

## CLINICAL RESEARCH

### Completed studies

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

(Funded by ICMR Task Force on HIV-TB)

#### Background

The duration of anti-tuberculosis treatment (ATT) among Human Immuno Deficiency Virus (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 Revised National Tuberculosis Control Programme (RNTCP) in India.

#### Aim

- To evaluate the efficacy of RNTCP Category-I treatment regimen (2EHRZ<sub>3</sub>/4RH<sub>3</sub>) among HIV-positive patients infected with TB and compare it with a 9-month intermittent anti-TB regimen with respect to reduction in failure and relapses

#### Methods

This was a randomized, controlled clinical trial with two arms, a 6-month regimen 2EHRZ<sub>3</sub>/4RH<sub>3</sub> and a 9-month regimen 2EHRZ<sub>3</sub>/7RH<sub>3</sub>. E: (ethambutol) 1200 mg, H: (isoniazid) 600 mg, R: (rifampicin) 450 mg in patients with <60kg/600 mg > 60 kg and Z: (pyrazinamide) 1500 mg with pyridoxine 10 mg, given thrice weekly throughout.

All HIV-positive patients diagnosed with pulmonary or extrapulmonary TB based on sputum smear and culture, fine needle aspiration cytology/biopsy/biochemical investigations of pleural fluid (PF) were included in the study if they fulfilled other eligibility criteria. Randomization was done in permuted block of four and stratified by CD4 cell count (<200 & >200 cells/cu.mm), and smear grading (0, 1+, 2+ and 3+). Treatment was fully supervised for the first 2 months and once a week thereafter. In cases of sputum smears being positive at the end of second month, the intensive phase was extended by four weeks. Patients were followed up every month with clinical examination, sputum acid fast bacilli (AFB) smear and culture for *M. tuberculosis*. Chest radiograph and CD4 counts were

performed at baseline, second 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 up to 36 months follow-up (clinical and/or bacteriological). Intent to treat and on-treatment analysis was performed.

## Results

**Study population:** Three hundred and thirty four patients were admitted and randomized to the study regimens. There were 7 exclusions in the efficacy analysis (4 - primary multi-drug resistant (MDR), 2 had regimen changed due to need of ART containing nevirapine and 1 patient had culture positive for *M.kansasii*). Out of the remaining 327 cases, 167 were allocated to 6-month regimen and 160 to the 9-month regimen. Two hundred and twenty seven of these patients had sputum culture confirmed TB: 117 were allocated to 6-month regimen and 103 to 9-month regimen. Seventy three cases were culture negative for pulmonary TB with clinico-radiological features including miliary and mediastinal TB and 27 cases had extrapulmonary TB.

The baseline characteristics of study population are given in table 1.

**Table 1:** Baseline characteristics

	Regimen 6M N = 167	Regimen 9M N = 160
Males (%)	78	74
Mean age (years) +range	33.7 ( 17 - 60)	34.3 ( 18 - 63)
Mean weight (kg)+ range	44.4 (27.6 - 65)	44.3 ( 18.5 - 73.7)
Sputum smear (% positive)	54	54
Sputum culture (% positive)	69	68
Median CD4 (cells/cu.mm) (inter-quartile range)	152 (82 – 304)	167 (83 – 270)

**Outcome:** At the end of treatment, 138 (83%) in 6-month regimen and 122 (77%) in 9-month regimen had a favourable response; the difference was non significant. There were 8 & 11 bacteriological failures and 4 & 5 patients with

clinical deterioration in the 6-month and 9-month regimens respectively. One case in regimen 6 and 3 cases in regimen 9 died due to TB during treatment. The regimen was changed due to toxicity to anti-TB treatment (ATT) in one patient in each of the regimens, and one patient in 9-month regimen required nevirapine-containing ART along with change of ATT.

The toxicity profile showed that 22 % of patients had minor toxicity, 3 patients had ATT temporarily withheld due to jaundice, for whom ATT was successfully reintroduced later. Only two patients had a permanent change in the regimen due to cutaneous toxicity to ATT. Drug toxicity was similar in both the groups.

**Baseline characteristics and outcome in sputum culture positive pulmonary TB:** Out of the 212 sputum culture confirmed pulmonary TB in the efficacy analysis (those who received more than 80% drug doses), 54% had smear positivity at start of treatment. Two-thirds of the patients had severe immunosuppression as evidenced by CD4 counts < 200 cells/cu.mm. Eighty nine percent of patients had pretreatment culture with *M. tuberculosis* sensitive to all first line anti-TB drugs. At the end of intensive phase, culture conversion was observed in 87% of the patients. Outcome at the end of treatment is given in table 2.

**Table 2:** Outcome in sputum culture positive patients

Outcome	6-month regimen (N=109)	9-month regimen (N=103 )
Favourable response, N (%)	93 (85%)	80 (78%)
Unfavourable responses, N	16	23
(i) Bacteriological failure	8	11
(ii) Clinical deterioration	3	1
(iii) TB death	1	3
(iv) Non-TB death	3	8
(v) Others	1	0

In patients with culture positive TB and declared cured, 19 (20%) in 6-month regimen and 7 (9%) in 9-month regimen had a bacteriological recurrence within

36 months from the time of starting treatment ( $p < 0.05$ ). Deaths during follow-up were similar in both the groups. The study results suggest that even though the 6-month and 9-month anti-TB regimens had similar efficacy at the end of treatment, there was a significant reduction in bacteriological recurrences with longer regimen of ATT. However, the 9-month regimen did not improve survival at 36 months, in the setting of limited access to ART.

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## **Preventive therapy for TB among HIV-infected individuals (Funded by United States Agency for International Development)**

### **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 testing (TST) (with 70% reduction in incidence and mortality reduced by 25%). However, the ideal duration of preventive therapy especially in TB-endemic countries is not known.

### **Aim**

- To study the efficacy of two different preventive therapy regimens [6 months of ethambutol (EMB) & isoniazid (INH) and 3 years of INH] in HIV-infected persons in reducing the incidence of TB and overall mortality

### **Outcome measures**

- Development of pulmonary or extrapulmonary TB
- Death due to TB

### **Study design**

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

The treatment regimens were as follows:

- EMB (800 mg) and INH (300 mg) daily for six months, self-administered, collected once in 15 days
- INH (300 mg) daily for 3 years (in lieu of lifelong prophylaxis) self-administered, collected once in 15 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 completely investigated and treated appropriately. All positive cultures were subjected to drug susceptibility tests. Attempts were made to ascertain the cause in all cases of death.

### **Results**

Of the 712 patients admitted to the study from March, 2001 – September, 2005, 632 were eligible for analysis. The baseline characteristics of the study patients are shown in table 3. The mean age, body weight, CD4 cell count and mantoux test reaction were comparable in both the groups.

A total of 247 patients from the INH arm and 283 from the EMB/INH arm have completed 36 months of follow-up as of 31<sup>st</sup> March, 2008.

Twenty patients in the EMB/INH arm and 15 in the INH group developed active TB giving a breakdown rate of 1.76 / 100 person years. Most of the breakdown in both the arms occurred in the first 12 months. There were 30 deaths in the EMB/INH arm while 23 deaths had occurred in patients who were on INH.

The toxicity pattern in both the groups was similar. Only one patient in the INH arm had termination of treatment because of severe jaundice.

The interim findings suggest that the 6 month - EMB/INH regimen is as effective as 3 years of INH in preventing TB among HIV-infected persons. Patients with lower CD4 cell counts were at higher risk of TB breakdown and death.

**Table 3: Baseline characteristics**

	EMB/INH – 6 months		INH - 36 months	
	n = 318		n = 314	
	Mean±S.D	Range	Mean±S.D	Range
Age (years)	29 ± 7	18 - 57	30 ± 6	18 - 30
Wt (kg)	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

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**A clinical trial to study the efficacy of two different once-daily antiretroviral regimens along with anti-TB treatment in patients with HIV-1 and TB  
(Funded by National AIDS Control Organization)**

**Background**

This randomized clinical trial was designed to study the efficacy and safety of two different once-daily antiretroviral (ARV) regimens along with ATT in HIV-infected TB patients. The specific aim was to study a once-daily regimen of didanosine + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP) along with standard ATT in patients with HIV and TB with CD4 cell counts < 250 cells/cu.mm. The primary outcome measure was suppression of viral load (< 400 copies/ml) after 24 weeks of ART. A secondary outcome was to study the utility of directly observed treatment (DOT) in this setting vs. self-administered ART. Pharmacokinetic studies were also carried out concurrently to study the interaction between rifampicin (RMP) and NVP/EFV as well as monitoring for development of drug resistance.

The pilot study was initiated in October, 2005 with recruitment at Chennai, Madurai and Vellore. Fifty seven patients (43 males and 14 females) were screened, of whom 20 were recruited to the study. These 20 patients consisted

of 17 males and 3 females, their age ranging between 22–44 years. Following the pilot study which lasted for one year, intake to the main trial was initiated in May, 2006 and was stopped in June, 2008 as per recommendation of the data safety and monitoring board (DSMB). As of March 31, 2008, 564 patients had been screened for the study at 5 centres (including 3 sites in Chennai, 1 in Vellore and 1 in Madurai). One hundred and thirty patients were admitted to the study (patient demographics in table 4). All patients were randomized at the end of intensive phase (2 months) of ATT: 70 patients received the EFV regimen and 57 the NVP regimen, 3 patients died before randomization. Seventy nine patients had pulmonary TB while the rest had extrapulmonary TB (pleural effusion, TB lymph node). Response to ATT was good with 87.5 & 96% of patients respectively becoming culture negative at the end of 2 & 6 months. Overall, cure/completion rate was 85%. Only one patient had adverse reaction to an anti-TB drug which required a change of treatment.

At the end of 6 months of ART, of the 70 patients randomized to receive EFV, 14 were still on treatment, 47 had completed 6 months of ART with viral load < 400 copies/ml, 5 had virologic failure, one patient died and one defaulted. In the NVP regimen, 37 of 57 patients had completed 6 months of ART with viral load < 400 copies/ml, 9 had virologic failure, 5 died, 3 defaulted and 2 were still on treatment. There were 8 serious adverse events equally distributed in both the 2 arms.

Overall, the immunological response to treatment was satisfactory with good improvement in CD4 cell counts (table 5).

The DSMB met on December 15, 2007 (for first interim analysis) and recommended that intake to the NVP regimen be withheld till further analysis. This was in view of the higher failure rates and deaths in the NVP arm compared to the EFV arm.

The second interim analysis was done and presented to the DSMB on June 14, 2008. The DSMB recommended that intake to the study be stopped and the data analysed and disseminated.

**Table 4:** Patient demographics

	Efavirenz (n= 70)	Nevirapine (n= 57)
Sex (M, F)	55, 15	44, 13
Age (years)*	35 ± 7.5	38 ± 7.8
Height (cm)*	161 ± 8.4	159 ± 7.1
Weight (kg)*	42.7 ± 8.5	41.6 ± 7.3
CD4 (cells/cu.mm)*	85 ± 60	83 ± 58
Viral load (copies /ml)**	3,62,000 (41,575 - 7,50,000)	2,82,000 (1,28,500 – 6,49,500)
Body Mass Index*	16.3 ± 2.7 (9.4 – 23.8)	16.4 ± 2.4 (10.8 – 22.4)

\* Mean ± SD

\*\* Median (range)

**Table 5:** Change in CD4 cell counts during ART

	Baseline	0 week	1 month	4 month	6 month
Efavirenz	95 ± 58	125 ± 84	255 ± 141	275 ± 125	325 ± 173
Nevirapine	87 ± 60	132 ± 82	238 ± 163	247 ± 166	283 ± 169

The above values are Mean ± SD

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## **Innate and adaptive immunity in children starting antiretroviral drugs in India**

**(Funded by Indo-US JWG Maternal and Child Health (NIH and ICMR))**

### **Background**

Currently, CD4 counts are the mainstay of immunologic assessment for HIV-infected adults and children on which treatment decisions are made. This study was aimed to identify other immunologic markers that can be predictive of disease outcomes in perinatally HIV-infected children.

## Aims

- To determine the relationship of naïve CD4 T-cells with total CD4 T-cells at study entry and with disease progression
- To determine the relationship of CD8<sup>+</sup> T-cells expressing CD127 (IL7R $\alpha$ ), with disease progression
- To determine the relationship of dendritic cells (numbers and function) with immunologic status

## Methods

Sixty ART naïve HIV-positive children (28 males/32 females) were screened and recruited to the study. Age ranged from 9 months to 13 years with median body mass index (BMI) of 14.5 (6.4–24.1). CD4 counts in the study subjects ranged between 131–2396 (median=728) cells/cu.mm and CD8 counts between 573–6086 (median=1585) cells/cu.mm. At each visit, all children were examined clinically and venous blood samples were collected for immunological and other assessments as per the following schedule:

### Schedule of evaluation

	Weeks				
	0	12	24	36	48
Clinical	✓	✓	✓	✓	✓
CBC	✓	✓	✓	✓	✓
Routine biochemical tests	✓		✓		✓
HIV RNA	✓		✓		✓
CD4 / CD8	✓	✓	✓	✓	✓
*Special immunology	✓	✓	✓	✓	✓
* Naïve CD4, T-cell receptor gene rearrangement excision circles, IL7R $\alpha$ in CD8 T-cells, DR <sup>+</sup> CD38 <sup>+</sup> CD8 T-cells, Dendritic cell phenotype and function					

The children were followed up to 48 weeks, after which they are referred to the nearest ART centre for management.

## Results

The number of patients enrolled in the study and their follow-up status as of March, 2008 is given in table 6.

**Table 6:** Details of patient enrollment and follow-up

	Baseline	1 <sup>st</sup> follow-up (12 weeks)	2 <sup>nd</sup> follow-up (24 weeks)	3 <sup>rd</sup> follow-up (36 weeks)	4 <sup>th</sup> follow-up (48 weeks)
No. of children	60	56	48	36	25

Nine children had been started on ART while 51 were not; all were monitored regularly as per treatment guidelines and protocol.

The major findings of the study were that naïve ( $CD45RA^+CD62L^+$ ) cells were greater in CD4 T-cells as compared to CD8 T-cells. A significant increase in the naïve CD4 T-cell population was observed in all the patients who were on ART. Expression of immune activation markers ( $CD38^+HLA-DR^+$ ) was greater in CD8 T-cells and inversely correlated with CD4 counts. A decrease in the immune activation markers was observed in all the patients who were on ART.

Expression of CD127, (IL-7R $\alpha$ ), a marker for memory cells, was reduced on CD8 T-cells and its expression correlated directly with CD4%. Although, the expression of CD127 on CD4<sup>+</sup> T-cells was low, it was not significant. Significant increase in the expression of CD127 was observed in ART-treated individuals.

Reduced number of dendritic cell (DC) subsets (mDC and pDC) was observed in HIV-infected children who were not on ART. We observed significantly greater expression of CD80 and CD83 in unstimulated compared to resiquimod stimulated whole blood. Their pDC subsets were responsive to stimulation by the TLR7/8 agonist resiquimod to produce IFN- $\gamma$  and TNF- $\alpha$ . Interestingly pDC TNF- $\alpha$  production was highly significant and inversely correlated to immune activation status in children with normal CD4 counts.

## Conclusion

In summary, immunologic assessments indicate that loss of naïve CD4/CD8 T-cells and CD127<sup>+</sup> CD8 T-cells is associated with immune activation. This may

prove useful as a marker of disease severity or recovery in HIV-infected children initiating ART. pDC functional deterioration was not apparent in relation to CD4 counts, but did correlate inversely with immune activation.

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## **Ongoing studies**

### **Randomised clinical trial to study the efficacy and tolerability of 3- and 4-month regimens containing moxifloxacin in the treatment of patients with sputum smear and culture positive pulmonary TB**

**(PROVCTRI/2008/091/000024)**

#### **Background**

Earlier clinical trials by the Tuberculosis Research Centre (TRC) have shown that while a 4-month daily regimen which included ofloxacin (OFX) in the intensive phase was successful in the treatment of sputum positive pulmonary TB, 4-month thrice weekly regimens with OFX, gatifloxacin or moxifloxacin (MFX) were less successful with high relapse rates. Following publication of the TRC clinical trial demonstrating the efficacy of an OFX-containing regimen in shortening TB treatment to 4 months (Indian Journal of Tuberculosis, 2002), there has been a global interest in the role of quinolones in the primary treatment of TB. MFX is now considered the most effective of quinolones for treatment of TB due to its many unique qualities. The TRC is now conducting a randomized clinical trial to study the efficacy and safety of 3- and 4-month MFX containing regimens for treatment of patients with sputum positive pulmonary TB. Newly diagnosed smear positive pulmonary TB patients are randomly allocated to 3-month or 4-month MFX regimens or a control 6-month regimen. The regimens being tested are as follows:

#### **Regimens**

3 RHZEM (RMP, INH, Pyrazinamide (PZA), EMB and MFX daily for three months) - treatment duration 3 months;

2 RHZEM/ 2 RHM (RMP, INH, PZA, EMB and MFX daily for two months followed by RMP, INH and MFX daily for two months) - treatment duration 4 months;

2 RHZEM/ 2 RHM thrice weekly (RMP, INH, PZA, EMB and MFX daily for two months followed by RMP, INH and MFX thrice weekly for two months) - treatment duration 4 months;

2 RHZEM/ 2 RHEM thrice weekly (RMP, INH, PZA, EMB and MFX daily for two months followed by RMP, INH, EMB and MFX thrice weekly for two months) - treatment duration 4 months;

2 RHZE thrice weekly/ 4 RH thrice weekly (RMP, INH, PZA and EMB thrice weekly for two months followed by RMP and INH thrice weekly for four months) - treatment duration 6 months.

The study is being conducted in Chennai and Madurai. The estimated sample size for this trial is 1650 patients; so far 200 patients have been enrolled to the trial.

The study is registered in the clinical trials registry of India. (PROVCTRI/2008/091/000024)

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### **Efficacy and safety of immunomodulator (*Mycobacterium W*) as an adjunct therapy in Category-II pulmonary TB**

**(Funded by Department of Biotechnology, India)**

#### **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 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 adverse reactions to the therapy.

#### **Aim**

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

## **Methods**

This study was being initiated by the Department of Science and Technology and was planned as a double blind, randomized, placebo controlled multicentric clinical trial. The patients were randomly chosen to receive either the vaccine or placebo along with the standard Category-II RNTCP regimen. Though it was initially proposed to admit 128 patients to the study, this number was restricted to 60 patients by the funding agency.

## **Results**

The study was initiated in March, 2006. In the two year period till March, 2008, 268 patients were registered, 115 screened and 59 enrolled into the study. Vaccine acceptability has been good among these patients. Of the 59 enrolled, 28 have completed treatment and are on follow up, 19 are still on treatment, 4 defaulted for treatment - 2 in the intensive phase and 2 in the continuation phase, 4 developed serious adverse events – 2 renal and 2 hepatic. Four patients required change of chemotherapy – 2 due to multidrug resistance, 1 due to clinical complication (hydropneumothorax), and one due to pregnancy. Two patients who had hepatic adverse events also had change of chemotherapy. This study is ongoing.

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## **Management of patients who fail on Category-II regimen of the TB control programme**

### **Background**

TRC has been doing the drug resistance surveillance of patients treated with RNTCP regimens in one TB unit in Tiruvallur district in Tamil Nadu, south India (1999 to 2005). In that survey, it was observed that there were 52 patients who failed to Category-II regimen. The drug susceptibility test (DST) results showed that 32% had multi-drug resistant TB (MDR-TB), 26% had drug-resistant organisms but were not MDR-TB (resistant to INH/Sm/SmINH/EMB), 29% harboured fully susceptible organisms, and in 13% there was no growth in the culture.

Directly observed treatment short course (DOTS) plus using standardized Category-IV regimen is being implemented in India in a phased manner. There is no report, on the feasibility and effectiveness and development of adverse reactions to the Category-IV regimen.

Similarly there is no guideline on the management of patients who fail on Category-II regimen but are non-MDR.

### **Aims**

- To assess the feasibility, effectiveness and development of adverse reactions of DOTS plus regimen compared to modified DOTS plus regimen
- To assess the treatment outcome of a re-treatment regimen for patients who fail on Category-II regimen and not having MDR-TB based on drug sensitivity test

### **Methods**

#### **Management of patients with MDR-TB**

**Eligibility criteria:** A patient whose TB is due to bacilli resistant to at least INH and RMP with or without resistance to other drugs will be eligible for the study. At least one sputum smear examined within 10 days of starting treatment should be positive for AFB.

**Treatment regimens:** Patients have been randomly allocated to one of the following regimens based on the drug resistance pattern (stratification based on resistance to first-line drugs alone or resistance to one or more of any second-line drug along with MDR-TB).

Regimen I: 6 (9) (kanamycin, OFX, ethionamide, PZA, EMB & cycloserine) 18 (OFX, ethionamide, EMB & cycloseine)

Regimen II: 6 (9) kanamycin thrice-weekly, (OFX, ethionamide, PZA, EMB & cycloserine) 18 (OFX, ethionamide, EMB & cycloserine)

**Regimen I:** It is a standardized treatment regimen approved by RNTCP (Category-IV regimen - DOTS-Plus) for the treatment of MDR-TB. It consists of

an intensive phase of 6 drugs for a period of 6-9 months followed by a continuation phase of 18 months of 4 drugs, administered daily.

**Regimen II:** Similar to regimen I but kanamycin given three days a week instead of daily administration.

### **Treatment duration**

All patients from Tiruvallur district are being hospitalized for the first 2 - 4 weeks of treatment. Later, they get discharged, with a 7-day supply of drugs including kanamycin. Treatment is being arranged from the nearest Primary Health Centre (PHC) as DOT. The drugs are supplied from TRC on a monthly basis. All patients from Chennai Corporation are being given treatment as DOT from TRC or at the subcenters by TRC staff.

### **Sample size:**

The estimated sample size for the study is 75 patients to each regimen.

### **Clinical and laboratory investigations:**

Before starting treatment patients undergo detailed history elicitation for previous second line ATT, chest X-ray, haemogram, liver and kidney function tests, pregnancy test for female patients, three sputum examinations for smear and culture for first and second line anti-TB drugs and enzyme linked immunosorbent assay (ELISA) for HIV antibodies.

After starting treatment, patients are being followed up every month and investigations repeated periodically. Patients are being monitored closely for adverse reactions.

### **Management of patients not having MDR-TB**

#### **Regimens**

Patients are allocated to one of the two regimens (stratification based on sensitivity to INH).

Regimen I: 6 kanamycin (RMP, EMB, PZA) 3 (RMP, EMB, PZA)

Regimen II: 6 kanamycin (RMP, EMB, PZA, INH) 3 (RMP, EMB, PZA, INH)

## **Sample size**

The estimated sample size for the study is 75 patients to each regimen.

**Outcome measures:** The following outcome measures will be analysed:

- Sputum smear conversion at 3 and 6 months of treatment
- Sputum culture conversion at 3 and 6 months
- Favourable bacteriological response at the end of treatment
- Adverse reactions to anti-TB drugs

Intake to the study was initiated in September, 2007 and upto 31<sup>st</sup> March, 2008, 24 patients have been recruited (17 in MDR and 5 in non MDR).

Recruitment of patients to the study is in progress.

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## **Utility of two antibiotic algorithms and repeat sputum smear microscopy to improve the efficiency of diagnosis in smear negative TB**

### **Background**

The diagnosis of smear negative pulmonary TB is vital, as such patients are likely to break down to smear positive cases if left untreated. A breakdown rate of about 28% in six months and 40% in two years has been reported. Importantly, nearly half of smear negative cases who require treatment develop active disease within the first three months.

### **Aims**

#### **Primary objectives**

- To assess the utility of two antibiotic algorithms to improve the efficiency of diagnosis in smear negative TB
- To study the role of repeat sputum microscopy in chest symptomatics with persistent symptoms after a course of antibiotics

#### **Secondary objectives**

- To study the proportion of TB patients among this group (confirmed by culture) and to examine the correlation of culture results with chest X-ray findings

- To study the etiological profile of respiratory infections and their sensitivity pattern and appropriateness of antibiotic algorithm

### **Methods**

Patients referred with cough of  $\geq 3$  weeks and 3 smears negative for AFB are registered. At TRC, the patients undergo 3 sputum examinations for AFB by smear and culture, and a chest X-ray is taken. They are randomly allocated to one of the following regimens for 10 days:

- Co-trimoxazole (sulphamethaxazole-800 mg, trimethoprim-160 mg) twice daily for 10 days.
- Doxycycline 100 mg twice a day on first day then once a day for 4 days followed by amoxicillin 500 mg three times a day for 5 days

After completion of the course of antibiotics, chest X-ray and sputum examinations are repeated, and patients are assessed for persistence of symptoms. If repeat sputum is negative by smear, and if X-ray is suggestive of TB they are started on Category-III regimen. If chest X-ray is abnormal but not suggestive of TB they are followed up for 6 months with monthly sputum examination.

All the patients are being reviewed with culture results. It is proposed to admit 700 patients to each antibiotic arm. Till 31<sup>st</sup> March 2008, 180 patients have been recruited.

Intake of patients to the study is in progress.

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### **Evaluation of a diagnostic algorithm for HIV-positive TB suspects who are initially smear negative**

**(In collaboration with NARI, Pune)**

#### **Background**

In the RNTCP, diagnosis of TB is based on sputum smear examinations – for patients with three negative smears, the response to a course of antibiotics is used to make a diagnosis of smear negative TB. In HIV-infected patients with active TB disease, sputum smears are more likely to be negative for AFB by

smear microscopy. The RNTCP bases diagnosis of TB on sputum smear examinations, and treatment consists of a course of antibiotics.

### **Aim**

- To determine the utility of initial chest X-ray and sputum culture (LJ solid media) in the diagnostic algorithm for TB among HIV-infected initially smear negative TB suspects

### **Methods**

This is a multicentric (Govt. Hospital for Thoracic Medicine, Tambaram, National AIDS Research Institute, Pune and TRC, Chennai) prospective study enrolling HIV-infected patients with suspected TB disease. Those suspects who are smear negative on initial sputum examination have a chest X-ray and sputum culture performed, receive a course of broad spectrum antibiotics, and are reviewed with a repeat chest X-ray after 15 days.

### **Results**

Up March, 2008 182 patients in Chennai and 68 patients in Pune have been enrolled. Interim analysis has been done on 114 patients (87 males, 27 females). Their mean age and body weight (SD) were 36 (9) years and 47 (9) kg respectively. The median CD4 cell counts were 191cells/cu.mm. Eighty one percent of the patients had cough and breathlessness for >3 weeks, 60% had fever for >2 weeks and 89% had weight loss. Twenty one patients (19%) had a positive TB culture initially. Seventy six patients (62%) had an abnormal chest X-ray, of whom 25% had a positive initial culture. Of the 76 patients with an abnormal chest X-ray, 34 (45%) demonstrated clinical and radiographic improvement after treatment with antibiotics.

Recruitment of patients to the study is in progress.

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## **Changes in HIV viral load in patients undergoing treatment for filarial infection**

**(Collaborative study with National Institute of Health, USA)**

### **Background**

This is a case-control study to determine whether treatment with DEC/Albendazole reduces viral load in patients with HIV and filarial co-infection. The total sample size required for this study is 138 (HIV/filarial–46, HIV alone–92). Two groups of patients are being recruited to the study. The first group comprises of patients with HIV and filarial infection (detected by serum antigen test). The second, or control group consists of patients with HIV infection, but not filariasis, matched for age, gender, HIV viral load and CD4 count. Patient recruitment is being done in TRC and YRG Care, Chennai. Screening of patients for this study started in May, 2007 at TRC; up to March, 2008, 156 patients were screened, of whom 23 (positives–7, controls–16) patients have been recruited to the study.

The study is ongoing.

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