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POST ATT STATUS OF PATIENTS WHO HAD CATEGORY II ATT - A Follow Up Study

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CERTIFICATE

Certified that this dissertation titled "POST ATT STATUS OF PATIENTS WHO HAD CATEGORY II ATT A FOLLOW UP STUDY" is a bonafide work done by Dr.K.THIRUPPATHI MD(TB&CD), Post graduate student of Institute of Thoracic Medicine, Madras Medical College, Chennai, under the guidance and supervision of PROF. R.ATHARUNISHA BEGUM, MD., DTCD., during the academic year 2003 – 2006.

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DECLARATION

I, **Dr.K. Thiruppathi**, declare that dissertation titled **POST ATT STATUS OF PATIENTS WHO HAD CATEGORY II ATT - A Follow Up Study** " is a bonafide work done by me at Institute of Thoracic Medicine, Chetput and Department Of Thoracic Medicine, Madras Medical College & Govt. General Hospital, Chennai-3 under the guidance of my Professor **Dr.R. Atharunnisa Begum M.D. (T.B. &C.D)**

This Dissertation is submitted to the Tamilnadu Dr.M.G.R.Medical University towards partial fulfillment of requirement for the award of **M.D. Degree Branch-XVII (T.B. AND RESPIRATORY DISEASES)**.

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CONTENTS

INTRODUCTION

Outcome surveillance is an essential tool to determine the effectiveness of the national effort to control Tuberculosis[1]. It provides an insight into the proportion of patients who complete treatment, experience complications, lose follow up or die. The main purpose of treatment outcome monitoring is to determine the outcome of potentially infectious cases and thus it provides information about the likely transmission of infection.

The Revised National Tuberculosis Control Programme (RNTCP), adopting the DOTS strategy advocated by World Health Organization (WHO), was implemented in 1993 in the country and has been scaled up rapidly since mid 1998. Based on a stringent diagnostic algorithm and history of previous TB treatment, the diagnosed cases under RNTCP are classified as 'New' and 'Re-treatment' cases for allotting an appropriate drug regimen to them.

Retreatment cases i.e. those who give history of previous TB treatment of more than one month, are put on Category II regimen. This category comprises smear positive 'Failures', 'Relapses', 'Treatment after Default (TAD)' and 'Others'. The question often posed by clinicians is regarding effectiveness of Cat II regimen for re-treatment cases, especially those with failures. It has been suggested that they may be treated with a stronger regimen since such cases are likely to harbor drug resistant organisms [2-3]. We conducted a retrospective study to evaluate the outcome of category II retreatment cases in a DOTS programme in Chennai city to examine if these concerns had any basis.

AIM OF THE STUDY

To evaluate the present status of a cohort of retreatment cases started on Category II ATT in the year 2002 in three tuberculosis units of Chennai city and to evaluate the effectiveness of Category II.

DESIGN OF THE STUDY:

Descriptive study

REVIEW OF LITERATURE:

Mycobacteria have played an extremely important role in influencing society through out its history[4]. Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, and rarely by other organisms of the "tuberculosis complex". Tuberculosis is most commonly transmitted by inhalation of infected droplet nuclei which are discharged in the air when a patient with untreated sputum positive TB coughs or sneezes. If the bacillus succeeds in infecting a person, only about 5%–10% of such infected persons (primary infection) develop active disease. In the remaining 90% to 95 % of infected persons, initial infection usually goes unnoticed. Tuberculin sensitivity appears within a few weeks of infection and initial lesions commonly heal leaving no residual changes except occasional pulmonary or tracheo-bronchial lymph node calcifications (primary complex).

Infection occurs almost exclusively through the respiratory route. The infection may then spread from the primary lung lesion to any part of the body via the blood stream, lymphatic and bronchial systems. Post primary TB (active TB disease) arises from endogenous reactivation of latent foci which remained dormant since the initial infection or exogenous re-infection. Post primary TB usually affects the lungs (more than 85%) but can involve any part of the body. Pulmonary TB which is sputum smear-positive is if untreated, TB leads to death within 2–3 years in at least half the patients. About 20 to 25% have natural healing and 25 to 30% remain positive and continue to spread the disease in the community.

Microbiology of Mycobacterium tuberculosis:

The main defining characteristic of the genus Mycobacterium is the property of "acid-fastness": that is, the ability to withstand decolorization with an acid-alcohol mixture after staining with such stains as Ziehl-Neelsen or auramine. In addition to their being acid-fast, the mycobacteria are primarily intracellular parasites, have slow rates of growth (except for the "rapid grower" category), obligate aerobes, and in normal hosts induce a granulomatous response in tissue.

Diagnosis Of Pulmonary Tuberculosis :

Sputum positive pulmonary TB patients are the main source of infection. It is estimated that an untreated smear positive pulmonary TB patient infects 10-15 persons annually. Therefore, it is very important to identify TB suspects and diagnose them early in order to effectively treat and make them non infectious.

Methods available for diagnosis of pulmonary tuberculosis:

- Sputum smear microscopy
- Chest X-ray
- Culture
- Tuberculin test

• Sputum smear microscopy:

This is the primary tool for diagnosing TB as it is easy to perform at the peripheral laboratories. It is not expensive. It is specific with low inter and intra reader variation. It is simple and requires minimum training. It can be used for diagnosis, monitoring and defining cure. Therefore, this is the key diagnostic tool used for case detection in RNTCP. If good diagnostic practices are followed, it is expected that at least 50% of the new pulmonary TB patients diagnosed will be smear-positive. A smear

is made, fixed and stained using the Ziehl-Neelsen staining technique. Sensitivity of detection of acid-fast organisms is increased by a fluorochrome staining procedure with auramine O, a fluorescent stain. This procedure requires use of a fluorescent microscope but is faster than acid-fast staining because the intensity of the fluorescent signal enables slides to be scanned at lower magnification.

Microscopic examination of sputum is, as a rule, the only way by which the diagnosis of pulmonary TB can be confirmed. Whenever TB is suspected, at least 3 specimens of sputum should be collected over 2 consecutive days and examined by microscopy.

Guidelines for collecting sputum for smear microscopy:

• First visit to the microscopy centre: When a TB suspect reports to the laboratory a specimen is collected on the spot. She/he is given a sputum container with the three times with his/her mouth open, cough out deeply from the chest, open the container, spit out the sputum into it and close the container tightly. This specimen is called a spot specimen. The patient is then given a similarly marked empty sputum container to collect a specimen early next morning and bring it to the laboratory. This specimen is called an early morning specimen.

• Second visit to the microscopy centre:

The early morning specimen brought by the patient is received and a further spot specimen is collected. Thus there will be three samples: SPOT-EARLY MORNING-SPOT. Obtaining a good sputum specimen is crucial for quality sputum microscopy. The following steps have to be observed to get good sputum specimen:

• Tasks performed before sputum collection:

Before a health worker collects a sputum specimen, the reasons for sputum collection have to be explained to the patient. The Laboratory technician/ health worker must ensure that the patient's full address is entered in the laboratory form.

• Tasks performed during sputum collection:

A specimen collected under the proper guidance of a health worker is likely to yield more conclusive results than one produced by a patient without any guidance. Sputum should preferably be collected in open air or in a vacant room with open windows. The health worker or the laboratory technician should stand behind the patient. The health worker should also ensure that no-one stands in front of the patient. If a patient coughs out only saliva, he should be asked to try again to bring out sputum. Patient must be asked to rinse the mouth before bringing out the sputum samples.

• Tasks performed after sputum collection:

Sputum specimens should be examined on the same day. In cases where sputum needs to be transported to a DMC it must be examined within a week after collection. Storage of sputum samples should be in cool place/ refrigerator. A smear is made, fixed and stained using the Ziehl-Neelsen staining technique

• <u>Chest X-ray:</u>

X-ray as a diagnostic tool is sensitive but less specific with large inter and intra reader variations. No shadow is typical of TB, 10-15% culture-positive cases remain undiagnosed and 40% patients diagnosed as having TB by X-ray alone may not have active TB disease. It is supportive to microscopy.

• Culture:

Definitive determination of species and antimicrobial susceptibility testing require culture of the organism. Culture of Mycobacterium tuberculosis bacilli is very sensitive and specific but is expensive as it requires a specialized laboratory set-up and results are available only after several weeks. If available, culture of tubercle bacilli may be helpful, although in sputum-negative cases a clinical decision to treat for TB based on X-ray findings and lack of response to broad-spectrum antibiotics would be more practical and also ensure prompt treatment. Culture and sensitivity testing is valuable for diagnosis and management of drug resistant tuberculosis, besides epidemiological surveillance and planning. Culture of sputum usually involves digestion and decontamination of the specimen before inoculating media. This process enables more uniform plating of the specimen and decreases bacterial overgrowth. For specimens other than sputum, digestion and decontamination are not required.

It is generally recommended that two different kinds of media be inoculated: usually an egg-based one, such as Lowenstein-Jensen, and an agar-based one, such as Middlebrook-Cohn 7H10.

Egg-based media are generally regarded as the reference standard [4]and may result in a larger number of positive cultures, whereas agar-based media enable earlier detection of growth. The main disadvantage of this procedures is the slow of mycobacteria which necessitates a mean incubation of 4-6 weeks on these conventional media.

Colonies of rapidly growing mycobacteria may be visible in 2 to 5 days, whereas colonies of the slower growing organisms appear in 2 to 6 weeks. Cultures showing no growth at 6 weeks are reported as negative, although they generally are kept for another 2 to 4 weeks before being discarded. Simply from observation of rates

of growth and pigment production, many of the non tuberculous mycobacteria can be differentiated from M. tuberculosis. A positive test for niacin production in essence confirms the isolate to be M. tuberculosis. In many laboratories, especially those processing large numbers of specimens, DNA probes are used routinely to identify mycobacteria grown in culture, thus obviating the need for many of the biochemical tests. Speciation of the non-tuberculous mycobacteria is important for separating pathogenic from nonpathogenic organisms and to indicate the initial approach to therapy on the basis of known drug susceptibility patterns of the various species.

Radiometric Culture Systems:

Radiometric culture systems incorporate 14C-labeled palmitic acid into a liquid culture medium. Growth of mycobacteria results in liberation of $^{14}CO2$ that can be measured by the detection device. The increased sensitivity of the system enables growth to be detected sooner, usually in 10 to 14 days[4]. As noted earlier, a positive NAP test or DNA probe testing confirms an isolate as being M. tuberculosis. Because identifying patients with tuberculosis early is desirable and because of concern with multidrug-resistant organisms, radiometric detection and sensitivity test systems should be used in hospitals in which large numbers of patients with tuberculosis are managed.

Nucleic Acid Amplification (NAA) Tests:

NAA tests include those that involve PCR amplification, transcription-mediated amplification (TMA), strand-displacement amplification (SDA), ligase chain reaction (LCR), and Q Beta replicase amplification. Each of these approaches has

strengths and weaknesses. In each test, either DNA or RNA is amplified to detectable levels. Currently, rapid amplification tests are licensed only for use with specimens in which AFB have been found. This limitation has been applied because the sensitivity of the tests for specimens that are smear-negative but culture-positive is not sufficiently high to exclude M. tuberculosis with a negative result of a rapid test.

Restriction Fragment Length Polymorphisms:

Analysis of insertion sequence patterns in genomic DNA of M. tuberculosis has been shown to be a useful tool for studying the epidemiology and transmission dynamics of tuberculosis. Restriction fragment length polymorphism (RFLP) analysis is based on the finding that tubercle bacilli possess repetitive DNA sequences. Of these sequences, IS6110 is the most widely used and is found in 2 to 25 copies per individual isolate or strain. The technique involves extracting DNA from cultured M. tuberculosis, digesting it with restriction endonucleases, separating the resulting fragments by gel electrophoresis, and then using Southern blot analysis with labeled components of these insertion sequences to create a unique, strain-specific DNA fingerprint. In outbreaks of tuberculosis among patients with acquired immunodeficiency syndrome (AIDS) in hospitals or in residential care facilities, isolates from multiple patients have shown precisely the same banding pattern, which indicates spread of infection within the facility. Although this technique requires considerable technical expertise, it can be used to track the spread of strains of M. tuberculosis through a population or to detect unsuspected sites and patterns of transmission, and thus it could have a significant impact on public health interventions

Drug Susceptibility Testing:

Determination of susceptibility to antimicrobial agents is of considerable clinical importance. Although several techniques are used for determining resistance, the proportion method is most commonly employed in the United States and Canada. This involves inoculating one or more dilutions of cultured mycobacteria on drug-free media and on media containing appropriate concentrations of anti mycobacterial agents. Resistance is generally considered to be present when the growth on the drug-containing medium is 1% or more of the control growth. The standard drug concentrations used for defining resistance to the first-line drugs are as follows: isoniazid, 0.2 g/mL; rifampin, 1.0 g/mL; ethambutol, 5.0 g/mL; and streptomycin, 2.0 g/mL. Susceptibility testing for pyrazinamide can be done only in a radiometric system. Testing of the second-line drugs is generally performed only in reference laboratories. Rapid radiometric measurements are also used to determine drug susceptibility and can provide results much more quickly than from cultures on solid media. The results obtained by this technique have been quite consistent with the results of standard test procedures.

• Tuberculin test:

Reactivity to tuberculoprotein is the hallmark of a cell-mediated immune response to M. tuberculosis. Stated differently, a positive response to an appropriate skin test antigen is assumed to be diagnostic of tuberculous infection. In fact, the tuberculin skin test is the only means of detecting tuberculous infection in persons who do not have clinical tuberculosis[4]; hence, it is important both in diagnostic and epidemiologic evaluations. Tuberculin test may be useful as an additional tool for diagnosing paediatric TB, in whom a positive test is more likely to reflect recent infection with TB and indicates a much higher risk of developing disease.

Extent of the Tuberculosis Problem

Nearly one-third of the global population, i.e. two billion people, are infected with Mycobacterium tuberculosis and are at risk of developing the disease. More than eight million people develop active tuberculosis (TB) every year, and about two million die[5] . More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years). There, an adult with TB loses on average three to four months of work time. This results in the loss of 20-30% of annual household income and, if the patient dies of TB, an average of 15 years of lost income[6]. In addition to the devastating economic costs, TB imposes indirect negative consequences - children leave school because of their parents' tuberculosis, and women are abandoned by their families as a result of their disease. Coinfection with the human immunodeficiency virus (HIV) significantly increases the risk of developing TB . At the same time, multidrug resistance, which is caused by poorly managed TB treatment, is a growing problem of serious concern in many countries around the world . Tuberculosis (TB) remains a major public health problem in India. About 40% of the population in India is estimated to be infected with TB bacillus. Every year approximately 1.8 million people develop TB and nearly 400,000 die from it. The annual incidence of smear positive TB is estimated to be 75 per 100,000 population (based on Annual Risk of Tuberculous Infection (ARTI) study done for the four zones of the country from 2000 to 2003. India accounts for one fifth of global incidence of TB and tops the list of 22 high TB burden countries. TB kills more adults in India than any other infectious disease.

In India, every day[7]:

• more than 5000 develop TB disease

• more than 1000 people die of TB (i.e. 1 death every 1.5 minutes)

The greatest burden of tuberculosis incidence and mortality in India is in adults aged 15 to 60 years, which include the most productive members of society. TB affects more men than women, but still kills more women than all causes of maternal mortality put together.

Every year due to TB (as per estimates made in 1997):

• More than 170 million work-days are lost

• nearly 300,000 school children dropout from the schools

• more than 100,000 women are rejected by their families

The HIV epidemic has the potential to worsen the TB situation, increasing the number of TB cases and accelerating the progression of TB infection to active disease. It is estimated that 50 to 60 % of HIV infected people will develop TB disease in their lifetime when compared to 10% of HIV negative persons infected with TB. Another challenge to TB control in India is multi-drug resistant TB (MDR-TB). Fortunately the data available to date shows that levels of MDR-TB remain relatively low, at around 3%, amongst new patients and 12% in re-treatment cases. However these relatively low percentage figures translate into large absolute number of MDR-TB cases, who can transmit their drug resistant disease to others and require effective treatment.

The problem of MDR –TB:

The phenomenon of drug resistance was detected very soon after the introduction of Streptomycin for the treatment of Tuberculosis in 1947. Today, with the greatly expanded efforts to strengthen Tuberculosis prevention and control programmes worldwide, there is growing concern about the currently reported and potential future rates of drug-resistant Tuberculosis, and more importantly, the emergence of strains

resistant to Isoniazid and Rifampicin, defined as multi-drug resistant TB, or "MDR-TB". 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, use of inappropriate non-standardized treatment regimens, irregular drug supply, poor drug quality, or rarely, erratic absorption of the medications.

The magnitude of the problem:

The emergence of strains of *Mycobacterium Tuberculosis* that are resistant to antimicrobial agents is a world-wide problem. In 1997, the first global report on drug resistance, published by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) Global Project on Anti-Tuberculosis Drug Resistance Surveillance, contained data from 35 countries. The 2nd and the 3rd reports, published in 2000 and 2004, provided data from 50 and 63 countries respectively[8,9]. The latter reported, the median prevalence of resistance to at least one drug among new TB cases as 10.2% (range 0 – 57.1%), with specific drug resistance being 5.9% for Isoniazid and 6.3% for Streptomycin[9].According to the said report, the median prevalence of MDR-TB amongst new cases worldwide was estimated to be 1.1% (range 0 – 14.2%). Higher rates of resistance were found amongst previously treated patients, with median prevalence of resistance to at least one drug and MDR-TB being 18.4% and 7.0% respectively[9].

In India, drug resistance patterns vary widely across different parts of the country. The data on drug resistance in 'new' cases has been variously estimated by different investigators[10]. The first nation wide survey conducted by Indian Council of Medical Research (ICMR) during the 1960s showed a resistance level of 8.2% to Isoniazid (H) alone, 5.8% to Streptomycin (S) alone, and 6.5% to both the drugs

(SH)[11]. Data published by the Tuberculosis Research Centre (TRC), Chennai have shown a gradual rise in the prevalence of resistance in 'new' cases over the past four decades, 3% to 17% for Isoniazid and 3% to 13% for Streptomycin. Drug resistance to Rifampicin emerged during the 1990s and data from the recent studies conducted by TRC and NTI, have reported MDR-TB levels between 0.5% to 3% in new cases and 12% amongst re-treatment cases[11-13]. A high prevalence of MDR-TB is mostly due to poor TB case management. Any intervention designed to treat and /or control MDR TB must place the highest priority on correcting such errors in TB management, in the public as well as the private sector, prior to incorporating treatment for MDR-TB cases into the programme. Under the operational conditions, it has been observed that less than 3% of new cases fail to the Category I treatment regimen and 6% fail amongst the retreatment patients treated with the RNTCP Category II regimen. It is being realized that, as DOTS programmes around the world become robust enough to manage the majority of patients who carry drug-sensitive strains, efforts should begin to provide better services for the minority of patients with MDR-TB[14-15].

Journey of tuberculosis control movement in India :

Era of Pre-chemotherapy:

Tuberculosis has been recognized as one of the most ancient diseases which finds a place in the works of Ancient Ayurvedic System practiced by Sushrutha, Charaka and others around 2500 BC. As we all know, 24th March 1882 is a landmark day, as on this day, Robert Koch announced the discovery of causative organism of TB. This brought to the forefront, a totally new era in the struggle against TB. Its relevance

continues till date. Koch's discovery inspired many facets of research in prevention, control and therapeutic aspects of the disease. Unfortunately, there was no breakthrough in the treatment of TB for a long time to come. The only available mode of treatment was isolation, providing good food and ventilation in a sanatorium. The development of anti-TB drugs was acquired and sporadic over a period of two decades starting from 1940s. Streptomycin and Para-Amino Salicylic Acid (PAS) were first introduced in 40s followed by Thioacetazone and Isonicotinic Acid Hydrazide (INH) in 50s. This gave a global impetus for treatment and control of TB. In 1951, these drugs were tried out on smaller scale in a limited number of patients in Indian doctors.

The Bhore Committee report in 1946 had come out with an estimate that there were about 2.5 million patients requiring treatment in the country and only a few thousand beds were available which indicated a wide gap that had to be bridged. The committee recommended establishment of an organized domiciliary service by setting up of TB clinics in the districts and mobile TB clinics for rural areas. The NSS was conducted (1955 to 1958) was an eye opener, which revealed that the problem of TB was uniformly distributed, both in the urban and rural population of the country. On an average, the bacillary cases were 4/1000 and X-ray active cases 16/ 1000.The National TB Control Programme (NTCP) formulated in 1962 and implemented throughout the country with limited resources was to create a good infrastructure in most parts of our country. A large number of key personnel of District TB Centers were trained in carrying out NTCP activities. It was also engaged in monitoring the TB control programme and providing feedback from time to time both to the central and state authorities.

Era of Conventional Chemotherapy (1961 -1986):

An integrated NTP was pilot tested in Ananthpur district of Andhra Pradesh during 1961 and thereafter the programme was launched in a phased manner throughout the country. The programme was expanded in a phased manner to cover 364 districts using R1 to R5 regimen and monitoring being taken up on a regional basis initially and thereafter NTI took up the monitoring work for the entire country. From the analysis of monitoring reports and the observations made in a number of studies, it stood out prominently that the compliance with anti-TB treatment for 12 to 18 months was a big problem under field conditions. Researchers had already demonstrated that the duration of treatment could be brought down to 6-8 months.

Era of Short course chemotherapy (1986 -1993):

At this juncture, the name that first strikes the mind is that of Dr. Wallace Fox who, through British Medical Research Council units in East Africa, India, Hongkong and Singapore, handed over the greatest gift to the world i.e., SCC. He is considered as the father of clinical trials for chemotherapy of TB. With the introduction of Rifampicin and Pyrazinamide in the developed countries in early 1960s, a new era started in the battle against TB. This has been a very important milestone in the fight against TB on a global scale which brought enormous hope of early TB control. This finding enabled to cut down the duration of treatment to 6 -8 months. In 1983, Tuberculosis Research Centre, Madras, pilot tested SCC in 18 districts of the country to assess the feasibility of its implementation on a larger scale. Government of India (GOI) agreed to the policy of implementation of SCC in 1986. In spite of the introduction of SCC, monitoring report as well as findings of some studies continued to show a high rate of defaulters and the disturbing trend of low compliance in SCC

districts. Following the global review of the programme WHO in 1993 declared TB as a global emergency.

Era of Directly Observed Treatment Short course:

(DOTS) -1993 -2005 In 1992, GOI-WHO carried out an in-depth review of TB programme in India as a part of global review and observed glaring deficiencies. In 1992, the Government of India, together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA), reviewed the national programme and concluded that it suffered from managerial weakness, inadequate funding, over-reliance on x-ray, non-standard treatment regimens, low rates of treatment completion, and lack of systematic information on treatment outcomes. As a result, a Revised National Tuberculosis Control Programme (RNTCP) was designed.

RNTCP - AN OUTLINE:

The RNTCP strengthens the existing NTP infrastructure by creating a sub-district-level supervisory team (known as the TB Unit), consisting of a treatment supervisor (Senior Treatment Supervisor, STS) and a laboratory supervisor (Senior TB Laboratory Supervisor, STLS). These are new posts. In addition, a medical officer from the general health system serves as Medical Officer—TB Control at sub-district level who is specifically allocated TB control duties in addition to his other duties. These 3 individuals constitute the management unit, which is responsible for overseeing operations in approximately a 5 lakh population including, on average, 5 designated

microscopy centers. More importantly, intensive modular training, supervision, and cross-checking of the work of the laboratory technician should ensure that reliable results are obtained.

DOTS – an overview:

The DOTS strategy has the following five components:

1 Sustained political commitment.

2 Access to quality-assured sputum microscopy.

3 Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including direct observation of treatment.

4 Uninterrupted supply of quality-assured drugs.

5 Recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance.

Directly Observed Treatment (DOT), in which a trained peripheral health worker or community volunteer watches as patients swallow all medicines, is fundamental to ensuring cure. DOT should be ensured for every dose in the intensive phase of treatment and at least the first dose of the week in the continuation phase. DOT is one of the five components of the DOTS strategy.

Classification of tuberculosis cases

It is important to classify cases of TB in order to determine the correct combination of drugs and duration of treatment. Classification of pulmonary cases should be based on at least 3 sputum smear examinations. Sputum should also be examined for cases of suspected extra-pulmonary TB if pulmonary symptoms are present.

Pulmonary tuberculosis

a. Smear-positive patient

A patient with at least 2 initial sputum smear examinations (direct smear microscopy) positive for acid-fast bacilli (AFB);

Or: A patient with one sputum examination positive for AFB and radiographic abnormalities consistent with active pulmonary TB as determined by the treating MO;

Or: A patient with one sputum specimen positive for AFB and culture positive for M.tuberculosis.

b. Smear-negative patient

A patient having symptoms suggestive of TB with at least 3 sputum examinations negative for AFB, and radiographic abnormalities consistent with active pulmonary TB as determined by the treating MO, followed by a decision to treat the patient with a full course of anti-TB therapy;

Or: A patient whose diagnosis is based on culture positive for M. tuberculosis but sputum smear examinations negative for AFB.

Extra-pulmonary tuberculosis

Extra-pulmonary tuberculosis (EPTB) is tuberculosis of organs other than the lungs, such as the pleura (pleurisy), lymph nodes, intestines, genito-urinary tract, skin, joints and bones, meninges of the brain, etc.

Diagnosis should be based on one culture-positive specimen from an extra-pulmonary site, or histological or radiological, or strong clinical evidence consistent with active extra-pulmonary TB followed by the treating MO's decision to treat with a full course of anti-TB therapy. Pleurisy is classified as extra-pulmonary TB. A patient diagnosed with both sputum smear positive pulmonary TB and extra pulmonary TB should be classified as a case of pulmonary TB.

TREATMENT :

The objectives of Tuberculosis treatment are:

• To decrease mortality and morbidity by ensuring cure, minimizing relapses and preventing development of drug resistance

• To decrease infections and break the chain of transmission of infection

• To achieve the above whilst minimizing side effects due to drugs

These objectives are achieved in RNTCP through intermittent (thrice weekly) treatment regimens given under direct observation for both pulmonary and extra-pulmonary tuberculosis patients. Treatment regimens for tuberculosis have emerged as a result of controlled clinical trials in India and other parts of the world. It has been proven that thrice-a-week (intermittent) treatment is as effective as daily treatment and produces lesser side effects.

RNTCP provides standardized anti-TB treatment in three categories.

Category of Treatment	Type of patient	Regimen
Category I	New sputum smear-positive Seriously ill new sputum negative Seriously ill new Extra-pulmonary	$2H_3R_3Z_3E_3+4H_3R_3$
Category II	Sputum smear-positive relapse Sputum smear-positive failure Sputum smear-positive Treatment After default, Others	$2H_3R_3Z_3E_3S_3+$ $1H_3\ R_3Z_3E_{3+}5H_3R_3E_3$
Category III	New sputum negative not, seriously ill	$2H_3R_3Z_3+4H_3R_3$

	New Extra-pulmonary, not seriously ill	

Definition of types of cases:

New

A TB patient who has never had treatment for tuberculosis or has taken anti tuberculosis drugs for less than one month.

Relapse

A TB patient who was declared cured or treatment completed by a physician, but who reports back to the health service and is now found to be sputum smear-positive.

Transferred in

A TB patient who has been received for treatment in a Tuberculosis Unit, after starting treatment in another unit where s/he has been registered.

Treatment after default

A TB patient who received anti-tuberculosis treatment for one month or more from any source and returns to treatment after having defaulted, i.e., not taken anti-TB drugs consecutively for two months or more, and is found to be sputum smear-positive.

Failure

Any TB patient who is smear-positive at 5 months or more after starting treatment. Failure also includes a patient who was treated with Category III regimen but who becomes smear-positive during treatment.

Chronic

A TB patient who remains smear-positive after completing a re-treatment regimen.

Others

TB patients who do not fit into the above mentioned types. Reasons for putting a patient .In this type must be specified.

Treatment outcome:

The patient's treatment outcome is identified by reviewing her/his Tuberculosis Treatment Card. The treatment outcome and the date the patient stopped treatment is written in the appropriate column in the Tuberculosis treatment card. The date on which the patient stopped treatment is the date of the last dose of drugs taken. The duplicate TB Treatment card and the used / partially used PWB of the patient should be immediately returned by the PHW to the PHI. The MO of the PHI should record the treatment outcome in the treatment card and sign it. The treatment card of the patients whose outcome has been declared and partially used PWBs, if any, should be handed over to the STS during his routine monthly visits.

Tuberculosis Register is kept at the Tuberculosis Unit which is at sub-district level and contains information on all TB patients registered in the area. The Tuberculosis Register is used to record the following information about the patient: Tuberculosis Number (TB No.); Date of registration; Name (in full), address, age/sex; Name of PHI; Date of starting treatment; Regimen/Category; Disease classification; Type of patient; Details of sputum examinations; Treatment outcome with date; Remarks; and Summary at the bottom of the page

Monitoring:

The programme is monitored on a quarterly basis from reports which include the report on case finding, sputum conversion, treatment outcomes and programme management. The programme has also evolved an in-built monitoring system. The quarterly reports are analyzed using the list of indicators at all levels, from the PHI, TU level, district, state to the centre. Detailed feedback on the performance of the districts is sent to the districts by the state at the end of every quarter in order to support the districts to improve performance. CTD gives additional feedback and helps in building the capacity of the state to monitor and evaluate the programme in their respective states. Besides the routine monitoring of the quarterly performance reports, the programme undertakes specific measures to monitor the programme implementation in the districts.

Achievements of RNTCP:

Starting in October 1993, the RNTCP was implemented in a population of 2.35 million in 5 sites in different states .The programme was expanded to a population of 13.85 million in 1995 and 16 million in 1996. In the past years RNTCP has been expanding rapidly as shown below:

Year	1998	1999	2000	2001	2002	2003	2004	2005
Population Covered cumulative, in millions	18	130	287	450	530	775	947	1059

- RNTCP is the largest and the fastest expanding programme in the world. Quality of services has been maintained during this rapid expansion.
- Treatment success rates have tripled from 25% to 86%. TB death rates have been cut 7-fold from 29% to 4%.
- Since its inception, the Programme has initiated over 4.4 million patients on treatment, thus saving nearly 8 lakh additional lives.
- During the year 2004, sputum positive case detection rate of 72% was achieved against the target of at least 70% and treatment success rate of 86% was achieved surpassing the global target of at least 85%..
- The one-billion population coverage mark was reached in March 2005[17]; Revised National Tuberculosis Control Programme (RNTCP) achieved a landmark in 2005 when DOTS services were extended to all the districts of the country[16].

Challenges:

The challenges ahead include the following: maintaining quality of services, addressing multi-drug resistance, dealing effectively with TB/HIV co-infection, wider involvement of other sectors, contributing to the strengthening of health systems, empowering communities, and promoting research. These components are central to the new WHO Global Stop TB Strategy. The union government admitted that the number of HIV positive persons has peaked to cross the five million mark. A few other risk factors for TB such as poverty, spatial proximity to infectious patient due to overcrowding in urban household settings, homelessness, smoking and co-morbidities like diabetes, silicosis, and malnutrition besides HIV/AIDS continue to exist unabated. The inter-play of multiple factors both on plus and negative side calls for monitoring of the situation on a continual basis. This will help us to keep our

responses timely and adequate. This brings in to focus the need to prioritize surveillance for TB to supplement RNTCP activities. National TB institutes at Chennai and Bangalore are already making inroads in operational research. It is imperative that a nationwide surveillance is implemented at the earliest so that early gains made by RNTCP can be carried forward.

In the context of control of TB, as for other diseases, it is important to evaluate the current burden of disease, to know how this has been changing over time, and to determine how it is likely to change in the future. It is also imperative to determine the effectiveness of ongoing TB control activities. An intelligent use of the available data and good understanding of the epidemiology helps design control strategies that are likely to be effective and are cost-effective too

The Revised National Tuberculosis Control Programme (RNTCP), adopting the DOTS strategy advocated by World Health Organization (WHO), was implemented in 1993 in the country and has been scaled up rapidly since mid 1998. Based on a stringent diagnostic algorithm and history of previous TB treatment, the diagnosed cases under RNTCP are classified as 'New' and 'Re-treatment' cases for allotting an appropriate drug regimen to them. Retreatment cases i.e. those who give history of previous TB treatment of more than one month, are put on Category II (Cat II) regimen. This category comprises smear positive 'Failures', 'Relapses', 'Treatment after Default (TAD)' and 'Others'.

Recently, concerns have been expressed that treatment with Category II regimen may not be effective since a single drug has been added to the failed regimen. It has been suggested that they may be treated with a stronger regimen since such cases

are likely to harbor drug resistant organisms. Quy et al.[2] provide evidence that the principle "do not add a single drug to a failing regimen" should be followed rigorously if one wants to ensure proper cure of cases who fail treatment with first-line drugs.

A prospective study was undertaken by **Sophia Vijay and V.H. Balasangameshwara, et al** [18] in the RNTCP centres of Bangalore Mahanagara Palike (BMP) to study the treatment outcome of patients treated with Category II regimen. A cohort of 226 smear and culture positive re-treatment cases, initiated on Category II regimen under DOTS, was followed up prospectively from April 1999 to September 2001. The cohort was interviewed at the initiation and end of treatment using a pre-tested semi-structured questionnaire to elicit details regarding past and present treatment. More than half of the study group (60%) was initially susceptible to all the regimen drugs. MDR –TB among the cohort was 12.8%. 'Treatment after default' cases constituted bulk of the cohort (65.5%) and 'defaults' among them were high. The overall favorable re-treatment outcome in the cohort was only 39.8% as a result of a high proportion of 'defaults' (43.8%). However, favorable outcome among those completing the prescribed duration of treatment was 75%, irrespective of pre-treatment drug susceptibility status. In addition, emergence of drug resistance, especially to Rifampicin, was negligible (1.8%) during current treatment despite the high default rate suggesting effectiveness of Category II regimen. Despite previous TB treatment, 60% of the study cohort was pre-treatment susceptible to all the four drugs despite the prevailing concept that a majority of the re-treatment cases have acquired drug resistance and may not respond to Category II regimen. Treatment adherence is crucial for the success of chemotherapy. Deaths being negligible, the overall high proportion of 'default' in the study group had considerably affected the expected favorable outcome,

which represents failure to keep patients on DOTS, rather than ineffectiveness of Category II regimen. The high default rate observed in the study area compared to the 15% average default rate among all patients on Cat II regimen from 1993 to 1998 in India is notable.

One of the important findings of this study is the emergence of Treatment After Defaults (TAD) as potential defaulters. TADs constituted a majority of the study group and were pre-treatment drug sensitive, and hence amenable to treatment, but continued to default during present treatment. The argument against Category II regimen for re-treatment cases by many physicians is the fear of adding a single drug to a failing regimen, causing emergence of further drug resistance, particularly MDR. Majority of the pre-treatment susceptible group in the present study, however, either became negative or remained susceptible. The overall emergence of resistance to Rifampicin during treatment under direct observation was negligible (1.8%), despite a high default rate. This further supports the robustness of the category II regimen given under direct observation, in preventing the emergence of drug resistance during treatment.

In another study by **T. Santha, P.G. Gopi, R. Rajeswari and N. Selvakumar et al**[19] to find out whether it is worth treating category I failure patients with Category II regimen .Sputum samples were collected from new sputum smear-positive patients declared 'failure' after treatment with Category I regimen under tuberculosis control programme using DOTS strategy from a rural area of Tamil Nadu. Of 1463 patients started on Category I regimen between May1999 and December 2002, 74 cases were declared as 'failures' (smear positive at 5/6 months of treatment). Sputum samples were collected from 60 (81%) of 74 'failures' and 27% (16 of 60) of

them were culture-negative for *M tuberculosis* and 17% (10 of 60) had organisms resistant to Isoniazid and Rifampicin (MDR TB). Their finding that nearly 80% of the 'failures' (as declared in the programme, based on smear results), have organisms susceptible to R, justifies the use of the currently recommended category II regimen for failures of category I treatment. They concluded that close monitoring of these patients will be required to identify failures early and if necessary, change of treatment can be considered for those patients who do not show any response to treatment with Cat II regimen at 3-months.

Quy et al[2] describes that it is the time to abandon the standard retreatment regimen with first-line drugs for failures of standard treatment . The study provides evidence that the principle "do not add a single drug to a failing regimen" should be followed rigorously if one wants to ensure proper cure of cases who fail treatment with first-line drugs. This study from Vietnam had reported 80% of Category I failure cases to have MDR TB. On the treatment regimen (2SRHZ/6HE), the findings of Quy et al. call for strategies to reduce amplification and, perhaps, failure among patients with primary drug resistance. As most resource-limited high-burden countries do not have the means to test every new case of tuberculosis for drug susceptibility at enrolment, innovation is needed to address the issue.

Regarding the retreatment regimen (2SHRZE/ 1HRZE/5H3R3E3), these results suggest its abandonment so that failure cases of the first-line treatment regimen can benefit from a stronger regimen. The principle raised previously, that such a retreatment regimen can still achieve bacteriological cure because of the possibility of susceptibility to R and E in this setting, is no longer valid for failure cases,[20] as this

study clearly shows that in such cases MDR-TB is the predominant pattern where tuberculosis control programmes are of good quality and no other reason for failure exists. Thus, if countries adopt culture and susceptibility testing for sputum smear-positive patients at the end of the intensive phase with 2SRHZ/6HE or 2RHZE/6RH, and MDR is confirmed, a retreatment regimen including second-line drugs should be mandatory. Patients with resistance to two or more first line drugs, other than MDR, may also be candidates for the addition of second-line drugs.[21] Standard retreatment regimens under programme conditions or tailored regimens through centers of excellence could be used, depending on feasibility issues and available Resources.[22-23] If culture and susceptibility testing are not available, standard retreatment regimens with secondline drugs can be attempted for use as soon as failure is declared, by means of smear microscopy after 5 months of treatment, as in Peru.

Some may perceive these suggestions as too radical, but international policy is an evolving process that needs to be adapted to emerging new evidence.Others may claim costs as the impeding issue. However, in the last few years funding for tuberculosis has increased substantially (although much more is needed), and what could not be done 20 years ago may be possible now.[24] The DOTS-Plus initiative of the WHO and partners is bringing hope, as concessionally lowpriced,

second-line drugs have been approved for use in 14 sites by the WHO-housed Green Light Committee under the DOTS framework following strict technical guidelines.[25] Given the encouraging results, the WHO has recently revised its policy for failure cases and recommended retreatment including second-line drugs in the presence of MDR-TB. Cure rates of failure cases treated with the retreatment regimen of first-line drugs alone in Vietnam and Peru are, respectively, 46% and 47%.[2,26].The success rate in

Morocco is only 57%. Such figures for countries with excellent tuberculosis control are simply unacceptable[27].

Re-treatment cases have a higher likelihood of drug resistance which may have been acquired through inadequate prior chemotherapy[26]. They are also more likely than new patients to harbour and excrete bacilli resistant to at least to isoniazid. The re-treatment regimen consists of 5 drugs in the initial phase and 3 drugs in the continuation phase . Three of the drugs RHE – are given through out the treatment . This standardized regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and/ or streptomycin. Under proper case management conditions , MDR-TB cases are those most at risk of failure in the re-treatment regimen[26].

The first alternative for the national tuberculosis programmes with limited resources is to use a Category II regimen, as for other re-treatment cases. However, failures to regimen I have a higher probability of being multi-drug resistant, particularly if the whole treatment was directly observed and included rifampicin in the continuation phase. Regimen II has poor results in MDR-TB cases (less than 50% cure rate). An option for countries implementing regimen IV with reserve drugs is to use this regimen in failures to regimen I with proven MDR-TB. This requires sufficient resources (clinical, laboratory and drugs), availability of culture and susceptibility testing, and capacity to maintain patients on treatment for long periods. Before regimen IV is routinely for those who fail Category I regimen, national tuberculosis programme should first strengthen the management of Category I patients, including putting all patients on directly observed treatment[26]. Only after further strengthening case

management practices should the programme move to provide reserve anti tuberculous drugs.

Failures to Category I treatment regimen may not always have MDR-TB[26], particularly if the entire treatment was not directly observed or if the continuation phase did not include rifampicin. National TB programmes may therefore provide the standard Category II re-treatment regimen until the results of susceptibility testing are known. This will enable a more efficient use of available resources. Culture and susceptibility should be performed as soon as patients fail treatment.

MDR-TB is one of the main causes of failure to a Category I treatment regimen in patients who are treated under strict observation. Studies conducted in Peru and Viet Nam, two countries in which DOTS has been implemented successfully, have shown that Category I treatment failures commonly have MDR-TB.

In programmes that have applied the strategy for several years chronic cases represent less than 2% of the total smear-positive PTB cases. Careful cohort analysis of these subgroups of re-treatment cases is essential to assess the magnitude of chronic cases and, whenever possible, the proportion of MDR-TB among chronic cases It would be irrational for any country to divert resources to regimens with reserve drugs if a large proportion of new infectious cases remain untreated or ineffectively treated and short-course chemotherapy with drugs has not reached its full therapeutic potential[26].

A programme-based study from Malawi by **Harries AD, Nyierenda TE, Kemp JR, et al** [28] had reported that none of the failures to first line treatment with

6HE in the continuation phase following an intensive phase of either 2SHRZ or $2HRZE_3$ had MDR TB. Of the 90 patients who failed their first course of treatment, 48 (53%) were cured by the programme and one patient (1%) completed treatment without a smear examination at 8 months. Altogether 17 (19%) patients died, four (4%) refused treatment, six (7%) had a treatment outcome other than cured, treatment completed or died, and for 14 (16%) there was no information available. Of the 90 patients who failed treatment, 31 (34%) had sputum specimens sent either to the Central Research Laboratory. Of these, 11 specimens grew organisms resembling *M. tuberculosis*. Of the remainder, two specimens grew organisms that were not *M. tuberculosis*, 15 were culture-negative and three were contaminated. Of the 11 cultures with *M. tuberculosis*, eight showed full sensitivity to all drugs tested, while three showed mono-resistance to isoniazid and full sensitivity to the other drugs. This study confirms that the Malawi NTP policy of offering a standard WHO retreatment regimen to failure cases is entirely appropriate.For failure patients started on a retreatment regimen the cure rate was 75%.

This study was country-wide, assessed the management of failed cases 2 to 3 years previously, and is therefore probably representative of the current management practices of treatment failures in Malawi. This study was country-wide, assessed the management of failed cases 2 to 3 years previously, and is therefore probably representative of the current management practices of treatment failures in Malawi.

Tuberculosis research centre Chennai in a controlled clinical trial of using standardized short-course regimens for treating newly diagnosed sputum smear positive (NSS) patients, 81% of 320 patients with H resistance, had favourable treatment outcome and 13% had bacteriological relapse, respectively, during a 24-

month period of follow up. Thus, 18 patients with resistance to H at the time of failure also are likely to respond to treatment with Cat II regimen. Another 27% were negative by culture and there is no cause for concern in treating these patients with Category II regimen.

According to **T. Santha et al** [29] the patients who have relapsed can achieve more than 80–90% cure if treated for 8–9 months with five drugs, including rifampicin, during the intensive phase and three drugs in the continuation phase, since more than 80% of the relapses occur with drug-susceptible organisms [30].

In patients who had incomplete prior treatment, response will depend upon the drugs and dosages given during the prior treatment and the duration of treatment since these factors influence subsequent drug susceptibility [31]. In well performing programmes, 70–80% of these patients are cured [32]. Smear-positive patients who have failed a directly observed short-course treatment or re-treatment regimen have a low probability of cure with regimens that include only first-line drugs, as the probability of resistance to several of the drugs is high. Treatment of these patients with reserve drugs for a long period (18–24 months) can achieve relapse-free cure in two-thirds of them at best .Most patients who default or relapse can be cured with a retreatment regimen. Thus, there is little potential for new drugs to increase cure rates. However, new drugs could promote tuberculosis control by reducing the duration or frequency of treatment. The most important cause of tuberculosis *treatment failure* among detected patients is non-completion of treatment, or default. The most important cause of tuberculosis programme failure is a low rate of treatment completion, as defaulting patients continue to transmit tuberculosis in the community, sometimes with acquired drug resistance.

Treatment success rates of at least 70–85% are necessary to ensure a substantial reduction in the incidence of tuberculosis. Systematic cohort analysis frequently reveals that less than half of patients who start treatment actually complete it. Treatment regimens capable of curing almost every tuberculosis patient have been available for more than 40 years, yet a large proportion of the patients detected have not been successfully treated. In a 1964 report of a community-based tuberculosis treatment programme in southern India using a regimen of isoniazid plus *p*aminosalicylic acid (PAS), only 64% of 123 patients were culture-negative after 12 months although the regimen was capable of a 90% cure rate [31]. The low level of success was attributed to failure of the health delivery services to maintain patient adherence to treatment. By the end of the 12-month period 27% of patients had refused treatment, 10% had died or moved, and fewer than half of the remainder had collected at least 80% of their medication.

In a a longitudinal survey and analytical studies, it was found that relapse still accounted for about 15–20% of the annual incidence of newly registered infectious cases.Controlled clinical trials in which patients were followed up regularly for 2 years or more have shown that the frequency of relapse is around 3–7% with standardized short-course chemotherapy. Similar results were obtained with either a 6-month regimen using rifampicin throughout the treatment period or 8 months if rifampicin was given only in the initial intensive phase of treatment. Approximately 80% of the relapses occur within the first 6 months of stopping treatment. More than 80% of relapses occur with organisms susceptible to the tuberculosis drugs used earlier [33] and hence their re-treatment does not pose a problem. It was also found that the individual risk of relapse among persons with a history of bacteriologically confirmed

tuberculosis varied substantially and was determined mainly by three factors: —whether treatment had been received or not (in case treatment was not given, the patient would be considered to have recurrent tuberculosis, not to have relapsed); —whether or not the regimen given was adequate and regularly taken; and —the time that had elapsed since smear/culture conversion to negative was achieved. The highest relapse rate is found in patients who have never received any treatment

(about 5% per annum) and the next highest rate (about 2%) in patients with prior inadequate treatment [34]. After 3–5 years, the risk in both groups diminishes appreciably, to about 1% [34] . In patients who have been adequately treated, the risk of relapse is too small to justify prolonged follow-up [35]. Thus, routine follow-up examinations are generally unnecessary. This conclusion was reached by the Centers for Disease Control of the Public Health Service in the USA [36], as well as by investigators who followed up patients treated in Scotland . The former stated [36] "Tuberculosis patients who complete adequate chemotherapy should be considered cured. They have no need for routine lifetime periodic recall for X-ray examination. Indeed, perpetuating life-time follow-up of such treated patients diverts clinic personnel and resources from the crucial task of providing services for those who really need them." However, ex-patients should be strongly advised to come for examination without delay if they develop symptoms suggestive of tuberculosis [35]. General practitioners and physicians who are likely to encounter patients with a history of previous tuberculosis should be informed about the possibility of relapse and the need to promptly evaluate recurrent respiratory symptoms (such as prolonged cough). However, it should also be understood that, among symptomatic ex-patients, cough is more the result of irreversible, bacteriologically quiescent lung damage than of recurrence of active tuberculosis disease .

Failure to begin a standardized retreatment regimen in Tuberculosis patients unresponsive to initial therapy may be the most important threat to the worldwide management of Tuberculosis, according to a U.S. Centers for Disease Control and Prevention (CDC) report. CDC *December 14th, 1998* The CDC report further found that inappropriate therapeutic additions or subtractions during treatment for Tuberculosis are also a significant threat.

The level of drug resistance in the community is closely related to the efficiency of treatment1. Multi-drug resistant (MDR) Tuberculosis is, to a large extent, the result of the past ineffective Tuberculosis programmes and practices. There is now an increased awareness about drug resistance posing as a major threat to patients and a challenge to Tuberculosis control programmes.

Observations show that a previous treatment outcome and current clinical and epidemiologic histories can be used to predict the development of MDR-TB and adverse outcomes in patients undergoing retreatment for TB. Such information may be useful for identifying appropriate patient candidates for programs such as directly observed therapy. [37]

Treatment outcome results serves as a tool to control the quality of TB treatment provided by the health care system. The aims of this study were to evaluate the treatment outcome for new culture positive pulmonary TB cases registered in Norway during the period 1996–2002, and to identify factors associated with non-successful treatment.In that study[1], the total treatment success rate for new culture positive pulmonary TB for the period 1996–2002 was 83%. This is close to the WHO

target of success rate of 85% of all smear positive cases. That study shows a default rate of 3%. Default can constitute a major public health problem. Although incomplete treatment can prevent patients from dying from TB, the patients may remain infectious and even develop MDR-TB. It is therefore worrying that several patients in their study who defaulted treatment had isolated INH resistant strains or MDR-TB prior to treatment. Language problems, lack of understanding of the patients' cultural background, lack of communication between primary health care and hospitals, frequent change of address and stigma related to TB might be some of the reasons for defaulting. DOT was used on an individual basis during the study period, especially when an increased risk of non-adherence was suspected, but it became mandatory in Norway from 2003 according to the new TB regulations . Adoption of this strategy will hopefully improve treatment adherence further.

Sophia Vijay, VH Balasangameswara et al[38] conducted a study to address the problem of default among cohorts of new and re-treatment cases treated under DOTS in a metropolitan city. The non-availability of more than one third of defaulters at final interview was mainly due to temporary migration to their native villages. This is a common occurrence in the urban environment , where people move from rural to urban areas for seeking employment. Failure to thrive in cities after an illness may compel them to return to their native habitat. This problem could be circumvented successfully through an efficient referral/transfer system as recommended in RNTCP.Provision of this facility should be made known to patients repeatedly during treatment.

Santha T et al [39]discussed about the progress of treatment and how it can be monitored? There are three approaches to monitor the progress of patients during treatment namely bacteriological, clinical, and radiographic assessment.

Bacteriological assessment:

Bacteriological assessment can be done by smear and culture. Although culture is more specific, it is time-consuming and costly and there is a delay in getting the results. Moreover, appropriate facilities are not universally available. Hence the management of patients is generally based on smear microscopy.

With short-course treatment, the organisms are killed rapidly, but dead bacilli may be excreted for some time, with the result that smears may be positive in some patients even when they are responding well to treatment .In monitoring treatment, culture examinations are merely confirmatory. It is exceptional for patients receiving treatment to be consistently negative on smear yet positive on culture.

Clinical assessment:

Clinical assessment of progress is largely subjective. Disappearance of clinical symptoms, general well-being, ability to resume normal activities, and weight gain are all pointers to clinical progress. Persistence or reappearance of symptoms plus weight loss – i.e. objective clinical deterioration – indicates the need for further investigations by sputum microscopy. Erythrocyte sedimentation rate and other tests are unreliable and unnecessary in monitoring progress. Clinical assessment is often the only means available for judging progress in extra pulmonary and smear-negative pulmonary tuberculosis. Weight gain is a valuable indicator in such cases.

Assessment by radiography:

Serial radiography is still preferred by many physicians. However, several studies have demonstrated that this can be very misleading for assessing the progress and eventual outcome of treatment. Patients may show radiographic improvement yet still discharge tubercle bacilli. Bacteriologically quiescent disease may be classified as treatment failure because of residual lesions on the X-ray, including cavitation. Patients with

persisting bacteriological negativity could show radiographic changes that would be interpreted as deterioration by expert assessors. In a study of 112 patients with bacteriologically quiescent disease, followed up by bacteriology and radiography for 4 years, radiographic changes in 35 patients (31%) were classified as deterioration. In 12 patients (11%), an increase in cavitation or appearance of cavitation was recorded. Clearly, assessment by radiographic changes alone can be very misleading [40].

To summarize microscopic examination of the sputum smear is a reliable and inexpensive method for assessing the results of treatment in initially smear-positive patients. Radiographic and clinical evaluations are unsatisfactory for assessing progress. Smear microscopy is also a valuable guide to progress and outcome: Examination of smear-positive patients at 2 months, 5 months, and at the end of treatment will give a good indication of the success of treatment in large-scale treatment programmes. Follow-up smears provide reliable information about patient progress and programme performance. However, the individual patient benefits from bacteriological assessment only if, in the event of treatment failure, another course of treatment with an effective regimen can be provided.

MATERIALS AND METHODS:

Data collection:

The study was conducted in the Institute of Thoracic Medicine, Chennai in the period from July 2005 to February 2006 .The study population is selected from three tuberculosis units of Chennai city, namely Pulianthope TU , Thanthai periyar TU and Saidapet TU. All the patients who received Category II anti-tuberculosis treatment in the year 2002 in those tuberculosis units were included for study. The indications for Category II were being relapse or treatment after default or failure or for other reasons. The details regarding treatment details, sputum status and treatment outcome at the end of Category II were collected from the tuberculosis register (T.R) available in the respective tuberculosis units. Postal cards were sent to the patient's addresses, requesting them to come to the institute for evaluation. The non responders were traced personally with the help of staff available at the concerned TUs and were interrogated at their door steps.

The patients were asked regarding their present symptoms with duration, past anti-tuberculosis treatment in a questionnaire. Then their sputum was collected in sputum cups and culture bottle. Sputum smear was examined using Ziehl-Neelsen method for the presence of acid fast mycobacteria. All the culture specimens were

collected in a sterile culture bottle containing trisodium citrate. The specimens were processed with sodium hydroxide (for decontamination) and then centrifuged. The inoculum is then inoculated in Lowenstein –Jensen medium. Chest skiagram was taken to all the patients. For those whose culture was positive for M.tuberculosis that specimen was sent to culture & sensitivity testing at Tuberculosis Research Centre.

Ziehl–Neelsen staining

1. Select a new unscratched slide and label the slide with the Laboratory Serial Number.

2. Spread sputum on the slide using a broomstick.

3. Allow the slide to air dry for 15–30 minutes.

4. Fix the slide by passing it over a flame 3–5 times for 3–4 seconds each time.

5. Pour filtered carbol fuchsin to cover the entire slide.

6. Gently heat the slide with carbol fuchsin on it until vapours rise. Do not boil.

7. Leave carbol fuchsin on the slide for 5 minutes.

8. Gently rinse the slide with tap water until all free carbol fuchsin stain is washed away.

9. Pour 25% sulphuric acid onto the slide.

10. Let the slide stand for 2–4 minutes.

11. Rinse gently with tap water. Tilt the slide to drain off the water.

12. If the slide is still red, reapply sulphuric acid for 1–3 minutes and rinse gently with tap water.

13. Pour 0.1% methylene blue onto the slide.

14. Leave methylene blue on the slide for 30 seconds.

15. Rinse gently with tap water.

16. Allow the slide to dry.

17. Examine the slide under the microscope using x40 lens to select the suitable area and then

examine under x100 lens using a drop of immersion oil.

18. Record the results in the Laboratory Form and the Laboratory Register appropriately .

Examination	Result	Grading	No. of fields to be examined
More than 10 AFB per oil immersion field	Positive	3 +	20
1–10 AFB per oil immersion field	Positive	2 +	50
10–99 AFB per 100 oil immersion fields	Positive	1 +	100
1–9 AFB per 100 oil immersion fields	Scanty	Record the exact number	200
No AFB in 100 oil immersion fields	Negative	0	100

Reports should state

- If the acid- fast bacilli were seen or not.
- If the acid-fast bacilli were seen , state the number of AFB seen
- Since the M.tuberculosis bacilli can not be microscopically distinguished from non tuberculous mycobacteria by smear examination, do not report species. A positive report should only state that "acid –fast bacilli" were seen.
- State the method by which the smear was examined (Ziehl-Neelsen or fluorescent microscopy)

Data analysis:

The data is entered in to the Microsoft Excel Work sheet and it is analysed using SPSS software.

The Definitions of various outcomes is as follows;

Determination of treatment outcomes	
If the patient	Then the treatment outcome is
Initially smear-positive patient who has completed treatment and had negative sputum smears, on at least two occasions, one of which was at completion of treatment.	cured
Sputum smear-positive case who has completed treatment, with negative smears at the end of the initial phase but none at the end of treatment. Or: Sputum smear-negative TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment. Or: Extra-pulmonary TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment.	Treatment completed
who died during treatment, regardless of cause.	Died
Smear-positive who is smear-positive at 5 months or more after starting treatment. Also, a patient who was initially smear-negative but who became smear-positive during treatment.	Failure
who, at any time after registration, has not taken anti-TB drugs for 2 months or more consecutively.	Defaulted

who has been transferred to another Tuberculosis Unit/District and his/her treatment results are not known.	Transferred out

RESULTS :

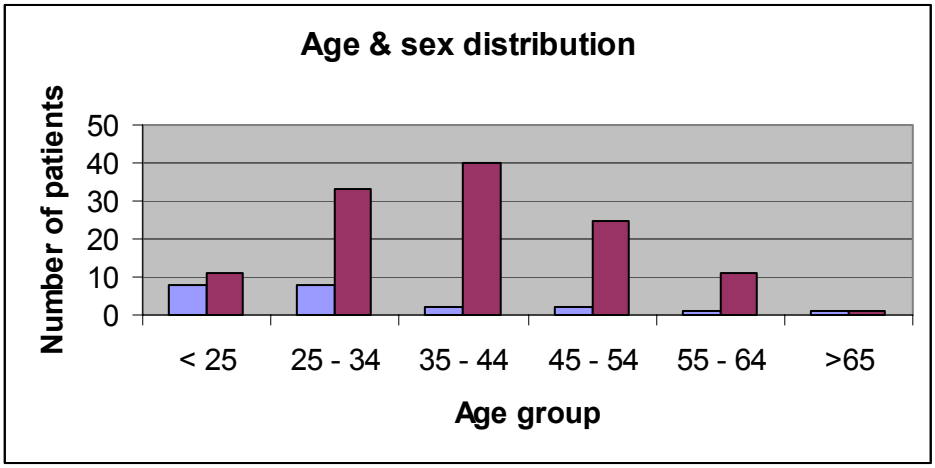
Break up of the total 143 patients who had ATT Category II:

Total no of patients registered	143
Died during treatment period	13
Remaining	130
Non traceable	27
Traced	103
Died in the follow up period	20
Sputum and chest Skiagram taken	83

Age & sex distribution of the 143 patients:

Age	Female	Male	Total
< 25	8	11	19
25 - 34	8	33	41
35 - 44	2	40	42
45 - 54	2	25	27
55 - 64	1	11	12
>65	1	1	2
Total	22	121	143

The above Table shows that more number of males(121) had Category II than females(22).

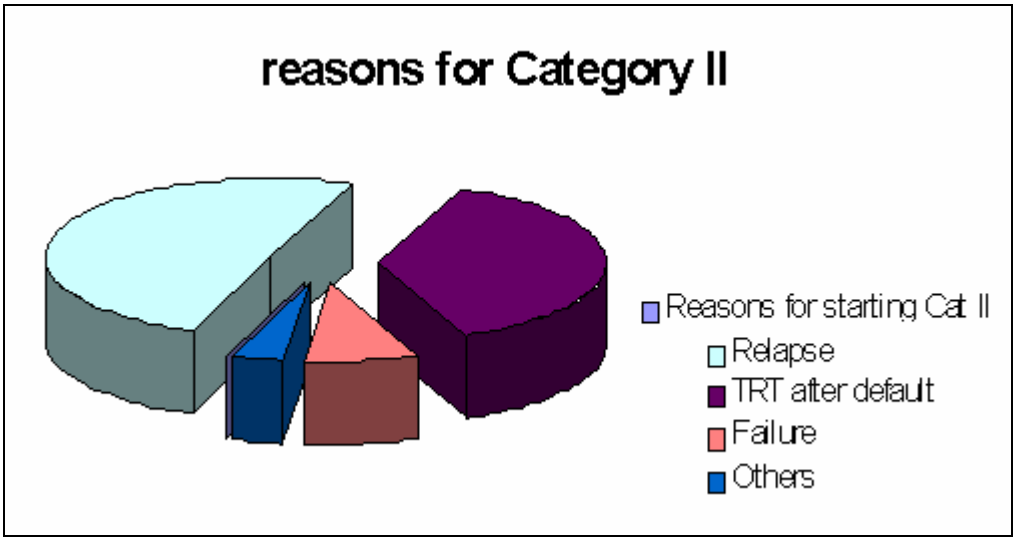


Reasons for starting Category II :

	Female	Male	Total	
	No	No	No	%
Relapse	17	55	72	50.3
TRT after default	1	53	54	37.8
Failure	2	10	12	8.4
Others	2	3	5	3.5
Total	22	121	143	100.0

$p < 0.01$ (Chi square)

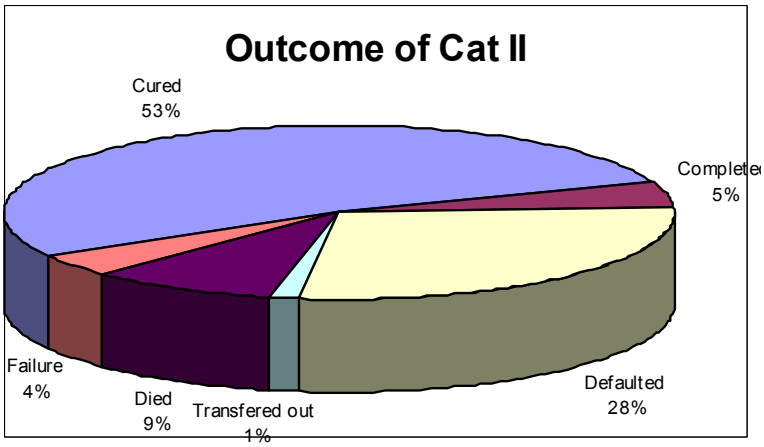
The above Table shows that Relapse is the most common reason for starting Category II (n=72), next common reason being Treatment After Default(n=54). More importantly the defaulters are mostly males. ($p< 0.01$).



Outcome of all the 143 patients registered under Category II:

	NUMBERS	%
Cured:	75	52.4
Completed:	7	4.9
Defaulted:	40	28.0
Failure:	6	4.2
Transferred out:	2	1.4
Died:	13	9.1
total	143	100

The above Table shows that 52.4% (n=75) patients were cured and 28%9(n=40) patients defaulted during treatment .Overall successful treatment completion rate was 58%.(cured + completed treatment)



Split up of outcome according to the reason for starting Category II:

Outcome at the end of Category II	Reasons for starting Category II								Total	
	Relapse		Treatment after default		Failure		Others			
	No	%	No	%	No	%	No	%	No	%
Cured	52	**72.2**	23	42.6	0	0.0	0	0.0	75	52.4
Completed	0	0.0	3	5.6	0	0.0	4	80.0	7	4.9
Defaulted	11	15.3	25	**46.3**	3	25.0	1	20.0	40	28.0
Transferred out	1	1.4	1	1.9	0	0.0	0	0.0	2	1.4
Died	5	6.9	2	3.7	6	**50.0**	0	0.0	13	9.1
Failure	3	4.2	0	0.0	3	25.0	0	0.0	6	4.2
Total	72	100.0	54	100.0	12	100.0	5	100.0	143	100.0

$p < 0.01$ (Chi square test)

The above Table shows that 72.2% (n=52)of the patients with relapse had cured at the end of Category II .Out of the 40 defaulters, 25 patients were already defaulters during Category I and now again defaulted during Category II. Regarding patients who had failure in Category I (N=12) 6 died during treatment period 3 met with failure in Category II .Death rate was high (50 %) in the failure group

Reasons for default:

Migrated	2
Alcoholics	19
Work pattern	14
Toxicity / new disease	3
Indifferent attitude	2

The above Table shows that alcoholism is associated with significant defaultness

Reasons for non-traceability:

Wrong address	4
Shifted	16
Homeless	5
Not willing	2

Co morbid conditions:

Diabetes mellitus	5
Alcoholism	25
HIV	3

Regarding comorbid conditions 5 had diabetes mellitus and 3 were HIV positives. All the three HIV positives were diagnosed only after receiving Category II.

Concordances of sputum smear with sputum culture:

Sputum smear	Sputum culture		
	Positive	Negative	Contaminated
Negative	0	70	3
1+	2	2	0
2+	3	0	0
3+	3	0	0

$p < 0.01$

The above Table shows that 70 smear negative patients were negative by culture also and all the culture positives(n=8) are positive by smear itself.. Only two patients who had positive smear had negative culture. This shows a good concordance between sputum and culture.

Outcome at the end of Category II Vs present culture status:

	Negative	Positive	Contamination	Total
	No	No	No	No
Cured	54	5	1	60
Completed	7	0	0	7
Defaulted	9	2	2	13
Failure	2	1	0	3
Total	72	8	3	83

p = Not significant

Among the 8 persons who are culture positive, five who were previously declared as cured, two were defaulters , one was failure at the end of Category II.

Present clinical status of patients Vs culture:

	Present Culture status		
	Negative	Positive	Total
Asymptomatic	13	2	15
Insignificant symptoms	57	1	58

Significant symptoms	5	5	10
Total	75	8	83

$p < 0.001$

(Insignificant symptoms = patients with cough,sputum,dyspnoea and constitutional symptoms for less than 3 weeks)
(significant symptoms = patients with cough,sputum,dyspnoea and constitutional symptoms for more than 3 weeks)

Outcome at the end of Category II Vs present clinical status:

	Asymptomatic	Insignificant symptoms	Significant symptoms	Died (during trt/follow up)	Non-traceable
Cured	11	43	6	8	7
Completed	2	4	1	0	0
Defaulted	2	9	2	10	17
Failure	0	2	1	2	1
Transferredout	0	0	0	0	2
Total	15	58	10	20	27

Regarding the clinical status of patients, majority of the patients have insignificant symptoms(N=58). There is good association (50%) between patients with significant symptoms and culture positivity. More importantly, 10 out of the 40 defaulters died (25%). On enquiring the cause for death of the defaulters , it was found mostly due to tuberculosis.

Present chest skiagram:

	Present Smear		
Radiologic feature	Negative	Positive	Total
Thinwalled cavity	8	0	8
Thick walled cavity	0	2	2
Fluffy nodular shadows	0	3	3
Pleural thickening	8	0	8
Fibrosis	28	0	28
Multiple patterns	3	4	7
Calcification	15	0	15
Normal	7	0	7
Total	69	9	78

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Outcome at the end of Category II Vs present radiological status:

	Thin walled cavity	Thick walled cavity	Fluffy nodular shadows	Pleural thickening	Parenchymal fibrosis	Multiple patterns	Calcification	Normal	Not available
Cured	6	1	3	7	19	3	13	5	18
Completed	0	0	0	1	3	1	0	2	0
Defaulted	2	1	0	0	5	1	0	0	29
Failure	0	0	0	0	1	2	2	0	3
T.O	0	0	0	0	0	0	0	0	2
Total	8	2	3	8	28	7	15	7	52

Chest skiagrams of patients with positive culture showed radiologic patterns like thick walled cavity and fluffy nodular shadows . Parenchymal fibrosis was the predominant radiological finding.

Sensitivity pattern of culture positives:

	INH	RIF	ETHAM	STREPTO	ETIHO	KANA	CIPRO
1	R	S	S	S	S	S	S
2	R	S	S	S	S	S	S
3	R	R	S	S	S	S	S
4	R	S	S	S	S	S	S
5	R	R	R	S	R	S	S
6	S	S	S	S	S	S	S
7	S	S	S	S	S	S	S
8	S	S	S	S	S	S	S

R = Resistant S = Sensitive

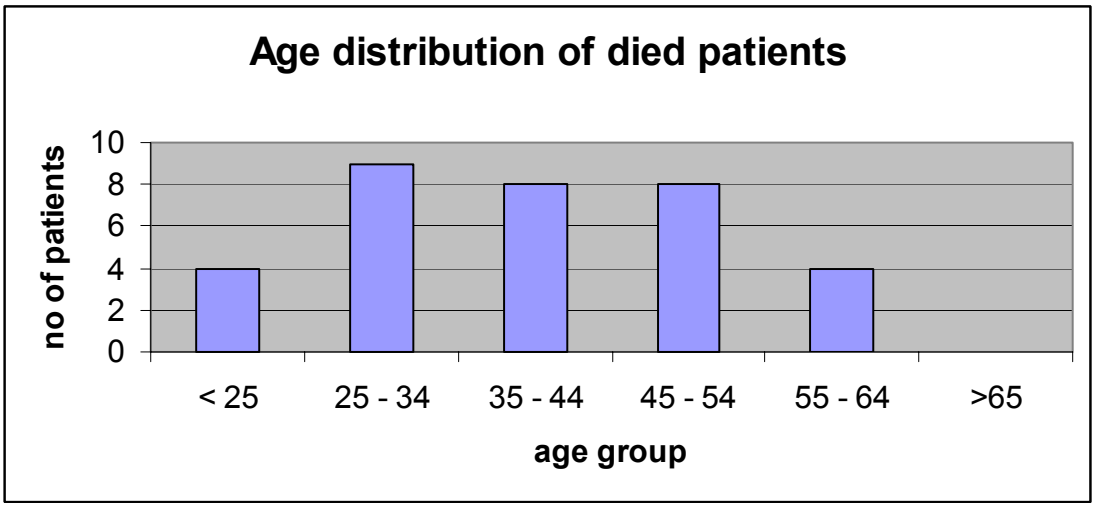
From the above table we find that three patients are sensitive to all the first line antituberculous drugs ; three patients are resistant to INH alone; one patient is resistant to both INH and rifampicin; one patient showed resistance to INH ,rifampicin and ethambutol.

Age wise distribution of died patients:

	Age	Total

	< 25	25 - 34	35 - 44	45 - 54	55 - 64	>65	
Died during follow up	3	6	4	6	1	0	20
Died during treatment	1	3	4	2	3	0	13
Total	4	9	8	8	4	0	33

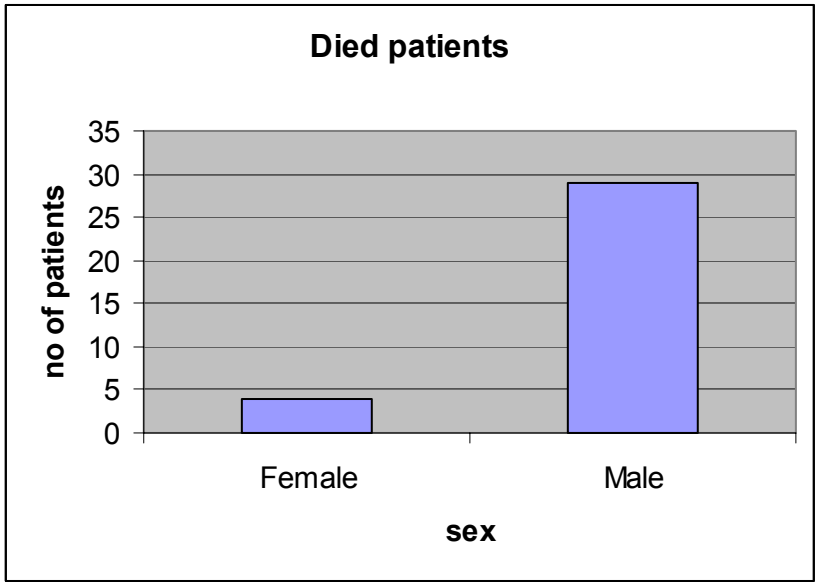
This table shows that age has not affected the death rate.



Sex distribution of died patients:

	Sex		
	Female	Male	Total
Died during follow up	4	16	20
Died during treatment	0	13	13
Total	4	29	33

This table shows that majority of deaths have occurred in males.


Died patients
no of patients
35
30
25
20
15
10
5
0
Female
Male
sex

DISCUSSION:

Totally 143 patients were registered for Category II in the three tuberculosis units in the year 2002. Out of the 143 patients, 13 patients died during the treatment period itself. We could not able to trace 27 patients. Finally 103 patients were traced. Out of them 20 patients died in the follow up period. 83 patients were subjected for sputum examination (smear & culture) and chest skiagram.

Relapse is the most common reason for starting Category II (72 patients 50%), next common reason being Treatment After Default. Twelve patients were started with Category II for failure in Category I.

When analysing the outcome at the end of Category II , 75 patients were cured (cure rate was 53%); 40 patients defaulted during treatment; 4 patients had failure with Category II. Overall successful treatment completion rate was 58% (cured + completed). Out of the 40 defaulters, 25 patients (46.3 %) were already defaulters during Category I and now again defaulted during Category II. Regarding patients who had failure in Category I (N=12) 6 died during treatment period 3 met with failure in Category II .Death rate was high (50 %) in the failure group.

In our study 72.2% (n=52)of the patients with relapse had cured at the end of Category II. This proves the point that most of the relapses will have drug susceptible organisms. According to **T. Santha et al** [29] the patients who have relapsed can achieve more than 80–90% cure if treated for 8–9 months with five drugs,

including rifampicin, during the intensive phase and three drugs in the continuation phase, since more than 80% of the relapses occur with drug-susceptible organisms [30]

This Table compares the outcomes of our study with outcomes of the Indian figures projected in the Research dissemination workshop conducted at Chennai in the January 2005.

	Research dissemination workshop Chennai 2005 [41] (%)	Our Study (%)
Cured	67.2	52.4
Completed	3.6	4.9
Defaulted	15.2	28
Failed	5.8	4.2
Died	7.5	9.1
Transferred out	0.6	1.4

Cure rate in our study is low as it is significantly influenced by high defaulter rate in our study (28%) than the results of research dissemination workshop which was conducted in Chennai in the year 2005 by **Dr. Fraser** from WHO (15.2%)**[41]**.

In a similar study by **Sophia Vijay, V.H. Balasangameshwara et al**[18] the overall favorable treatment outcome was 39.8% (cure 33.6%), treatment completion rate (6.2%) with 43.8% of patients having defaulted from treatment.

When looking at the various reasons for defaultness, alcoholism was the main reason. The next common reason was the work pattern. Persons with wandering jobs like drivers, businessmen, merchants and daily laborers had poor compliance during treatment.

Under the operational conditions, it has been observed that less than 3% of new cases fail to the Category I treatment regimen and 6%(our study 5.8%) fail amongst the retreatment patients treated with the RNTCP Category II regimen. It is being realized that, as DOTS programmes around the world become robust enough to manage the majority of patients who carry drug-sensitive strains, efforts should begin to provide better services for the minority of patients with MDR-TB[14-15]

In study by **Sophia et al**[18]the overall high proportion of 'default'(43.8% Vs 28% of our study) in the study group had considerably affected the expected favorable outcome, which represents failure to keep patients on DOTS, rather than ineffectiveness of Category II regimen

In a study by **Sophia et al**[38] those predicted at risk of default with DOT in a metropolitan setting are most likely to be males, alcoholics, and those missing one or more doses in IP particularly after twelfth dose. In addition, re-treatment patients belonging to the type TAD and having poor knowledge of disease are also likely to default.

Among the 83 patients traced , 8 are positive by culture (10%). Among the 8 persons five who were previously declared as cured at the end of Category II, two were defaulters , one was failure. The reasons for the previously cured patients

becoming culture positive may be due to relapse or reinfection. Only one patient from the failure group became culture positive. But , since the number of failure patients in the study population is low and six of them already died, we can not draw any significant conclusion from this point.

Regarding the need for regular follow up , The highest relapse rate is found in patients who have never received any treatment (about 5% per annum) and the next highest rate (about 2%) in patients with prior inadequate treatment [34]After 3–5 years, the risk of relapse in both groups diminishes appreciably, to about 1% [34] . In patients who have been adequately treated, the risk of relapse is too small to justify prolonged follow-up [35]. Thus, routine follow-up examinations are generally unnecessary. This conclusion was reached by the Centers for Disease Control of the Public Health Service in the USA [36], as well as by investigators who followed up patients treated in Scotland . The former stated [36] "Tuberculosis patients who complete adequate chemotherapy should be considered cured. They have no need for routine lifetime periodic recall for X-ray examination. Indeed, perpetuating life-time follow-up of such treated patients diverts clinic personnel and resources from the crucial task of providing services for those who really need them." However, ex-patients should be strongly advised to come for examination without delay if they develop symptoms suggestive of tuberculosis [35]. General practitioners and physicians who are likely to encounter patients with a history of previous tuberculosis should be informed about the possibility of relapse and the need to promptly evaluate recurrent respiratory symptoms (such as prolonged cough).

Regarding the culture and sensitivity , three patients are sensitive to all the first line antituberculous drugs ; three patients are resistant to INH alone; one

patient is resistant to both INH and rifampicin; one patient showed resistance to INH ,rifampicin and ethambutol. Interestingly that patient failed in both Category I and II. So among the 83 patients subjected for the culture examination 8 are positive(10%); two patients are having multi-drug resistant tuberculosis.

According to **T. Santha et al** [29] more than 80% of the relapses occur with drug-susceptible organisms [30].

Tuberculosis research centre Chennai in a controlled clinical trial of using standardized short-course regimens for treating newly diagnosed sputum smear positive (NSS) patients, 81% of 320 patients with H resistance, had favourable treatment outcome and 13% had bacteriological relapse, respectively, during a 24-month period of follow up. Thus, 18 patients with resistance to H at the time of failure also are likely to respond to treatment with Cat II regimen. Another 27% were negative by culture and there is no cause for concern in treating these patients with Category II regimen.

In study by **Sophia et al[18],** Despite previous TB treatment, 60% of the study cohort was pre-treatment susceptible to all the four drugs despite the prevailing concept that a majority of the re-treatment cases have acquired drug resistance and may not respond to Category II regimen. Treatment adherence is crucial for the success of chemotherapy. The overall emergence of resistance to Rifampicin during treatment under direct observation was negligible (1.8%), despite a high default rate. This further supports the robustness of the category II regimen given under direct observation, in preventing the emergence of drug resistance during treatment.

Failures to Category I treatment regimen may not always have MDR-TB, particularly if the entire treatment was not directly observed[26].

A programme-based study from Malawi by **Harries AD, Nyierenda TE, Kemp JR, et al,** of the 90 patients who failed treatment, 31 (34%) had sputum specimens sent either to the Central Research Laboratory. Of these, 11 specimens grew organisms resembling *M. tuberculosis*. Of the remainder, two specimens grew organisms that were not *M. tuberculosis*, 15 were culture-negative and three were contaminated. Of the 11 cultures with *M. tuberculosis*, eight showed full sensitivity to all drugs tested, while three showed mono-resistance to isoniazid and full sensitivity to the other drugs. This study confirms that the Malawi NTP policy of offering a standard WHO retreatment regimen to failure cases is entirely appropriate.

In analyzing deaths, it was found that more number of males died than females; death rate is not influenced by age . On enquiry more number of deaths were due to tuberculosis.

CONCLUSIONS:

The purpose of the present study is to address the often-posed query regarding effectiveness of Category II regimen for re-treatment.

In Our study the cure rate is 53% and overall successful treatment completion rate is 58%. Since that was the early days of implementation of the programme and the number of staff exclusively available were less, the outcome of the patients who had Category II is acceptable .

46.3 % of Category I defaulters again defaulted in Category II. Recommendations to be formulated concerning management of TB patients with respect to the risk of treatment default.

In the three year follow up it is found that five of the cured patients of Category II now found to be positive by culture. This stresses the importance of prompt evaluation of patients who have completed the treatment in the presence of recurrent chest symptoms.

Out of the 83 patients subjected for culture examination, only five patients showed drug resistance and among the five patients only two were having multi drug resistant tuberculosis. With this low incidence of drug resistance , Category II will be adequate under programme conditions for the management of re-treatment cases.

SHORT COMINGS OF THE STUDY:

- We are not able to trace about 27 patients.
- We are not able to trace many of the defaulters
- The number of patients in failure Category is less
- Pretreatment chest skiagrams and culture sensitivity was not available

Bibliography

1. Delphine Antoine and Clare French -First Annual Report on Tuberculosis Treatment Outcome Surveillance in England, Wales and Northern Ireland Outcome Results on Tuberculosis Cases Reported in 2001.

2 .HTW Quy, NTN Lan, MW Borgdoff et al. Drug susceptibility among failures and relapse cases of tuberculosis: Is standard re-treatment regimen adequate? *Int J Tuberc Lung Dis* 2003; 7(7): 631-636.

3 A. M. Chavez Pachas, R. Blank, M. C. Smith Fawzi, J.Bayona, M. C. Becerra, C. D. Mitnick. Identifying early treatment failure on Category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. International Journal of Tuberculosis & Lung Diseases.2004; 8(1):52–58

4 . Philip C. hopewell, Barry R. Bloom, Text book of Respiratory Medicine by Murray and Nadel , 3rd edition, Chapter 34.

5. Dye C et al. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. Journal of the American Medical Association, 1999, 282(7):677- 686 (http://jama.ama- assn.org/issues/v282n7/toc.html).

6. Ahlburg D. The economic impacts of tuberculosis. Geneva, World Health Organization, 2000 (document WHO/CDS/STB/2000.5)

7. Central TB Division .New Delhi. Technical and Operational Guidelines for Tuberculosis Control, October 2005.

8 Anti-tuberculosis drug resistance in the world. Report No. 2: Prevalence and trends. The WHO/IUATLD Global Project on anti-tuberculosis drug resistance surveillance. World Health Organization, Geneva: WHO/CDS/TB/2000. 278.

9 Anti-tuberculosis drug resistance in the world. Report No.3. The WHO/IUATLD Global Project on anti-tuberculosis drug resistance surveillance. World Health Organization, Geneva: 2004.

10 Paramasivan CN, Venkataraman P. Drug resistance tuberculosis in India. *Indian J Med Res* 2004; 120: 377-386

11. Central TB Division, New Delhi: Summary and recommendations of the expert group meeting on drug resistance surveillance held at TB Research centre, Chennai, 5-26th September 1997.

12 Mahadev B, Kumar P, Agarwal SP, et al. Surveillance of drug resistance to anti-tuberculosis drugs in districts of Hoogli in West Bengal and Mayurbhanj in Orissa. *Indian J Tuberc* 2005; 52: 5-10.

13 . Tuberculosis Research Centre. Trends in initial drug resistance over three decades in a rural community in South India. *IndianJ Tuberc* 2003; 50: 75-86.

14 Espinal M, Christopher Dye. Can DOTS control multi drug resistant tuberculosis? *Lancet* 2005; 365: 1206-1209.

15 . Christopher Dye, Marcos A Espinal, Catherine J. Watt, et al. Worldwide incidence of Multidrug- Resistance tuberculosis.*Journal of Infectious diseases* 2002; 185:197-202.

16. Dinesh Kumar Sharma, Jatinder Singh .Editorial Note:
TB News from India: January-February 2006

17 .S.P. Agarwal, Sophia Vijay, P. Kumar, L.S. Chauhan The History of Tuberculosis Control in India:Glimpses through Decades tbcindia.org

18.Sophia Vijay1, V.H. Balasangameshwara2, P.S. Jagannatha3, V.N. Saroja4, B. Shivashankar5 and P. Jagota6re-treatment outcome of smear positive tuberculosis cases under dots in bangalore city *Ind. J Tub., 2002,49,195*

19 .T. Santha, P.G. Gopi, R. Rajeswari, N. Selvakumar, R. Subramani, V. Chandrasekaran, B. Rani,A. Thomas and P.R. Narayanan . Is it worth treating category I failure patients with Category II regimen? [*Indian J Tuberc 2005; 52:203-206*].

20.Rieder H L, Arnadottir T, Trébucq A, Enarson D A. Tuberculosis treatment: dangerous regimens? Int J Tuberc Lung Dis 2001; 5: 1–3.

21.Iseman M D, Huitt G A. Treatment of multidrug-resistant tuberculosis. In: Bastian I, Portaels F, eds: Multidrug-resistant tuberculosis. Dordrecht, The Netherlands: Kluwer Academic Publishers, 2000.

22.Suarez P G, Suarez P G, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet 2001; 359: 1980–1989.

23 . Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med 2003; 348: 119–128.

24.The Global Fund to Fight AIDS, Tuberculosis and Malaria.Progress report 2003. http://www.globalfundatm.org/background.Accessed 1 June 2003.

25 .Gupta R, Cegielski J P, Espinal M, et al. Increasing transparency in partnership for health—introducing the Green Light Committee. Trop Med Int Health 2002; 7: 970–976.

26.World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 3rd ed. WHO/CDS/TB/2003.313. Geneva, Switzerland: WHO, 2003.

27. Marcos A. Espinal *World Health Organization Stop Tuberculosis Strategy and Operations*

28.A. D. Harries,* T. E. Nyirenda,*† J. R. Kemp,‡ B. S. Squire,‡ P. Godfrey-Faussett,§ F. M. L. Salaniponi* Management and outcome of tuberculosis patients who fail treatment under routine programme conditions in Malawi

Int J Tuberc Lung Dis 7(11):1040–1044 © 2003 IUATLD

29 K. Toman.Text book of tuberculosis. Questions and answers WHO . chapter 58.253-255.

30. Cao JP et al. Two-year follow-up of directly-observed intermittent regimens for smearpositive pulmonary tuberculosis in China. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:360–364.

31. Datta M et al. Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme. Tubercle and Lung Disease, 1993,74:180–186.

32. *Global tuberculosis control. WHO Report 2001*. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.287).

33.Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. International Journal of Tuberculosis and Lung Disease, 2001, 5:40–45.

34.Grzybowski S et al. Reactivations in inactive pulmonary tuberculosis. *American Review of Respiratory Disease*, 1966, 93:352–361.

35.*WHO Expert Committee on Tuberculosis. Ninth report.* Geneva,World Health Organization,1974 (WHO Technical Report Series, No. 552).

36. Recommendations for health department supervision of tuberculosis patients. *Morbidity and Mortality Weekly Report*, 1974, 23:75–76.

37.Mathew et al (CHEST 1997; 111:1162-67).

38. Sophia Vijay1 VH Balasangameswara2, P S Jagannatha3, VN Saroja4 and P Kumar Defaults among tuberculosis patients treated under dots in Bangalore city : a search for solution.*Ind. J Tub., 2003, 50,185.*

***39.*Santha T et al , K. Toman.Text book of tuberculosis. Questions and answers WHO ch 57.250-252.**

40.Fox W. The chemotherapy of tuberculosis in developing countries.In: Heaf F, Rugsby NL eds,recent advances in respiratory tuberculosis . London,Churchill.1968:127-159.

41 Dr Fraser WHO India.RNTCP Category II regimen in Retreatment cases Research dissemination workshop.Chennai 2005

ABBREVIATIONS:

CTD	Central Tuberculosis Division
DOTS	Directly Observed Therapy Short course
DMC	Disignated Microscopy Centre
EPTB	Extra Pulmonary Tuberculosis
INH	Isonicotinic acid Hydrazide
MDR-TB	Multi Drug Resistant Tuberculosis
NSS	New sputum Smear positives
PAS	Para Amino Salicylic acid
PHI	Peripheral Health Institution
PTB	Pulmonary Tuberculosis
RNTCP	Revised National Tuberculosis Control Programme
TU	Tuberculosis Unit
TAD	Treatment After Default
WHO	World Health Organisation

MASTER CHART

S.NO	AGE	SEX	REASONS	COMPLIANCE	OUTCOME	COMORBID CONDITIONS	PRESENT SMEAR	PRESENT CULTURE	CLINICAL STATUS	CHEST SKIAGR
1	23	1	1	1	1	0	0	0	2	5
2	25	1	1	1	1	0	4	4	6	9
3	32	1	1	1	1	0	0	0	2	4
4	21	1	1	1	1	0	0	0	2	1
5	36	1	1	2	3	2	4	4	6	9
6	56	0	1	1	1	1	1	1	3	6
7	21	1	1	5	5	0	4	4	5	9
8	35	1	1	1	1	2	2	1	3	3
9	27	0	3	1	6	0	4	4	4	9
10	25	1	4	1	3	0	4	4	6	9
11	36	1	3	1	5	0	4	4	5	9
12	43	1	3	1	5	0	4	4	5	9
13	30	1	1	1	1	0	0	0	2	9
14	24	1	2	2	3	0	4	4	4	9
15	38	1	1	1	1	0	4	4	4	9
16	48	1	1	1	1	0	4	4	4	9
17	32	1	1	4	5	0	4	4	5	9
18	33	1	3	3	3	2	0	2	2	1
19	38	1	2	2	3	2	3	1	2	2
20	44	1	2	1	1	1	0	0	1	1
21	52	1	2	1	1	0	0	0	2	5
22	50	1	1	1	1	2	1	0	3	3
23	55	1	1	3	3	0	4	4	6	9
24	57	1	1	5	5	0	4	4	5	9
25	35	0	1	1	1	0	0	0	2	5
26	42	1	2	3	3	2	4	4	4	9
27	18	0	1	1	1	0	0	0	2	8
28	68	1	2	2	3	0	4	4	6	9
29	58	1	2	2	3	2	4	4	6	9
30	22	0	4	1	2	0	0	0	2	8
31	38	1	3	2	5	0	4	4	5	9
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37	26	0	3	1	6	0	3	1	3	6
38	21	0	1	3	4	0	4	4	6	9
39	46	1	1	1	1	0	0	0	2	5
40	65	1	1	1	1	0	4	4	6	9
41	43	1	1	1	1	0	4	4	6	9
42	35	1	1	1	1	0	0	0	2	1
43	40	1	2	2	3	2	4	4	6	9
44	52	1	2	1	1	0	0	0	2	4
45	22	1	2	2	3	0	4	4	4	9
46	38	1	2	3	2	0	0	0	2	5
47	36	1	2	5	5	0	4	4	5	9
48	62	1	4	1	2	0	0	0	1	4
49	48	1	1	1	1	0	0	0	2	7

50	26	1	3	2	3	0	4	4	4	9
51	42	1	1	1	1	1	0	0	1	5
52	30	1	1	1	1	0	2	1	1	6
53	51	1	2	1	1	0	0	0	2	7
54	60	1	3	4	5	0	4	4	5	9
55	60	1	1	1	1	0	4	4	4	9
56	40	1	1	1	1	0	0	0	2	5
57	40	1	2	3	3	0	4	4	6	9
58	35	0	1	1	1	0	0	0	2	5
59	55	1	1	1	1	0	4	4	4	9
60	45	1	2	2	3	0	0	0	2	5
61	45	1	2	2	4	0	4	4	6	9
62	47	0	2	1	2	0	0	0	2	5
63	48	1	1	1	1	0	4	4	4	9
64	25	0	1	1	1	0	4	4	4	9
65	21	0	1	1	1	0	0	0	1	5
66	42	1	1	1	1	0	0	2	2	4
67	40	0	4	1	2	0	0	0	2	5
68	17	0	1	3	6	0	4	4	6	9
69	50	1	3	5	5	0	4	4	5	9
70	35	1	2	1	1	0	0	0	2	9
71	45	1	2	1	1	0	0	0	1	4
72	33	1	3	5	5	0	4	4	5	9
73	43	1	3	2	6	3	0	0	2	6
74	50	1	1	1	1	0	0	0	2	5
75	29	0	1	1	6	0	4	4	4	9
76	53	1	2	4	5	0	4	4	5	9
77	34	1	1	1	1	0	4	4	6	9
78	28	1	1	1	1	0	0	0	2	7
79	45	1	1	1	1	0	0	0	2	7
80	30	1	1	1	1	0	0	0	2	8
81	59	1	1	5	5	0	4	4	5	9
82	46	1	1	1	1	0	4	4	4	9
83	45	1	1	1	1	0	0	0	2	5
84	30	1	1	2	3	0	4	4	6	9
85	37	1	1	1	1	0	0	0	2	4
86	17	0	1	1	1	0	0	0	1	8
87	38	1	1	3	3	2	0	0	1	5
88	45	1	1	2	3	0	4	4	6	9
89	33	1	1	5	5	0	4	4	5	9
90	28	1	1	3	3	0	4	4	6	9
91	55	1	2	2	3	0	4	4	4	9
92	45	1	2	1	1	0	4	4	4	9
93	50	1	1	1	1	0	0	0	2	5
94	59	1	2	1	1	0	0	0	2	4
95	26	0	1	2	3	0	4	4	4	9
96	55	1	1	1	1	0	0	0	3	1
97	46	1	2	1	1	0	0	0	2	7
98	44	1	2	2	3	2	0	2	3	6
99	46	0	1	1	1	0	0	0	2	7
100	27	1	2	1	1	0	0	0	2	7
101	42	1	2	1	1	2	1	1	3	2

102	41	1	1	1	1	2	0	0	2	5
103	57	1	1	1	1	0	4	4	6	9
104	16	0	1	1	6	0	0	0	2	5
105	38	0	1	1	1	0	0	0	2	1
106	30	1	2	2	3	2	0	0	1	7
107	48	1	1	2	3	2	4	4	6	9
108	34	1	2	2	3	0	4	4	4	9
109	48	1	2	1	1	0	0	0	1	8
110	27	1	2	2	3	3	4	4	6	9
111	35	1	2	1	1	0	3	1	1	3
112	45	1	2	1	1	0	4	4	6	9
113	42	1	2	2	3	2	0	0	2	9
114	45	1	2	1	3	0	0	0	2	5
115	24	1	1	1	1	0	0	0	1	7
116	27	1	2	1	1	0	0	0	1	7
117	56	1	2	2	3	3	0	0	2	1
118	30	1	2	2	3	2	0	0	2	7
119	25	1	2	1	1	0	0	0	2	5
120	41	1	2	1	1	0	0	0	2	5
121	35	0	1	1	1	0	0	0	2	5
122	40	1	1	1	1	0	0	0	2	5
123	43	1	2	1	1	2	1	0	3	6
124	36	1	2	3	3	0	4	4	4	9
125	23	1	1	1	1	0	0	0	2	5
126	33	1	2	1	1	0	0	0	2	1
127	27	1	2	1	2	0	0	0	3	6
128	35	1	2	2	3	2	0	0	2	5
129	37	1	2	2	3	2	4	4	6	9
130	45	1	2	1	1	1	0	0	2	7
131	52	1	1	1	1	0	0	0	2	4
132	26	1	1	1	1	0	4	4	6	9
133	55	1	2	2	3	0	0	0	2	5
134	26	1	1	3	3	2	4	4	4	9
135	35	1	2	1	1	0	0	0	2	7
136	46	1	1	2	3	0	4	4	6	9
137	29	1	1	1	1	2	0	0	2	9
138	30	0	1	1	1	0	0	0	1	7
139	33	1	2	2	3	2	4	4	6	9
140	52	1	2	1	1	1	0	0	2	5
141	21	1	2	1	1	0	0	0	2	5
142	45	1	2	2	3	2	4	4	6	9
143	66	0	1	1	1	0	0	0	2	8

KEY TO MASTER CHART:

SEX:

MALE	**1**
FEMALE	**0**

REASONS FOR CATEGORY II:

RELAPSE	**1**
TREATMENT AFTER DEFAULT	**2**
FAILURE	**3**
OTHERS	**4**

COMPLIANCE:

REGULAR TREATMENT	**1**
DEFAULTED IN I P	**2**
DEFAULTED IN C P	**3**
DIED IN 1 P	**4**
DIED IN C P	**4**

OUTCOME AT THE END OF CATEGORY II:

CURED	**1**
COMPLETED	**2**
DEFAULTED	**3**
TRANSFERRED OUT	**4**
DIED	**5**
FAILURE	**6**

COMORBID ILLNESS:

DIABETIC	**1**
ALCHOHOLISM	**2**
HIV	**3**
NIL	**0**

PRESENT SPUTUM SMEAR:

NEGATIVE	**0**
ONE PLUS	**1**

TWO PLUS	**2**
THREE PLUS	**3**
NOT DONE	**4**

PRESENT SPUTUM CULTURE:

NEGATIVE	**0**
POSITIVE	**1**
CONTAMINATED	**2**
NOT DONE	**4**

PRESENT CLINICAL STATUS:

ASYMTOMATIC	**1**
INSIGNIFICANT SYMPTOMS	**2**
SIGNIFICANT SYMPTOMS	**3**
DIED DURING FOLLOW UP	**4**
DIED DURING TREATMENT	**5**
NOT TRACEABLE	**6**

PRESENT CHEST SKIAGRAM:

THIN WALLED CAVITY	**1**
THICK WALLED CAVITY	**2**
FLUFFY NODULAR SHADOWS	**3**
CALCIFIC NODULES	**4**
PARENCHYMAL FIBROSIS	**5**
MULTIPLE PATTERNS	**6**
PLEURAL THICKENING	**7**
NORMAL	**8**
NOT TAKEN	**9**