

Medicine and Society

The Revised National Tuberculosis Control Programme in India: Time for revision of treatment regimens and rapid upscaling of DOTS-plus initiative

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INTRODUCTION

India's Revised National Tuberculosis Control Programme (RNTCP) is based on the 'Directly observed therapy, short course' (DOTS) approach of the Global TB Strategy of WHO. This strategy emphasizes case-finding by sputum-smear examination and the administration of protocol-based standardized short-course therapy under direct observation, at least during the initial phase. The revised programme has improved case-finding facilities, made available short-course chemotherapy in an uninterrupted manner, increased the cure rates, and has provided data on adherence and outcome. The RNTCP adopted the operational and managerial strategy suggested by WHO, and also based its treatment regimens on the WHO guidelines on treatment of tuberculosis published in 1997, which recommended either daily or 3 times a week administration of drugs as equivalent options for use.¹ The 2003 WHO guidelines for treatment of tuberculosis were revised substantially in 2004,² perhaps in response to the challenges posed by drug-resistant tuberculosis and the unsatisfactory outcome of the previously recommended regimens, particularly in some patients with a previous history of treatment.³ In a departure from previous recommendations, WHO now recommends daily administration as the preferred dosing schedule for all categories of patients, and considers intermittent regimens optional.² A single regimen has now been recommended for all new cases, irrespective of the site of disease or status of the sputum smear. To improve case management of patients with drug-resistant tuberculosis, it has also incorporated recommendations for drug susceptibility testing and use of second-line drugs in selected patients with a previous history of treatment for tuberculosis (category II patients under the RNTCP classification). However, the RNTCP, apart from launching a DOTS-plus initiative in pilot sites, has not altered the dosing schedule or the content of the regimens and is still following the decade old WHO guidelines.¹

We focus on the treatment components of the DOTS regimens in India, highlight concerns related to efficacy of treatment in new as well as previously treated cases based on the Indian and international evidence, and suggest an urgent revision of the RNTCP guidelines on management of tuberculosis in India.

TREATMENT OF NEW PATIENTS (CATEGORY I) IN INDIA

Concerns over longer term outcomes with fully intermittent regimens in the RNTCP

The outcome being reported by the RNTCP in patients with smear-positive pulmonary tuberculosis is the cure rate, defined in the programme by a negative sputum smear at the end of the treatment. The definition of cure in the RNTCP is a negative smear examination, which has its own limitations, as bacillary counts <10 000 organisms/ml in sputum can be smear-negative.⁴ The RNTCP reports an average national cure rate of 83% for new patients at the end of treatment.⁵ However, the efficacy of treatment regimens in tuberculosis is judged not only by a high cure rate, but also by a low rate of relapse on follow up, with rates of <5% considered acceptable for treatment regimens.⁶

Most cases of relapse follow completion of treatment fairly closely and occur within 6–12 months. The RNTCP does not follow up patients for relapses and many patients who do suffer a relapse, default or fail treatment do not return to the programme.⁷

There is a paucity of data on longer term outcomes with the regimens given in the RNTCP. However, the limited published evidence has consistently suggested that the risk of relapse has been higher than acceptable in patients who receive fully intermittent thrice-weekly or twice-weekly regimens in trial and in programme conditions.^{8–10} In a rural and urban cohort of patients treated under the RNTCP, 12% and 11.4% patients, respectively, relapsed during follow up of durations up to 2.5 years.^{8,9} Only one-third of the cohort, which consisted of patients who did not smoke, were fully adherent and had susceptible acid-fast bacilli. The relapse rate among them was <5%.⁸ A study conducted by the Tuberculosis Research Centre (TRC) in 1997 showed that twice as many patients on intermittent regimens relapsed compared with those on the daily regimen (10% v. 5%).¹⁰

The problem with higher relapse rates with fully intermittent therapy assumes even greater importance in the Indian context, where initial drug resistance to a key drug such as INH is expected to be 20%–25% in programme conditions.¹¹

Studies show that the risk of relapse with the use of fully intermittent regimens increases further in the event of initial drug resistance to INH and reaches unacceptable levels. In the TRC study the rate of relapse in fully intermittent twice-weekly regimens was up to 25%, while a daily regimen fared much better with a relapse rate of 8%.¹⁰ This study concluded that in view of such poor performance, these fully intermittent twice-weekly regimens were unsuitable for use in the RNTCP. Even with fully intermittent thrice-weekly regimens used in the RNTCP, in the setting of INH

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resistance, a relapse rate of 20% during an 18-month period in patients with INH resistance was documented, an outcome which would be considered unacceptable.⁸

Tuberculosis is a leading opportunistic disease and a cause of death in patients with HIV. A recent report from the TRC of a recurrence rate of 39% after cure with the 6-month fully intermittent regimen used in the RNTCP, in a relatively small cohort of Indian patients with HIV-associated tuberculosis, is disturbing, although a number of factors including poor immune status, re-infection and drug malabsorption can be implicated in these patients.¹²

Although intermittent therapy has been in use for 50 years, there is a paucity of formal comparative studies conducted with methodological rigour, between daily and fully intermittent forms of therapy, with regard to cure rates as well as relapse rates. Observational and cohort studies have demonstrated high cure rates, similar to daily therapy,^{13,14} but a Cochrane review in 2001 identified and analysed only one study of 1981, where daily administration of drugs was directly compared with a fully intermittent regimen (which is not similar to the regimen used in the RNTCP).¹⁵ Although the bacteriological cure was comparable in the two groups, the fully intermittent therapy group had higher relapse rates. The Cochrane review acknowledged that the size of the study was insufficient to determine if this was a true effect or had arisen by chance, and called for larger studies comparing fully intermittent regimens directly with daily regimens with adequate follow up to establish equivalence between these two forms of drug administration.

Since the publication of the Cochrane review, evidence has accumulated on the better long term efficacy of daily regimens. The results of a nested case-control study showed that thrice-weekly treatment increased the risk of relapse compared with daily regimens (odds ratio 3.92, 95% CI: 1.78–8.63).¹⁶ A systematic review of 20 published trials concluded that the risk of relapse is related to the total dose administered and that the relapse rate remains within the acceptable limit of 5% only with either daily 6-month regimens or regimens that incorporate a daily intensive phase followed by a thrice-weekly continuation phase.¹⁷ A multicentre randomized trial of WHO-recommended regimens showed a significant advantage of daily therapy with a higher percentage of conversion to culture negativity at 2 months, and a lower percentage of unfavourable results (relapses, deaths) at 12 months.¹⁸ A recent systematic review on the long term efficacy of DOTS regimens was prompted by the observation of a high recurrence rate (even in patients with susceptible bacilli) after treatment in a successful DOTS programme.¹⁹ It noted wide heterogeneity in recurrence rates of up to 14% and concluded that 'few studies have assessed the ability of standard DOTS regimens to result in lasting cure for patients treated under routine programmatic conditions'.¹⁹

Fully intermittent regimens have been advocated as they lower cost and make direct observation of drug intake easier. Yet, if they compromise the longer term outcomes of therapy, and lead to higher and unacceptable relapse rates, especially in a setting of INH resistance, their disadvantages may well outweigh the benefits of ease of direct observation of each dose. In India, direct observation of therapy is limited to the intensive phase of therapy as well as for one of the thrice-weekly doses administered in the maintenance phase, with 32 of the 72 doses being self-administered by the patient. If the RNTCP has achieved satisfactory outcomes even with this partial form of DOT, then in view of operational considerations, it is reasonable to implement the same in the intensive phase, maintain close supervision of the patient to

maintain levels of adherence and, in line with the WHO revised recommendations, implement a daily therapy-based regimen as the preferred option.

TREATMENT OF PATIENTS WITH HISTORY OF PREVIOUS TREATMENT (CATEGORY II) IN RNTCP

Concerns over the suboptimal end-of-treatment outcomes and the need for revision of diagnostic and treatment strategies

There is an even clearer case and a stronger public health imperative for revision of management guidelines for category II patients in India. Nearly 0.2 million category II patients with tuberculosis, often treated by one or more healthcare providers, are registered by the RNTCP every year.⁵ They comprise 26% of the smear-positive patients reported annually,⁵ and constitute a major public health risk as they form the reservoir of drug-resistant tuberculosis including multidrug-resistant (MDR) tuberculosis. Prevalence of INH resistance in this group ranges from 47.7% to 87.1% while resistance to both INH and rifampicin (i.e. of MDR tuberculosis) in this group has ranged from 8.1% to 80.6%.^{20,21} In terms of the number of cases with MDR-TB, India ranks among the highest in the world. India, China and the Russian Federation contribute an estimated 62% of the global incidence of MDR-TB.²² Now, even resistance to many second-line drugs, known as extensively drug-resistant (XDR) tuberculosis, which makes tuberculosis virtually untreatable, has been reported from India.²³

The end-of-treatment outcomes of category II patients has been suboptimal with the treatment regimens administered by DOTS and the RNTCP—much below the global target cure rate of 85%. A study of treatment outcomes has shown that only about half of re-treatment patients and only a quarter of MDR-TB patients were cured successfully with the current standardized short course therapy under DOTS across 6 nations.³ The results of treatment in an urban as well a rural cohort from southern India were both below 50%, with a default rate exceeding 40%.^{24,25} While DOTS is an excellent means of preventing acquired resistance, it is not an effective means of treating patients with resistant tuberculosis.²⁶

Improvement in treatment outcomes in these patients needs a revision of the classification of these patients, the diagnostic tests to which they are subjected, and the antituberculosis drugs that are used for their treatment.

First, the clubbing together of heterogeneous groups of patients within a single category in the present RNTCP guidelines (which owes its origin to the 1997 WHO guidelines¹) is fallacious. A single therapeutic category (category II) was created to address patients with previous treatment, regardless of whether the patients stopped taking treatment, had failure of treatment or relapsed after a previous cure. Studies have shown that patients with treatment failure are most likely to harbour MDR-TB strains, while those with default or relapse have a lower rate of MDR-TB, and may well have drug-sensitive strains if the infecting strain was drug-sensitive at the onset of therapy.²⁷ The 2003 WHO guidelines have correctly separated category II patients with a history of default or relapse from those with treatment failure, and suggested different treatment regimens and strategies for the two groups.² We believe that the RNTCP too should follow this example. The present provision of a single regimen for all patients in category II violates the basic principles of tuberculosis chemotherapy in patients with treatment failure, i.e. to never add a single new drug to a failing regimen.²⁸ For example, for those who fail the category I regimen (2HREZ/4HR) under RNTCP, the category II regimen (2SHREZ/1HREZ/5HRE) merely adds streptomycin. This error of choice

results in a higher risk of failure as well as creates additional resistance to drugs including the development of MDR-TB—a phenomenon known as amplifier effect of short course chemotherapy. In a report from India, the treatment success of the above regimen in category II treatment failure patients was as low as 18.2%,²⁴ while in a report from Peru, 83% MDR patients who had failed the retreatment regimen acquired additional resistance.²⁹ WHO has revised this recommendation for patients with treatment failure, and an expert from its Stop TB initiative noted that, ‘It is time, therefore, to close the chapter on cases [patients] who fail the treatment regimen with first-line drugs and receive poor retreatment regimens based on the same drugs that, of note, are not used in high-income countries.’³⁰ The continued use of this regimen for patients with treatment failure in India is a cause for concern.

Second, in patients with a previous history of treatment, and especially those with treatment failure, diagnostic strategies should move beyond smear microscopy to include access to drug susceptibility testing as suggested in the recent WHO guidelines. In a recent study in India, patients with failure to the category I regimen have been noted to have a 17% prevalence of MDR-TB.³¹ Subjecting such patients to drug susceptibility testing only after they do not convert to smear negativity after 4 months of a category II regimen, as suggested by the DOT-Plus initiative of the RNTCP, will introduce further delays in their access to effective therapy.³² Patterns of drug resistance can either be confirmed on individualized drug susceptibility testing (DST) or be inferred from drug resistance surveillance (DRS) data in representative categories of patients. There is a need for access to such testing and data, which at the moment is not being addressed, even in patients with treatment failure to category I or II regimens. The results of an International Clinical Epidemiology Network study, concluded in 2004, which could provide drug resistance surveillance data across 4 states, is still awaited.

Finally, category II patients, especially those with treatment failure, require access to second-line drugs as part of individualized or standardized retreatment regimens, based on patterns of drug resistance.

It should be noted that while fully intermittent dosing is still an option in the treatment of patients with susceptible bacilli, there is a consensus among guidelines against their use in the treatment of drug-resistant tuberculosis.^{28,33} The American Thoracic Society guidelines state: ‘Intermittent therapy should not be used in the treatment of drug-resistant tuberculosis, except perhaps for injectable agents after an initial phase (usually 2–3 months) of daily therapy.’²⁸

DECREASING THE BURDEN OF DRUG-RELATED ADVERSE EFFECTS IN RNTCP REGIMENS

A need for doses appropriate for Indian patients

Irregularity in drug intake or premature interruption of treatment is one of the major impediments to the success of treatment. The RNTCP aims to prevent these by direct observation of drug intake. Interruption of treatment or default, as it is as termed in the RNTCP, is multifactorial and related to the patient, treatment, provider and programme-related factors. In tuberculosis as in other diseases, treatment-related factors such as adverse effects of drugs, apart from true or perceived lack of efficacy, can lead to default. Adverse effects of antituberculosis drugs can appear in the first few weeks of therapy, often before the patient has had any noticeable improvement in symptoms.

In the RNTCP, among patients who complete therapy and particularly in those who default, a substantial number have been

reported to complain of treatment-related adverse effects.³⁴ In a study of 4310 patients (including 729 defaulters) who underwent treatment in the RNTCP across 4 states, drug-related side-effects were the leading reason cited for discontinuation of treatment.³⁵ Similarly, in a rural cohort of patients from the RNTCP, 42% of patients as well as 34% of their DOTS providers cited drug-related side-effects as the leading cause of non-compliance with treatment.³⁶ The rates of drug-induced toxicity such as hepatotoxicity with INH and rifampicin are higher (8%–39%)³⁷ than those reported in the West (~2.5%).³⁸ One factor implicated in most studies on tuberculosis chemotherapy in India is malnutrition, which decreases drug metabolism and leads to a higher risk of toxicity.^{39,40}

There is a high prevalence of undernutrition among Indian patients with tuberculosis. In rural Chhattisgarh, in our programme, in 1069 unselected adult patients with tuberculosis (during 2003–2005), the median weight of adult men was 42.8 kg and of adult women 35.3 kg. Such weights are not unique to the less developed states in India. In a cohort of 656 patients in Tamil Nadu, 14–87 years of age, 43.9% weighed <40 kg.⁴¹ The doses of antituberculosis drugs in the RNTCP need to take into account the body weights of Indian patients to decrease the rates of adverse effects. In an article published in 1986 on drug toxicity, the TRC concluded: ‘There is a tendency for Indian patients to receive high drug dosages in terms of body weight, as fixed doses which have been established for heavier western patients are transferred without adjustment to light-weight Indian patients.’³⁷ However, the RNTCP in its recommendation in 1997 stated: ‘For adults, drugs will be given in the recommended number of pills/capsules irrespective of body weight.’⁴² Later, the RNTCP recommended that adult patients weighing <30 kg be given regimens according to body weight.⁴³ However, the doses of drugs in the RNTCP continue to be a cause for concern, especially in the case of INH, a drug which can result in major side-effects such as drowsiness, peripheral neuropathy and hepatotoxicity. The RNTCP recommends a standard dose of INH 600 mg thrice weekly for all patients >30 kg weight, perhaps with the understanding that this would be the appropriate dose for most patients in India. The current WHO guidelines recommend an INH dose of 10 mg/kg administered thrice weekly.² According to these guidelines the 600 mg dose of INH would be considered appropriate only for patients with weights >55 kg (<5% of our patients, and perhaps a similar minority of TB patients in India).² Other guidelines recommend a dose of INH of 15 mg/kg thrice weekly to ensure a maximal post-antibiotic effect required in intermittent therapy.^{28,44} With reference to this higher dose, patients in India who weigh 30–39 kg (which in our programme would constitute 75.2% of adult women and 35.4% of adult men) are still receiving higher than the maximally safe dose of INH. The RNTCP needs to make available regimens with doses appropriate for weight bands such as 30–39 kg to decrease the frequency of drug toxicity and the consequent default by patients due to adverse effects.

THE DOTS-PLUS INITIATIVE FOR THE TREATMENT OF MDR-TB IN INDIA

Needs to be rapidly upscaled and made commensurate with the magnitude of the problem

MDR-TB has been documented in India since the 1980s but there has been a continued lack of provision of treatment regimens effective against it in the national programme. The DOTS-Plus initiative of the RNTCP, designed to provide access to treatments effective against MDR-TB in phase II of the RNTCP, was launched

in 2007 starting with Gujarat. It now needs expeditious implementation and there is an urgent need for upscaling. According to recent estimates, 87 413 new cases of MDR-TB occur in India per year among all cases of tuberculosis (range: 33 180 to 228 655).²² The present plans of providing access to MDR-TB treatment to 100 patients nationwide in the first year and 5000 patients eventually, are grossly inadequate and need to be revised.^{5,45} Otherwise a large number of patients will continue to be deprived of access to effective therapy, who will propagate the public health disaster of MDR-TB, before dying a premature death. As Farmer *et al.* have noted, the arguments against aggressive treatment of MDR-TB in resource-poor countries are flawed on clinical, epidemiological, analytical and moral grounds, and that 'It is too expensive *not* to treat MDR-TB now, when only a small fraction of all TB cases are resistant to our best drugs.'⁴⁶

To conclude, we suggest that the RNTCP, which is based on the DOTS strategy of WHO should, in line with the new WHO recommendations, use daily therapy as the preferred option. There is a need to improve the cure rates of re-treatment cases by diagnosing drug resistance early, especially in treatment failure cases and treating them effectively using second-line drugs when deemed necessary. Marcos Espinal of WHO's Stop TB Initiative, while referring to the need to replace the current re-treatment regimen for failures of standard treatment, provides a perspective: 'It is neither biomedically correct nor programmatically, ethically or financially appropriate to perpetuate a policy when new evidence speaks clearly against it.'³⁰ The RNTCP should respond to the issues relating to the treatment regimens of tuberculosis in India. It is time, nearly 4 years after the WHO revised its recommendations, that the treatment regimens in the RNTCP are revised, so that the end of treatment as well as long term outcomes in previously treated and new patients are improved. A disease, which affects millions of the most vulnerable and marginalized Indians in the prime of their lives, and continues to exact a heavy toll of an estimated 370 000 deaths annually,⁵ deserves no less.

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