A Dissertation on

SPUTUM STATUS OF SPUTUM POSITIVE PULMONARY TUBERCULOSIS PATIENTS WHO HAVE COMPLETED CATEGORY I ATT UNDER DOTS TREATMENT

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CERTIFICATE

This is to certify that this dissertation entitled "**SPUTUM STATUS OF SPUTUM POSITIVE PULMONARY TUBERCULOSIS PATIENTS WHO HAVE COMPLETED CATEGORY I ATT UNDER DOTS TREATMENT**" submitted **by Dr. A. KARTHICK RAMALINGAM** to the Tamilnadu Dr. M.G.R medical University is in partial fulfilment of the requirement of the award of M.D DEGREE (BRANCH-I) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation entitled "**SPUTUM STATUS OF SPUTUM POSITIVE PULMONARY TUBERCULOSIS PATIENTS WHO HAVE COMPLETED CATEGORY I ATT UNDER DOTS TREATMENT**" was done by me at Government Stanley Medical College and Hospital during 2011-2014 under the guidance and supervision of Prof. Dr. P. Vijayaraghavan M.D. and Prof. Dr. Sridhar M.D., DTRD., The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfilment of requirement for the award of M.D. Degree (Branch-1) in General Medicine.

Place :

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ABBREVIATIONS

ATT	Anti Tuberculosis Treatment (ATT)
DOTS	DIRECTLY OBSERVED TREATMENT SHORT COURSE
PAS	PARA –AMINO SALICYLIC ACID
WHO	WORLD HEALTH ORGANISATION
RNTCP	REVISED NATIONAL TUBERCULOSIS CONROL PROGRAMME
HIV	HUMAN IMMUNO DEFICIENCY VIRUS
MDR	MULTIDRUG RESISTANT
INH	ISONIAZID
CNS	CENTRAL NERVOUS SYSTEM
RFLP	RESTRICTION FRAGMENT LENGTH POLYMORPHISM
DST	DRUG -SUSCEPTIBILITY TESTING
XDR	EXTENSIVELY DRUG –RESISTANT
FLD	FIRST LINE DRUGS
SLD	SECOND LINE DRUGS
AFB	ACID FAST BACILLI
BMI	BODY MASS INDEX

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SPUTUM STATUS OF SPUTUM POSITIVE PULMONARY TUBERCULOSIS PATIENTS WHO HAVE COMPLETED CATEGORY I ATT UNDER DOTS TREATMENT

BACKGROUND: DOTS remains the cornerstone in global efforts towards tuberculosis control. In India DOTS based guidelines given by RNTCP remains the standard of care for treatment of tuberculosis. New smear positive patients treated under RNTCP programme have a cure rate of 88% on completing treatment.

AIMS & OBJECTIVES: To assess the bacteriological status of patients after one year of completion of primary chemotherapy under new smear positive category in RNTCP. To assess the effectiveness of cure obtained in that regimen and factors associated with increased chance of relapse.

METHODS: The study is a prospective study. New smear positive patients who have registered under DOTS programme in the period October 2011 to March 2012 and declared cured are selected in two zones around Stanley medical college. Patients with immunosuppressive illness were excluded from the study. Their current sputum bacteriological status is assessed by sputum smear examination and culture in a spot sputum specimen. Risk factors associated with relapse are also evaluated by means of questionnaire, clinical examination, biochemical test, radiological assessment. Patients who are bacteriologic ally active were started on category II as per RNTCP norms. The sampling method is non probability sampling-convenient sampling. Radiological assessment intended in the protocol was not done during the study.

RESULTS: Sputum AFB culture of the 49 patients showed positive culture in three patients. . The relapse of pulmonary TB among patients who have completed ATT under RNTCP is 6 % at the end of one year. One out of three patients revealed SH resistance.

CONCLUSION: Evaluation of primary resistance prior to treatment may help in avoiding future relapses.

KEY WORDS: Tuberculosis, New smear positive, Relapse, DOTS, RNTCP, AFB, ATT.

INTRODUCTION

New sputum positive pulmonary tuberculosis patients are started on category I Anti Tuberculosis Treatment (ATT) under DOTS. New smear positive patients are treated with a 6 month regimen. In the first two months called the intensive phase patients are treated with four drugs that include rifampicin(R), isoniazid (H), pyrazinamide (Z) and Ethambutol (E). Intensive phase is followed by continuation phase in which only isoniazid and rifampicin is taken for four months. In both the phases drugs are given three days in a week called intermittent regimen.

The primary goals of treatment of sputum positive pulmonary tuberculosis patients are to kill tubercle bacilli rapidly, prevent the emergence of drug resistance and eliminate the persistent bacilli from the host's tissues to prevent relapse [(1)]. Patients started on ATT usually become sputum negative at the end of 2 to 3 months (80% -90%). At the end of 6 months of category I the cure rate achieved among new smear positive patients is 88% [(2)]. The data about relapses that occur from this 88% is lacking. Those patients who report spontaneously to the health sector and found to have relapsed are put on category II regimen. The present study is to determine how many of these patients who have been

cured with category I under programme conditions are able to maintain their bacteriological negativity at the end of one year period .From the earlier studies it has been found that most of the relapses occur within one year of completion of primary chemotherapy. Hence a cohort of patients who have completed or cured from their smear positive status and completed one year post treatment status are included in the study. In these patients sputum smear examination and culture for acid fast bacilli are done to look for bacteriological activity.

AIM OF THE STUDY

To identify patients who are bacteriologically active one year after completion of their primary chemotherapy.

OBJECTIVES OF THE STUDY

1) To assess the effectiveness of cure obtained from category I regimen under programme conditions.

2) To assess presence of co morbid illnesses and other risk factors as a causative or helping factor in the development of relapse.

3) Whether drug resistance has any role causing relapse.

REVIEW OF LITERATURE

INTRODUCTION

Tuberculosis is caused by bacillus Mycobacterium tuberculosis. It continues to be a major health challenge that the global community is facing. Currently it is the second major cause of mortality due to infectious agent superseded only by Human Immunodeficiency Virus [(2)]. Infection mainly affects the lung (pulmonary). It can also affect the extra pulmonary sites. The great burden of tuberculosis in developing world is in the active age group 15 to 60 years of age [(3)].

EVOLUTION OF TUBERCULOSIS TREATMENT

Tuberculosis control measures were started as a global measure. Cure of the sputum positive pulmonary tuberculosis patients is the only effective way in which spread of tuberculosis in the community can be controlled[(5)]. Drugs effective against tuberculosis became available in 1944 after the discovery of streptomycin when it was isolated from Streptomyces griseus by Waksman. Initially streptomycin monotherapy was used. It resulted in emergence of drug resistance and treatment failure. P- Amino salicylic acid was discovered in1949. It was found that when PAS given along with streptomycin prevented the emergence

of drug resistance. Isoniazid was discovered in 1952. Because of its low toxicity, high effectiveness and low cost it got incorporated into all primary regimen since then. Till these times treatment of tuberculosis was predominantly sanatorium based. In 1956 from trials in Madras it was demonstrated that ambulatory and domiciliary care was equally effective in treatment of tuberculosis. It was demonstrated that domiciliary care did not increase the chance of family members getting affected by tuberculosis. The most effective drug against tuberculosis rifampicin became available in 1960. It was observed that even with good health education patients did not take drugs regularly and this lead to the development of drug resistance so directly observed treatment was recommended as the standard of care in tuberculosis treatment. Intermittent regimen was demonstrated to be as effective as daily regimen in the treatment of tuberculosis in1964. Various trials around the world demonstrated that 6 to 8 months of treatment with combination of drugs were highly effective in treatment of tuberculosis. It was shown that even in smear positive severe cavitatory lung lesion addition of rifampicin decreased the duration of treatment with less relapse rate. Addition of pyrazinamide during the intensive phase of treatment was found to decrease the duration of treatment to 6 to 8 months. In 1980 regimens were tried with duration of treatment less

than 6 months. All these regimens were associated with a high relapse rate and hence were discontinued.

SCIENTIFIC BASIS IN THE EVOLUTION OF TUBERCULOSIS TREATMENT

Mycobacterium tuberculosis is slow growing aerobic bacteria. Its doubling time is 18 hours and can remain dormant for a long time. In a pulmonary lesion due to tuberculosis there will be a large number of bacilli in rapidly dividing state (in a cavitatory lesion it is 10^8 & in case of a nodular lesion without a communicating bronchus it is 10^2 [10] and there will be a bacilli population with a slow metabolic rate. The chance of having drug resistant bacilli is more when the bacilli load is very high even before initiation of treatment.

The chance of a drug sensitive bacilli to survive and remain latent even in the presence of adequate concentration of potent drugs like isoniazid and streptomycin is also there if the bacilli have a slow metabolic rate. Only drugs like rifampicin and pyrazinamide are effective against these slow multipliers. Regimens used to treat tuberculosis should contain at least 2 drugs for which the organism is susceptible and usually the patients are treated with four drugs during the intensive phase to avoid the emergence of drug resistance [6]

DIRECTLY OBSERVED TREATMENT SHORT COURSE

With the advent of potent drugs the duration of therapy decreased. Pyrazinamide availability decreased the duration of treatment from 8 months to six months. It was found that instead of daily regimen twice weekly or thrice weekly intake of drugs were also equally effective. These observations made the world health organisation to recommend that DOTS therapy should be the basis of treatment in tuberculosis patients. In DOTS during the intermittent therapy the drugs should be taken under the supervision of a health care personnel.

Before the introduction of Directly Observed Treatment Short course by WHO treatment regimens were chaotic and were not standardised. Treatment was not properly monitored. So treatment of sputum positive patients failed to make any impact on the incidence of tuberculosis in the community. Post introduction of DOTS most countries adopted it and regimens used against tuberculosis were uniform. These measures resulted in the better outcome of treatment. Today relapse, default, treatment failure have come down because of the monitored treatment under DOTS. Because of better treatment of sputum positive patients, incidence of tuberculosis has started to come down.

The DOTS strategy assures a compulsory and free availability of good quality drugs to all tuberculosis patients and necessitates drug administration under direct supervision, thereby ensuring the requisite regimen compliance[7]

After the introduction of DOTS the incidences of tuberculosis have come down. WHO launched its next programme against tuberculosis “The Stop TB strategy”.

The components of Stop TB Strategy are,

- Pursue high quality DOTS expansion and enhancement.
- Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations.
- Contribute to health system strengthening based on primary health care.
- Engage all care providers.
- Empower people with TB, and communities through partnership.
- Enable and promote research.

The Stop TB Strategy has the following end points

Vision: TB free world

Goal: to dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the Stop TB Partnership targets.

Objectives

- Achieves universal access to high quality care for all people with TB
- Reduce the human suffering and socioeconomic burden associated with TB
- Protect vulnerable population from TB, TB/HIV and drug resistant TB
- Support development of new tools and enable the timely and effective use.
- Protect and promote human rights in TB prevention, care and control

Targets: MDG 6, Target 6.c; Halt and begin to reverse the incidence of TB by 2015.

- 2012: Reduce prevalence of and death due to TB by 50% compared with a baseline of 1990.

- 2050: eliminate TB as a public health problem (defined as <1 case per 1 million population per year)

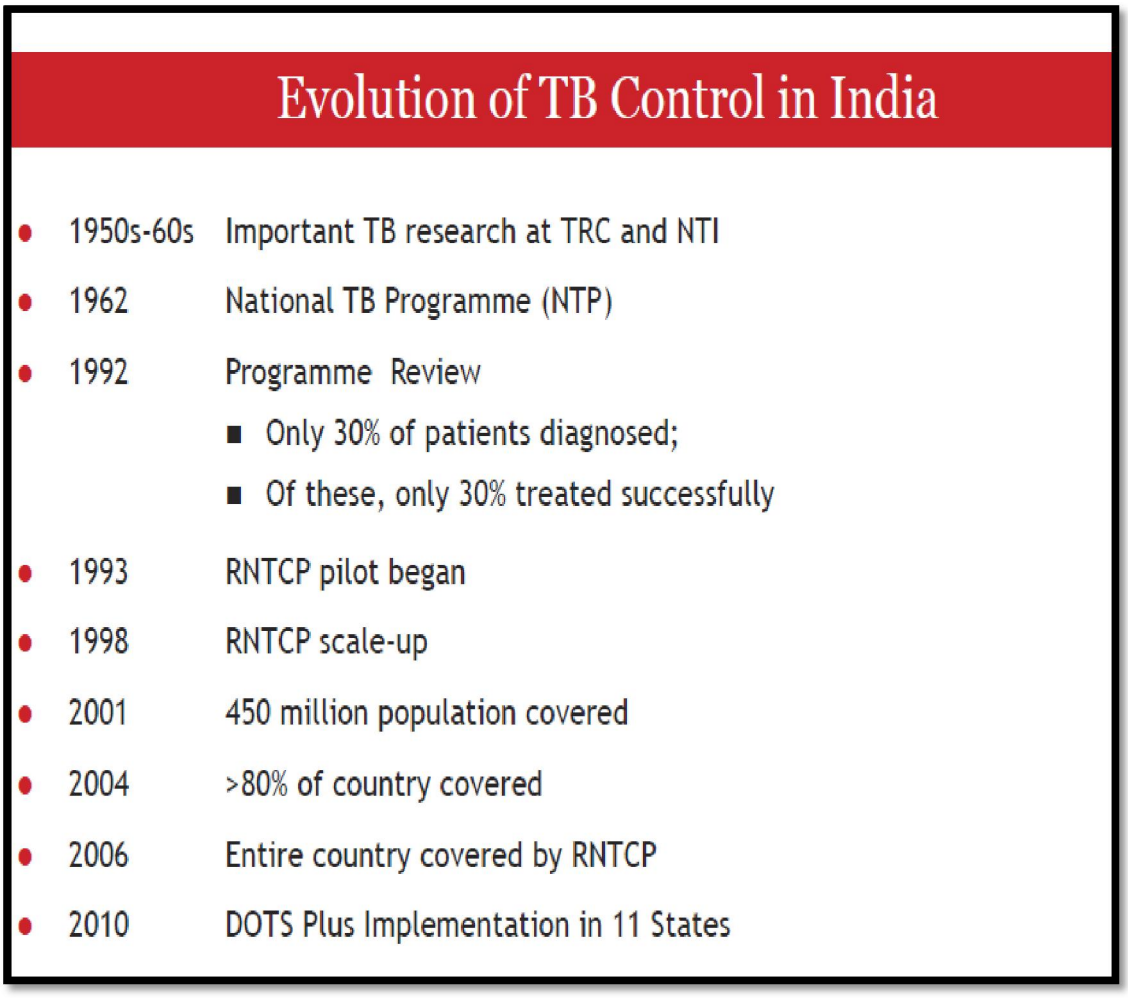
Currently incidence of tuberculosis is coming down at rate of 2% per year. Global incidence of tuberculosis in 2012 is 8.6 million cases. Mortality due to tuberculosis in the same year is 1.3 million cases. In developed world incidence initially was controlled but now with emergence of HIV incidence of tuberculosis in the developed world started increasing. Among the 8.6 million TB patients 13% were HIV positive.

TUBERCULOSIS CONTROL IN INDIA

Before the recommendation of DOTS by WHO tuberculosis treatment evolved in India from a predominantly sanatorium based therapy to a domiciliary care. In 1962 the National Tuberculosis control programme (NTP) was implemented. After in practice for more than three decades it was observed that drug adherence was still a major problem. In 1992 after a comprehensive review of tuberculosis control programme in India it was found that less than half of the patients with tuberculosis received accurate diagnosis and less than half were effectively treated. Several factors lead to the failure of NTP. They were,

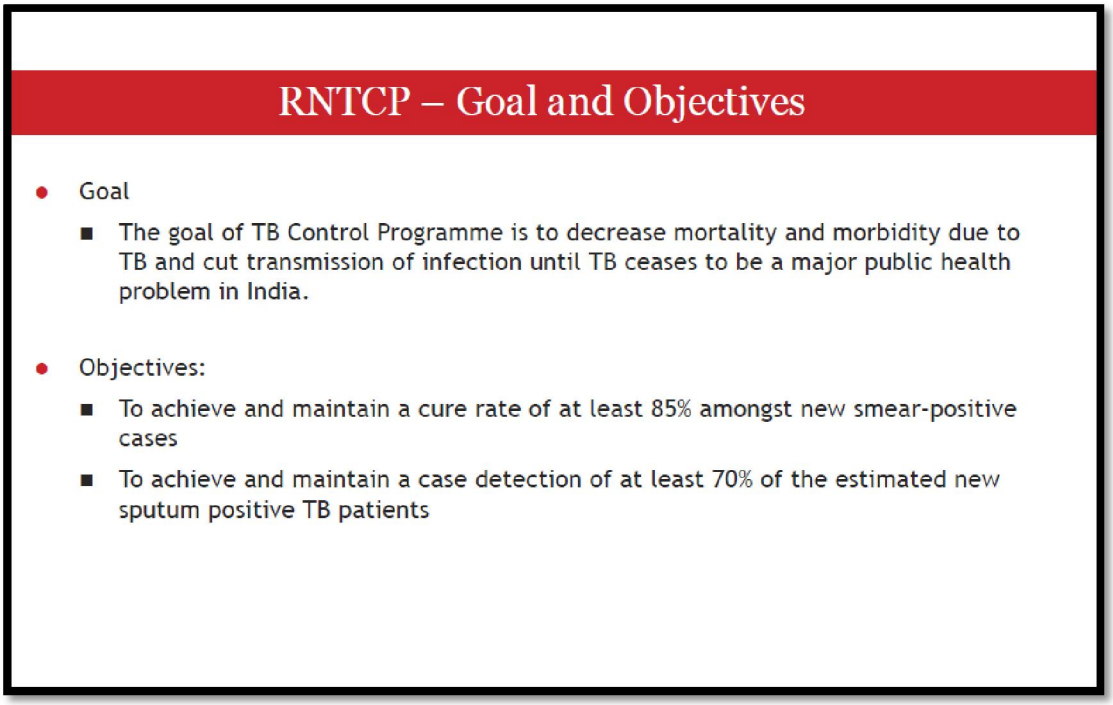
- Under utilization of laboratory services
- Unnecessarily complicated treatment regimens
- Shortage of drugs
- Treatment completion was not assessed systematically.

These factors that lead to the failure of NTP was analysed in detail and Revised National Tuberculosis Control Programme was introduced in 1993. In 2006, 100 % national coverage was achieved under RNTCP.RNTCP was based on DOTS recommended by WHO.



REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME

India has one fifth of world tuberculosis patients. India has the largest tuberculosis load more than any other country. India accounts for 26% of world tuberculosis load. The prevalence of tuberculosis in India is 2.8 million cases. The incidence of tuberculosis is 2.2 million cases. Incidence among HIV positive patients is 0.13 million. Mortality due to tuberculosis in India is 0.39 million. The largest impact is in the age group 15 -60 years. This is found due to socioeconomic factors and the dependence of members of the family over this age group for earning and the exposure the age group receive in the community [(26)]. In India DOTS was adopted under Revised National Tuberculosis Control Programme in 1993.Objective of RNTCP is to detect at least 70 percent of new smear positive patients and to cure at least 85 percent of those new smear positive patients.



The Revised national tuberculosis control programme has improved case finding facilities, made available short course chemotherapy in an un interrupted manner, increased the cure rates, and has provided data on adherence and outcome.

Guidelines for treatment of tuberculosis were revised in 2010 by WHO. In a departure from the previous recommendations the WHO has now said that daily regimen is the preferred dosing regimen compared to the intermittent. Regimen [37]. In RNTCP still intermittent regimen is used .A study done by Tuberculosis Research Centre in 1997 showed that twice as many patients on intermittent regimens relapsed compared with those on daily regimen(10% Vs 5 %)[40]. Although the bacteriological care was comparable in the two groups, the fully

intermittent therapy group had higher relapse rates. In a systematic review of 20 published trials it was concluded that the risk of relapse is related to the total dose of administered and the relapse rate remains within acceptable limit of 5 % only with either daily regimen or regimens that incorporate a daily regimen in the intensive phase[42]. Daily regimen showed a higher percentage of culture negativity at 2 months and less unfavourable outcomes (relapse, death) at 12 months[43].

In current RNTCP guidelines new smear positive patients are treated with a 6 month regimen. In the first two months called the intensive phase patients are treated with four drugs that include rifampicin(R), isoniazid (H), pyrazinamide (Z) and Ethambutol (E). Intensive phase is followed by continuation phase in which only isoniazid and rifampicin is taken for four months. It is recommended that the 2HRZE/ 6HE regimen previously used to be phased out since it is associated with more relapse and death than 2HRZE/4HR. A 12 month regimen is advised for TB meningitis in which ethambutol is replaced by streptomycin. For bone and joint TB the recommended regimen is for 9 months.

REGIMEN FOR TREATMENT OF TUBERCULOSIS [4]

Category of cases	Intensive Phase	Continuation Phase
New cases	2 month of HRZE	4 month of HR
Previously treated cases		
Failure cases	Empirical MDR regimen	18-24 months
Relapse/Default cases	2HRZES/1 HRZE/5HRE Regimen to be modified after DST	

RNTCP Recommendation[7]

RECOMMENDED DRUG DOSAGES UNDER THE RNTCP

Drug	Dose in mg (thrice a week) in adults	Dose in mg per kg body weight (thrice a week) in children
• Isoniazid	600	10 - 15
• Rifampicin	450*	10
• Pyrazinamide	1500	35
• Ethambutol **	1200	30
• Streptomycin	750***	15

NOTE : * Patients weighing > 60 kg are given an additional 150 mg of Rifampicin.
** Ethambutol is not given to children < 6 years of age.
*** Patients > 50 years of age or weighing < 30 kg are given 500 mg of Streptomycin.

WHO ESTIMATED BURDEN OF TUBERCULOSIS IN INDIA, 2011

	Number (Millions) (95% CI)	**Rate Per 100,000 Persons (95% CI)**
Incidence	2.3 (2.0–2.5)	185 (167–205)
Prevalence	3.1 (2.0–4.6)	256 (161–373)
Mortality	0.32 (0.21–0.47)	26 (17–39)
	Number (Millions) (95% CI)	**Percent (95% CI)**
HIV among estimated incident TB patients	0.11 (0.075–0.16)	5% (3.3–7.1%)
MDR-TB among notified pulmonary TB patients	0.064 (0.044–0.075)	5.3% (3.6–6.2%)
Notified New pulmonary TB patients	0.021 (0.015–0.027)	2.1% (1.5–2.7%)
Notified Re-treatment pulmonary TB patients	0.043 (0.039–0.048)	15% (13–17%)

ANTI TUBERCULOSIS DRUGS

ISONIAZID

Isoniazid is a hydrazide of isonicotinic acid. It was first synthesized in Prague in 1912. It's effectiveness in treating tuberculosis was demonstrated in 1952. It is effective only against tuberculosis and

not against any other organism. One of the most powerful anti tuberculosis drug that is active against both intracellular and extracellular bacilli. More marked action is seen in rapidly dividing organisms and less activity is seen against slow multipliers. It easily penetrates the cell membrane and it is widely distributed among body fluids with good CNS penetration.

Peak drug concentration of INH is more important than sustained blood levels of the drug so single dose on a day is preferred rather than divided doses[17]. It's a potent drug with less toxicity and available at a low cost. It's also used in the treatment of latent tuberculosis and in chemo prophylaxis of tuberculosis.

Use of INH is associated with peripheral neuropathy, blood dyscrasias, hyperglycaemia and liver damage more so in slow acetylators. Infrequently it is associated with psychosis and generalized epileptic convulsions. Both these complications can occur in any patient irrespective of their acetylator status. Peripheral neuropathy is the most common toxic manifestation. In HIV co infected patients the chance of having peripheral neuropathy is high. The frequency of developing peripheral neuropathy increases with dose of INH. Peripheral

neuropathy is more common in diabetics, chronic kidney disease patients, malnourished patients, alcoholics and slow acetylators.

To prevent peripheral neuropathy pyridoxine (10-20 mg daily) can be added to regimen. High doses of pyridoxine should be avoided as it may reduce the effectiveness of isoniazid [18]. INH induced hepatotoxicity is more common in those more than 35 years of age. It can be reversed if drug is discontinued early but fatal hepatotoxicity can occur [19, 20].

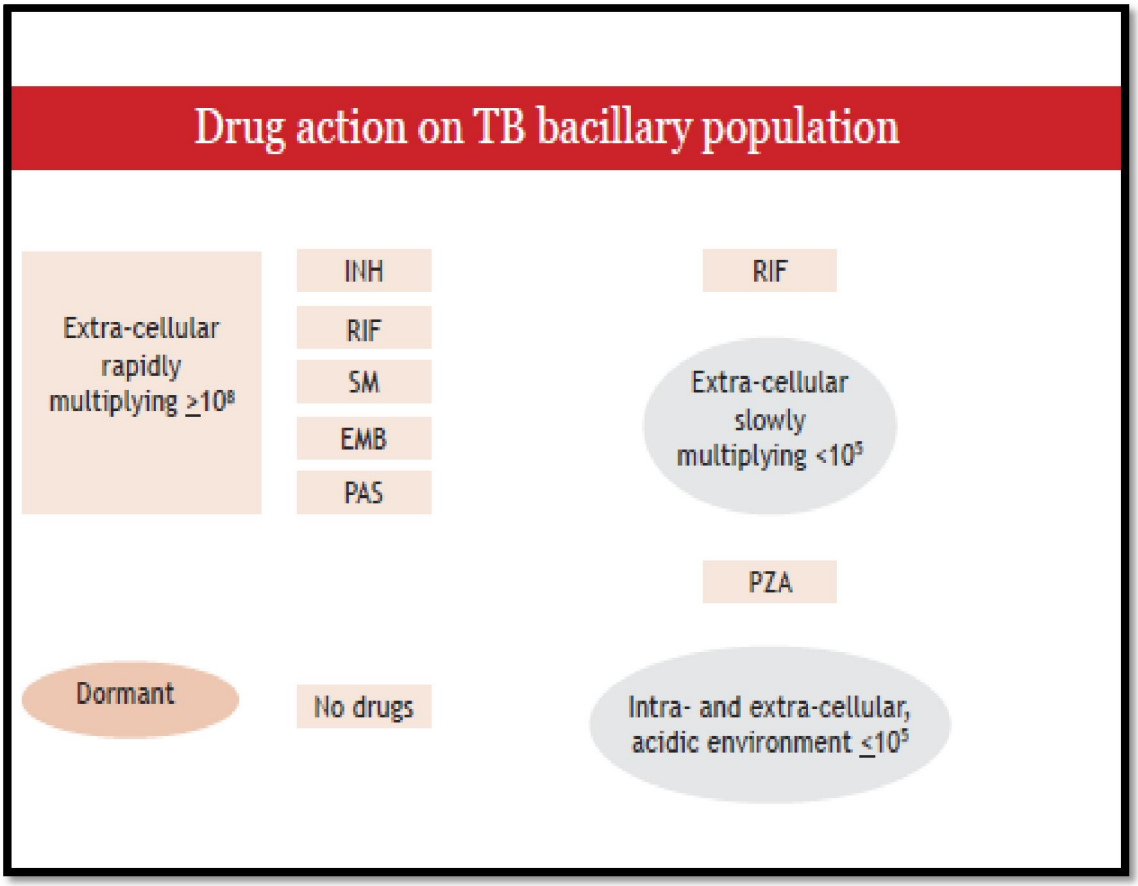
RIFAMPICIN

Rifampicin is a semisynthetic antibiotic. It was introduced in 1965. It was found that the non toxic oral dose of rifampicin produces serum concentration that was 100 times more than the dose needed to inhibit the growth of tubercle bacilli. This led to trials that it can be used to reduce the duration of treatment [21]. It became the single most important drug in the short course regimen. Bactericidal drug that is active against dormant bacteria. It is usually taken one hour before food or 2 hours after food since food reduce rifampicin absorption. It is associated with gastritis, purpura, thrombocytopenia and nephrotoxicity.

Dose of rifampicin used is 10 mg/kg with a maximum dose of 600mg. it can cause orange -red discolouration of body fluids. Usually given as 450 mg. Of patients weigh more than 60 kg it is 600 mg.

Rifampicin produces more adverse reactions with intermittent regimen than daily regimen. It rarely causes cholestatic liver injury. Flu like syndrome is observed only with intermittent regimen [22]. If a patient with rifampicin develops shock, renal failure, purpura or acute haemolytic reaction the drug need to be stopped and never be used again. Minor adverse effects were to be avoided patient should be on more frequent dosages than intermittent regimen and drug dose can be reduced.

Rifampicin has a number of drug interactions because of the fact that it induces hepatic cytochrome oxidase. Rifabutin is a long acting congener that affects enzymes less [28,30]. Rifapentene is longer acting drug with similar activity against M.tuberculosis [29,30].



STREPTOMYCIN

It was isolated by Waksman. Bactericidal drug that is active on rapidly dividing bacteria. It acts on extracellular bacilli. It doesn't penetrate cell wall. It is given in a dose of 0.75g and if the patient weight is less than 35 kg 0.5g is used. If age is more than 50 years only 0.5g is used. It causes predominantly vestibular damage rather than deafness. Risk increases with dose and age of the patient. It occur more in patients with age more than 40 years. Vestibular damage presents with vertigo, ataxia, tinnitus and loss of hearing.

Once patient reports symptoms suggestive of vestibular damage drug dosage is reduced or drug is stopped. If treatment is continued it may result in permanent damage more so in patients with renal damage. Renal damage can also occur. It is avoided in patients with myasthenia gravis since it can affect neuromuscular conduction. It is contraindicated in pregnancy as it can cause fetal eighth nerve damage.

PYRAZINAMIDE

Primarily it acts on slow-multiplying bacilli and it augments the action of rifampicin. It helped in reduction of the duration of treatment [(27)]. Dosage is 35 mg/kg body weight. It is associated with hepatotoxicity and hyperuricemia. Asymptomatic increase in uric acid is seen in many patients but symptomatic gout is rare. Hepatotoxicity is rare when used without rifampicin. But used along with rifampicin, chance of developing hepatotoxicity is high

ETHAMBUTAOL

Among the first line drugs it is the only bacteriostatic drug. It is a synthetic drug. It is associated with retro bulbar neuritis. It produces impaired vision with decrease in visual acquity and red-green colour blindness. Ocular toxicity is dose dependent. Rarely occur if less than 15mg/kg is given daily[(24,25)]. Not used in young children as they cannot

report visual disturbance. Visual disturbance improves if the drug is stopped or dosage is reduced before permanent damage occurs. Dosage used is 30 mg/kg in intermittent regimen.

RANKING OF DRUGS WITH RESPECT TO THEIR TYPE OF ACTIVITY

Drugs	Early bactericidal	Sterilizing activity	Prevention of emergence of drug resistance
Isoniazid	++++	++	++++
Rifampicin	+++	++++	+++
Streptomycin	+++	-	++
Pyrazinamide	++	+++	+
Ethambutol	+	-	++

TREATMENT OUTCOME IN RNTCP

Patient treated under RNTCP are categorised under the following at the end of treatment or during the course of treatment

Cured

Initially sputum smear –positive patient who has completed treatment and had negative sputum smears on two occasions, one of which was at the end of the treatment.

Treatment completed

Initially sputum smear -positive patient who has completed treatment with negative smears at the end of the intensive phase/two months in the continuation phase, but none at the end of the treatment is declared as treatment completed. Or initially sputum smear negative patient who has received full course of treatment and has not become smear-positive at the end of treatment

Treatment Failure

Any TB patient who remains smear positive 5 months or more after initiation of the treatment and not put on MDR-TB treatment.

Defaulted

A patient after treatment initiation has interrupted treatment for 2 consecutive months or more.

Relapse

A tuberculosis patient who was declared cured or treatment completed by a physician and who reports back to health facility and is now found to be sputum smear –positive.

The definition of cure in the RNTCP is a negative smear examination which has its own limitations, as bacillary counts< 10,000 organisms/ml in sputum can be smear negative [38].

TREATMENT OUTOMES

6.1 million TB cases were notified to WHO in 2012. Among them 5.7 million cases were newly diagnosed cases. 0.4 Million cases were previously diagnosed cases. India and China together account for 39% of the notified cases. 87% of the new cases are treated successfully. 87% of new smear positive patients are treated successfully. 56 Million Patients have been treated successfully since introduction of DOTS saving 22 million lives.

In India the percentage of retreatment case is high when compared to other countries. The causes for retreatment of patients are defaulter, failure of treatment and relapse. Relapse rate in India is almost 10 % which is much higher than the relapse rate in most countries. Most of the relapse in India is due to drug irregularity, initial drug resistance, alcohol and smoking [12]. The percentage of retreatment smear positive cases among all smear positive patients is 24 % (under RNTCP) [11].In patients registered for CAT I ATT the rate of default is 12% and rate of treatment failure is 5%[15] . In one study reported by Thomas the relapse

rate was as high as 12.3% [12]. Relapse rate in international studies were found to be 3.3% [13]. 50 % of relapses were found to occur in first 6 months [15]. 68.5% of relapses were found to occur in the first 1 year. The median interval between declaring cure and relapse was found to be 212 days (7 months). Among relapse cases the incidence of drug resistance was found to be 20% [12]. The outcome of treatment of relapse cases were better than treatment of default and failure cases but less effective when compared to new smear positive cases. 76.4% of relapse cases treated had positive outcome. The outcome of treatment failure cases was 53.85% and for default cases were 55.85% [16].

RELAPSE OF TUBERCULOSIS

In tuberculosis the time interval between the infection and disease manifestation is highly variable from a few weeks to even years. So development of active pulmonary tuberculosis in a patient previously treated for pulmonary tuberculosis may be because of activation of the previous infection or a reinfection by a fresh strain of Mycobacterium tuberculosis [33, 34]. Activation of latent tuberculosis occurs when immunity of the patient decreases because of concurrent illness or if immunity is modified by drugs.

To differentiate between endogenous reactivation and exogenous reinfection DNA finger printing is needed. Restriction fragment length polymorphism is used to differentiate relapse of tuberculosis from reinfection from a different strain of Mycobacterium.

Distinguishing between endogenous reactivation and exogenous reinfection is important because,

- If reinfection is common in the population then isoniazid drug prophylaxis in a previously treated patient following an exposure to active pulmonary tuberculosis may be prudent.
- If reinfection is common in the community then a new drug or drug regimen may not be judged properly in the community.
- Natural infection will not give protection if reinfection is common in the community. Vaccine production for tuberculosis will be affected because of this[32].

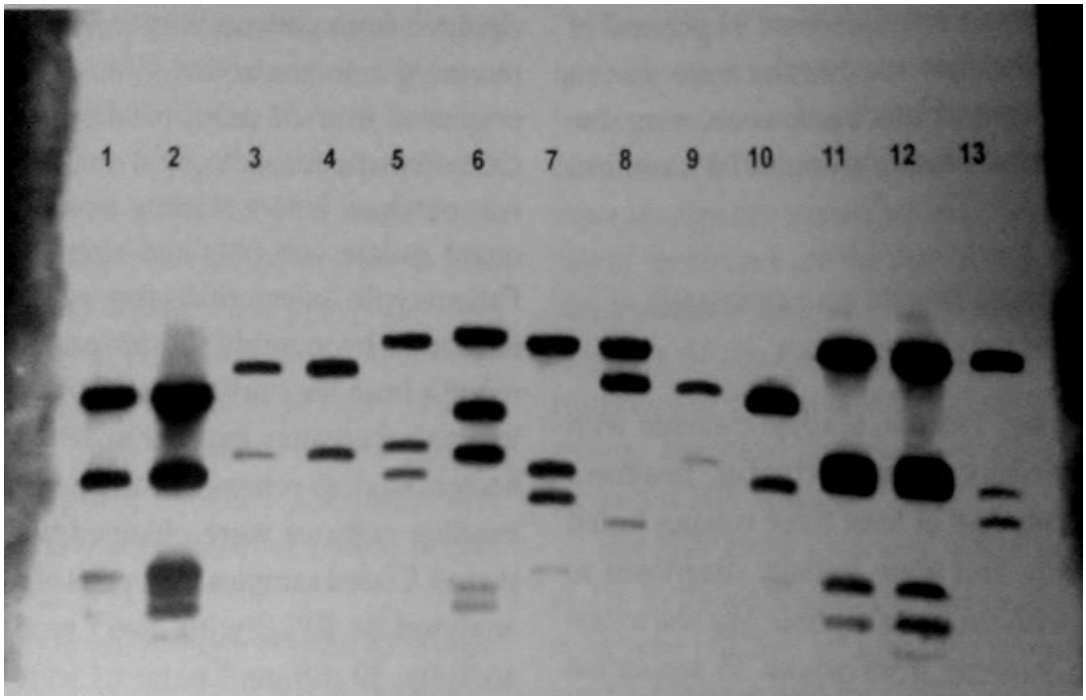
TO DIFFERENTIATE REINFECTION FROM REACTIVEATION

Restriction length polymorphism is used in differentiating reinfection from reactivation of tuberculosis by the following two methods [35,36].

- If the strain of the initial infection is known then the RFLP of the current strain can be done and compared.

- If the initial strain is not known RFLP is done for patients who come with relapse from the same community. If two or more patients have a same strain then they are said to be a cluster. If in the same community another relapse patient RFLP is of a different pattern then he is said to have a endogenous reactivation.

Restriction Fragment Length polymorphism



Restriction Fragment length polymorphism pattern of the pre- and post treatment isolates. lane 1 and 2 shows the pre and post treatment

isolate of a patient and lane 3 and 4 shows the pre and post treatment of the next patient and so on.

Most of the relapses that occur were found to occur during the first 6 months following treatment with ATT. The rate of relapse comes down as the time after completion of treatment increases.

THE FACTORS ASSOCIATED WITH RECURRENCE OF THE DISEASE: [8,9,14]

- Extensive disease
- Cavitations
- Severe lung lesion
- HIV
- Alcoholism
- Diabetes mellitus
- Male
- Smoker
- Concomitant illness
- Underweight
- Irregular treatment
- Illiteracy
- Overcrowding in residence
- Drug resistance

Sex and weight has not been found to be a significant factor in relapses in India.

Whether DOTS is given as intermittent regimen or continuous regimen for patient to come to health care facility on a regular basis for a period of 6 months needs time, money and energy more so in difficult terrains where reaching a health care facility may be a problem. These factors affect the regularity of treatment a factor found to influence relapse of tuberculosis.

Immunosuppressive illness like diabetes, HIV has increased the relapse of treated patients. Patients started on cancer chemotherapy, corticosteroids, immunomodulatory therapy, monoclonal antibodies all can decrease patients immunity and cause relapse of tuberculosis.

Decrease in weight gain during the course of treatment is also associated with increased in relapse of tuberculosis. Weight gain of less than 5 % with treatment is associated with increased chance of relapse.

Patient who get infected with a drug resistant strain or develop resistance during the course of treatment have an increased chance of treatment failure and relapse. Drug resistance to rifampicin during the start of treatment is associated with an increase in relapse of tuberculosis.

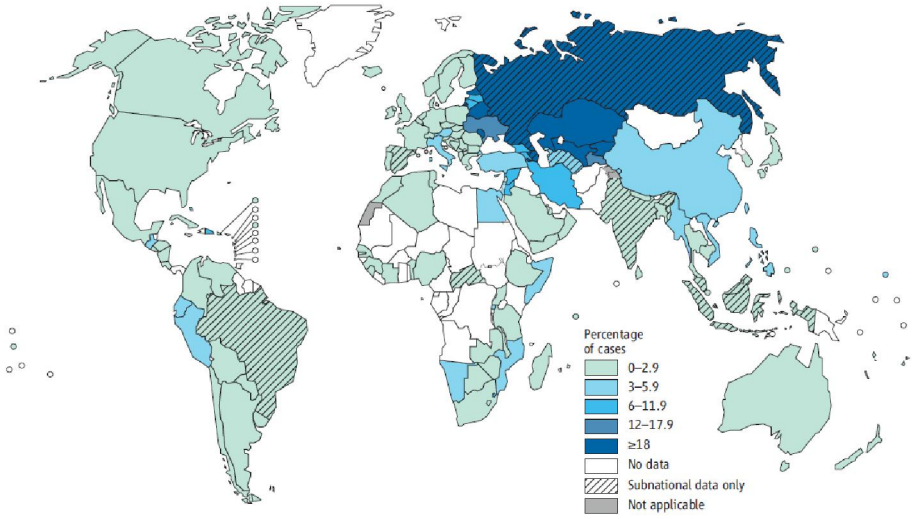
Patients who have taken treatment irregularly are twice at risk than who have taken treatment regularly to develop relapse. Smoking has been associated with a three percent chance of relapse than the general population.

DRUG RESISTANT TB

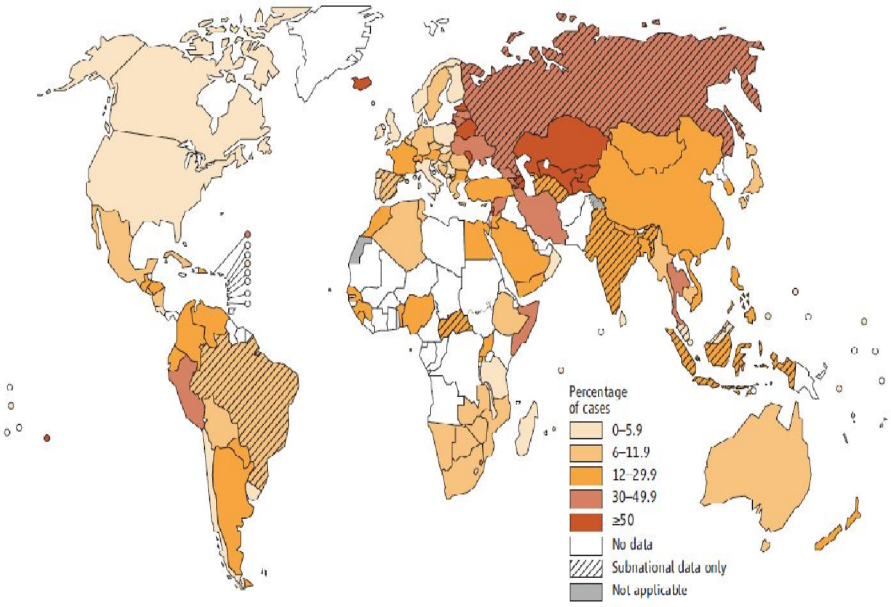
Resistance to rifampicin and isoniazid is called MDR TB. Resistance to rifampicin, isoniazid, a second line injectable and fluroquinlone is called XDR TB.

Globally around 3 % of the newly diagnosed TB patients are MDR TB. In the retreatment group the figure is around 20.2 %.in some areas like the eastern Europe and central Asia the rates may be as high as 20% in the CAT I and more than 50% in CAT II. There is an estimated 300000 cases of MDR in 2012 and half of these cases were reported from India, China and Russia. Extensively drug resistant tuberculosis has also been reported. 92 countries have so far reported the occurrence of XDR-TB. Among the MDR-TB 9.6% is found to be XDR-TB. In India 26% of pulmonary tuberculosis patients are found to be MDR-TB. 2.2 % of the newly diagnosed sputum positive patients were found to be MDR TB and 15% of retreatment patients in India is found to be MDR TB[(2)].

Percentage of new TB cases with MDR-TB[a]



Percentage of previously treated TB cases with MDR-TB[a]



METHODS TO DO DST

3 methods are used in RNTCP to detect drug resistance.

- The conventional solid egg based Lowenstein- Jensen media.
- Liquid culture media MGIT
- Rapid molecular diagnostic methods like Line probe assay and Xpert MTB/Rif

The conventional Lowenstein Jensen media in which the organism is grown in a media that contains the drug and drug resistance is noted is called phenotypic DST. The advantage of phenotypic DST is that it is available for more ATT drugs. It is reliable in the case if INH, Rifampicin and streptomycin. It is less reliable in the case of Ethambutol.

Molecular DST are methods in which the presence of gene mutations are noted. They are also genotypic DST.

The advantages of molecular method are,

- Speed of diagnosis
- Standardised testing
- Fewer requirements for laboratory bio safety.

But molecular methods are better to detect only rifampicin resistance and they are used less in other drug resistance detection.

Time taken for reporting DST by various methods:

- LJ media - 84 days
- MGIT - 42 days,
- LPA - 72 hours and
- Xpert/Rif - 2 hours.

LINE PROBE ASSAY(LPA)

It involves the following steps[45]

1. DNA is extracted from *M. tuberculosis* isolates (indirect testing) or directly from clinical specimens (direct testing).

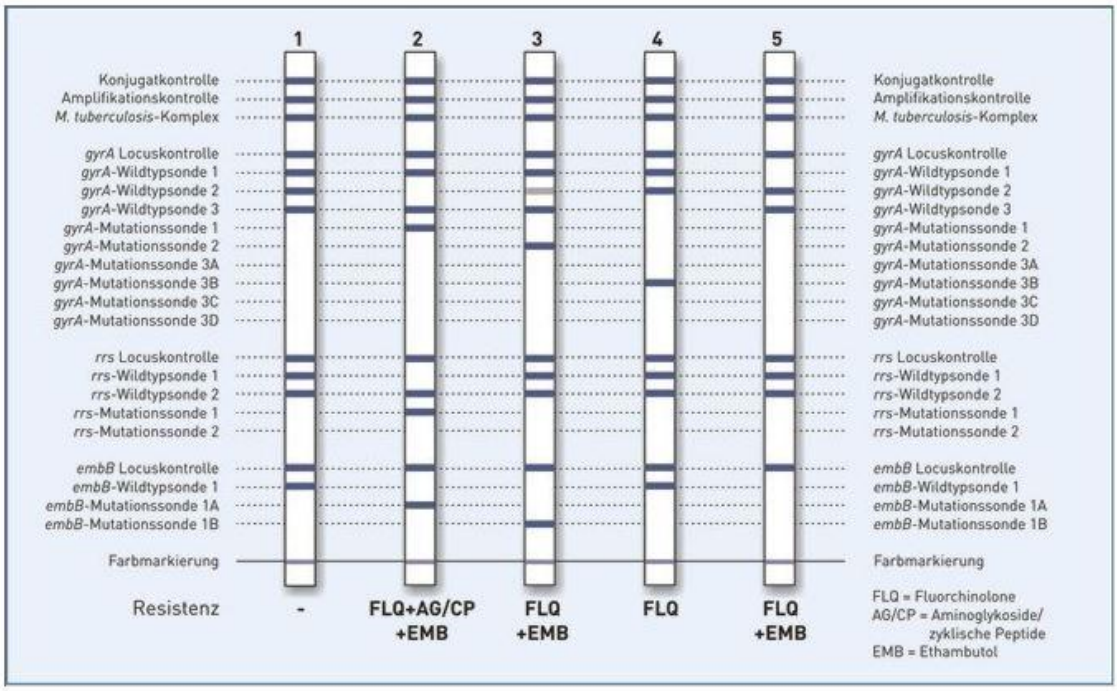
2. Polymerase chain reaction (PCR) amplification of the resistance-determining region of the gene under question is performed using biotinylated primers.

3. Labeled PCR products are hybridized with specific oligonucleotide probes immobilized on a strip.

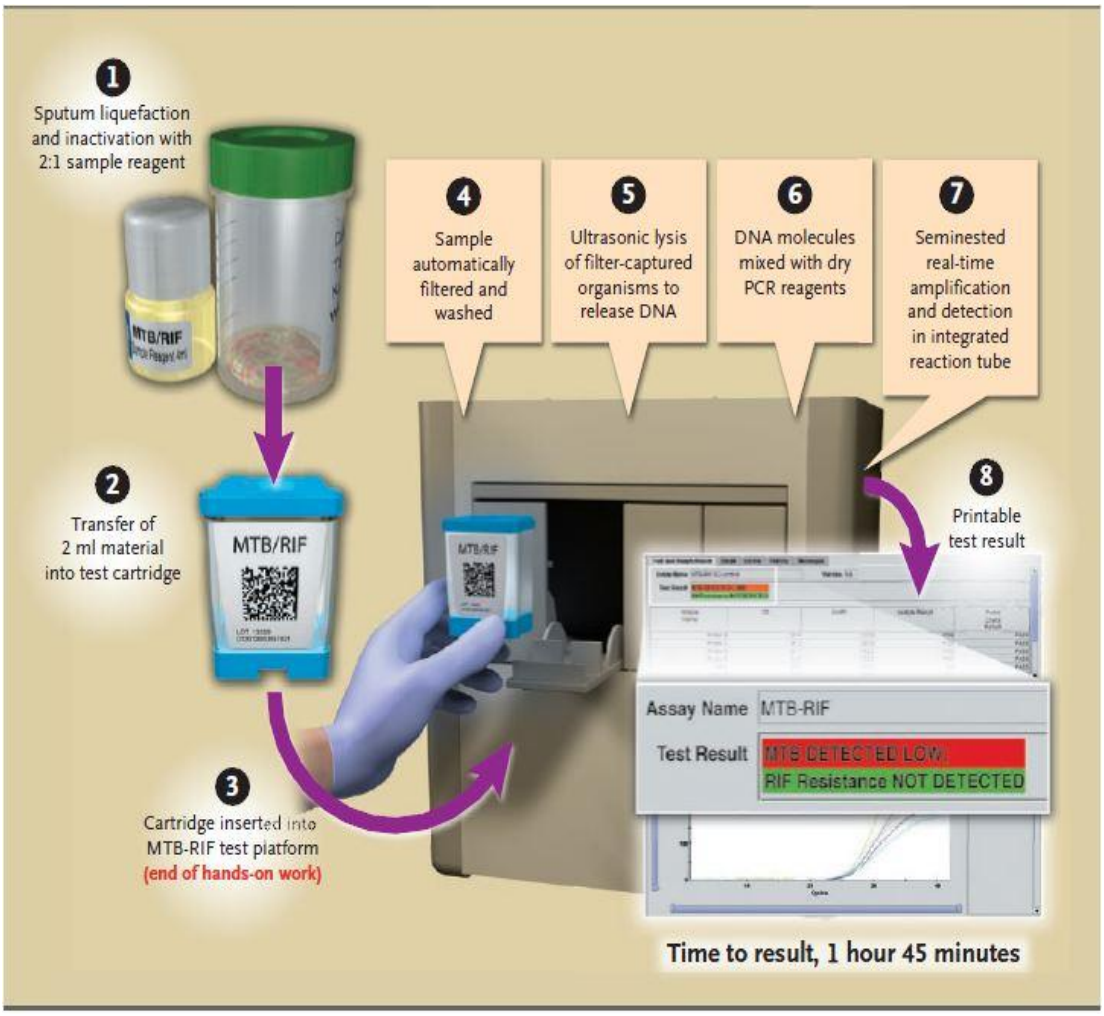
4. Captured labeled hybrids are detected by colorimetric development, enabling detection of the presence of *M.*

tuberculosis complex, as well as the presence of wild-type and mutation probes for resistance.

5. If a mutation is present in one of the target regions, the amplicon will not hybridize with the relevant probe. Mutations are therefore detected by lack of binding to wild-type probes, as well as by binding to specific probes for the most commonly occurring mutations. The post hybridization reaction leads to the development of coloured bands on the strip at the site of probe binding.



STEPS IN DOING XPERT MTB/RIF



THE CHOICE OF METHOD TO BE USE IN DRUG SUSCEPTIBILITY TESTING[46]

MDR Diagnostic Technology	Choice
Molecular DST	First
Liquid culture isolation and LPA DST	Second
Solid culture isolation and LPA DST	Third
Liquid culture isolation and DST	Fourth
Solid culture isolation and DST	Fifth

TREATMENT OF MDR TB & XDR TB

Drug Resistance	Definition
Monoresistant TB	Resistance to only one of the first line TB drugs e.g. isonizid
Multi Drug-Resistant TB (MDR)	Resistant to both isonizid and rifampicin, two of the commonest first line drugs classically used to treat TB
Extensively Drug resistant TB (XDR)	MDR TB resistance plus resistance to any fluoroquinolone (a class of second line drugs) plus resistance to at least one of the injectable second line drugs. XDR TB was first famously documented in Africa in 2006

Regimens to be used in the treatment of MDR and XDR TB are given in RNTCP guidelines. The drugs used in the treatment of drug resistant TB are grouped in to five groups based on the drug class, their efficacy in the treatment of tuberculosis and the experience in using these drugs in the treatment of tuberculosis.

GROUPING OF ANTI-TB DRUGS

Grouping	Drugs
Group 1: First-line oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable anti-TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vm).
Group 3: Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4: Oral second-line anti-TB agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); *para*-aminosalicylic acid (PAS)
Group 5: Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); Clarithromycin (Clr)

RNTCP recommends uniform regimen in the treatment of drug resistant tuberculosis but treatment is complicated by the following factors,

- Presence of drug resistance to one of the second line drugs at the baseline. (Eg) Resistance to fluroquinolone.
- Drug intolerance and treatment discontinuation is more common with the drug resistant regimen.

Poor response to treatment with the second line regimen should alert the clinician to look for other causes of poor response like drug compliance, further development of drug resistance.

MDR TB patient should be started on initial MDR regimen and should be subjected to DST during the course of treatment as and when indicated. The indications for second line DST are

- Persistent culture or smear positive at six months of treatment
- Culture or smear reversal during the course of treatment.

It is preferred to have DST to the second line drugs during the start of treatment. But the problem is the availability of facilities to do

DST to second line drugs. So in places where base line second line DST cannot be done it is better not done.

If a patient started on the MDR TB regimen remains culture positive at the end of six months the intensive phase is extended by one month at a time and the culture is repeated. Extension can be done three times so that the maximum period of intensive phase is 9 months. While repeating the culture to rule out XDR TB sensitivity is seen for kanamycin and ofloxacin if facilities permit capreomycin sensitivity is also seen.

MDR TB REGIMEN

In the intensive phase 6 drugs are used. In the continuation phase 4 drugs are used. Intensive phase is for 6-9 months and the continuation phase is for 18 months.

- Drugs used in the intensive phase are kanamycin, levofloxacin, ethionamide, cycloserine, ethambutaol and pyrazinamide.
- Drugs used in the continuation phase are Levofloxacin, Ethionamide, Ethambutol and Cycloserine

CHANGES MADE IN REGIMEN IN SOME SPECIAL SITUATIONS ARE:

- If patient is intolerant to kanamycin it is replaced by capreomycin if injectable option is not feasible then PAS is given.
- If any oral second line drug intolerance is present then PAS is used.
- Capreomycin is used in place of kanamycin if baseline resistance is present to kanamycin
- If drug resistance to ofloxacin is present at the base line then a combination of moxifloxacin with PAS should be used in place of levofloxacin.
- Baseline resistance to both kanamycin and capreomycin needs patient evaluation and treatment for XDR TB

INTEGRETED ALGORITHM FOR DR-TB TREATMENT

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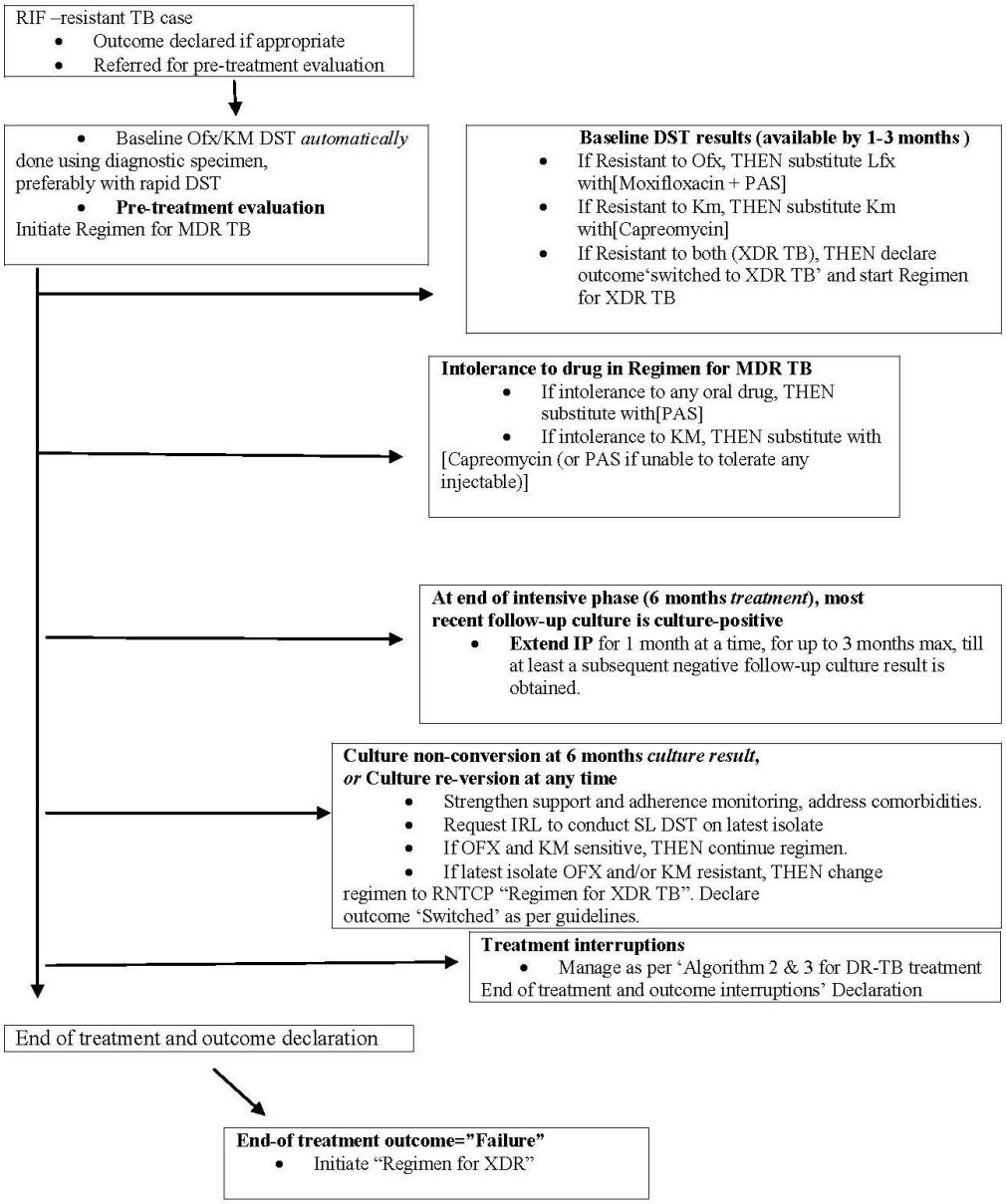


MDR regimen drugs are given as single daily dose. Drugs are given supervised for 6 days of a week. It is given unsupervised for 1 day in a week (Sunday). Injection is avoided on Sunday only oral drugs are given. Pyridoxine is given to all patients in MDR regimen.

REGIMEN FOR MDR TB DOSAGE AND WEIGHT BAND RECOMMENDATIONS

S.No.	Drugs	16-25 Kgs	26-45 Kgs	46-70 Kgs
1	Kanamycin	500 mg	500 mg	750 mg
2	Levofloxacin	250 mg	750 mg	1000 mg
3	Ethionamide	375 mg	500 mg	750 mg
4	Ethambutol	400 mg	800 mg	1200 mg
5	Pyrazinamide	500 mg	1250 mg	1500 mg
6	Cycloserine	250 mg	500 mg	750 mg
7	Pyridoxine	50 mg	100mg	100mg

If a patient gains 5 kg or more during treatment he can be switched over to the next weight band. If he loses weight more than 5 kg he can be shifted to another weight band. The change in band group can be done when the next supply of drugs comes not necessarily once the patient has gained weight.

REGIMEN FOR XDR TB

The intensive phase is for 6 to 12 months. It consists of 7 drugs . Capreomycin , PAS, moxifloxacin, high dose INH, clofazimine, linezolid, amoxicillin with clavulanic acid.

- The continuation phase is for 18 months and it has six drugs. They are

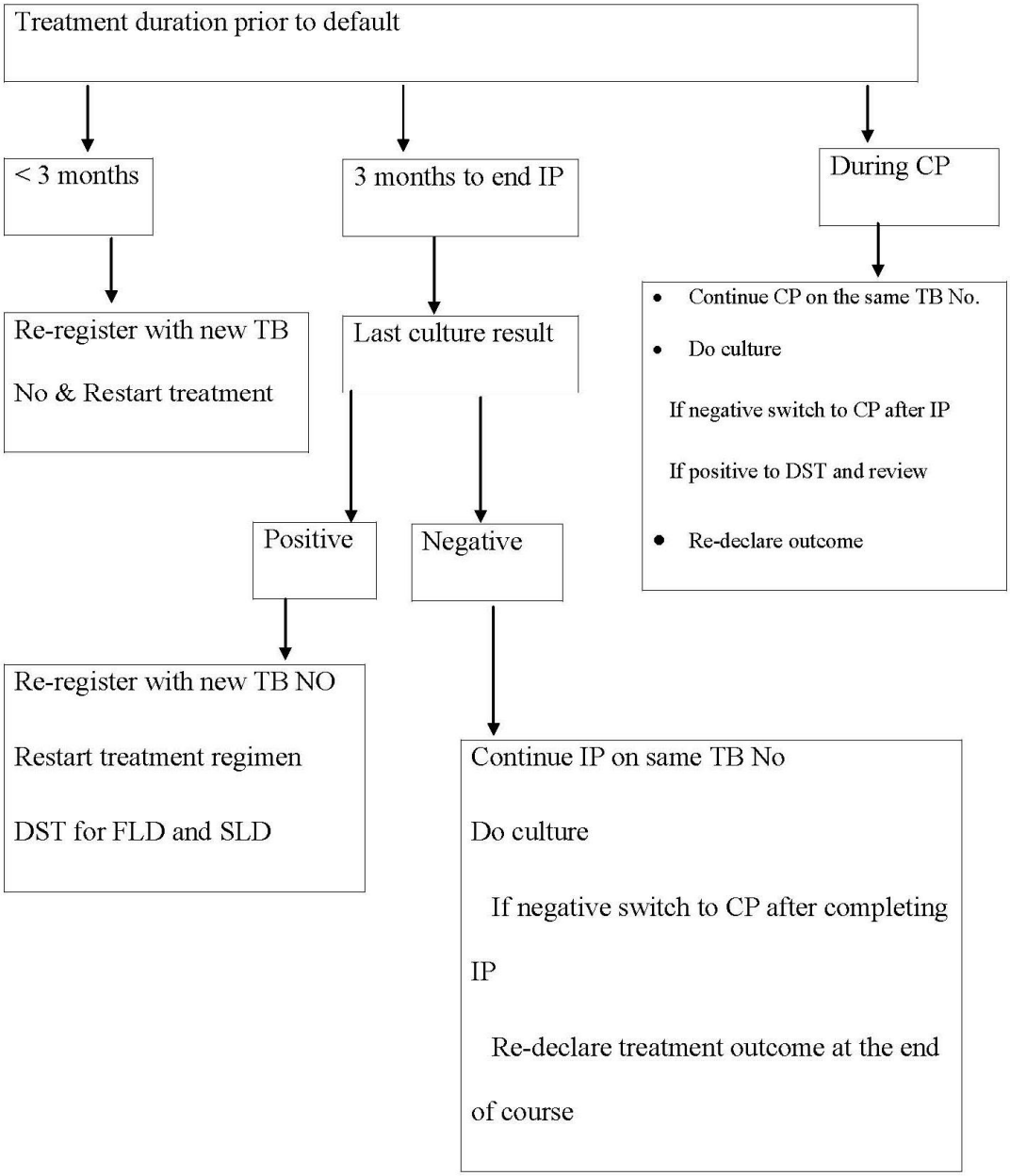
PAS, moxifloxacin, high dose INH, clofazimine, linezolid, amoxicillin with clavulanic acid.

Similar to MDR TB treatment it is 6 days supervised treatment with one day of unsupervised treatment.

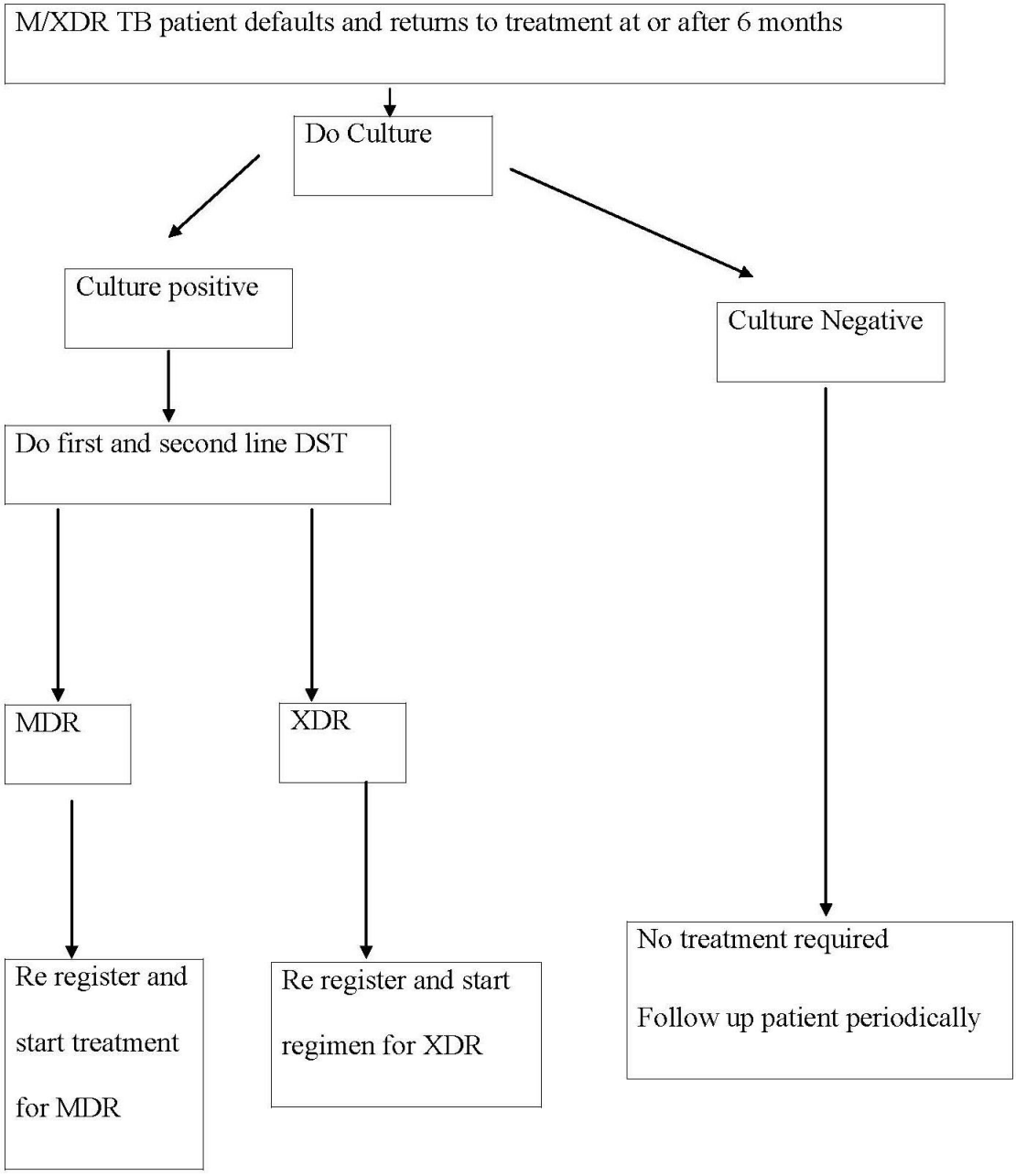
REGIMEN FOR XDR TB DOSAGE AND WEIGHT BAND RECOMMENDATIONS DRUGS

Drugs	**Dosage/day**	
	45 kg or less	>45 Kg
Capreomycin	750 mg	1000 mg
PAS	10 mg	12mg
Moxifloxacin	400 mg	400 mg
High Dose INH	600 mg	600 mg
Clofazimine	200mg	200 mg
Linezolid	600 mg	600 mg
Amoxyclav	875/125 mg	875/125 mg
Pyridoxine	100 mg	100 mg

Algorithm for patients on MDR/XDR regimen who have defaulted treatment and returned within 6 months.(ALGORITHM 2)



Management of Patient on MDR & XDR Regimen who Return for Treatment after 6 months (ALGORITHM 3)



MATERIALS AND METHODS

INSTITUTIONAL EHICAL COMMITTEE APPROVAL

Obtained

PERIOD OF STUDY

January 2013- August 2013.

PLACE OF STUDY

Stanley medical college and Zone I and Zone II in Chennai under RNTCP

STUDY DESIGN

Prospective Study

SAMPLE SIZE

49 patients were included in the study.

INCLUSION CRITERIA

Patients who have enrolled for ATT under RNTCP during the period October 2011 to March 2012 and declared cured or those who have completed treatment are included in the study.

EXCLUSION CRITERIA

- Patients who are having
  - Human Immunodeficiency Viral infection,
  - renal failure
  - Malignancies
  - any other immunosuppressive illnesses
- Patients who are known to have contact with MDR TB patients.

STUDY METHODOLOGY

Patients who have enrolled for ATT under category I as new smear positive during the last quarter of 2011 and first quarter of 2012 and completed ATT or declared cured are selected. Two fresh spot sputum samples are taken for AFB stain and culture sensitivity. A chest X Ray PA view will be done for all these patients to assess their present radiological status. Biochemical investigations like blood urea, sugar (random), serum creatinine, serum bilirubin will be done. Retro virus status of the individual will also be assessed. A questionnaire is administered to the patients to assess their present clinical status. An initial assessment of the patient will be made from the clinical assessment, radiological assessment and sputum smear status. Sputum smear is examined in Stanley medical college RNTCP department by immunofluorescenc microscopy.

Sputum culture is done in LJ medium at National institute of research in tuberculosis. If sputum culture cannot be given on the same day of collection of specimen it is stored in cold storage device and given within 72 hours to the laboratory.

If the patient is found to be sputum smear negative the final assessment will be done with the sputum culture for AFB results. If any co morbid illness or risk factors are encountered a detailed assessment of the respective illness or risk factor will also be done. Those patients who are found to be smear positive for AFB will be initiated on category II ATT as per RNTCP norms. Those patients whose sputum cultures are positive will be subjected to sensitivity studies to assess the drug resistance if any and started on appropriate ATT.

OBSERVATIONS

49 patients were included in the study. Of the 49 patients sputum smear examination for AFB was positive for 2 patients and culture for mycobacterium tuberculosis was positive for 3 patients.

AGE

The mean age of male patients included in the study was 41.45(S.D 16.30) and female patients was 36.36(S.D 14.40). 36 patients were under the age of 50 and 13 patients were 50 years and above.

Table 1: **Mean Age distribution of the patients**

Age	Male	Female
Number of Observations	38	11
Mean Age	41.45	36.36
Standard Deviation	16.30	14.40

CHART 1

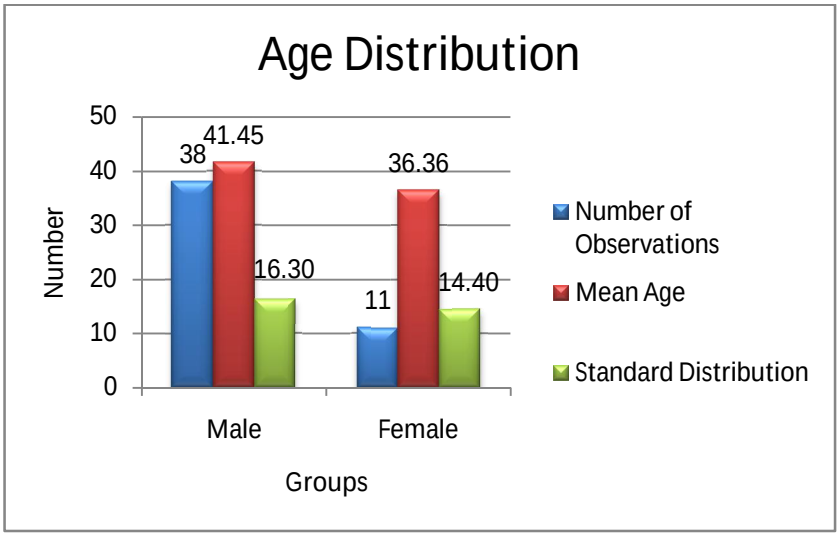


Table 2: Percentage of different Age groups

Age	Frequencies	Percentage
(11-20)	5	10
21-30	10	20
31-40	10	20
41-50	10	20
51-60	6	12
61-70	6	12
71-80	2	4
Total	49	100

Of the three relapse patients two patients were of less than 50 years of age and 1 was more than 50 years of age.

Table 3: Age & Relapse

Age in Years	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
<50	36	2	0.7059	0.0586 to 8.5060	0.7839
≥50	13	1			

By conventional criteria the association between the TB relapse and age is considered to be not statistically significant since $p > 0.05$.

GENDER

Among the 49 patients 38 patients were male patients and 11 patients were female patients. All the three patients who were bacteriologically active were male patients.

CHART 2

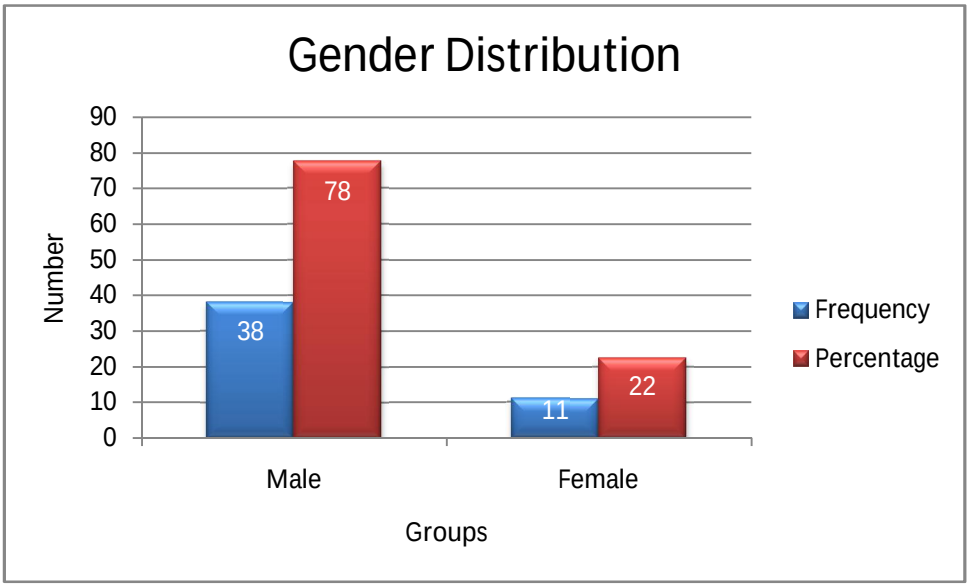


Table 4: Gender Prevalence

Gender	Frequency	Percentage
Male	38	78
Female	11	22
Total	49	100

TABLE 5: GENDER & RELAPSE

Gender	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Male	38	3	2.2676	0.1088 to 47.2605	0.5972
Female	11	0			

By conventional criteria the association between the TB relapse and gender is considered to be not statistically significant since $p > 0.05$.

SYMPTOMS AT PRESENT

29% of patients were symptomatic among the study group.

CHART 3

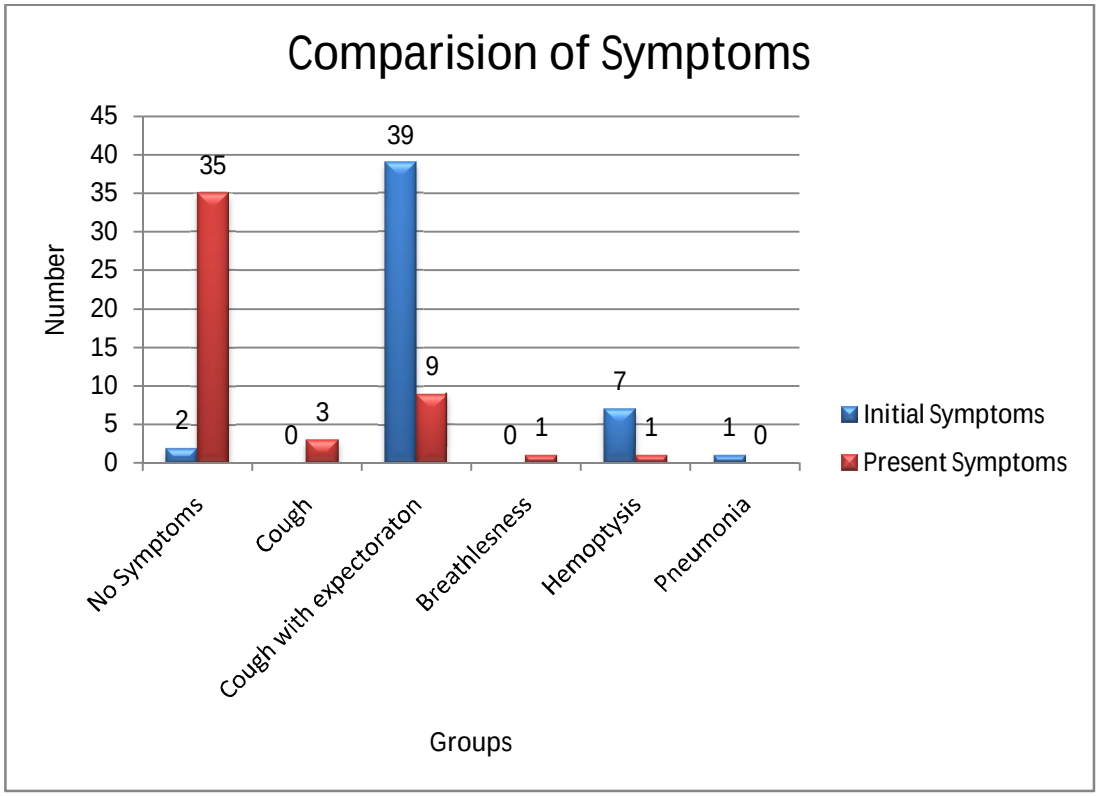


Table 6: Patients Symptoms

Symptoms	Initial Symptoms	Percentage	Present Symptoms	Percentage	P value
No Symptoms	2	4	35	71	
Cough	0	0	3	6	0.3198
Cough with expectoration	39	80	9	18	0.0286
Breathlessness	0	0	1	2	0.3198
Haemoptysis	7	14	1	2	0.0001
Pneumonia	1	2	0	0	0.0817
Total	49	100	49	100	

Fisher's exact test

By conventional criteria the association between the appearance symptoms (cough with expectoration and haemoptysis) during regular ATT and presently after completion of treatment are considered to be statistically significant since $p < 0.05$.

This indicates that there is a true difference among groups and the difference is significant. In simple terms symptoms of TB occur more frequently among patients before initiation of ATT in comparison to patients who have completed ATT. This difference is true and significant and has not occurred by chance.

In contrast, we can conclude that ATT is effective in reducing the symptoms of tuberculosis, especially cough with expectoration and haemoptysis there is a 78% significant reduction in cough with expectoration and 86% significant reduction in haemoptysis.

Table: 7 Patients with Fever

Fever	Frequency	Percentage
Fever+	3	6
Fever-	46	94
Total	49	100

Table: 8 Fever & Relapse

Fever	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Fever+	3	0	1.7755	0.0756 to 41.7249	0.7215
Fever-	46	3			

By conventional criteria the association between the TB relapse and appearance of fever is considered to be not statistically significant since $p > 0.05$.

Table: 9 Patients with Loss of Appetite

Loss of Appetite	Frequency	Percentage
Present	4	8
Absent	45	92
Total	49	100

Table: 10 Relapse & Loss of Appetite

Loss of Appetite	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Present	4	0			
			1.3492	0.0597 to 30.5080	0.8507
Absent	45	3			

By conventional criteria the association between the TB relapse and loss of appetite is considered to be not statistically significant since $p > 0.05$.

Table: 11 Patients with Loss of Weight

Loss of weight	Frequency	Percentage
Yes	4	8
No	45	92
Total	49	100

Table: 12 Relapse & Loss of Weight

Loss of weight	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Yes	3	0	1.7755	0.0756 to 41.7249	0.7215
No	46	3			

By conventional criteria the association between the TB relapse and loss of weight is considered to be not statistically significant since $p > 0.05$.

ANTHROPOMETRY

The mean weight of the male patients in the study was 57.11(S.D 7.45) and for female patients it is 47.36(S.D 6.68).

CHART 4

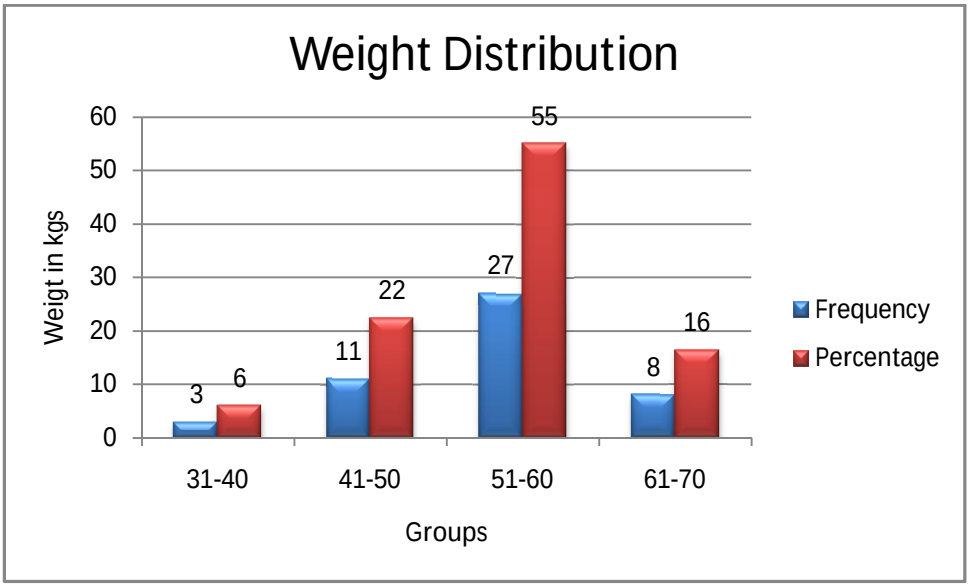


Table 13: Mean Weight of the Patients

Weight in Kg	Male	Female
Number of Observations	38	11
Mean	57.11	47.36
Standard Deviation	7.45	6.68

Table 14: Weight & Relapse

Weight in Kg	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
< 50	6	1	4.100	0.3126 to 53.7735	0.2826
≥ 50	43	2			

By conventional criteria the association between the TB relapse and weight is considered to be not statistically significant since $p > 0.05$.

The mean height of the male patients included in the study was 162.71(S.D 5.34) and female patients was 151.91(S.D4.95). Two patients with relapse were over 160 cm in height and one patient with relapse was under the height of 160 cm

Table 15: Height Distribution

Height in cm	Frequency	Percentage
141-150	6	12
151-160	16	33
161-170	26	53
171-180	1	2
Total	49	100

Table 16: Mean Height of Patients

Height in cm	Male	Female
Number of Observations	38	11
Mean	162.71	151.91
Standard Deviation	5.34	4.95

By conventional criteria the association between the TB relapse and height is considered to be not statistically significant since $p > 0.05$.

CHART 5

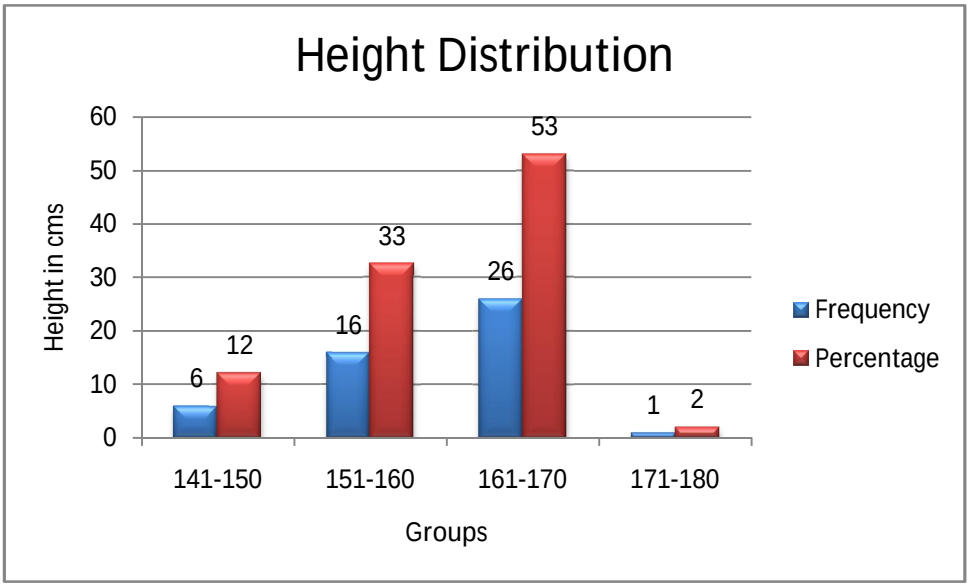


Table 17: Height & Relapse

Height in cm	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
< 160	21	1	0.6500	0.0550 to 7.6867	0.7325
≥ 160	28	2			

Of the 49 patients only 7 were under weight. The entire relapse was found in the normal BMI group.

CHART 6

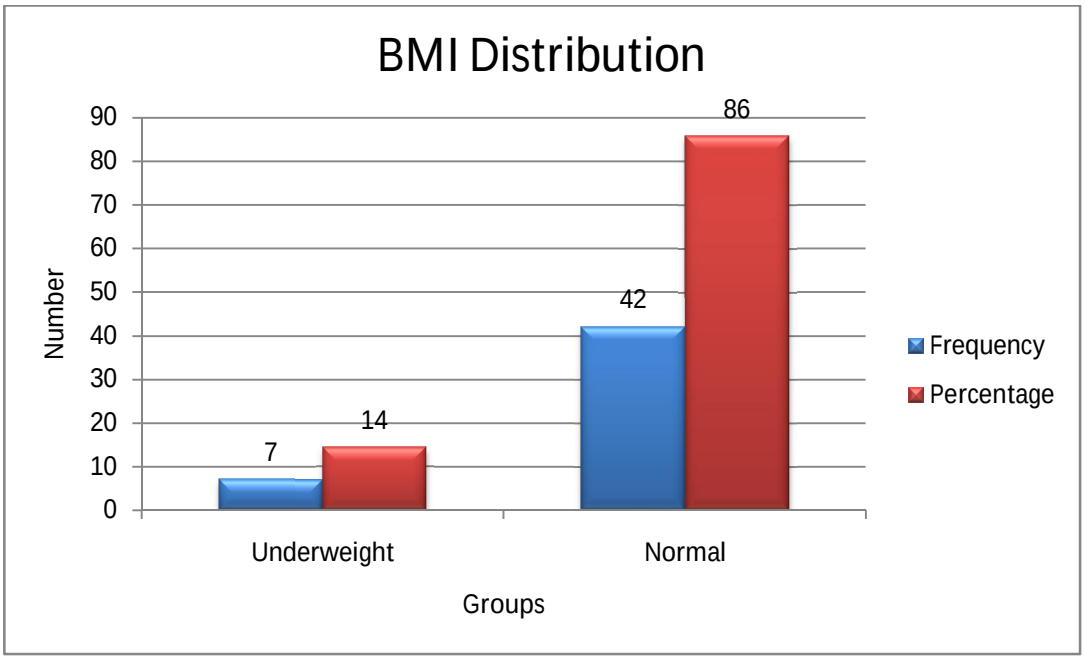


Table 18: BMI Distribution

BMI	Frequency	Percentage
Underweight	7	14
Normal	42	86
Total	49	100

Table 19: Mean BMI of Patients

BMI	Male	Female
Number of Observations	38	11
Mean	21.52	20.52
Standard Deviation	2.23	2.71

Table 20: BMI & Relapse

BMI	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Underweight	7	0	0.7524	0.0351 to 16.1165	0.8556
Normal	42	3			

By conventional criteria the association between the TB relapse and BMI is considered to be not statistically significant since $p > 0.05$.

DRUG RESISTANCE

Two patients were sensitive to all the first line drugs. One patient had resistance to isoniazid and streptomycin

Table 21: Bacteriological Status

Culture & DST	Frequency	Percentage
No Growth	46	94
Growth with Sensitive	1	2
Growth with Resistance	2	4
Total	49	100

CHART 7

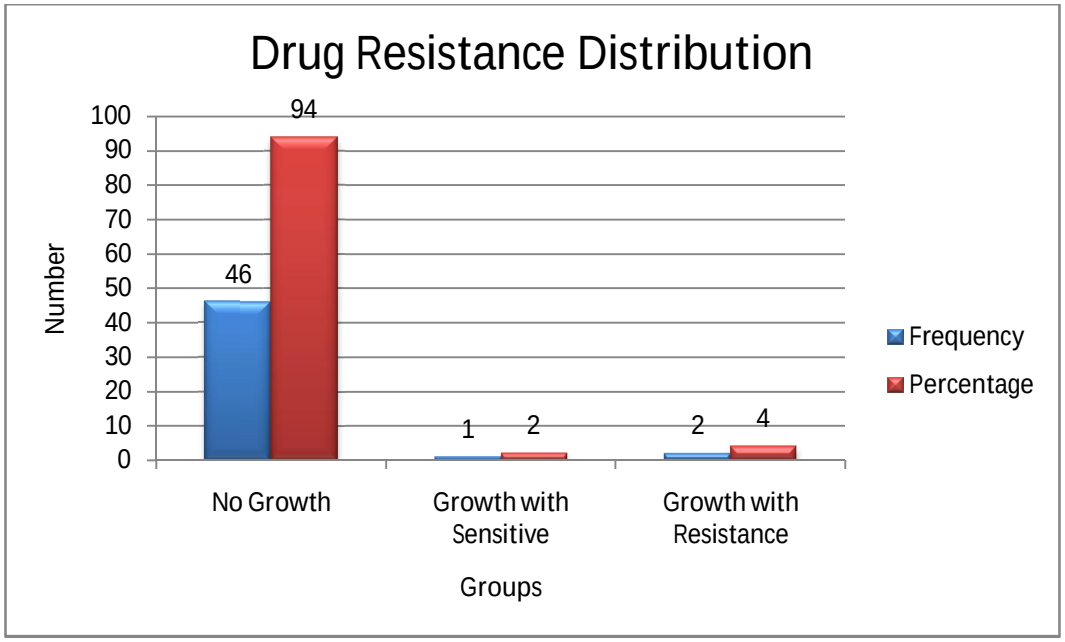


Table 22: Drug Resistance & Relapse

DR	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
DR+	1	1	55.8000	1.7814 to 1747.8124	0.0221
DR-	48	2			

By conventional criteria the association between TB relapse and Drug resistance is considered to be statistically significant since $p < 0.05$.

Since the 95% CI of 1.7814 to 1747.8124 does not include 1.0, the increased odds (OR 55.8000) of drug resistance to anti tuberculosis drugs among patients TB relapse reaches statistical significance. This increase in odds of drug resistance among TB relapse patients is true and significant and has not occurred by chance.

It means that the patients who have a relapse of TB infection have 55.8 times the risk of developing drug resistance compared to patients who do not have relapse of Tab infection. 66.7% of the patients with TB relapse had Drug susceptible mycobacterium.

ALCOHOL STATUS

CHART 8

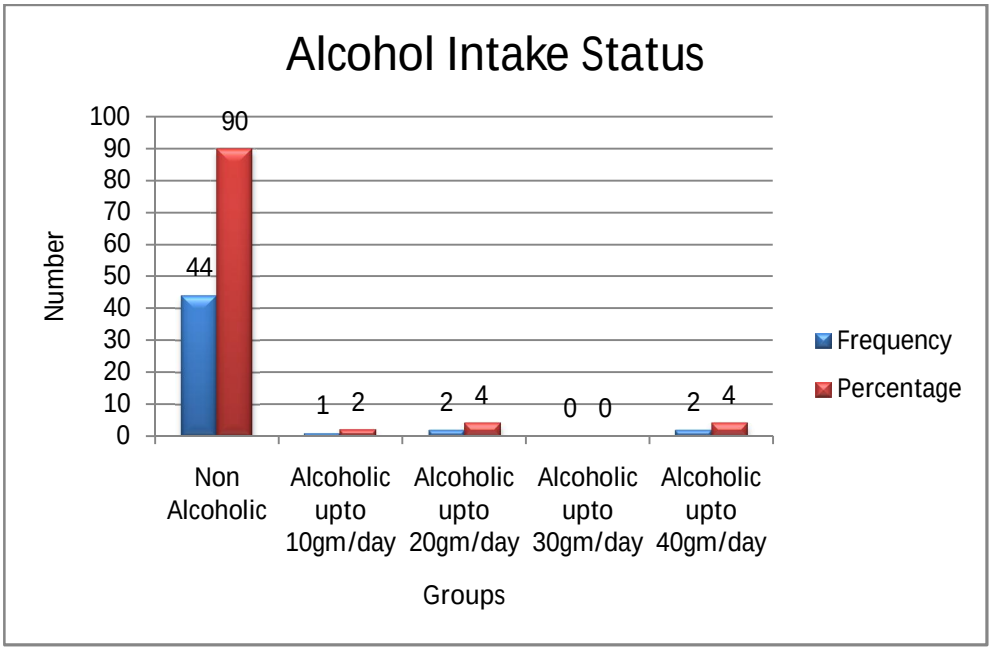


Table 23: Percentage of Alcoholics

Alcohol Intake	Frequency	Percentage
Non Alcoholic	44	90
Alcoholic up to 10gm/day	1	2
Alcoholic up to 20gm/day	2	4
Alcoholic up to 30gm/day	0	0
Alcoholic up to 40gm/day	2	4
Total	49	100

Table 24: Alcohol & Relapse

Alcohol Intake	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Alcoholic	5	0	1.0779	0.0489 to 23.7807	0.9621
Non Alcoholic	44	3			

By conventional criteria the association between the TB relapse and alcohol intake is considered to be not statistically significant since $p > 0.05$.

SMOKING

11 patients were smokers of them only one of them showed bacteriological activity.

Table 25: Distribution of Smokers and Non Smokers

Smoking	Frequency	Percentage
Non Smoker	38	78
Smoker upto 10 pack years	3	6
Smoker upto 20 pack years	3	6
Smoker upto 30 Pack years	4	8
Smoker upto 40 pack years	1	2
Total	49	100

CHART 10

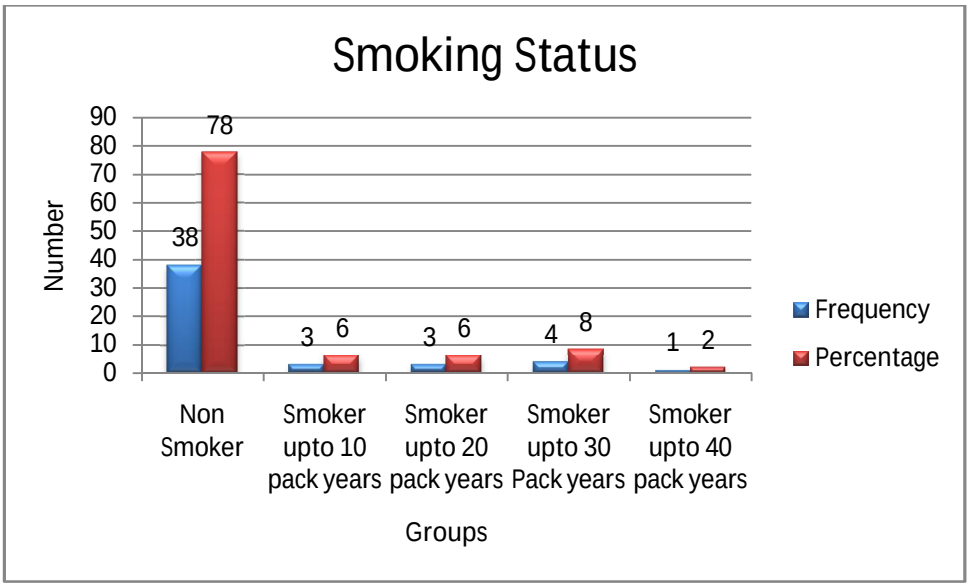


Table 26: Smoking & Relapse

Smoking	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Smoker	10	1	2.3125	0.1862 to 28.7185	0.5142
Non Smoker	39	2			

By conventional criteria the association between the TB relapse and smoking is considered to be not statistically significant since $p > 0.05$.

PRE EXISTING LUNG DISEASES:

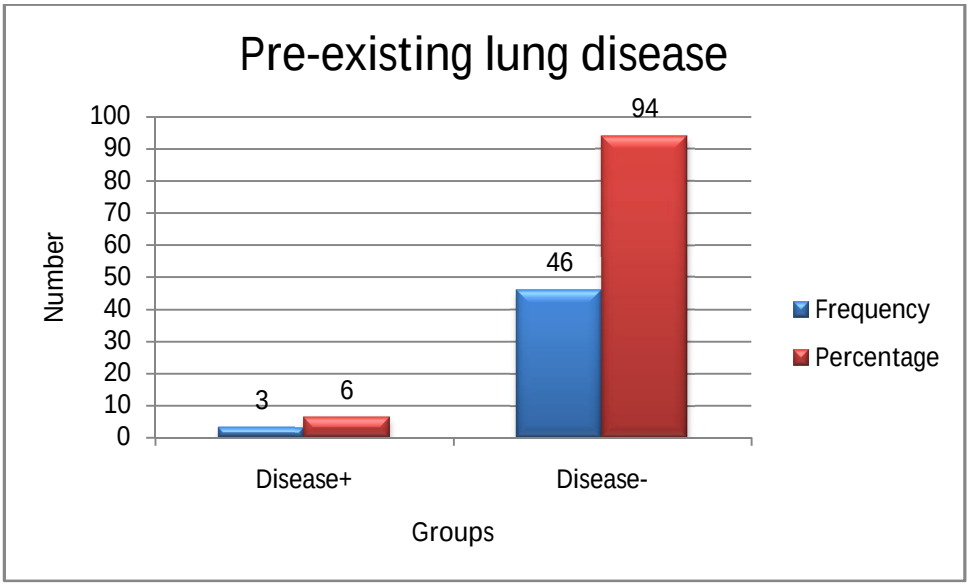
3 patients had history of pre-existing lung disease. None of the relapse patients had any prior history of lung disease.

Table 27: Lung Disease and Relapse

Pre-existing lung disease	Number of Observations	Relapse	Odds ratio	(95%CI)	P value
Disease+	3	0	1.7755	0.0756 to 41.7249	0.7215
Disease-	46	3			

By conventional criteria the association between the TB relapse and pre-existing lung disease is considered to be not statistically significant since $p > 0.05$.

CHART 11



RESULTS

1. The average age of the patients with relapse of TB is 44.
2. The relapse of pulmonary TB among patients who have completed ATT under RNTCP is 6%(n=49)
3. Patients with primary drug resistance may have more chance of relapse (OR 55.8, CI 1.78 to 1747.81)
4. The clinical manifestations are much less is patients with TB relapse (33% when in comparison 67% during ATT)

DISCUSSION

Sputum positive Pulmonary Tuberculosis patients treated under RNTCP in India show a cure rate of 88% [2]. Relapse of the treated patients vary in different population varying between 0 to 14 % [9]. In International studies the relapse rate in culture based studies was found to be 3.6% [13], but in India the relapse rate is high 10% [14]. In present study the relapse rate was around 6%. In another study from South India the relapse rate was found to be 4.8% among the non smokers who have taken ATT regularly without evidence of drug resistance [12].

Majority of the patients are asymptomatic at present (71%). Of the symptomatic patients the most common symptom is productive cough followed by dry cough. Other symptoms with which the patients have presented are breathlessness and haemoptysis. Of the relapse patient's only one patient was symptomatic. The constitutional symptoms present in the study group individual were fever, loss of appetite, loss of weight. None of the relapse patients had constitutional symptoms. The relapse patients usually present with less of clinical manifestations.

Statistical analysis of age, height and BMI of the current study population showed no difference in different groups of the study based on these parameters. Age and weight has been shown to be significant factors of relapse in various studies [12] but in the present study relapse was not associated with these factors

Male gender has been associated with increased chance of relapse[9,12], which correlates with the present study where the relapse rate is found to be high in males (100%). This could be a selection bias since 78 % of the study population were males and only 22% were females. The difference may also be because of the increased prevalence of tuberculosis of tuberculosis in male [2], increased access of males to health care facility. In India the male to female ratio of notification of tuberculosis is high (2.2) compared to the global ratio of 1.9.

20% of relapse was associated with MDR TB in previous studies[2]. In the current study no relapse patient was found to have MDR TB. Two patients of the current study had isolates that were sensitive to all first line drugs. One patient had resistance to isoniazid and streptomycin. His sputum AFB isolate was sensitive to rifampicin and hence could not be classified as MDR TB. In fully intermittent therapy in Indian context initial INH resistance is expected to be 20-25% under programme conditions [41]. In daily regimen the chance of

INH resistance is 8%[40]. In patients who come for retreatment the presence of INH resistance ranges from 47.7% to 87.1% [44].

In the present study relapse was not associated with diabetes mellitus. In previous studies diabetes was associated with an increased risk of relapse of tuberculosis [31]. Diabetes mellitus is also associated with an increased risk of severe disease and retreatment.

In the present study alcohol was not associated with an increased risk of relapse. But in previous studies alcohol was found to be associated with increased chance of relapse [12].

In the present study relapse rate that was found after one year of completion of ATT was 6%. The relapse rate that is acceptable on follow up of sputum positive pulmonary tuberculosis patients is< 5 %[39]. Most of the relapse has been found to occur in 6 to 12 months after completion of ATT. In RNTCP patients are not followed up following treatment completion for relapse. Many patients who relapse, fail or default do not return to the programme[15]. There is a paucity of data on the long term outcomes with the regimens given in the RNTCP.

LIMITATIONS OF THE STUDY

- Small sample size
- Use of spot sputum specimen
- Radiographic evaluation which was in the initial protocol was not done during the study period
- Non randomized method of sampling
- There may be a male bias in the selection of cases in the study
- The study did not differentiate between relapse relapse due to reinfection from relapse due to endogenous reactivation

CONCLUSIONS

1. Clinicians should impressed about the probability of relapse of TB within the first year of completion of ATT.

2. Sputum re-evaluation at regular intervals starting 3 months after completion of treatment should be performed especially among high risk patients with co morbidities and HIV.

3. The relapse rate under the DOTS programme can be reduced by ensuring that patients take their treatment regularly and are counselled effectively about drug resistance.

4. Evaluation of primary resistance prior to treatment may help in avoiding future relapses.

5. Early patient retrieval mechanism should be implemented effectively to maintain regularity in TB treatment. This will prevent relapse and drug resistance.

6. The combination of both the relapse in TB and increased development of drug resistant Mycobacterium potentially carries a risk of global spreading, with serious implications for TB

control and the achievement of the United Nations Millennium Development Goals.

7. Given the growing epidemic of DM worldwide, it is necessary to add DM prevention and control strategies to TB control programmes and vice versa and to evaluate their effectiveness. The combination of both diseases potentially carries a risk of global spreading, with serious implications for TB control and the achievement of the United Nations Millennium Development Goals.

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PROFORMA

S.No Date

Name Age Sex

TB No Zone DOTS site

Height Weight

RBS	mg/dl
Urea	mg/dl
Creatinine	mg/dl

T.Bilirubin	mg/dl
SGOT	IU/L
SGPT	IU/L
ALP	IU/L
T.Protein	g/dl
Albumin	g/dl

HIV I & II

CXR-PA view

Sputum AFB: Sputum culture:

If Culture positive DST

INH

Rifampicin

QUESTIONNAIRE

Symptom for which pulmonary TB was diagnosed

Symptom at present

Fever

LOA

LOA

Anti Tuberculosis Treatment:

Started	
Completed	
Duration	
Regularity	
Outcome	

Contact with MDR patient

DM

Treatment regular/ Irregular

HIV

Pre-existing lung disease

Renal disease

Chronic liver disease

Alcohol
g/wk

Type		Duration	
Amount		No.of days /wk	

Smoking pack years

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Prospective study on sputum status of sputum positive Pulmonary tuberculosis patients who have completed category I ATT under DOTS treatment

Principal Investigator : Dr.A.Karthik Ramalaingam

Designation : PG in.M D (Gen.Med)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 07.02.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

27/6/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI

Name	Age	Gender	AFB	C/S	resistance	DM	PUL.D	alcohol	smoke	sym now	Fever	LOA	LOW	weight(kgs)	height(cms)	Height(m)	Height(m^2)	BMI	RBS	Initial symptom
Gunalan	62	1	0	0	0	0	0	1	3	3	0	0	0	51	164	1.64	2.69	18.96	141	5
selvaraj	35	1	0	0	0	1	0	0	0	0	0	0	0	60	161	1.61	2.59	23.15	113	0
karthikeyan	17	1	0	0	0	0	0	0	0	0	0	0	0	59	158	1.58	2.50	23.63	104	2
moses murali	64	1	0	0	0	1	0	0	2	2	0	0	0	62	168	1.68	2.82	21.97	296	2
anandaraj	40	1	0	0	0	1	0	0	1	0	0	0	0	60	162	1.62	2.62	22.86	120	2
suri	40	1	0	0	0	0	0	2	3	2	0	0	0	55	158	1.58	2.50	22.03	113	4
V.sundaramoorthy	64	1	0	0	0	0	0	0	0	0	0	0	0	70	168	1.68	2.82	24.80	92	2
subramani	41	1	0	0	0	1	0	4	1	0	0	0	0	64	172	1.72	2.96	21.63	213	2
vijayakumar	57	1	0	0	0	1	0	0	0	0	0	0	0	59	163	1.63	2.66	22.21	230	2
selvaraj	59	1	0	0	0	0	1	0	0	2	1	1	1	60	166	1.66	2.76	21.77	132	2
rajkumar.A	25	1	0	0	0	0	0	0	1	1	0	0	0	64	161	1.61	2.59	24.69	85	2
abdul hussain	28	1	0	0	0	0	0	0	0	2	1	1	1	42	165	1.65	2.72	15.43	90	2
thulukannam	48	1	0	0	0	0	0	0	2	1	0	1	0	45	168	1.68	2.82	15.94	102	2
Athilingam	32	1	0	0	0	0	0	0	0	0	0	0	0	64	169	1.69	2.86	22.41	105	2
balamurali	23	1	0	0	0	0	0	0	0	0	0	0	0	70	169	1.69	2.86	24.51	111	2
raja.S	48	1	0	0	0	1	0	0	0	0	0	0	0	51	162	1.62	2.62	19.43	143	2
N.Vedhagiri	57	1	0	0	0	1	0	0	0	0	0	0	0	57	158	1.58	2.50	22.83	132	2
B.Selvaraj	49	1	0	0	0	1	0	0	0	0	0	0	0	54	160	1.6	2.56	21.09	98	2
purushothaman	28	1	0	0	0	0	0	0	0	0	0	0	0	55	167	1.67	2.79	19.72	123	2
shankar	37	1	0	0	0	1	0	4	3	2	1	1	1	69	169	1.69	2.86	24.16	340	4
madurai	73	1	0	0	0	0	1	0	0	0	0	0	0	58	163	1.63	2.66	21.83	98	2
murugesan	65	1	0	0	0	1	0	0	0	2	0	0	0	46	159	1.59	2.53	18.20	87	2
govindharaj	35	1	0	1	1	0	0	0	0	0	0	0	0	49	159	1.59	2.53	19.38	87	4
ravi	58	1	0	0	0	1	1	2	3	0	0	0	0	37	142	1.42	2.02	18.35	92	2
abdul khadar	73	1	0	0	0	1	0	0	4	2	0	0	0	70	168	1.68	2.82	24.80	132	4
samuel.R	15	1	0	0	0	0	0	0	0	0	0	0	0	52	156	1.56	2.43	21.37	138	2

Rashool	25	1	0	0	0	0	0	0	0	0	0	0	0	54	164	1.64	2.69	20.08	116	2
jagadeesh	17	1	0	0	0	0	0	0	0	0	0	0	0	58	166	1.66	2.76	21.05	102	2
mahesh	22	1	0	0	0	0	0	0	0	0	0	0	0	56	158	1.58	2.50	22.43	118	2
Rajesh	33	1	0	0	0	0	0	0	0	0	0	0	0	59	162	1.62	2.62	22.48	89	2
Babu	53	1	1	1	3	0	0	0	2	2	0	0	0	58	163	1.63	2.66	21.83	94	2
Thirumoorthy	48	1	0	0	0	0	0	0	0	0	0	0	0	60	166	1.66	2.76	21.77	112	2
jayaraman	35	1	0	0	0	0	0	0	0	0	0	0	0	60	161	1.61	2.59	23.15	103	2
jeganathan	43	1	1	1	2	0	0	0	0	0	0	0	0	58	166	1.66	2.76	21.05	119	0
Anbhazhagan	27	1	0	0	0	0	0	0	0	0	0	0	0	58	164	1.64	2.69	21.56	131	2
kumar	31	1	0	0	0	0	0	0	0	0	0	0	0	58	163	1.63	2.66	21.83	85	2
ramesh	44	1	0	0	0	0	0	0	0	0	0	0	0	60	159	1.59	2.53	23.73	80	2
saraswathy	24	1	0	0	0	1	0	0	0	2	0	0	0	48	156	1.56	2.43	19.72	265	2
Pushpa	61	2	0	0	0	1	0	0	0	4	0	0	1	44	147	1.47	2.16	20.36	510	4
pushpa	29	2	0	0	0	0	0	0	0	0	0	0	0	38	149	1.49	2.22	17.12	123	4
abinaya	18	2	0	0	0	0	0	0	0	0	0	0	0	45	158	1.58	2.50	18.03	95	4
vanitha	55	2	0	0	0	1	0	0	0	0	0	0	0	56	154	1.54	2.37	23.61	260	2
fathima	45	2	0	0	0	0	0	0	0	0	0	0	0	35	150	1.5	2.25	15.56	99	2
aysha	42	2	0	0	0	1	0	0	0	1	0	0	0	46	149	1.49	2.22	20.72	386	2
tamilselvi	26	2	0	0	0	0	0	0	0	0	0	0	0	50	153	1.53	2.34	21.36	117	2
priya	19	2	0	0	0	0	0	0	0	0	0	0	0	52	157	1.57	2.46	21.10	118	2
sivagami	37	2	0	0	0	0	0	0	0	0	0	0	0	56	156	1.56	2.43	23.01	134	2
v.lakshmi	44	2	0	0	0	0	0	0	0	0	0	0	0	49	142	1.42	2.02	24.30	98	2
Narasamma	65	2	0	0	0	0	0	0	0	0	0	0	0	50	156	1.56	2.43	20.55	108	2