

## 2. CLINICAL RESEARCH

### Ongoing studies:

#### **Efficacy and safety of immunomodulator (*Mycobacterium W*) as an adjunct therapy in category II pulmonary tuberculosis**

#### **Background:**

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 tuberculosis (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.

#### **Aim:**

- To study the cure rate in Category II pulmonary TB patients after the addition of the *Mycobacterium w* vaccination to standard anti-TB drugs

#### **Methods:**

This study is planned as a double blinded, randomized, placebo controlled multicentric clinical trial. It is being initiated by the Department of Science and Technology. The patients are randomly chosen to receive either the vaccine or placebo along with the standard category II Revised National TB Control Programme (RNTCP) regimen. One hundred and twenty eight patients are proposed to be admitted to the trial.

#### **Results:**

The study was initiated in March 2006, and in one year period 57 patients were screened and 30 were included in the study (18 relapses, 4 failures and 8 treatment defaulters of Category I). Vaccine acceptability has been good among these patients. During the intensive treatment phase, 4 patients developed serious adverse reactions (2 rifampicin (R) - induced renal failure and 2 hepatotoxicity). This study is on going.

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## **Evaluation of chemotherapy regimens for tuberculosis in HIV infected persons**

### **Background:**

The duration of anti-TB treatment (ATT) among HIV positive patients with TB is still a contentious issue. A 6-month intermittent (3 times/week) regimen is the standard treatment for TB in the RNTCP in India and many countries.

### **Aims:**

- To evaluate the efficacy of RNTCP treatment regimens among HIV patients infected with TB
- To compare the efficacy of a 6-month versus a 9-month intermittent anti-TB regimen among HIV positive patients with TB with respect to reduction in failure and relapses

### **Methods:**

This study was planned as a prospective randomized controlled clinical trial to compare the efficacy of a 6 months' regimen (Regimen A-2EHRZ<sub>3</sub>/4RH<sub>3</sub>) with 9 months' regimen (Regimen B – 2EHRZ<sub>3</sub>/7RH<sub>3</sub>). The dosages of ATT were as follows: ethambutol (E) 1200 mg, isoniazid (H) 600 mg, R 450 mg in patients with < 60 kg and 600 mg in patients with body weight ≥ 60 kg and pyrazinamide (Z) 1500 mg with pyridoxine 10 mg, given thrice weekly.

All HIV positive patients with pulmonary TB were diagnosed based on sputum smear and culture and lymphnodal TB by FNAC/Biopsy. Patients with exudative effusion suggestive of TB or miliary TB were included in the study. Randomization was done by permuted block scheme and stratified by CD4 cell count (< 200 & ≥ 200 cells/cu.mm), and smear grading (0, 1+ & 2+, 3+). Treatment was fully supervised for the first 2 months, then once a week. The intensive phase was extended by 4 weeks if sputum smears were positive at the end of 2<sup>nd</sup> month. Patients were followed up every month with clinical examination, sputum AFB smear and culture for *M. tuberculosis*. Chest radiograph and CD4 counts were done at baseline, 2<sup>nd</sup> month and at the end of therapy. None of the patients were on antiretroviral therapy (ART) during the treatment period. End points of the study were sputum culture negativity at the

end of treatment and relapses during follow-up for sputum culture positive cases and clinical improvement with radiological clearance for sputum culture negative cases. On -treatment analysis was performed.

**Results:**

**Study population:** Of the 334 receiving the study regimens, 65 were excluded in the efficacy analysis [2-early deaths, 14 cases who had confirmed non-tuberculous cause of death, 2-primary multidrug resistant-TB (MDR-TB), 17 cases -<80% treatment taken, 29 cases who had no definite evidence of TB and 1 had regimen changed due to need of ART containing nevirapine (NVP)]. Of the remaining 269 cases, 140 received regimen A and 129 received regimen B. Two hundred and one out of 269 cases had sputum culture confirmed pulmonary TB, of which 106 received regimen A and 95 received regimen B. Of the remaining 68 cases, 16 had TB lymphadenitis, 8 had TB pleural effusion, 4 had miliary TB (without culture confirmation) and 40 had smear and culture negative pulmonary TB with persistent X-ray findings and respiratory symptoms. The baseline characteristics of study population are given in table 2.1.

**Table 1.1:** Baseline Characteristics of study participants (n=273)

	Regimen A – 6M n = 140	Regimen B – 9M n = 129
Males (%)	81	74
Age (Years)	34 ± 7	34 ± 8
Weight (kg)	44 ± 7	44 ± 9
Sputum smear (% positive)	58%	57%
Sputum culture (% positive)	76%	74%
Median CD4	165 (range 82 – 308)	173 (range 90 – 295)

**Outcome:**

At the end of treatment, 126 (90%) in regimen A and 111 (86%) in regimen B had a favourable response. There was no statistically significant difference between the outcomes of two regimens. There were 8 and 11 bacteriological failures and 4 and 3 clinical deterioration in regimen A and regimen B respectively. One case in regimen A and 3 cases in regimen B died during treatment due to TB.

Regimen was changed due to toxicity to ATT in one patient in regimen A and 1 patient required NVP- containing ART along with change of ATT in regimen B.

The toxicity profile showed that 18% of patients had minor toxicity, 3 cases had ATT temporarily withheld due to jaundice which was successfully reintroduced. Only one had a permanent termination of the regimen due to cutaneous toxicity to ATT. Drug toxicity was similar in both the groups.

The results suggest that the 6-month and 9-month anti-TB regimens had similar efficacy, and addition of 3 months of ATT in the 9-month regimen as compared to 6 month regimen had no added benefit.

**Follow Up:** Follow up is ongoing to find out the relapse rate. Restriction fragment length polymorphism (RFLP) is being done to differentiate true relapses from re-infection.

(PI-Dr.Soumya Swaminathan; soumyas@trchennai.in; Funded by ICMR Task Force on HIV-TB)

## **Preventive therapy for TB in HIV infected individuals**

### **Background:**

Available evidence indicates that preventive therapy for TB reduces the frequency of active TB in HIV-positive subjects by about 50% to 60%. Protection is greatest in adults with a positive tuberculin skin test (TST) (70% reduction in incidence, mortality reduced by 25%). Ideal duration of preventive therapy, especially in TB-endemic countries is not known.

### **Aims:**

- To study the efficacy of two different preventive therapy regimens in HIV infected persons in reducing the incidence of TB and overall mortality
- To find out if a long duration/life long regimen with H daily is superior to a 6-month regimen of H and E

### **Outcome Measures:**

1. Development of pulmonary or extra-pulmonary TB
2. Death due to TB

### **Study Design:**

The study was conducted as a two-armed prospective randomized clinical trial among HIV- positive patients without active TB.

The treatment regimens were as follows:

1. E (800 mg) and H (300 mg) daily for six months, self-administered, collected once in fifteen days
2. H (300 mg) daily for 3 years (in lieu of life long prophylaxis) self administered, collected once in fifteen days

Subjects in both study groups received 10 mg of pyridoxine daily during treatment. Patients were followed up for a period of three years from the time of admission to the study. Clinical examination and relevant investigations were done every three months. Patients suspected to have TB at any time were fully investigated and treated appropriately. Any positive culture was subjected to drug susceptibility tests (DST). The cause was ascertained in all cases of death.

**Results:**

Of the 711 patients admitted to the study from March 2001- Sep 2005, 635 were eligible for analysis. The mean age, body weight, CD4 cell count and Mantoux were comparable in both the groups (Table 2.2). One hundred and seventy eight patients from the H arm and 175 from the EH arm have completed 36 months of follow-up as of March 2007. Thirty four patients in the H arm and 39 in the EH arm have been initiated on ART, because of falling CD4 cell counts. Eighteen patients in the EH arm and 18 in the H group developed active TB giving a breakdown rate of 1.76 / 100 person years respectively. Most of the breakdown in both the arms had occurred in the first 12 months. Number of deaths in the H arm were 21 (2.06 / 100 person years) as compared to 29 (2.84 / 100 person years) in the EH arm. Majority of the deaths had occurred between 12–24 months. The toxicity pattern was also similar in both the groups. In only one patient in the H arm, the treatment had to be terminated because of severe jaundice.

**Table 2.2: Baseline Characteristics**

	EH 6 MONTHS		H 36 MONTHS	
	n = 320		n = 315	
	Mean±S.D	Range	Mean±S.D	Range
Age (yrs)	29 ± 7	18 -57	30 ± 6	18 - 30
Wt (kgs)	51± 10	32 – 79	50 ± 11	30 - 97
CD4 (cells/cu.mm)	337±257	35-1125	330±224	12-1247
Mx (mm)	9 ± 10	0.0-40.0	8 ± 9	0.0-35.0

The interim findings suggest that the 6 months of EH regimen is as effective as 3 years of H in preventing TB among HIV-infected persons. Patients with lower CD4 cell counts are at higher risk of TB breakdown and death.

(PI: Dr.Soumya Swaminathan; soumyas@trcchennai.in. Funding: USAID)

**A clinical trial to study the efficacy of two different once-daily anti-retroviral regimens along with anti-TB treatment, in patients with HIV-1 and TB**

**Background:**

People with HIV infection are at increased risk for developing TB. Though most patients respond well to ATT, they develop other opportunistic infections and deteriorate rapidly. Recurrence of TB is also more frequent. Timely use of ART co-administered with ATT could reduce these complications thereby improving mortality and long term outcome.

**Aims:**

**Primary:**

- To compare the efficacy and safety of two different once-daily ART regimen of didanosine + lamivudine (3TC) + efavirenz (EFV)/Nevirapine along with standard ATT in patients with HIV and TB with CD4< 250 cells/cu.mm.

**Secondary:**

- To compare the efficacy of ART given under partial supervision (observed three times a week) with unsupervised treatment (once a month supply)

**Methods:**

The study is a prospective randomized controlled clinical trial with patients given standard ATT (2EHRZ<sub>3</sub>/4HR<sub>3</sub>) as DOTS and randomized to receive ART regimen containing either NVP or EFV along with ddl and 3TC at the end of intensive phase of ATT. ART is given as DOTS for 6 months (8 months after start of ATT) and then patients are randomized if virologically suppressed to either DOTS or NON-DOTS arm. Recruitment of patients to the study is being done at Chennai, Madurai and Vellore. The primary outcome measure is suppression of viral load after 24 weeks of ART. A secondary outcome variable is to study the utility of DOT in this setting vs. self-administered ART at the end of 24 months. Pharmacokinetic studies are being planned concurrently to study the interaction between R and NVP/EFV.

Two hundred and seventy one patients have been screened (182 males and 89 females), out of which 81 have been recruited (63 males and 18 females) up to March 2007, 41 randomized to EFV regimen and 33 to NVP regimen. The mean weight and age of patients on admission was 42 (SD-8.6) and 35 (SD-7.4) respectively. The median CD4 cell counts of the study subjects was 84 cells (range: 3-232), the median viral load was 2,33, 000 copies/ml. The study is in progress.

(PI: Dr.Soumya Swaminathan; soumyas@trchennai.in. Funding: National AIDS Control Organization, India)