Original Articles

Long term follow up of HIV-infected patients with tuberculosis treated with 6-month intermittent short course chemotherapy

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ABSTRACT

Background. Tuberculosis occurs in 60%–70% of HIV-positive persons in India. The outcome of HIV-positive patients treated with 6-month intermittent short course antituberculosis regimens in India is not well described.

Methods. This was a prospective observational feasibility study of 71 patients with HIV and tuberculosis who were treated with category I regimen of the Revised National Tuberculosis Control Programme (ethambutol, isoniazid, rifampicin and pyrazinamide thrice weekly for the initial 2 months followed by rifampicin and isoniazid thrice weekly for the next 4 months). Sputum was examined by smear and culture for *Mycobacterium tuberculosis* every month up to 24 months. Chest X-ray, CD4 cell count and viral load were done prior to and at the end of treatment. None of the patients received antiretroviral therapy.

Results. We present here the treatment response of patients with sputum culture-positive pulmonary tuberculosis to category I regimen. By efficacy analysis, among 43 patients treated with category I regimen, sputum smear conversion was observed in 79% and culture conversion in 82% at the second month. A favourable response was seen in 72% of patients. The mean (SD) CD4% fell from 12.6 (5.9) to 8.9 (4.9) ($p<0.001$) with no significant change in mean (SD) CD4 cell count (169 [126] to 174 [158]; ns) at the end of treatment. Viral load change from $1.8x10^5$ at baseline to $1.3x10^5$ at the end of treatment was not statistically significant. Thirty-one patients, who completed the full course of treatment, were declared cured and were followed up for 24 months. Twelve had recurrent tuberculosis (39%); 16 of 43 (37%) patients had died by the end of 24 months, two-thirds due to causes other than tuberculosis.

Conclusion. Though the early bacteriological response to intermittent short course antituberculosis regimen was satisfactory, the overall outcome was adversely affected by the high mortality (during and after completion of treatment) and recurrence rate among HIV-infected patients with tuberculosis. Immune status deteriorated in spite of antituberculosis treatment, highlighting the need for antiretroviral treatment in addition to antituberculosis treatment to improve the long term outcome. The results of this pilot study need to be confirmed by larger studies.

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INTRODUCTION

The human immunodeficiency virus (HIV) epidemic has had a major impact on the worldwide incidence of tuberculosis (TB). It is estimated that nearly 2 billion people are infected with *Mycobacterium tuberculosis*, 40 million are HIV-infected and over 12 million have dual infection with *M. tuberculosis* and HIV.[1,2] A prospective study at the Tuberculosis Research Centre (TRC), Chennai found a TB incidence rate of 6.9/100 person-years (95% CI: 4.1–9.6) in patients infected with HIV without a significant difference between initially tuberculin-positive and -negative subjects.[3] The growing number of patients with HIV-related TB is placing increasing pressure on the already heavily burdened TB control programme and resources.

Intermittent short course regimens have been proven to be highly effective and well tolerated in HIV-uninfected patients with TB.[4] However, reports characterizing the outcome of intermittent short course chemotherapy among patients with HIV-associated TB are few. Though some studies[5–7] have shown a good short term response to standard short course antitubercular therapy (ATT), considerable uncertainty remains regarding some aspects such as effectiveness under programme conditions, recurrence of TB and mortality. It is important for the Indian TB control programme to know whether or not patients with TB co-infected with HIV can be treated with the standard regimens used in the Revised National

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Tuberculosis Control Programme (RNTCP).[8] We report the results of a feasibility study in a group of patients with HIV and TB who did not have access to antiretroviral therapy (ART) and were treated with standard intermittent short course therapy used in the RNTCP. Patients were followed for 24 months after completing ATT.

METHODS

This was a prospective, observational, feasibility study. Between July 1999 and June 2000, HIV-infected individuals referred to TRC and those admitted in Government Hospital of Thoracic Medicine (GHTM), Tambaram, Chennai were assessed for their eligibility to participate in the study. Patients were enrolled if they were ambulatory and at least 15 years of age, had at least one sputum smear-positive for *M. tuberculosis* or had radiological or histopathological evidence of extrapulmonary TB. Almost 50% of our study population were from outside the city but were willing to attend the clinic as required. Pregnant and moribund patients were excluded from enrolment to the study. A history of patients having received ATT was elicited and patients were categorized and treated as per the RNTCP guidelines.

A standard questionnaire containing demographic, medical and behavioural characteristics was administered and all patients underwent a physical examination. Baseline investigations included a chest X-ray and examination of two overnight and one spot sputum specimens by direct smear microscopy and culture for mycobacteria. Cultures were subjected to species identification and those positive for *M. tuberculosis* were tested for sensitivity to isoniazid (H), ethambutol (E), streptomycin (S) and rifampicin (R).[9,10] Evaluation of baseline hepatic and renal functions, and serological testing for HIV were done for all patients. HIV screening was done using the Tridot rapid test (J. Mitra, India) and positive tests were confirmed by Comb Aids rapid test (Span Diagnosis, Surat, India) and also by enzyme-linked immunosorbent assay (Labsystems, UK). National guidelines and policy concerning HIV testing and related issues (informed consent, confidentiality, pre- and post-test counselling) were adhered to. Haematological and immunological parameters were measured. CD4%, CD8% and CD4, CD8 cell counts, CD4:CD8 ratio were determined using flow cytometry (Simultest-IMK Lymphocyte kit and a Becton Dickinson FAC scan) and viral load was measured using Cobas Amplicor automated viral load monitor (Roche amplicor, V3.1).

All eligible patients (i.e. patients >15 years of age, no history of TB or receiving ATT with current evidence of pulmonary or extrapulmonary TB) received the standard short course ATT regimen category I, as recommended by RNTCP.[8]

Category I consists of ethambutol, isoniazid, rifampicin and pyrazinamide thrice weekly for the initial 2 months (intensive phase; $2EHRZ_3$), followed by rifampicin and isoniazid thrice weekly for the next 4 months (continuation phase; $4RH_3$).

The drug dosages were: isoniazid 600 mg, ethambutol 1200 mg, pyrazinamide 1.5 g, streptomycin 0.75 g and rifampicin 450 mg for patients weighing ≤60 kg. For those weighing ≥60 kg the dose of rifampicin was increased to 600 mg. Tablet pyridoxine 10 mg was given with each dose of ATT. Fixed drug combinations were not used. The study protocol was approved by the scientific advisory and the ethics committees of the TRC, Chennai and written informed consent was obtained from the patients.

Monitoring during treatment and follow up

All patients received treatment under supervision during the intensive phase and were supplied drugs once weekly during the continuation phase. Community DOT (directly observed treatment) providers were arranged for those patients unable to attend the clinic as required during the continuation phase. Field investigators from the hospital visited these community DOT providers every month to supervise and educate them on how to dispense ATT drugs, how to maintain the DOT notebook, etc. When these patients attended the centre for monthly examination, besides doing a thorough clinical examination, regularity of their drug intake was checked by re-questioning them, performing a urine examination for acetyl-INH and by checking their DOT notebooks, which should have been duly dated and signed by their DOT providers. If a patient had missed an appointment, a health visitor made a home visit the next day, if the patient lived in the city. Otherwise a letter was posted to him or to his DOT provider. Subsequently, a social worker and a medical officer made home visits, if necessary. These visits were continued until the patient was either retrieved or 'lost'; loss being defined as continuously defaulting for more than 1 month. Any complaint suggestive of an adverse reaction volunteered by a patient during the treatment period was recorded and a clinician elicited further details. If the complaints were related to the ATT drugs administered, suitable action was taken wherever necessary.

All patients were monitored at monthly intervals for 2 years following completion of treatment. Follow up examinations included clinical assessment, regularity of drug intake and monitoring of adverse drug reactions. Three sputum specimens during treatment and two specimens during follow up were examined at monthly intervals up to 2 years by microscopy and culture. If a culture grew *M. tuberculosis* it was tested for sensitivity to first-line drugs to monitor the emergence of drug resistance. Chest X-ray was done at the second month and at the end of treatment while blood examination for liver functions and immunological parameters was done at the end of ATT (6 months) and at any other time considered necessary (clinical deterioration). During follow up patients who were late for their scheduled appointment by 15 days were contacted at their homes, and all attempts made to motivate them to attend the clinic at the earliest. Patients in this cohort received co-trimoxazole (1 double strength tablet daily) along with medications for intercurrent illnesses and other opportunistic infections. After completing treatment if the sputum smears/culture became positive at any time they had a chest X-ray, were re-evaluated clinically and managed appropriately. None of the patients in this study received ART because ART was not available in government hospitals during this period and since all our patients were from the lower socioeconomic stratum none of them could afford ART.

Outcome measures

A patient was considered to have had

1. a favourable response, if all the 6 cultures were negative during the last 2 months of treatment.
2. an unfavourable response, if one or more cultures were positive in the last 2 months of treatment, sputum smear positivity at 5 months or more after starting treatment (treatment failure), death due to TB, a change of treatment for clinical/radiographic deterioration or for persistent culture positivity.
3. a recurrence of TB, if one or more cultures became positive or there was clinical/bacteriological deterioration during follow up among patients who had a favourable response at the end of treatment.

Statistical analysis

Statistical analysis was done using the statistical package for social sciences (SPSS version 13). Descriptive analysis was done for demographic details and the difference between variables at baseline and at end of therapy was assessed by paired *t*-test. An efficacy analysis was done for patients who had received more than 80% of the prescribed chemotherapy. For all tests, $p<0.05$ was considered statistically significant.

RESULTS

Of the 71 patients given the category I regimen, the majority were men (83%) with ages ranging from 18 to 55 years with a median age of 33 years (mean [SD] age: 33.5 [7.2] years) and weight ranging from 28 kg to 73 kg with a median weight of 40 kg (mean weight: 41.4 [7.6] kg). At the time of enrolment, most patients had a combination of two or more symptoms such as cough or fever and weight loss. Extensive parenchymal opacity was the commonest chest X-ray abnormality followed by miliary mottling; 24 patients had more than 1 radiological lesion; 65% of patients had positive sputum smears, while culture positivity was seen in 73% (*n*=55) of patients initially. Among patients who had a drug sensitivity pattern available (*n*=52), 43 (83%) had organisms that were sensitive to all the first-line TB drugs, 15% were resistant to isoniazid and 4% had MDR TB. The mean CD4% was 12.5% (range 2%–29%), mean CD4 count 169 (126) cells/cmm while the median viral load was 188 000 (interquartile range (IQR): 41 100 to 1 157 200 copies/ml). Regularity of drug intake was monitored by questioning the patient, urine examination for acetyl-INH and through visits to monitor the community DOT providers as described earlier. Only patients with more than 80% of drug intake were considered for the efficacy analysis.

Of the 71 patients, 28 patients were excluded from the efficacy analysis due to various reasons: initial culture negativity (*n*=16), <80% of drug intake (*n*=9), or death within 1 month of starting treatment (*n*=3). Among the 43 patients available for efficacy analysis, favourable response, defined as culture negativity at the end of treatment with clinical and radiological improvement, was

TABLE I. Laboratory parameters (mean [SD]) at baseline and end of treatment (paired)

Parameter	*n*	Baseline	End of treatment	p value
Weight (kg)	55	41.4 (7.6)	48.1 (9.3)	<0.001
Haemoglobin (g/dl)	55	11.1 (2.7)	11.7 (1.8)	0.005
Total lymphocyte count (cmm)	33	1305 (644)	1902 (1160)	<0.05
CD4%	37	12.6 (5.9)	8.9 (4.9)	<0.001
CD4 cell counts (mm^3)	34	169 (126)	174 (158)	ns
Median viral load (IQR) (copies/ml)	14	188 000 (41 100–1 157 200)	132 000 (16 400–614 000)	ns

IQR interquartile range

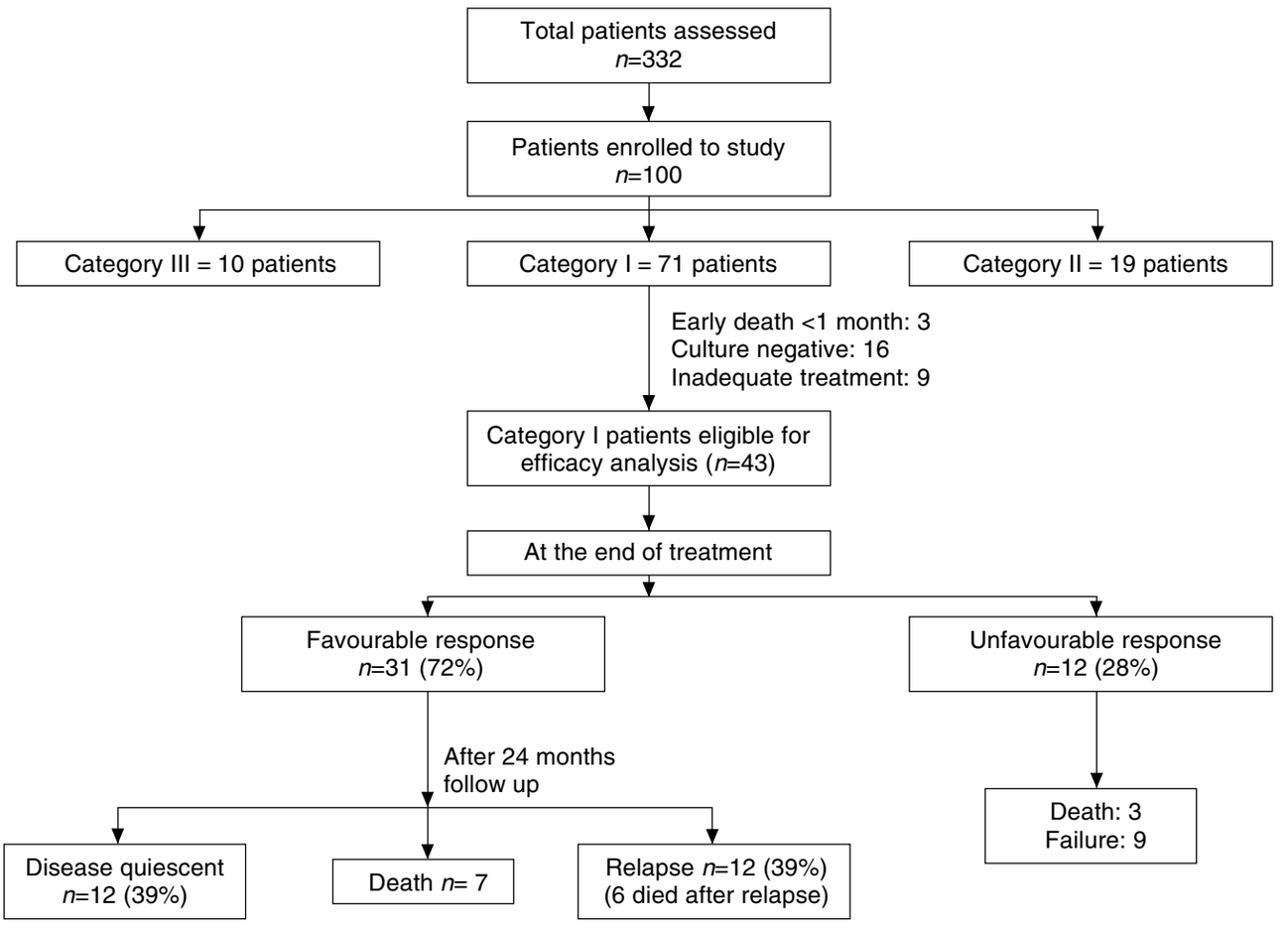

FIG 1. Schematic presentation of study population and outcome

seen in 31 patients (72%). At the end of treatment, 12 patients (28%) had unfavourable response in the form of death (*n*=3) or treatment failure (*n*=9) (Fig. 1). Sputum smear conversion among the initial smear-positive patients at second month was 79% and culture conversion was 82%. Table I shows a comparison of various parameters at baseline and at the end of treatment among patients who had paired data available. There was a significant improvement in weight, haemoglobin and absolute lymphocyte count at the end of ATT, while the CD4% declined significantly.

Adverse drug reactions attributable to ATT (rifampicin) occurred in one patient in our study. The patient developed acute hepatitis, elevated liver enzymes more than 3 times the upper limit of normal and bleeding diathesis about 25 days after starting ATT. In view of the above symptoms the patient was changed to a regimen that did not include rifampicin. She improved subsequently and completed her course of chemotherapy. Gastrointestinal reactions such as nausea, vomiting and epigastric disturbance were seen in a few patients that were managed symptomatically with reassurance and antacids. None of them required any modification in their drug dosages or regimen.

Long term follow up

At the end of 24 months of follow up, among patients who had a favourable response to category I regimen (*n*=31), 12 patients had quiescent disease, 7 had died and 12 had recurrence of TB.

Of the 12 patients with recurrent TB there were 11 men and 1 woman (age range 21–38 years). The majority of recurrences (7 of 12) occurred within the first 6 months of completion of treatment. Of these 12 patients, 7 had a high bacteriological load of 2+ or more in their initial sputum culture, 9 patients had organisms susceptible to all first-line ATT drugs at the beginning and 10 of them were severely immunocompromised, even at baseline, with CD4 cell counts <200 cells/cmm (Table II). Patients who developed recurrence were significantly older than those who did not. None of the other variables were significantly different even though there was a trend towards lower initial CD4 counts and weight, and higher smear grading in the recurrence group.

Of the 71 patients, excluding the initial culture negatives (*n*=16), 55 patients were considered for death analysis. Nineteen (35%) of them had died by the end of 24 months of follow up at various time points which included early death within 1 month (*n*=3), death during treatment (*n*=3), death during follow up (*n*=7) and death after recurrence (*n*=6). Considering the 43 patients eligible for efficacy analysis, 16 patients (37%) died by the end of 2 years of follow up, 6 of them being after recurrence of TB.

TABLE II. Comparison of pre-treatment characteristics of HIV-infected TB patients who developed a recurrence of TB versus those who remained quiescent

Characteristic	Recurrence (*n*=12)	Quiescent (*n*=12)
Mean (SD) age (in years)	36.7 (5.4)	30 (5.1)*
Sex ratio (M:F)	11:1	9: 3
Mean (SD) weight (in kg)	41.2 (4.6)	45.0 (7.9)
Mean (SD) CD4%	11.8 (6.5)	16.4 (8.4)
Mean (SD) CD4 cell count	156 (162)	272 (251)
Pre-treatment sensitivity		
Pansensitivity	9	11
MDR TB	1	–
Not available	2	1
Sputum smear grading		
0 to 1+	7	11
2+ to 3+	5	1
Sputum culture grading		
0 to 1+	5	6
2+ to 3+	7	6

* p value <0.001 MDR TB multidrug resistant tuberculosis

DISCUSSION

In this prospective observational study, we have shown that among HIV-infected individuals with TB who were treated with category I regimen and were regular with treatment, the initial bacteriological response to ATT was good. Overall, however, only 72% of patients (31/43) had a favourable response while 28% (12/43) had an unfavourable response at the end of treatment which included death, treatment change and culture positivity. Both cure and death rates compare unfavourably with rates reported for HIV-negative TB patients treated under the RNTCP.[10]

Many reports[5–7,11] have shown that 6- and 9-month courses of ATT regimens containing isoniazid and rifampicin are highly effective in TB patients with HIV disease, with high cure but variable recurrence rates. Two studies[6,7] describing the results of 6-month therapy for TB in HIV-positive patients have shown cure rates, at the end of treatment, of 59% and 81%, respectively. Our results showed that patients with HIV infection and culture confirmed pulmonary TB who take regular treatment have a favourable response of 72% when treated with a 6-month intermittent regimen. This cure rate is less than the 85% reported in the RNTCP from most parts of India. This may be due to the selected group of patients with advanced stage of HIV disease in our study. The possible reasons for treatment failure could be malabsorption of drugs exacerbated by diarrhoea and other associated opportunistic infections. We have earlier demonstrated that patients with advanced HIV disease have evidence of malabsorption and low blood levels of ATT drugs.[12]

A survey to determine the proportion of initial and acquired drug resistance among patients with pulmonary TB in Tamil Nadu showed 81% of organisms susceptible to all first-line drugs, isoniazid resistance in 15.4%, rifampicin resistance in 4.4% and resistance to isoniazid and rifampicin in 3.4% of previously untreated cases.[13] Recent reports[14,15] on the prevalence of drug resistance among HIV-infected TB patients from Chennai and Pune have shown that it was similar to HIV-negative patients from the same geographical area. This study confirms the finding that the majority of HIV-infected TB patients have drug-susceptible organisms and that MDR TB is still fairly low in this population.

Recurrence of TB in HIV-infected patients is a serious problem and may be due to re-activation or re-infection with a new strain of *M. tuberculosis*. Recent observations[16] in countries endemic for HIV/TB suggest that recurrence rates following TB treatment may be unacceptably high in HIV-infected individuals, even when the DOT strategy recommended by WHO[17] is followed. Studies done in various parts of the world have reported a recurrence rate of TB in HIV-infected persons ranging from 4.6% to 9% in non-endemic areas[6,18,19] and 50% to 62% in TB-endemic areas.[16,20] In our series, recurrence of TB was observed in 39% of category I patients followed up to 24 months. This high rate could be due to the advanced stage of HIV disease in this group with two-thirds of patients having a CD4 cell count <200 cells/cmm at presentation, as recurrence of TB is more likely to occur among severely immunocompromised patients.[21] Another reason could be exposure to TB in the hospital environment as many patients were admitted for a long duration and were exposed to other sputum-positive TB patients in the wards thus increasing the

chances of re-infection with different strains of *M. tuberculosis*. This raises the issue of implementing proper infection control procedures in hospital wards and segregation of infectious patients to prevent nosocomial spread of TB. We have earlier described TB recurrence due to re-infection with a new strain of *M. tuberculosis* in a patient with advanced HIV disease.[22] Further studies using molecular techniques such as restriction fragment length polymorphism (RFLP) are required to find out the proportion of recurrences due to re-infection in India. Further, treatment was not fully supervised in the continuation phase in our study as many patients were from remote places and we had to depend on community DOT providers for drug administration and concealed irregularity is a possibility. A recent study from our centre showed that irregular treatment, smoking and pre-treatment drug resistance were strong risk factors for recurrence.[23] In this study of HIV-infected TB patients, those who developed recurrent TB had poorer immune status, lower body weight and a higher sputum smear grading initially, though the differences were not statistically significant. One of them had MDR TB to begin with and another 6 developed rifampicin resistance at the time of recurrence. The development of rifampicin resistance is of concern and could imply three things. First, if the patients were irregular when intermittent chemotherapy was not supervised, this could have led to drug resistance. Second, malabsorption of drugs could have led to development of rifampicin resistance because of subtherapeutic blood levels of one or more ATT drugs; the third possibility is that re-infection occurred with a drug-resistant strain of *M. tuberculosis*

Several other aspects of our results are pertinent to the management of HIV-related TB**.** The clinical features of our patients have been described in detail earlier; the most common presenting symptoms were cough and weight loss followed by fever.[24] Of the 71 HIV-positive cases treated with category I regimen, 65% were smear-positive for acid-fast bacilli. This indicates that smear microscopy done diligently could be a sensitive diagnostic tool even in the presence of HIV infection. This is contrary to the general belief that sputum smears are more likely to be negative in HIV-infected individuals.[4]

The association of TB and high viral loads portends a more rapid course of HIV disease, even in patients in whom TB is treated and cured.[25] Patients in our study had high viral loads, which did not decrease significantly after treatment. While there was no significant change in CD4 cell counts, there was a significant decrease in CD4% indicating progressive immunosuppression. CD4 absolute count is influenced by the total lymphocyte count, which was found to increase significantly after treatment of TB. The CD4% is a more reliable and independent marker of disease progression and response to treatment in such situations.

A few previous studies have reported the 1-year mortality for HIV-infected TB patients to be 20%–25%.[26,27] Studies have also shown that early death in cases of HIV-related TB was more likely due to TB, whereas late death was due to other HIV-related complications.[28,29] Due to the non-availability of free ART during the course of our study and since most of our patients were from the lower socioeconomic group they did not have access to ART. Sixteen of our 43 patients (37%) died by the end of 2 years, two-thirds due to causes other than TB. Of the 16 deaths, 6 patients died after recurrence of TB. Thus, the long term prognosis for patients with HIV and TB is poor, particularly when there is limited access to ART.

The results of our study must be interpreted with caution and cannot be generalized. The number of patients studied was relatively small and treatment was not supervised completely; in many instances community DOT providers were used. However, the study provides valuable preliminary data, which can be used to plan future research studies. Larger studies are required to determine if there is a CD4 lymphocyte level below which the risk of recurrence of TB is increased, which could identify patients for whom the duration of ATT should be extended. A randomized clinical trial is under way at the TRC comparing a 9-month regimen with the standard RNTCP 6-month regimen in the treatment of HIV-associated TB. The mortality reported here underscores the need for access to ART for HIV-infected individuals and those who present with TB would form a good target group for ART.

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Surveillance for risk factors of cardiovascular disease among an industrial population in southern India

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ABSTRACT

Background. We assessed (i) the risk of cardiovascular disease in an industrial population in Chennai, southern India and (ii) whether the status of treatment and control of diabetes and hypertension would be different in an industrial population, which is provided free healthcare, compared with the general population of Chennai.

Methods. Subjects residing in the residential areas of 2 industries (Indian Airlines and Integral Coach Factory) in Chennai in southern India were recruited. The subjects were employees ($n = 440$) selected by an age- and sex-stratified random sampling method, and their family members ($n = 727$) in the age group of 20–69 years; a total of 1167 subjects. Fasting plasma glucose, lipid estimations and anthropometric measurements were done in all the subjects. Information on demographic and lifestyle determinants was obtained using a questionnaire. Diabetes was diagnosed using the American Diabetes Association criteria and metabolic syndrome was defined by the Adult Treatment Panel III criteria with modified waist definition for Asian Indians.

Results. Age-adjusted prevalence of major risk factors for cardiovascular disease using the 2001 Census of India were as follows: diabetes 11.9%; hypertension 25.4%; dyslipidaemia 40.2%; hypertriglyceridaemia 28.3%; overweight (body mass index ≥ 23 kg/m^2) 60.2%; and metabolic syndrome 34.1%. Use of tobacco in any form was present in 22.9% of men and 0.5% of women; 79% of the subjects followed a sedentary lifestyle. Among subjects receiving medication, 42.1% of subjects with diabetes and 55.3% of subjects with hypertension had their disease under adequate control. A comparison of these results with the general population of Chennai showed that the industrial population had a higher prevalence of cardiovascular risk factors in spite of having better access to healthcare facilities.

Conclusions. The prevalence of cardiovascular disease was high in this industrial population of Chennai. Although the overall treatment and control of diabetes and hypertension was better than that in the general population, it was still inadequate and this emphasizes the need for greater awareness about non-communicable diseases.

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INTRODUCTION

Cardiovascular disease (CVD) is predicted to be the most common cause of death globally, including in India, by 2020.[1] The prevalence of CVD and its risk factors are high in migrant people of Asian Indian origin compared with the host population.[2,3] The growing burden of CVD[4] is due to the increasing prevalence of cardiovascular risk factors such as diabetes, hypertension, dyslipidaemia, overweight or obesity, physical inactivity and use of tobacco. It is known that CVD occurs at least a decade earlier in Asian Indians compared

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