Chapter - ONE

Introduction
Chapter 1

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World Health Organization (WHO) declared tuberculosis (TB) a global health emergency over 10 years ago and still an emergency today. Globally, TB rates continuously rising leading to increased burden of disease. It is a major killer of women, rivaling maternal mortality and a prime cause of death in people with human immunodeficiency virus (HIV). Children are particularly vulnerable to TB infection as they are often held close and breathed on. One-third of the world's population is latently infected with the tubercular bacillus \textit{(M. tuberculosis)} that causes TB. Only a small proportion of people will develop active TB, because in most of the people tubercular bacilli latently present without any symptoms called latent TB (Broekmans \textit{et al.}, 2005).

Tuberculosis affects the lungs in more than 85% of cases. This form of disease is called pulmonary tuberculosis, but \textit{M. tuberculosis} can attack any part of the body such as the kidney, spine, genital organs, skin, brain etc. Pulmonary tuberculosis with sputum smear positive results is infectious form of TB. People leaving with or coming in contact with a patient who has undiagnosed or untreated infectious tuberculosis (in particular, smear positive) has the risk of getting infection. Therefore it is very important to identify suspects who have symptom of tuberculosis early in the course of the disease and ensure their treatment (Managing the Revised National Tuberculosis Control Programme in your area, 2005). If not treated properly, TB disease can be fatal. Tuberculosis spread through droplet infection (in the air) from infected person to another healthy person. The bacteria are put into the air when a person with active TB disease of the lungs or throat coughs or sneezes. However, not everyone infected with TB bacteria becomes sick. People who have latent TB infection do not have any symptoms, and cannot spread TB to others. People with active TB disease can be treated and cured if they seek medical help. Even, people with latent TB infection can take medicine so that they will not develop active TB disease. When a person breathes in TB bacteria from surrounding infected air, the bacteria can settle in the lungs and begin to grow. From there, they can move through the blood to other parts of the body, such as the kidney, spine, lymph node, genital organs, brain etc. TB in the lungs or throat can be infectious. TB in other parts of the body, such as the kidney or spine is usually not infectious. This form of TB is called extra-pulmonary TB (EPT).
The emergence of resistance to drugs used to treat tuberculosis (TB) and particularly multidrug-resistant TB (MDR-TB), has become a significant worldwide public health problem in a number of countries and an obstacle to effective TB control (Central TB Division, 2006). MDR-TB, defined as resistance to at least isoniazid and rifampicin, two of the most potent anti-tuberculosis (anti-TB) drugs, is a reflection of poor management of TB cases. Drug resistance develops either due to infection with a resistant strain, or as a result of inadequate treatment such as when a patient is exposed to a single drug, or because of selective drug intake, poor compliance, use of inappropriate non-standardised treatment regimens, irregular drug supply, poor drug quality, or rarely erratic absorption of medications (Andrews et al., 2007; Jain and Dixit, 2008; Alcaide and Santin, 2008; Jassal and Bishai, 2009).

MDR-TB is posing a potential threat to tuberculosis control in the country. Continuous monitoring of drug resistance trends is essential in order to assess current interventions and their impact on the TB epidemic. Though drug resistance against isoniazid and rifampicin has been frequently reported in India, the available information is hospital-based, using non-standardised methodology and may not have used quality controlled laboratories for drug susceptibility testing (DST). A series of representative drug resistance surveillance studies are being undertaken in selected states in accordance with the WHO global surveillance of drug resistance project (RNTCP status reports, 2008). Available data from the earlier district-wise and now state representative surveys in Gujarat and Maharashtra have found about 3% MDR-TB among new cases and 12–17% among cases with a previous history of anti-TB treatment. Data from studies conducted by Tuberculosis Research Centre (TRC) and National Tuberculosis Institute (NTI), have found MDR-TB levels of less than 1% to 3% in new cases and around 12% in retreatment cases (Paramasivan et al., 2002; Mahadev et al., 2005). It is estimated that 424,000 cases of MDR-TB occur annually, representing 14% of the global burden of TB (Zignol et al., 2006).

In India, the available information from the several drug resistance surveillance studies conducted in the past suggest that the rate of MDR-TB is relatively low in India, this translates into a large absolute number of cases and as yet the management of patients
with MDR-TB is inadequate. Specific measures are being taken within the Revised National Tuberculosis Control Programme (RNTCP) to address the MDR-TB problem through appropriate management of patients and strategies to prevent the propagation and dissemination of MDR-TB.

It is well known that resistance levels are higher in areas with a poorly performing Directly Observed Treatment Short-Course (DOTS) program. Use of inadequate regimens and inappropriate directly observed treatment (DOT) leads to increase in drug resistance levels in the community. It has been acknowledged that good treatment is a pre-requisite to the prevention of emergence of resistance. RNTCP recognizes that implementation of a good quality DOTS programme is the first priority for TB control in the country (Paramasivan, 2003). Therefore in every DOTS implementing unit of the country, DOTS would be prioritised above DOTS-Plus with the view that DOTS reduces the emergence of MDR-TB and therefore the need for DOTS-Plus over time.

In the year 2006, Mortality and Morbidity Weekly Report (MMWR) for the first time reported on the detection of extensively drug resistant TB popularly known as XDR-TB. XDR-TB, defined as tuberculosis caused by \( M. tuberculosis \) strain, which is resistant to at least isoniazid and rifampin, among the first-line anti-TB drugs in addition to resistance to any fluoroquinolones and and at least one of three injectable second-line drugs, namely amikacin, kanamycin or capreomycin (Banerjee et al., 2008; Jain and Dixit, 2008). Worldwide prevalence of XDR-TB is estimated to be 6.6% in all the studied countries among multidrug-resistant \( M. tuberculosis \) strains. The emergence of XDR-TB strains is a reflection of poor tuberculosis management, and controlling its emergence constitutes an urgent global health reality and a challenge to tuberculosis control activities in all parts of the world, especially in developing countries and those lacking resources and as well as in countries with increasing prevalence of HIV/AIDS (Alcaide and Santin, 2008; Jain and Mondal, 2008). Patients with XDR-TB have poor outcomes, prolonged infectious periods and limited treatment options. To prevent an epidemic of untreatable XDR-TB, improvements in XDR-TB surveillance, increased laboratory capacity for rapid detection of drug-resistant strains, better infection control and the development of new therapeutics are urgently needed (Banerjee et al., 2008; Jain and Mondal, 2008).
Information on the identification and management of adverse reactions should be available when patients are treated with category IV regimen. It addresses the following:

- Monitoring for early detection of adverse reactions
- Commonly encountered adverse reactions with second line drugs
- Strategies for managing adverse reactions.

Close monitoring of patients is necessary to ensure that the adverse effects of category IV anti-TB drugs are recognized early by the DOT provider. DOT makes it possible to closely monitor patients. Patients will not be asked any leading question to elicit any adverse reaction (Furin et al., 2001). However, if the patient makes any spontaneous complaint, he/she will be interrogated in detail and the necessary action taken. Commonly, patients will volunteer if they experience any adverse effects. The DOT provider should be trained to recognize adverse reactions like nausea, vomiting, diarrhoea, skin rashes, ototoxicity, peripheral neuropathy, psychiatric symptoms and jaundice (Chaulk et al., 1994; Iseman, 2000; Chan et al., 2004; Torun et al., 2005). In addition to clinical monitoring, certain laboratory investigations may be required to detect certain occult adverse effects.

A major adverse reaction to one of the first-line anti-TB drugs, which results in discontinuation of that drug, has several implications. During the course of therapy there may be considerable morbidity, even mortality, particularly with drug-induced hepatitis, which have been reported in past. Alternative agents may have greater problems with toxicity and are often less effective, so that treatment must be prolonged, with challenges to ensure compliance. As a result the risk of treatment failure and relapse are higher (Yee et al., 2003). Hence monitoring is crucial, but costly. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug-related adverse effects.

Therefore, the present study was designed to monitor the incidence of ADRs and their possible mechanism(s) during combination anti-tuberculosis therapy. There is genetic variation in the metabolism of isoniazid, leading to slow and fast metaboliser. Predetermined pattern of acetylation helps in individualisation of treatment and reduce the risk of treatment failure and occurrence of adverse reactions.