

Clinical response of newly diagnosed HIV seropositive & seronegative pulmonary tuberculosis patients with the RNTCP Short Course regimen in Pune, India

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Received January 27, 2010

Background & objectives: In the Revised National Tuberculosis Control Programme (RNTCP) in India prior to 2005, TB patients were offered standard DOTS regimens without knowledge of HIV status. Consequently such patients did not receive anti-retroviral therapy (ART) and the influence of concomitant HIV infection on the outcome of anti-tuberculosis treatment remained undetermined. This study was conducted to determine the results of treatment of HIV seropositive pulmonary tuberculosis patients with the RNTCP (DOTS) regimens under the programme in comparison with HIV negative patients prior to the availability of free ART in India.

Methods: Between September 2000 and July 2006, 283 newly diagnosed pulmonary TB patients were enrolled in the study at the TB Outpatient Department at the Talera Hospital in the Pimpri Chinchwad Municipal Corporation area at Pune (Maharashtra); they included 121 HIV seropositive and 162 HIV seronegative patients. They were treated for tuberculosis as per the RNTCP in India. This study was predominantly conducted in the period before the free ART become available in Pune.

Results: At the end of 6 months of anti-TB treatment, 62 per cent of the HIV seropositive and 92 per cent of the HIV negative smear negative patients completed treatment and were asymptomatic; among smear positive patients, 70 per cent of the HIV-seropositive and 81 per cent of HIV seronegative pulmonary TB patients were cured. Considering the results in the smear positive and smear negative cases together, treatment success rates were substantially lower in HIV positive patients than in HIV negative patients, (66% vs 85%). Further, 29 per cent of HIV seropositive and 1 per cent of the HIV seronegative patients expired during treatment. During the entire period of 30 months, including 6 months of treatment and 24 months of follow up, 61 (51%) of 121 HIV positive patients died; correspondingly there were 6 (4%) deaths among HIV negative patients.

Interpretation & conclusions: The HIV seropositive TB patients responded poorly to the RNTCP regimens as evidenced by lower success rates with chemotherapy and high mortality rates during treatment and follow up. There is a need to streamline the identification and management of HIV associated TB patients in the programme with provision of ART to achieve high cure rates for TB, reducing mortality rates and ensuring a better quality of life.

Key words Anti-retroviral therapy - HIV - HIV-TB - RNTCP - seropositive - sputum - tuberculosis

Tuberculosis is a major public health problem globally as well as regionally. In Asia, the prevalence of HIV infection in TB patients has been lower than that reported from sub-Saharan Africa¹. In urban areas in India, a series of referral center surveys from the late 1990's reported an increasing prevalence of HIV among TB patients²⁻¹². Raizada *et al*¹² provided information from community based surveys on tuberculosis patients in different regions of India and showed a HIV prevalence varying from 1 to 13.8 per cent in 15 different districts in India¹². In India, more than 50 per cent of HIV seropositive subjects have been shown to develop active tuberculosis at least once in their lifetime^{13,14}. Thus, managing HIV associated TB could be a problem in areas where HIV prevalence is high.

In the Revised National Tuberculosis Control Programme (RNTCP) in India, the target of 85 per cent cure rate has been attained. A recent report indicates a success rate of 87 per cent in 2009¹⁵. This, however, is a mean of results achieved throughout the country with a HIV prevalence of 0.29 per cent¹⁶. The distribution of HIV infection is uneven and there are six States which have HIV prevalence over 1 per cent. In such areas, the prevalence of HIV infection in TB patients may be high, which could in turn affect the efficacy of the RNTCP regimen.

In the TB Control Programme in India, routine screening for HIV infection was not being carried out in tuberculosis patients till recently. Hence, many patients were being treated for tuberculosis under programme conditions without knowledge of the presence or absence of concurrent HIV infection. However, in high HIV prevalence States, there is a provision for routine referral of all TB patients for voluntary HIV-counselling and testing.

The current RNTCP regimens in India are highly effective in the management of tuberculosis patients without HIV infection. There was insufficient information about their efficacy in HIV associated TB. Hence, the Indian Council of Medical Research (ICMR), New Delhi, commissioned two Task Force studies in Pune and Chennai to determine the efficacy of the directly observed intermittent short course RNTCP regimens in pulmonary tuberculosis patients having concurrent HIV infection. The present study reports on the outcome of the study conducted in Pune.

Material & Methods

This prospective observational study was undertaken at the Chest Clinic in Talera Hospital located in the Pimpri Chinchwad area of Pune. This clinic serves as the District TB Centre (DTC) for the Pimpri Chinchwad Municipal Corporation (PCMC) area under the Revised National Tuberculosis Control Programme of India. The DTC at Talera Hospital has a good record of implementation of the RNTCP and is located in an area with a high prevalence of HIV infection. Between 11 to 31 per cent of the new TB patients attending the Talera Clinic had concurrent HIV infection, similar to that reported earlier from other TB clinics in the Pune region¹⁷.

The study was initiated after getting approvals from the institutional Ethics Committee at the National AIDS Research Institute (NARI). Newly diagnosed pulmonary tuberculosis patients were tested for presence of HIV infection after informed consent was obtained. Subjects with or without HIV infection who were willing to participate in the study were enrolled, after obtaining written consent, between September 2000 and July 2006 when the required target for enrollment in each arm of the study was attained. These patients had never been treated for TB or had taken anti-tuberculosis drugs for less than one month. After enrollment, they were treated with the RNTCP regimen for 6 to 7 months and were followed up for a period of two years after the completion of their treatment for pulmonary tuberculosis with periodic visits at three monthly intervals. Sputum examination was carried out at the 2nd, 4th and 6th month as required by RNTCP. All HIV seropositive pulmonary tuberculosis cases were treated with Category I regimen, while HIV seronegative patients were treated with either Category I or Category III regimens as per RNTCP guidelines. During the period of anti-TB treatment, if the subject failed to turn up for treatment, suitable action was taken as described in the RNTCP to ensure regularity in anti-TB treatment. At the time of the initiation of the study, free antiretroviral therapy was not yet available in India. Whenever a death occurred in the hospital, the hospital records were reviewed for the cause of the death. However, if the death occurred outside the hospital setting, a verbal autopsy was carried out by discussions with the subject's relatives or friends.

Diagnosis of active pulmonary tuberculosis: Individuals with a history of cough of 3 wk duration or more and not responding to routine line of management for

upper respiratory tract infection were advised to give three sputum samples (usually two spot and one early morning collection) for sputum smear examination for acid fast bacilli (AFB) using the Ziehl-Nielsen Method and the smears were graded as per WHO standards¹⁸.

Smear positive pulmonary tuberculosis patients were diagnosed using the following criteria as per the RNTCP guidelines: (i) Two or three smears positive for AFB and (ii) One sputum smear positive for AFB with radiographic abnormalities consistent with active pulmonary tuberculosis. Smear negative pulmonary tuberculosis was diagnosed if three sputum smears were negative for AFB but evidence of radiographic abnormalities of active tuberculosis was present after two weeks of antibiotic treatment for routine bacterial infections of the respiratory tract¹⁹.

Detection of HIV infection: All patients were given pre-test counselling and tested for anti-HIV antibodies by enzyme-linked immunosorbent assay (ELISA) (Detect HIVMC, Biochem Immunosystems Inc., Canada) after obtaining written informed consent. The reactivity in ELISA was confirmed by a rapid test (HIVTRI-DOT, Biotech Inc., India). After the HIV antibody test results were available, post test counselling was provided to all the pulmonary tuberculosis patients tested.

Inclusion and exclusion criteria: Patients were eligible for enrollment in the study if they were aged 18 yr or more, had newly diagnosed pulmonary TB, had no history of previous treatment for TB, had knowledge of their HIV status, resided within 20 km of study site, assessed to be cooperative and willing for DOTS therapy as judged by counselor, had no major complications of HIV disease like encephalopathy, renal or hepatic disease, malignancy or any end stage disease and did not have any medical condition that might interfere with the management of the pulmonary tuberculosis like diabetes, convulsions, serious cardiac or renal disease. Since the study protocol required a follow up period for two years after completion of the anti-TB treatment, the study subject should have been willing to come for follow up for a period of two years after the anti-TB treatment had been completed.

Pre-enrollment assessment and investigations: The patients were admitted under RNTCP. After confirming the presence of pulmonary tuberculosis, pretest counselling was carried out and after obtaining consent, blood was collected for HIV testing.

Regimens used for the study participants: The patients were routinely treated as a part of the RNTCP, using

DOTS strategy. All HIV seropositive pulmonary tuberculosis patients were treated with the category I anti-TB regimen.

All HIV seronegative smear positive TB patients received category I regimen while the smear negative patients were treated with the category III regimens as per the guidelines of the RNTCP.

The patients were treated with an initial intensive phase lasting for 2 months followed by a continuation phase, which lasted for 4 months. In the intensive phase, three to four anti-TB drugs were administered thrice weekly depending on the category of treatment prescribed; all the thrice weekly doses were given under direct observation. In the continuation phase, the number of anti-TB drugs administered was reduced to two and only the first dose of the week was given under direct supervision while the remaining two doses in the week were self administered. All the drugs were administered thrice a week in the following doses (mg): isoniazid (600), rifampicin (450, 600 if weight more than 60 kg), pyrazinamide (1500), ethambutol (1200).

Patients who failed on the initial treatment with category I or category III regimens or who had a bacteriological relapse were treated with the category II regimen.

Investigations during treatment and follow up: Sputum smear examination was done on two specimens each at 2, 4 and 6 months of anti-TB treatment. Radiologic examination was carried out at 0, 2 and at 6 or 7 months. CD4 counts were determined in a majority of the patients. To determine the degree of immune-suppression in the enrolled patients, the CD4 counts were estimated in freshly collected blood in EDTA containing vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) Fifty μ L of whole blood samples were stained with 20 μ l of liquid antibody reagent (MultiTEST CD3 FITC, CD8 PE, CD45 PerCP and CD4 APC, Cat no.340491, Becton Dickinson, USA) and mixed with the reference beads (TruCOUNT tubes, Cat No: 340334, Becton Dickinson). After incubation for 15 min the RBCs were lysed and the tubes were acquired on the FACSCalibur using the automated MultiSET software (Becton Dickinson, USA). The absolute CD4 counts were expressed as cells/ μ l³.

Free ART was not available for the HIV seropositive patients in Pune till January 2005. Subjects enrolled after January 2005 were referred to the ART center at Sassoon General Hospital, Pune, for free ART. During follow up of the subjects, if there was clinical evidence

of any opportunistic infection, the subject was admitted at Talera Hospital for investigations and treatment of the opportunistic infection.

Deaths: Deaths occurring during the study period were analyzed for all enrolled subjects separately during the period of treatment (0 to 6 months) and during the subsequent follow up period of 7 to 30 months.

Response to treatment: Depending on the response to treatment, the study subjects were classified as cured, completed treatment, failure cases, defaulters or those transferred out to other districts based on the RNTCP definitions¹⁹.

Follow up after completion of treatment: After the completion of TB treatment, subjects were followed up at 3 monthly intervals for up to two years and if symptoms and signs of recurrence of tuberculosis occurred, they were investigated with sputum AFB smear examination and chest radiograph. Radiographic examination of the chest was carried out once a year during the 24 months of follow. If a relapse or recurrence of tuberculosis was confirmed, the subjects were retreated with the category II RNTCP regimen.

Sample size: The sample size of 60 was chosen so that at least 50 evaluable subjects would be available in each of the two HIV positive arms. The enrollment of HIV negative TB patients was made concurrently till the desired number of HIV positive patients had been admitted.

The four arms in the study were HIV+ve sputum AFB+ve; HIV+ve sputum AFB-ve; HIV-ve sputum AFB+ve; and HIV-ve sputum AFB-ve.

Analysis of data was carried out using the SPSS software Version 14.0.

Results

In all, 283 subjects were enrolled, including 121 HIV seropositive and 162 HIV seronegative patients with pulmonary tuberculosis. Sixty (50%) of the 121 HIV seropositive patients and 113 (70%) of the 162

HIV seronegative patients had sputum smears positive for AFB (Table I).

The patients ranged from 18 to 60 yr with 102 (84%) of the 121 HIV+ve patients and 133 (82%) of the 162 HIV negative patients being in the age group of 21 to 40 yr.

Outcome after 6 months of anti-TB treatment: At the end of 6 months of treatment, among smear negative patients, 62 per cent of the 61 HIV seropositive and 92 per cent of the 49 HIV negative patients completed treatment and were asymptomatic; among smear positive patients, 42 (70%) of the 60 HIV-seropositive and 92 (81%) of 113 HIV seronegative pulmonary TB patients were cured (Table II). Considering the results of HIV smear positive and smear negative patients together, nine (7.4%) of the 121 HIV seropositive and 18 (11.1%) of the 162 HIV seronegative patients defaulted on anti-TB treatment. Treatment success rates were substantially lower in HIV positive patients. Thus, 66 per cent (80 of 121) of the HIV seropositive and 85 per cent (137 of 162) of the HIV seronegative patients had a favourable response to treatment ($P<0.0005$). Of those who were AFB smear positive at the initiation of anti-TB treatment, only one HIV seronegative TB patient was smear positive at the end of treatment and none was smear positive at the end of treatment in the HIV seropositive TB group of patients.

Mortality rates were significantly higher in HIV positive patients. Thus, 24 per cent (29 of 121) HIV seropositive and 1 per cent (2 of 162) HIV seronegative tuberculosis patients expired during treatment ($P<0.001$). Except for one HIV seropositive tuberculosis patient, who died due to non-TB causes, all other patients had active tuberculosis at the time of death. Of the 29 HIV infected patients who died, 10 expired in the first month of treatment. None of the HIV seropositive tuberculosis patients received anti-retroviral therapy since free ART was not available for HIV/TB patients in Pune prior to 2005, and in the initial stages of the ART programme, ART drugs were available only to a limited extent.

Table I. Gender distribution of the HIV seropositive and HIV seronegative tuberculosis patients

Sex	HIV negative		HIV positive		Total
	Sputum AFB +ve	Sputum AFB -ve	Sputum AFB+ve	Sputum AFB-ve	
Male	83	43	47	53	226
Female	30	6	13	8	57
Total	113	49	60	61	283

Table II. Treatment outcome at end of anti-TB treatment (6 months)

Treatment outcome	HIV negative		HIV positive		Total
	Sputum AFB +ve	Sputum AFB -ve	Sputum AFB+ve	Sputum AFB-ve	
Favourable response					
Cured	92	0	42	0	134
Treatment completed	0	45	0	38	83
Unfavourable response					
Expired	0	2	10	19	31
Treatment failure	3	0	2	0	5
Defaulted	16	2	5	4	27
Transferred out	2	0	1	0	3
Total	113	49	60	61	283

The status of patients at 30 months: Of the 162 HIV seronegative tuberculosis patients, two died before completion of anti-TB treatment. Of the remaining 160 subjects, four expired, of whom 3 deaths were due to tuberculosis and 1 due to non-TB causes. Among 121 HIV seropositive tuberculosis patients, 29 expired before the completion of the anti-TB treatment. Of the remaining 92 who were alive at the end of 6 months of anti-TB treatment, 32 died during the follow up period, 14 due to tuberculosis, 7 due to AIDS related causes other than tuberculosis and 11 due to unknown reasons (Table III).

Overall, in the 162 HIV seronegative tuberculosis patients, there were 6 (4%) deaths (5 TB, 1 non-TB). In the 121 HIV seropositive tuberculosis patients, there were 61 (51%) deaths (43 TB, 18 non-TB). The differences in mortality between the HIV negative and positive groups were significant ($P < 0.001$).

CD4 counts: The mean CD4 counts in HIV seropositive tuberculosis patients was significantly lower than in HIV negative patients ($P < 0.001$) (Table IV). It is seen that many HIV positive patients had moderate or severe immunosuppression as reflected by the low CD4 counts. Thus 82 per cent of the seropositive patients had CD4 counts of 350 cells/ μ l or less compared with 8 per cent of the seronegative patients ($P < 0.001$).

Eleven seronegative and 2 seropositive patients who defaulted during treatment were excluded from the analysis of the relationship between initial CD4 count and death occurring during the period of treatment (0-6 months) (Table V). Among seronegative patients with CD4 counts, only 1 of 102 died, with an initial CD4 count in the range 200 to 230 cells/ μ l. In contrast, 17 of 18 seropositive patients who died, had CD4 counts of less than 350, including 15 who had counts less than 200 cells/ μ l. The mean CD4 counts in those who

Table III. Status of the enrolled patients at 30 months

Status	HIV Seronegative	HIV Seropositive
	Healthy / symptom free	127
TB deaths <1 month	1	19
1 – 6 months	1	10
7 – 30 months	3	14
Non-TB death (including AIDS)	1	18
Recurrences / relapses	7	2
Transferred out	2	3
Defaulter / lost to follow up	20	6
Total	162	121

Table IV. Pre-treatment CD4 counts in HIV+ve and HIV-ve TB patients

CD4 counts (cells/ μ l)	HIV -ve (n=113)	HIV+ve (n=91)
>500	78	3
351 – 500	26	13
200 – 350	8	17
<200	1	58
Overall mean \pm SD	660 \pm 269	181 \pm 165*

* $P < 0.001$ compared to HIV-ve group

expired during treatment was 111 \pm 118 cells/ μ l. In HIV seropositive subjects who remained alive at the end of anti-TB treatment, the mean CD4 count was 199 \pm 132 cells/ μ l before starting anti-TB treatment and was 299 \pm 199 at end of anti-TB treatment.

Discussion

The thrice weekly category I regimen has had a consistently high cure rate of over 85 per cent in the treatment of sputum positive pulmonary TB cases in India²⁰. In the study area of Talera, the success rate

Table V. Deaths during treatment related to initial CD4 counts

Pre-treatment CD4 counts (Cells/ μ l)	HIV seronegative (n=102)		HIV seropositive (n=89)	
	Total	Died	Total	Died
>500	68	0	3	0
351 – 500	25	0	13	1
200 – 350	8	1	16	2
<200	1	0	57	15

(13 patients who defaulted during treatment have been excluded)

of 92 per cent achieved in HIV negative TB patients in the current study compares favourably with the national average. In patients with HIV positive TB, however, the success rate was significantly lower. Such a high mortality in TB/HIV patients during a 30 month period brings into focus the need for providing ART and co-trimoxazole prophylaxis in addition to the RNTCP regimen to reduce the morbidity and mortality associated with the management of TB/HIV. Presence of a significant number of HIV associated TB cases could substantially reduce the overall efficacy of the RNTCP regimen in situations where TB/HIV patients form a substantial part of the TB patient population. In urban areas of Pune city in Maharashtra, about 30 per cent of the TB patients are dually infected¹⁷. While the mortality in such TB patients is largely due to tuberculosis, deaths due to other AIDS related causes have also contributed to the overall mortality. None of the patients in the study received anti-retroviral treatment.

The response of HIV-TB patients to treatment with the thrice weekly RNTCP category I regimen was also investigated in two studies at the Tuberculosis Research Centre, Chennai, India. In one study, on 55 patients followed up to 30 months, 35 per cent died at various time points²¹; in the second study, the mortality in HIV/TB patients by the end of 36 months was 36 per cent²². In our study as well as in the Chennai studies, the high mortality rates were associated with the presence of high degree of immunosuppression in the HIV/TB patients as evidenced by the low CD4 counts in most patients.

The high mortality associated with HIV/TB had also been noted in several studies in Africa. There is thus adequate justification for addition of ART and co-trimoxazole prophylaxis to ATT for success in the management of HIV associated TB²³⁻²⁸.

The Indian programme is cognizant of the need of routine identification of HIV positive persons among

TB patients in areas with high prevalence of HIV and currently has a programme of effective co-ordination between RNTCP and National AIDS Control Programme (NACP) with cross referrals between the two programmes. This system is in operation now and is working efficiently. Since TB/HIV patients now receive ATT and ART, mortality due to TB and other AIDS related causes would be lower than the high mortality rates observed in TB/HIV patients treated with ATT alone.

Realizing the gravity of identification of HIV positives among TB patients, the World Health Organization has now recommended that all TB patients in HIV endemic areas or countries should be offered HIV test. Further, recent WHO treatment modalities have been simplified by recommending that all TB/HIV patients should receive ART regardless of the CD4 count and also receive co-trimoxazole prophylaxis during the period of anti-TB treatment²⁹. Earlier, the WHO recommendation had provided for compulsory ART in TB/HIV patients with CD4 counts of less than 200 with an option to treat those with CD4 counts in the range of 200-350 cells/ μ l with ART.

The interaction between rifampicin and many of the ART drugs necessitates either avoiding one or the other of the ART or ATT drugs or to complete a course of anti-TB treatment first and then start ART drugs. The latter policy would be inadequate since mortality among TB/HIV patients occurs early - many die within the first three months of treatment. Some of these deaths could be prevented by initiating ART within a short period of starting ATT. Results of a retrospective study in San Francisco have shown that it is possible to reduce the mortality associated with tuberculosis in HIV infected individuals by initiating anti-retroviral therapy³⁰. Indeed, studies are ongoing to determine at what stage of anti-TB treatment should ART be initiated.

Another matter of concern is the large number of HIV/TB patients who attained bacteriological negativity (and designated as cured) at the end of treatment and yet exhibited signs of active TB during the 24 months of follow up, indicating that in the RNTCP, routine follow up of the HIV seropositive TB cured cases may be needed to look for evidence of recurrence of tuberculosis.

There are certain deficiencies in this study carried out under the programme conditions of the RNTCP. This study was primarily conducted during the period before free ART was available in India, when the guidelines for ART and prophylaxis in HIV infected TB patients were not clearly available. The lack of ART and co-trimoxazole prophylaxis for the study participants could have contributed to the increased mortality in HIV associated TB patients. Since ART was not administered to the study participants, the onset of immune reconstitution inflammatory syndrome (IRIS) in the study participants could not be studied. Similarly, the drug – drug interaction of antiretroviral and anti-tuberculosis medications could not be studied as antiretroviral therapy was not administered to the study participants.

Since the study was carried out using RNTCP guidelines for diagnosis and management of tuberculosis, results of the sputum culture for *Mycobacterium tuberculosis* were not available. CD4 count results were available but HIV-1 viral load results were not available in the study participants. Thus the increased mortality reported in this study needs to be interpreted in the presence of these deficiencies.

In areas where HIV prevalence is high, efforts are needed to identify TB patients who are HIV positive, design a schedule of ATT and ART treatment for them, monitor such patients for bacteriological response, recurrence of TB disease and occurrence of other opportunistic infections and other AIDS related conditions. Current efforts of co-ordination between RNTCP and NACO are timely and hopefully will not only reduce mortality in TB/HIV patients but also enhance their quality of life.

Acknowledgment

This study was undertaken at the RNTCP TB Clinic at Talera Hospital with financial and technical support from the ICMR Special Task Force on HIV/TB.

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