Abstract:
Multi Drug Resistant Tuberculosis (MDR TB) is resistant to Isoniazid (INH) and/or Rifampicin (R). Government of India started implementing Directly Observed Treatment, Short Course (DOTS) strategy under Revised National Tuberculosis Control Programme (RNTCP) since 1997, the country has come a long way. This study is undertaken to analyse the outcome results of MDR-Tb under PMDT. This is a retrospective analytical study of 90 patients who were registered in District Tuberculosis Control Centre (DTCC), Visakhapatnam during the period of January 2012 to December 2012. Observed results were, cure rate was 45.6%, defaulters were 7.8%, deaths were 33.3% and failures were 5.6%. Rapid diagnostics like Line Probe Assay (LPA) will reduce the time in MDR diagnosis and treatment. This will reduce the death rate in the long term. Default rate can be further reduced by intensifying health education, strengthening family support and improving nutritional status.

Key words: Isoniazid, Line Probe Assay, MDR-TB, PMDT, Rifampicin, RNTCP.

Introduction:
Tuberculosis, one of the oldest diseases known to affect humans, is a major of deaths worldwide. This disease, which is caused by bacterium of the Mycobacterium tuberculosis (MTB), which is a part of the complex of organisms including M. bovis (cattle) and M. africanum (human) which usually affects the Lungs, although other organs are involved in up to 1/3rd of cases. If properly treated, TB caused by drug- susceptible strains is curable in virtually all cases. If untreated the disease may be fatal within 5 years in 50-65% of cases [1]. In 2010, an estimated 8.8 million incident cases occurred and TB was estimated to account for nearly 1.5 million deaths, making it the second most common cause of the death due to an infective disease [2].

M. bovis infection arises from drinking non-sterilized milk from infected cows. M. tuberculosis spreads by the inhalation of aerosolised droplet nuclei from other infected patients.
INH is a tuberculocidal drug. The most plausible mechanism of action of INH is inhibition of synthesis of Mycolic acids which are unique fatty acid component of Mycobacterial cell wall. This may explain the high selectivity of INH for Mycobacteria. The lipid content of Mycobacteria exposed to INH is reduced. A gene labelled inhA and kasA which function in Mycolic acid are the targets of INH action. The sensitive Mycobacteria concentrate INH and convert it by a Catalase- Peroxidase enzyme into an active metabolite. This then forms adduct with NAD that inhibits inhA and kasA genes. The most common mechanism of INH resistance is by mutation of the Catalase - Peroxidase (kat G) gene so that the bacilli do not generate the active metabolite of INH. Another possible mechanism is resistance based of efflux of INH from the bacterial cell.

Rifampicin is a semi- synthetic derivative of derivative of Rifamycin B obtained from Streptomyces mediterranei. Rifampicin is bactericidal to M. tuberculosis and many other gram-positive and gram-negative bacteria like Staphylococcus aureus, N. meningitidis, H. influenzae, E. coli, Klebsiella, Pseudomonas, Proteus and Legionella. Rifampicin inhibits DNA dependent RNA synthesis. Probably, the basis of selective toxicity is that mammalian RNA polymerase does not avidly bind Rifampicin. Rifampicin resistance is due to mutation in rpoB gene reducing its ability for the drug [3].

India is home to over 25% of world’s tuberculosis (TB) cases and ever since government of India started implementing DOTS Strategy under Revised National TB Control Program (RNTCP) since 1997, the country has come a long way. Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients. This improper use is a result of a number of actions including, administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals [4]. The entire country is covered with DOTS by 2006 and treatment success rate improved since then. However, the emergence of multidrug-resistant tuberculosis (MDRTB) has become a challenge all over the world, and it is creating an obstacle to the effective management of TB in our country.

World Health Organization (WHO) estimates that between 220,000 and 400,000 MDRTB occurred among TB cases notified in the world in 2011. About 60% of these occurred in Brazil, Russian Federation India, China, and South Africa alone (BRICS Countries). India has the second highest burden of MDRTB cases following China [5]. RNTCP started a WHO recommended DOTS PLUS program in a phased manner for the systematic treatment of MDRTB in 2007. By Feb 2013, programmatic management of drug-resistant tuberculosis (PMDT) services were available in 35 states of the country (including Union Territories), 638 districts covering a population of 1089 million (92%) and were rapidly scaled up to include remaining districts by 24th March 2013 [6].

As per the drug resistance surveillance surveys in Gujarat, Maharashtra and Andhra Pradesh, estimated proportion of MDRTB is 2.1% (1.5-2.7%) in new TB cases and 15% (13-17%) in previously treated cases [7]. Global data show that 32% of relapse cases actually have MDRTB.

Materials and Methods:

In the present study, retrospective analysis was done on 90 MDRTB patients who were registered at the DTCO centre, in the GHCCD, Andhra Medical College, Visakhapatnam, during the period from January 2012 to December 2012.

All the 90 patients consecutively enrolled in the study were diagnosed with MDRTB at the IRL, Hyderabad and RNTCP certified C&DST Laboratory, Visakhapatnam, located in the building of GHCCD. Prior to the diagnosis, all the patients were MDR-TB suspects as per the RNTCP strategy at the time of the study, i.e., patients who failed category (CAT) I regimen and CAT II patients whose sputum was positive at the end of 4th month or later. The patients belonged to Visakhapatnam District. The two-sputum samples of the MDR suspects who were sputum positive were collected in Falcon tubes and transported in cold chain from the respective designated microscopy Centre (DMCs), some to RIL, Hyderabad and some to the C&DST Laboratory in our hospital. The C&DST Laboratory is attached to AMC and supported by FIND, WHO and Central RB Division (CTD) through state, and its first accreditation was done in 2011. All the sputum positive samples of the MDRTB suspects were
subjected to LPA and results were available in 2-3 days. When the results were inconclusive, the culture was repeated on LJ culture medium, and the culture isolate was tested with LPA. All the follow-up cultures were also tested on LJ medium. All the confirmed MDR-TB cases were traced, counselled and referred to DR-TB centre, GHCCD for pre-treatment assessment and initiation of CAT IV regimen.

As per the program guidelines, all the patients underwent thorough clinical evaluation including height and weight recording, complete blood count, blood sugar, liver function tests, renal function tests, thyroid stimulating hormone, urine examination, pregnancy test in women of childbearing age group and HIV testing after counselling and Chest X-ray examination.

During the stay at the DR-TB centre, which is a 24 bedded ward (12 for males and 12 for females) with air-borne infection control measures in place as per the guidelines, the patients were initiated on CAT IV regimen consisting of 6 (9) Km Ofx Eto Cs Z E/18 Ofx Eto Cs E. Patients were discharged 1-2 weeks after initiation of CAT IV. Trained DOTS Providers arranged through concerned DTO administered the drugs under supervision, counselled the patients and family and took care to identify and refer them to the DTO/DR-TB centre in the event of adverse drug reactions (ADRs).

Follow-up sputum smear and culture examination was done at the end of the months 3, 4, 5, 6 and 7 and at 3 monthly intervals from 9th month onwards till the completion of treatment (9, 12, 15, 18, 21, 24 months). The sputum smear microscopy was done at the concerned DMC and culture was done on LJ medium at C&DST Laboratory, GHCCD. If any of the cultures in the last 3 quarters was positive, it was followed by monthly culture in the following 3 months. Based on the culture reports of 4th, 5th, 6th months, the Intensive Phase (IP) was extended to 1-3 months. After discharge from DR-TB centre, the respective DTOs reviewed the patients at monthly intervals during IP and 3 monthly intervals during CP until the end of the treatment. Patients were evaluated for clinical improvement, weight changes and possible adverse reactions.

Treatment outcome results are classified as follows: Cure, Defaulter, death, treatment completed, treatment failure and still on treatment.

Cure: An MDR-TB patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to 15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.

Treatment completed: An MDR-TB patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of bacteriological results.

Death: An MDR-TB patient who dies for any reason during the course of MDR-TB treatment

Treatment failure: Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12-15 months are positive, or if any of the final three cultures are positive.

Treatment default: An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reasons.

Transfer out: An MDR-TB patient who has been transferred to another reporting unit (DOTS Plus site in this case) and for whom the treatment outcome is not known. Till the time the DOTS Plus services are available across the country, the Cat IV patients can be transferred out only to those districts, within or outside the state, where these services are available. If a Cat IV patient moves from one district to another, both of which are covered by the same DOTS plus site, transfer out will not be required.

Treatment stopped due to adverse drug reactions: A patient on MDR-TB treatment who develops severe adverse reactions and could not continue the MDR-TB treatment in spite of the management of the adverse reactions as per the defined protocols and decision has been taken by the DOTS-Plus site committee to stop treatment.

Treatment stopped due to other reasons: A patient on MDR-TB treatment who could not continue the MDR-TB treatment for any other medical reason (than adverse drug reactions), and a decision has been taken by the DOTS-Plus site committee to stop treatment.

Switched to Category V treatment: A Category IV patient who during treatment is identified as an “XDR-TB suspect” and who is found to have XDR-TB on testing by an NRL, who subsequently has had their Category IV treatment stopped and RNTCP Category V treatment initiated.
Still on treatment: An MDR-TB patient who, for any reason, is still receiving their RNTCP CAT IV treatment at the time of the submission of the RNTCP DOTS-plus Treatment Outcome Report.

Results:
A total of 97 patients confirmed with MDR-TB cases registered at District Tuberculosis Control Centre (DTCC), Visakhapatnam between January 2012 and December 2012. Of these 97 cases, detailed information is not available for 7 cases. In the remaining 90 cases, 60 were males and 30 were females. Of 60 males age ranges from 15-70 and in females it ranges from 17-65 years. Among the 90 cases, 63 were resistant to both INH and Rifampicin and 27 were resistant to Rifampicin only. Among 63 which were resistant to both, 39 were males and 24 were females. Among 27 patients who were resistant to Rifampicin only, 21 were males and 6 were females.

Culture Conversion: Patients will be considered Culture converted after having two consecutive negative cultures taken at least 1 month apart.

Time to Culture Conversion: It is calculated as the interval between the date of MDR-TB treatment initiation and the date of the first of these two negative consecutive cultures (the date that the sputum specimens are collected for culture should be used).

At the end of 3rd month among 90 patients observed, culture conversion occurred in 61 patients and remained positive in 7 patients. By the end of third month number of deaths occurred were 14 and defauters were 8.

By the end of 6th month out of 70 patients, culture conversion occurred in 49 patients and remained positive in 8 patients. Deaths occurred in 4 patients, defaulters are 8 and 1 patient was transferred to Guntur District.

At the end of 10th month, out of 61 patients’ culture conversion seen in 41 patients and remained positive in 4 patients. Deaths and defaulters were 5 and 11 respectively.

At the end of 14th month out of 58 patients’ culture conversion seen in 41 patients and remained positive in 3 patients. Deaths and defaulters were 7 each.

Table 1: Outcome Results of the patients in the respective months

<table>
<thead>
<tr>
<th>Category</th>
<th>3rd month</th>
<th>6th month</th>
<th>10th month</th>
<th>14th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture Converted</td>
<td>61</td>
<td>49</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Culture Positive</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Died</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Defaulters</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Transferred</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

4 female patients were associated with HIV-positive. Out of 4, 3 were died during the follow-up.1 after 6 months and remaining 2 after one year. The remaining 4th patient was a failure case.

The treatment outcome results were analysed. 41 out of 90 cases were cured, 7 were defaulters, 30 were died, 5 cases were failures, 4 patients were still on treatment and 3 were transferred to other districts. None were diagnosed with XDR-TB.

Discussion:
In the present study of 90 patients males are 60 with a predominance of 67% with 60, while
females were 30 constituting about 37%. Of 60 males age ranges from 15-70 and in females it ranges from 17-65 years. In the present study, Line Probe Assay (LPA) shows a mono resistant pattern to Rifampicin in 30 patients out of 90 patients. Among 27 patients, 21 were males and 6 were females. 63 patients were resistant to both INH and Rifampicin. Of these, 39 were males and 24 were females.

In the present study, culture converted were 61 out of 90 (68%) by the end of 3rd month, 49 out of 70 (70%) by the end of 6th month. By the end of 10th month 41 out of 61 were culture converted i.e. 68% and at the end of 14th month out of 58, 41 (71%) were culture converted. This shows there is a 4% improvement of culture conversion.

By the end of 3rd month, deaths were reported 14 (15.2%). By the end of 6th month deaths were 4 i.e. 6.7% and by the end of 10th month out of 5 deaths (8%) and at the end of 14th deaths were 7 i.e. (12%). The total number of deaths for a period of 2 years was 30.

By the end of 3rd month, cultures remained were 7 (7.8%). By the end of 6th month, 8 i.e. 11.4% and by the end of 10th month 4 (7%) and at the end of 14th month 7, i.e. (5%). This shows there is a decline in culture positive rate by 2.8&

By the end of 3rd month defaulters were i.e. 9%, by the end of 6th month 11.4% and in the 10th month 11 patients i.e. 18% and by the end of 14th month 7 patients i.e. 12%. This shows an increase in defaulters. Among 30 deaths, 3 were diagnosed as HIV positive and all of them were females.

Barely deaths indicate extensive damage to Lungs of the patients. Defaulter’s rate varied from 7-8. Data about Adverse Drug Reactions and Diabetes mellitus is not available.

Analysis of treatment outcome results showed that cure rate was 45.6%. Worldwide studies demonstrated a cure rate varying from 38 100%. Our cure rate is low when compared to the 66% of Joseph et al and 61% of Singla et al [8, 9]. Yet our cure rates are higher than the 39% of Visakha et al. [10] and 37% of Thomas et al. [11]. The defaulters rate 7 out of 90 and death rate of 30 out of 90. The present study explains the cure rate of 45.6%.

When enquired into the reasons for defaulting. It is observed that the defaulted patients lacked family support were reluctant to consume large number of pills for a period of 24 months. Some had very low nutritional status and did not want to go on with the treatment and attributed minor adverse effects to the drugs.

The overall treatment success rate is 48% according to the data available from 60 countries across the world [5]. The global target of treatment success rate is 75% which can be achieved with rapid scale-up of RNTCP services and more number of certified laboratories adopting rapid diagnostic methods. RNTCP strategy of case detection also has changed with the new A, B, C criteria for an MDR suspect. This will also help in the detection of disease in early stage before permanent lung damage occurs.

To make the patients more knowledgeable about their condition and for better adherence, strong health education to the patient as well as the family members is highly important. More intense monitoring and early identification and management of ADR also help to reduce default rates which will have an impact on the success rate.

This study had few limitations that it is a small sample, and it was in the early months of PMDT services at our hospital. Therefore, the study group was largely made up of pooled up patients with MDRTB, which may have had an impact on the treatment outcome. There were also some initial

<table>
<thead>
<tr>
<th>Table 2: Comparison of the present study with other studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Compariso n</td>
</tr>
<tr>
<td>Present study</td>
</tr>
<tr>
<td>Thomas et al.</td>
</tr>
<tr>
<td>Joseph et al.</td>
</tr>
<tr>
<td>Jain et al.</td>
</tr>
<tr>
<td>Visakha et al.</td>
</tr>
<tr>
<td>Singla et al.</td>
</tr>
</tbody>
</table>
operational difficulties because of which this study lacks data of BMI, radiological features and history of contact details.

**Conclusion:**

The cure rate with PMDT in the present study is 46% which is below overall treatment success rate (48%). The global target of 75% can be achieved with widespread use of rapid diagnostics like Line Probe Assay (LPA), which will reduce the time for diagnosis and treatment of MDRTB. This will help in reducing death rate in the long term which will have an impact on success rate. The default rate can be further reduced by intensifying health education, improving family support and nutritional status.

**Acknowledgement:**

We would like to thank Dr. Vasundhara, District Tuberculosis Control Officer (DTCO), Visakhapatnam for her support in retrieving the data relating to the patients. We would also wish to thank Dr. Usharani Namballa, Associate Professor, Government Hospital for Chest and Communicable Diseases (GHCCD), Visakhapatnam for helping in preparation of manuscript and giving feedback and suggestions.

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

**Source of Funding:** Nil

**Source of Conflict:** None

**References:**