 2021 to 3.31 lakhs in 2022. The number of cases reported in a year also went down from 29.4 lakh in 2021 as per the previous method to 27.4 lakh in 2022, according to the data.

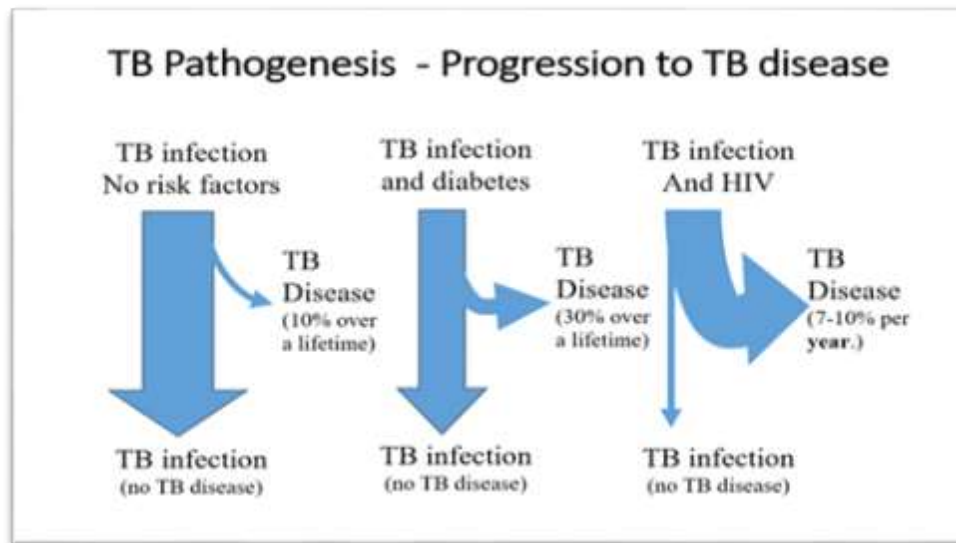
The report shows that India reached its 2023 target of initiating treatment in 95% of patients diagnosed with the infection. It says 58% of those

diagnosed were offered a test to check whether their infection was resistant to the first line drugs, an increase from 25% in 2015. The programme recommends drug susceptibility treatment to ensure that people who may have drug resistant TB are able to access the therapies from the get go instead of being treated with the first-line therapy initially.

ACCORDING TO MINISTRY OF HEALTH & FAMILY WELFARE

More than 40% of the population in India carry Tuberculosis infection in their body but only 10% get TB disease: Chief Medical Officer, National Tuberculosis Institute

Most common cause of infertility in our country is



Tuberculosis: Director, National Tuberculosis Institute

“TB is a highly infectious disease; if not treated timely, it can

Figure 2 TB PATHOGEN TO TB DISEASES

result in even death”

Tuberculosis is caused by a bacterium known as Mycobacterium Tuberculosis. Most often, it affects the lungs. The disease can easily spread from the infected person’s cough droplets; this makes it a highly infectious disease. If not treated on time, TB can even result in death.

Incidence of TB is quite high across the world. Out of the total cases, more than 26% are from India. This includes both multidrug-resistant TB and HIV TB cases.

TB Infection and TB Disease

TB infection is not the same as TB disease, explains Dr. Ravichandra C.

“TB infection is there in one-third of the world population; that doesn’t mean they are suffering from TB. More than 40% of the population in India carry TB bacteria in their body but they may not suffer from TB disease.

There is only 10% chance that someone infected with TB bacteria to catch TB disease.”- Dr. Ravichandra C., Chief Medical Officer, NTI

Estimated	Global	India
Incidence	99,00,000 (127/ lakh)	25,90,000 (188/ lakh)
Deaths (excluding HIV)	12,80,000 (17/ lakh)	4,93,000 (36/ lakh)
HIV TB cases	7,87,000 (10/ lakh)	53,000 (3.8/ lakh)
HIV TB deaths	2,14,000 (2.7/ lakh)	11,000 (0.78/ lakh)

Figure 3 TB GLOBAL & INDIA DATA

GLOBAL SCENARIO

According to WHO, TB is a worldwide pandemic. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, while half of all new cases are in six Asian countries, viz., Bangladesh, China, India, Indonesia, Pakistan and Philippines. A WHO fact sheet dated March 2010[[10](#)] on tuberculosis stated that overall one third of the world's population (over 2 billion) is currently infected with the TB bacillus. According to it, every second, someone in the world is newly infected with TB bacilli and 1 in every 10 of these newly infected people will become sick or infectious later in life. Since concurrent infection with HIV weakens the immune system, people with co-infection of HIV and TB are much more likely to develop TB; it is a leading cause of death among HIV-positive people. In Africa, HIV is the single most important factor contributing to the increase in the incidence of TB since 1990. The same fact sheet[[10](#)] stated that in 2008, globally speaking, there were 9.37 million new cases of TB, with the African region and the Southeast Asian region (SEAR) having a share of 30% and 34%, respectively. However, the estimated incidence rate in Sub-Saharan Africa is nearly twice that in the SEAR with over 350 cases per 100,000 individuals of the human population. In the same year 2008, an estimated 1.3 million people died from TB. The highest number of deaths was in SEAR, while the highest mortality per capita was in the African region. The global community woke up to this disease when, in 1993, WHO declared TB as a global emergency. It was estimated that by 2004, the world as a whole would have achieved the Millennium Development Goal (MDG) of halting and reversing the incidence to half of its 1990's prevalence and mortality rate. Now the revised time limit to achieve that MDG is by 2015.[[13](#)]

The southeast asian region (SEAR) of the WHO is critically important from the global perspective. It is home to 25% of the world human population; and with 30% of the world's poor living in this region, it suffers from high burdens of communicable and noncommunicable diseases, against a background of relatively poor health infrastructure. Progress in global health will not be possible without visible progress in this region. Six of the 14 million deaths in this region are caused by communicable diseases,

which in turn result in 42% of all the disability-adjusted life years lost.[[14](#),[15](#)]

About 3.6 million persons are estimated to be living with HIV/ AIDS in SEAR. This region is distinguished by a complex, heterogeneous HIV epidemic at different stages, both within countries and across the region. For example, approximately two thirds of the estimated HIV burden in India is in the six states in the south and northeast, which make up only one third of the country's population. In the four states in southern India, the HIV prevalence appears to be slowly decreasing. In Indonesia, where the overall prevalence of HIV is low, three provinces have been reported to have much higher rates of HIV. In other countries, such as Bangladesh and Nepal, increasing HIV prevalence among high-risk groups, such as intravenous drug users (IDUs), has raised concerns about the potential risk of a generalized HIV epidemic in these countries.[[15](#)]

Tuberculosis (TB) is airborne infectious disease caused by *Mycobacterium tuberculosis* [[1](#)]. It is one of the ten top causes of death worldwide from curable infectious diseases. Globally there were estimated 10.4 million new TB cases, and 600,000 new cases with resistance to rifampicin, 490,000 had multidrug-resistant tuberculosis (MDR-TB) cases and 1.7 million people died from TB.

Current WHO-assisted ongoing TB control program

In 1992, Government of India, together with the WHO and the Swedish International Development Agency (SIDA), reviewed the national program and concluded that it suffered from managerial weaknesses, inadequate funding, over-reliance on x-ray, nonstandard treatment regimens, low rates of treatment compliance and completion and lack of systematic information on treatment outcomes.[[22](#)] Around the same time, in 1993, WHO declared TB to be a global emergency and devised the DOTS strategy and recommended that all countries adopt this strategy. This strategy was built on five pillars, viz., political commitment and

continued funding for TB control programs, diagnosis by sputum smear examinations, uninterrupted supply of high-quality anti-TB drugs, drug intake under direct observation and accurate reporting and recording of all registered cases.

World Bank acknowledged that the DOTS strategy was the most economical health intervention and agreed to provide credit assistance for the NTCP, initially for the coverage of a population of 271 million persons, which was later revised to cover a population of 730 million persons. Presently, other bilateral and multilateral agencies, Danish International Development Agency (DANIDA), Department for International Development (DFID), US Agency for International Development (USAID), Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria (GFATM), Global Drug Facility (GDF) and WHO are providing invaluable support to the program. The Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria is the single biggest source of external funding for TB control.[\[23\]](#)

To give new thrust and to revitalize the NTCP, with assistance from the above-mentioned international agencies, in 1997, the Revised National TB Control Program (RNTCP) was launched.[\[24\]](#) It formulated and adopted the internationally recommended DOTS strategy, as the most systematic and cost-effective approach to revitalize the TB control program in India. Political and administrative commitment to ensure the provision of organized and comprehensive TB control services; reliable and early diagnosis through smear microscopy; an uninterrupted supply of good-quality anti-TB drugs; effective and patient-friendly treatment with short-course chemotherapy (SCC) given under direct observation; and accountability through proper reporting and recording and through effective supervision was heavily emphasized.[\[25\]](#) Today, India's DOTS program is the fastest-expanding and the largest program in the world in terms of patients initiated on treatment; and the second largest, in terms of population coverage.

HIV AND TB

People who are HIV-positive and infected with TB are 20 to 40 times more likely to develop active TB than people not infected with HIV living in the same country.[26] TB is a leading cause of death in people with HIV infection, accounting for more than a quarter of the 2 million AIDS deaths in 2008; it is the commonest HIV-associated opportunistic disease in the world[27]; it accelerates HIV disease progression, increasing infectivity and reducing HIV treatment efficacy.[28,29]

In India, there were 2.5 million people living with HIV and AIDS (PLHIV) at the end of 2007, while the incidence of TB was approximately 1.8 million cases per year.[30] The interaction between HIV and TB in persons co-infected with HIV and TB is bidirectional and synergistic. The level of immunosuppression determines clinical presentation of the resulting disease.[31,32] Pulmonary involvement occurs in about 75% of all HIV/TB-infected patients.[33,34] It was observed that the most frequent extra-pulmonary form of TB in HIV-positive people is that with involvement of the lymph nodes, with cervical region being the commonest.[35] Co-infection of HIV and TB also results in more rapid development of MDR-TB.[36,37]

A national policy to coordinate common activities for HIV/AIDS and TB has been formulated by the National AIDS Control Organization and the Central TB Division. TB and TB/HIV interventions are reciprocally included in the national policies of both programs.[30] Among the 1.5 million TB cases reported under the national program in 2008, an estimated 73,720 cases were HIV-infected. Implementation of the revised “*national framework of joint TB/HIV collaborative activities*” began in early 2008, and interventions now cover the entire country. An “*intensified TB/HIV package*” initiated in 2008 is now being implemented in 11 states and in districts of other states with high HIV prevalence, covering a total population of over 400 million. Indian government plans to cover the entire country with the intensified package by 2012.[21]

Current guidelines (National AIDS Control Organization, 2007) recommend that irrespective of HIV status of the patient, TB requires a minimum of 6 months of treatment — with 4 drugs (including Rifampin) in the intensive phase and 2 drugs in the continuation phase.[30] Treatment consists of Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB) and Pyrazinamide (PYZ) for 2 months followed by INH and RIF for 4 months, given either daily or intermittently. It further classifies the currently available antiretroviral (ART) agents as follows: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, chemokine receptor antagonists and entry (fusion) inhibitors. A reduction by 80% in incident TB in HAART (highly active antiretroviral therapy)-treated patients (treated with a combination of at least 3 ART drugs) was demonstrated as compared to ART-naïve HIV-infected persons in Brazil.[38] Regimens recommended for use in India for HIV/TB patients are a combination of 2 NRTIs with Efavirenz or, less commonly, Nevirapine. The NRTI combinations used commonly are Zidovudine with Lamivudine; Stavudine with Lamivudine; Tenofovir with Lamivudine; and rarely “Abacavir with Lamivudine” or “Didanosine with Lamivudine.”[30]

A commonly observed side effect of HAART is immune reconstitution inflammatory syndrome (IRIS), which is defined as transient worsening of existing symptoms, signs or radiographic manifestations or transient appearance of new symptoms, signs or radiographic manifestations after initiation of HAART. Tuberculosis is the most frequent pathogen associated with IRIS, of which, lymph node enlargement is the commonest manifestation. In one study, the incidence of IRIS in TB alone was 2%; with HIV co- infection, it was 7%; and in those started on HAART, it was 36%.[39] Surveillance for HIV infection among TB patients has been previously conducted in special surveys, and now relies upon routine reporting of HIV status of TB patients. Based on pilot-testing of decentralized delivery of co-trimoxazole preventive therapy (CPT) for HIV-infected TB patients in three high-HIV-prevalence districts of Andhra Pradesh, CPT for HIV-infected TB patients has been included in

the national policies. PLHIV are eligible for free HIV care at a network of antiretroviral treatment (ART) centers. These centers are located in medical colleges, mainly staffed and operated by the State AIDS Control Societies, and a few are situated within the facilities of private or NGO partners. As of September 2009, 217 ART centers were operating in the country, in addition to ten Regional Centers of Excellence providing state-of-the-art services for PLHIV.[30]

CURRENT CHALLENGES

Even today in India, two deaths occur every three minutes from TB. Major challenges to control TB in India include poor primary health-care infrastructure in rural areas of many states; unregulated private health care leading to widespread irrational use of first-line and second-line anti-TB drugs; spreading HIV infection; poverty; lack of political will; and, above all, corrupt administration. A collaborative effort is in progress between NTCP and National Rural Health Mission (NRHM), which is a reform initiative of which the goal is to improve primary health care in rural areas. In addition to this, NTCP has established several initiatives in coordination with the private sector and the Indian Medical Association (IMA) to improve TB care. Surprisingly, in India, people are still under the impression that TB is a disease of poor people, mostly of those living in slums. The rich and affluent persons need to know that their cooks/servants/drivers can be asymptomatic carriers of this deadly disease, right in their mansions, and hence they can potentially get infected with TB even without stepping into these slums. The consumption of unpasteurized milk or dairy products made from raw milk is another potential source of TB for humans, as there is ample evidence that bovine TB (*Mycobacterium bovis*) gets transmitted to humans.[6,7]

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