

CLINICAL RESEARCH



Studies Completed:

The long term status of sputum positive pulmonary tuberculosis patients successfully treated with short course chemotherapy

Background:

Information on the long-term clinical, radiological and bacteriological status of patients successfully treated with short course chemotherapy (SCC) regimens — both daily and intermittent — remains largely unknown. However, data on the long term follow up of patients treated with short course chemotherapy would be of great value while analyzing the long term impact of the disease and its treatment.

Aim:

To carry out a one time assessment of the clinical, bacteriological and radiological status including estimation of quality of life and pulmonary function of sputum positive pulmonary TB patients successfully treated with short course chemotherapy regimen at 15-20 years after completion of treatment.

Methodology:

All sputum positive pulmonary TB patients who were started on treatment during the period 1986-1990 at the centre and completed 60 months follow up, formed the study population.

In this prospective study, the patients were subject to the following investigations:

- (i) Detailed history regarding re-treatment taken for TB;
- (ii) Information collected on smoking, alcoholism, respiratory symptoms and co-morbid conditions like diabetes, hypertension, bronchial asthma, cardiac and renal problems;
- (iii) Clinical examination, X-ray chest – PA view, sputum examination by smear and culture for *M. tuberculosis*, urine examination for albumin, sugar, other relevant blood tests, pulmonary function test and ECG. Further, to assess the quality of life the St. Georges Respiratory Questionnaire and the WHO DASII Questionnaire were used.

Results:

Out of the 601 patients treated during 1986-1990, 364 were eligible for the study. This included 163 treated daily and 201 with an intermittent regimen. The mean period of long term follow-up was 16.5 years (range 15-18 yrs). Fig.1 gives the current status of the study population. Sixteen per cent migrated and as for the remaining patients, the coverage was 87 per cent.

Mortality:

Fifty two patients expired (14 per cent). The mean age of these patients was 50 years, and of them, five were females.



Re-treatment:

There were 25 patients (7 per cent) retreated for TB. Out of the 25 patients, 23 were re-treated for pulmonary TB and two for extra pulmonary TB (brain tuberculoma, TB lymphadenitis). The majority of these patients (i.e. 21 of them) were started on re-treatment at the centre after duration of 10 years from the initial treatment for pulmonary TB.

Profile of patients:

The mean age of the 198 patients was 46 years (range 27-73 years). There were 124 (63 per cent) males, among whom 62 (50 per cent) were smokers.

Clinical:

As many as 58 (29 per cent) patients had complaints such as cough or dysnoea, pertaining to the respiratory system. However, clinical signs and respiratory system examination was almost normal in 99 per cent of the patients.

Bacteriology:

Sputum smear negativity was seen in 193 (97 per cent) and culture negativity in 196 (99 per cent). Among the 5 who had positive smears, 3 were culture negative, while 2 of the patients' cultures, grew atypical mycobacteria, *M. kansasii*.

Radiology:

Among the 86 per cent of patients with abnormal chest x-ray, fibrosis alone was present in 62 (36 per cent); calcification alone in 41 (24 per cent). The features of both, fibrosis and calcification, was seen in 59 (35 per cent) of the patients. There were 28 (14 per cent) patients with a normal chest x-ray.

Radiological progress when compared with x-ray taken 15-20 years ago showed that 157 (79 per cent) patients had the same radiological pattern. Five (3 per cent) patients showed an improvement, which was marked by the decrease in the distribution and extent of lung involvement due to the disease. Eleven (6 per cent) patients had fresh lesions and they had respiratory complaints frequently in the past two years. Among them, 8 of them were smear and culture negative, while 3 were smear positive. Of these, 2 had positive cultures of *M. kansasii*. One patient had pericardial effusion.

Electrocardiogram (ECG):

ECG findings were normal in 160 (81 per cent) of the patients. Features suggestive of corpulmonale were observed in 21 (11 per cent) of the patients, with predominant findings of right arterial overload and right ventricular enlargement.

Spirometry:

Pulmonary function tests were performed in 148 patients, which showed that the lung function was normal in 57 (39 per cent) of them, while 47 (32 per cent) and 10 (7 per cent) showed restrictive and obstructive type of disease respectively. Combined (both restrictive and obstructive) type of disease pattern was observed in 34 (23 per cent).



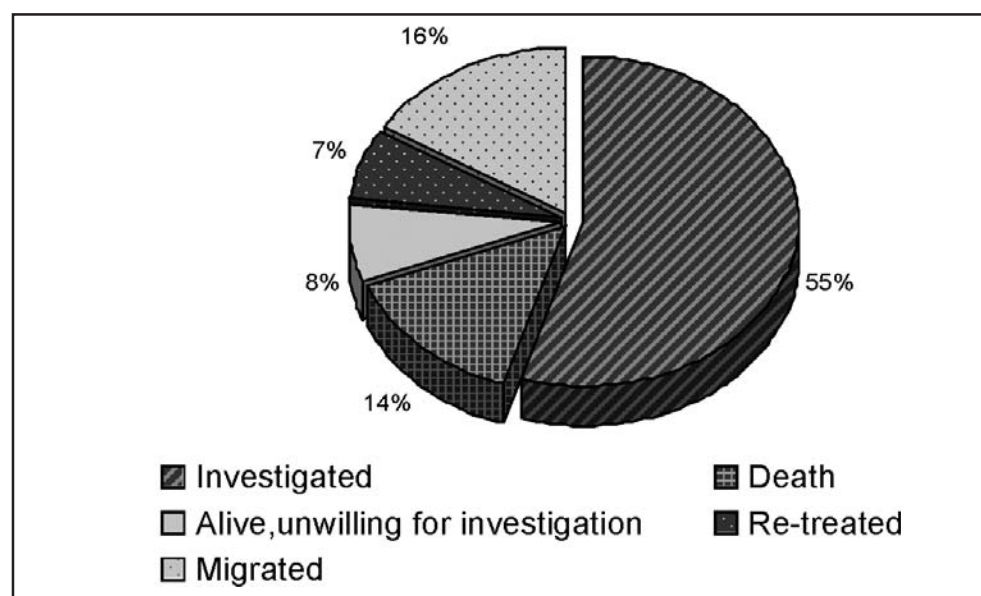
Males had significant lung function impairment as compared to females ($p < 0.001$). Among the males, lung function was interpreted as normal in 41 per cent, restrictive type in 20 per cent, obstructive type in 10 per cent, and combined type in 29 per cent. Lung function impairments were similar when it came to smokers and non-smokers.

Among the females, 34 per cent, 54 per cent and 12 per cent had normal lung function, restrictive and combined disease patterns respectively. None of them had an obstructive type of disease. Yet restrictive type of disease was observed more in females ($p = 0.01$). The data collected on the quality of life of these patients, is being analyzed.

Conclusion:

The study has shown that it is possible to get information on 84 per cent of the TB patients treated 15 to 20 years earlier. We observed that 71 per cent had no respiratory complaints and all investigated patients were culture negative for *M. tuberculosis*. Fourteen per cent had normal chest x-ray, while the remaining had residual lesions. The ECG evidence of cor pulmonale was present in 11 per cent. The lung function was normal in 39 per cent.

Fig.1: Current status of the cohort of pulmonary TB patients treated with short course chemotherapy 15 – 20 yrs ago



Studies in progress:

Study of the efficacy and tolerability of moxifloxacin and gatifloxacin containing regimens in the treatment of patients with sputum positive pulmonary TB

Background:

A randomized clinical trial carried out by TRC has demonstrated that patients with sputum-positive pulmonary TB, can successfully be treated with a four-month regimen that substituted ofloxacin (OFX) for ethambutol (EMB) in the four-drug intensive phase given daily (IJT 2002).



However, a similar regimen administered thrice weekly was less successful (TRC Annual Report 2003-04). Meanwhile, the newer generation of fluoroquinolones, moxifloxacin (MFX) and gatifloxacin (GFX), have shown to have more potent anti-mycobacterium activity compared to OFX. Therefore it was decided to study the efficacy and safety of thrice-weekly MFX and GFX regimens in the treatment of patients with smear-positive pulmonary TB. This was done in a randomized clinical trial.

Methods:

Newly diagnosed sputum smear-positive pulmonary TB patients residing in or around Chennai and Madurai, who fulfill the inclusion criteria are randomly allocated to one of the following three treatment regimens:

Regimen 1: 2GHRZ₃ / 2GHR₃. GFX, isoniazid (INH) and rifampicin (RMP) thrice weekly for four months with pyrazinamide (PZA) for the first two months.

Regimen 2: 2MHRZ₃ / 2MHR₃. MFX, INH and RMP thrice weekly for four months with PZA for the first two months.

Regimen 3: 2EHRZ₃/4HR₃ as a control regimen. INH and RMP thrice weekly for six months with EMB and PZA for the first two months.

It is proposed to admit 300 patients to each arm. The study is being conducted in Chennai and Madurai.

Results:

The study was started in May 2004 and 391 patients have been enrolled till April 2006. This includes 141 patients in regimen 1, 92 in regimen 2 and 158 in control regimen (Regimen 3). The study is ongoing.

Efficacy and safety of immunomodulator (*Mycobacterium w*) as an adjunct therapy in category II pulmonary TB

The immunomodulator containing *Mycobacterium w* was developed by the National Institute of Immunology, New Delhi in 1980. It has been found to be useful in the prevention of TB in experimental animals. A pilot study conducted to evaluate the role of *Mycobacterium w* in improving sputum conversion rate in pulmonary TB, showed that the conversion rate was faster when *Mycobacterium w* was added to the short course chemotherapy. Immunomodulators work against persistors, which may result in reducing the relapse rates. The addition of immunomodulator to chemotherapy is well tolerated and does not increase the adverse reactions to the therapy.

A double blinded, randomized, placebo controlled, multicentric clinical trial has been initiated by the Department of Science and Technology. This is being done with the object of studying the cure rate in Category II pulmonary TB patients after the addition of the *Mycobacterium w* vaccination to standard anti-TB drugs. The patients are randomly chosen to receive either the vaccine or placebo along with the standard category II RNTCP regimen. One hundred and twenty eight patients are proposed to be admitted to the trial. The study has begun in March 2006, and so far 3 patients have been enrolled.



Evaluation of chemotherapy regimens for TB in HIV infected persons (Funded by ICMR Task Force on HIV-TB)

Background:

The duration of anti-TB treatment among HIV positive patients with TB, is still a contentious issue. A six-month intermittent (3 times a week) regimen is the standard treatment for TB in RNTCP in India and many countries.

Aim:

1. To evaluate the efficacy of RNTCP treatment regimens among HIV patients infected with TB
2. To compare the efficacy of a six-month versus a nine-month intermittent anti-TB regimen among HIV positive patients with TB

Methodology:

This is an ongoing, prospective, randomized, controlled clinical trial.

Arm A: Six-month regimen 2EHRZ₃/4RH₃.

Arm B: Nine-month regimen 2EHRZ₃/7RH₃

The drug dosages are EMB: 1200 mg, INH: 600 mg, RMP: 450mg in patients with <60kg/600 mg >60 kg and PZA:1500 mg with Pyridoxine 10 mg), given thrice weekly.

All those HIV positive patients diagnosed with TB, based on sputum smear and culture or radiologically suggestive of TB, were included in the study. Randomization was done by a permuted block scheme and stratified by a CD4 cell count (<200 & ≥200 cells / cu.mm), and smear grading (0, 1+ & 2+, 3+). Treatment was fully supervised for the first two months, then brought down to once a week. The intensive phase was extended by four weeks if sputum smears were positive at the end of second month. Follow up of patients was done every month with clinical examination, sputum AFB smear and culture for *M. tuberculosis*. Chest radiograph and CD4 counts were done at baseline, during the second month and at the end of the therapy. None of the patients were on antiretroviral therapy (ART) at the time of intake. End points of the study are sputum culture negativity at the end of treatment and relapses during follow-up. Intent to treat analysis and on treatment analysis, will be performed.

Results:

Up to March 2006, 382 patients were admitted to the study. Forty two patients were treated with the RNTCP Cat II regimen and separately analyzed. Six patients were initially excluded. Out of the 334 patients, 230 had pulmonary TB confirmed by sputum culture. Fifteen patients were excluded for treatment analysis (13 had less than 80 per cent of drug dosage and there were two early deaths).

Among the 215 patients included in the analysis, 110 were allocated to regimen A (six months) and 105 were allocated to regimen B (nine months). The baseline demographic and other characteristics of the patients admitted to the two treatment arms are given in Table 1.



Seventy seven per cent of the patients had smear positivity. The median CD4 cell counts were 132 and 167 cells / cu.mm in both the regimens. The mean age of the patients was 35 years. The CD4 count was under 200 cells / cu.mm in 66 per cent of the patients suggesting severe immunosuppression. At the end of the intensive phase, sputum smear conversion rate was 61 per cent while culture conversion was 87 per cent. Among patients available at the end of treatment (n=172), the culture negativity at the end of treatment was 98 per cent and 95 per cent in the two regimens respectively (Fig.2). Overall, there was an 83 per cent favourable response in regimen A and 76 per cent in regimen B (Table 2). Change of treatment due to bacteriologic or clinical deterioration (failure) and deaths in the two arms are shown.

Drug susceptibility pattern of the organisms isolated from pre treatment sputum culture, showed that 86 per cent of the organisms isolated were susceptible to all anti-TB drugs, and that resistance to both INH and RMP (MDR-TB) was seen in 2 per cent of the patients. Occurrence of adverse reactions was similar in both groups. A follow up is ongoing to study the relapse rates.

Table 1: Baseline characteristics (n=215)

	Regimen A 6m (n=110)	Regimen B 9m (n=105)
Males %	84.5	74.3
Mean Age (Years)	34.1	34.8
Mean Weight (kg)	43.4	43.1
Sputum smear positivity %	76	78

Fig.2: Smear and Culture Results at the end of treatment (n=172)

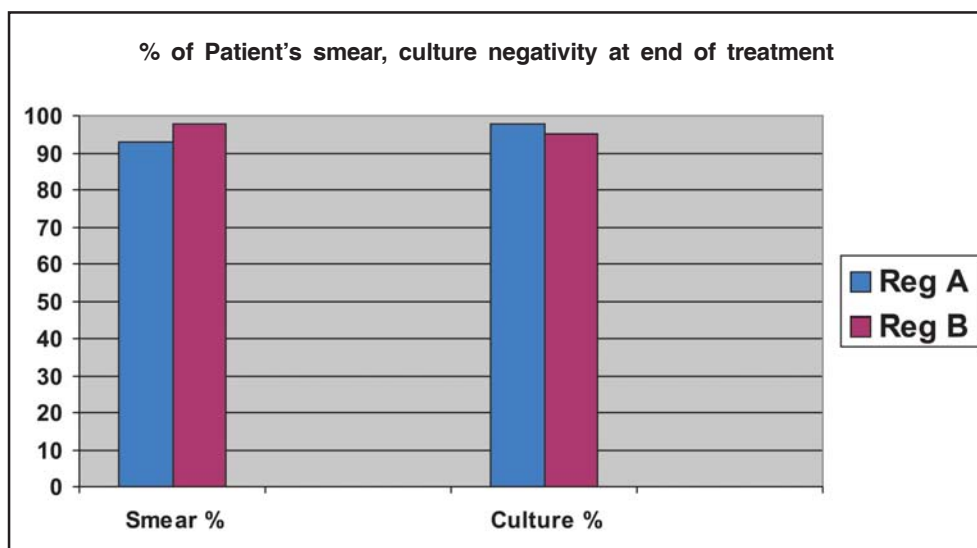


Table 2: Outcome on treatment

Outcome		Regimen A (n=109)	Regimen B (n=102)
Favourable		91 (83%)	78 (76%)
	Rx changed	13 + 1 (Toxicity)	14
Unfavourable	Total deaths (with active TB)	4 (1)	10 (3)



Preventive Therapy for TB in HIV-infected persons (Funded by USAID)

Background:

Persons co-infected with *M. tuberculosis* and HIV, have a 5-8 per cent annual risk and a 50 per cent or greater lifetime risk of developing active TB.

The increased risk of developing TB among the HIV-infected prompted a need to consider institution of preventive measures, so that HIV positive patients are enabled to avoid the risk of progression to clinical TB.

Aims:

The study is being done to compare the efficacy of 2 regimens (INH 300 mg daily for 3 years versus EMB 800 mg with INH 300 mg daily for 6 months) in reducing the incidence of TB and mortality among HIV-infected persons.

Methods:

HIV positive persons greater than 15 years without evidence of active TB and meeting eligibility criteria were randomly selected to receive either of the 2 regimens (INH 300 mg daily for three years or EMB 800 mg with INH 300 mg daily for 6 months, stratification based on tuberculin test reaction of 5mm). Patients collected the drugs for self-administration once in 15 days and surprise home visits were done to check the pill count and also collect urine for acetyl INH measurements. All patients were given Pyridoxine 10 mg daily. Clinical examination was done every 3 months, while complete investigations including chest X-ray, sputum examination and CD4, CD8 counts done every 6 months, and at any time if clinical deterioration was present. Follow up is for 3 years and end points are development of TB and death.

Results:

Seven hundred and eleven patients have been admitted to the study up to March 2006. Seventy nine were excluded for various reasons (pre treatment culture positive-29, treatment less than 80 per cent - 41, treatment changed within 1 month - 8, early deaths within 1 month - 1). Out of the 632 patients in analysis, 317 were allocated to 6 months of EMB-INH daily and 315 to 36 months of INH daily.

Table 3 shows the baseline characteristics of patients admitted to both arms. Among patients who had completed 36 months, (as on March 31, 2006), 108 in EH regimen and 103 in INH regimen, TB developed in 16 and 12 patients respectively. The follow-up is in progress.



Table 3: Baseline characteristics

	6EH (n=317)		36H (n=315)	
	Mean \pm S.D.	Range	Mean \pm S.D.	Range
Age (Years)	29.8 \pm 7.2	18 - 57	30.3 \pm 7.0	18 - 60
Weight (kgs)	50.7 \pm 9.8	30 - 79	49.3 \pm 10.2	30 - 97
Mx-mm	7.8 \pm 9.6	0 - 40	7.4 \pm 9.3	0 - 35
	Median	25-75 Percentile	Median	25-75 Percentile
CD4	337	208-529	330	194-475

Exercise limitation in patients treated for Pulmonary TB

Background:

The long-term functional sequelae of pulmonary TB are not well described. Pulmonary TB is a wasting disease, which also affects skeletal muscle mass, limiting manual work capacity.

Aim:

To measure maximal work capacity and cardio respiratory functions in patients treated for smear positive pulmonary TB with standard short course chemotherapeutic regimens. This data would be compared to that obtained from healthy age and sex-matched controls.

Methods:

Oxygen consumption (VO₂ max), carbon dioxide production (VCO₂), minute ventilation (VE), heart rate (HR) and workload were measured with a progressive incremental exercise test using the Jaeger oxycon-pro metabolic cart and a treadmill. Oxygen saturation was monitored with a pulse oxymeter. Sixty four patients who had completed a course of anti-TB therapy and 72 sex, age and height matched controls from the same ethnic group were studied.

Result:

The mean height of patients and controls was similar. But weight ($p < 0.02$) and BMI ($P < 0.01$) were significantly lower among TB patients. The metabolic and ventilatory parameters at peak exercise in patients and controls are shown in Table 4. Male TB patients had significantly lower aerobic capacity and minute ventilation at maximal exercise and achieved lower peak heart rate. When corrected for body weight, the maximal oxygen consumption was similar. The peak heart rate achieved was lower among patients, though all achieved an RER > 1 , indicating they had exercised maximally. Further, 20 per cent of patients and three per cent controls, had desaturation at maximal exercise.



Conclusion:

Patients treated for pulmonary TB have exercise limitation as demonstrated by lower peak heart rate, VO₂ max and maximal ventilation. Males are affected more than females. A significant proportion of patients desaturated at maximum exercise. These findings suggest that the work capacity of patients treated for pulmonary TB is significantly impaired and this could affect their quality of life.

Table 4: Cardio-respiratory parameters at maximal exercise in controls and TB related patients

	PATIENTS				CONTROLS			
	Females (n=29)		Males (n=35)		Females (n=35)		Males (n=69)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Load (Watts)	123**	54.7	204**	103.1	196	57.0	311	81.2
VO ₂ (ml/min)	1237	326.1	1872**	562.8	1410	389.2	2449	591.5
VCO ₂ (ml/min)	1345**	397.7	2066**	788.7	1678	508.0	2923	782.7
VE (L/min)	40*	11.3	60**	24.1	46	11.7	79	22.7
HR (/min)	158	25.8	160	35.9	171	16.0	171	32.4
RER	1.089**	0.15	1.0834**	0.18	1.186	0.133	1.191	0.12
VE/VO ₂	31		30		31		32	
VE/VCO ₂	28.*		28		27		27	
ETO ₂ (%)	16.07*	0.8	15.65*	1.1	16.2	0.8	16.1	0.9
ETCO ₂ (%)	5.19*	0.67	5.6	0.95	5.4	0.93	5.5	0.74
**P<0.01	compared to controls							
*P<0.05								

Nutritional assessment and supplementation in HIV-infected patients with and without TB (Funded by World Food Programme, New Delhi)

Background:

Tuberculosis and HIV infection are known to be separately associated with malnutrition. TB might worsen the course of HIV associated immunosuppression and therefore reduce the rate of survival among HIV-infected subjects. Despite the high prevalence of TB and malnutrition among HIV seropositive patients, data concerning the nutritional status of TB/HIV co infected patients in developing countries like India, is scarce.

Aims:

1. To document the occurrence of baseline macro and micronutrient deficiencies in HIV infected individuals in south India and correlate that with their immune status.
2. To test the efficacy of an intervention in the form of a nutritional supplement and quantitate changes in nutritional, biochemical and immunological parameters over a period of 6 months.



Methods:

The study was started in July 2003. HIV infected persons without TB and those who had completed therapy for TB, formed the study population. A baseline clinical, anthropometric and dietary assessment along with laboratory investigations (hematology, biochemistry and immunology) was done for all patients at the time of enrollment to the study.

Patients were divided into two groups: The first group, the intervention group, received a high calorie, high protein supplement called "Indiamix" supplied by the World Food Programme, New Delhi. Each patient had to consume 100gms per day, which supplies an additional 400 calories and 15gms of protein. The other group, the control group, did not receive the nutritional supplement for the first six months. Patients were followed up clinically (including dietary assessment and anthropometric measurement) every three months and hematological, biochemical and immunological investigations, were repeated every six months. Body composition was measured by BIA and fat content and fat-free mass calculated. The study has been completed and data analysis is ongoing.

Interim results:

Six hundred and sixty two patients were enrolled into the study. Of these, 551 patients received the supplement (cases) and 111 did not receive any supplement for a period of 6 months. The latter group served as controls for the study. At the end of a 6-month follow up, data is available for 288 patients, that is, 83 controls and 214 cases. Baseline characteristics like age, sex, socioeconomic status, body weight and BMI, were comparable between the two groups. Ninety per cent of the patients were from the lower socio-economic strata with the mean age being 31.5 ± 6 years. Table 5 shows the changes in various parameters after 6 months of nutritional supplementation.

Conclusion:

After 12 months of nutritional supplementation, there was a significant increase in weight, BMI, mid arm circumference, hemoglobin and CD4 cell count in the supplemented group compared to controls. Maximum improvement was observed in the lowest CD4 cell strata. The study findings suggest that nutritional supplementation can help to improve nutritional status and delay disease progression in HIV positive persons.

Table 5: Changes in nutritional parameters after 6 months of supplementation

Subjects (n=214)	BL	12 months	p value
Mean \pm SD			
Weight	49.9 \pm 9.73	51.2 \pm 10.35	<0.001
BMI	20.6 \pm 3.59	21.1. \pm 3.75	<0.001
MAC	23.9 \pm 3.28	24.7 \pm 3.71	<0.001
n=195			
Hb	11.6 \pm 1.69	12.2 \pm 1.68	0.001
CD4	376 \pm 234	422 \pm 251	0.001
Controls (n=78)	BL	6 months	p value
Weight	51.9 \pm 12.88	52.0 \pm 12.17	NS
BMI	21.28 \pm 4.77	21.35 \pm 4.39	NS
MAC	24.1 \pm 4.39	24.4 \pm 4.58	NS
Hemoglobin	12.1 \pm 1.69	12.1 \pm 1.57	NS
CD4 cell counts	448 \pm 278	396 \pm 286	0.033

MAC - Mid arm circumference