

Review Article

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Current trends in chemotherapy of tuberculosis

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After streptomycin, which heralded the era of antibacterial chemotherapy for tuberculosis (TB), many important advances have made available treatment regimens that are almost 100 per cent curative. Randomised clinical trials by the Tuberculosis Research Centre, in Chennai and British Medical Research Council in East Africa and in the Far East have helped to establish many of the principles of antituberculosis chemotherapy. With successes have also come fresh challenges. *Mycobacterium tuberculosis* becomes rapidly resistant to the drugs used against it and in the last decade, the HIV epidemic has had an adverse impact on the global epidemiology of tuberculosis, with many countries in Sub-Saharan Africa experiencing a 2-3 fold increase in their TB burden. While the currently recommended treatment regimens are very effective, they have failed to control the burden of TB in the developing countries due to less than satisfactory implementation of the control programmes. Faced with the dual threat of multidrug resistant TB and the HIV/facilitated increase in TB, the WHO has instituted a Global TB Control Programme based on the directly observed treatment shortcourse (DOTS) strategy. Much of the principles of this strategy have come out of research in India. As part of this strategy, the Government of India is implementing a Revised National Tuberculosis Control Programme (RNTCP). Under the RNTCP standardized treatment regimens are prescribed for different treatment categories. Already more than 80 per cent of the population is covered by this Programme and full coverage is slated for 2005. Meanwhile, fresh research is ongoing to shorten treatment duration, a measure that should greatly aid TB control.

Key words Adverse reaction - chemotherapy - multidrug resistance - short course - tuberculosis - RNTCP - DOTS

The treatment of tuberculosis (TB) has witnessed many important changes over the years. With the advent of effective antimycobacterial chemotherapeutic agents in the early 1950s, the two main biological obstacles to successful treatment of TB were the high rate of failure during treatment and the high risk of relapse after treatment. The former was due to the selection of drug resistant mutants of *Mycobacterium tuberculosis* during the initial stages of treatment when the bacterial populations in the lesions were large. Relapse was due to the regrowth

of viable organisms that had persisted in the latent state. To overcome these obstacles it was necessary to give the patients a three-drug combination initially and secondly to continue the treatment for 18 to 24 months with two drugs.

With the introduction of rifampicin the outlook for treatment of TB changed dramatically. It was no longer necessary to give streptomycin daily for three months initially to prevent failure. The relapse rate also came down steadily even though the duration of

treatment was considerably shorter. This was possible because complete, or almost complete sterilization of the lesions became feasible with the introduction of rifampicin and pyrazinamide.

Principles of treatment of tuberculosis

To understand the principles of the treatment of TB it is necessary to study its evolution over the years. For a disease that has been in existence since antiquity and has left its imprint on the history of mankind, specific treatment aimed at the causative agent became available for the first time only in 1944 with the discovery of streptomycin by Selman Waksman^{1,2}. Before that time empirical measures such as blood letting, horse riding, sea voyages, graded exercise, absolute bed rest, calcium, injections of extracts of gold or other heavy metals, artificial pneumothorax or peritoneum, thoracoplasty, and various other exotic remedies were practiced, usually in the setting of a sanatorium, and without much success³. Soon after the discovery of streptomycin, para aminosalicylic acid (PAS) in 1949, and isoniazid in 1952 became available, heralding the era of effective antituberculosis chemotherapy. The main objective of treatment of TB in the early years of chemotherapy was to prevent the emergence of drug resistance. This required treatment for a prolonged duration of 18 to 24 months. The discovery of rifampicin in the late 1960s and the rediscovery of the antimycobacterial activity of pyrazinamide soon after, were major breakthroughs in the treatment of TB that made it feasible to shorten the duration of treatment considerably. Randomised clinical trials carried out by the British Medical Research Councils (BMRC) in East Africa and Hong Kong and the Tuberculosis Research Centre (TRC) of the Indian Council of Medical Research in Chennai, India, served to establish many of the principles of the chemotherapy of TB^{4,5}. The stage for these important developments was set by the landmark clinical trial by the TRC, Chennai (then called the Tuberculosis Chemotherapy Centre) in the late 1950s showing that TB could be treated effectively on an outpatient basis and did not require admission in a sanatorium⁶. This study not only established the bacteriological efficacy of the treatment regimen in curing the patient, but also showed that the close contacts of those patients

treated at home were not at a greater risk of developing TB compared to the contacts of those treated in the sanatorium⁷. The global impact of the findings of this study is now well recognized and domiciliary treatment for TB became the therapeutic policy for developing countries⁸.

The first reports of effective short-course treatment for TB came from East Africa^{9,10}. In a randomized clinical trial the efficacy of four 6-month regimens (streptomycin and isoniazid, streptomycin, isoniazid and rifampicin, streptomycin, isoniazid and pyrazinamide, streptomycin, isoniazid and thioacetazone) was compared with a standard 18-month regimen of isoniazid and thioacetazone for the treatment of patients with pulmonary TB. It was found that the 3-drug combination of streptomycin, isoniazid and rifampicin resulted in sputum conversion in all the patients at the end of treatment and a relapse rate of only 3 per cent. This study was the forerunner of several other studies on short-course chemotherapy in East Africa and other countries including India, which helped to identify the specific role of each drug in the multi-drug treatment regimen, its role in the particular phase of treatment, to establish dosage levels, to identify drugs suitable for intermittent drug dosing, delineate ideal treatment durations and document adverse reactions of individual drugs and regimens⁵.

In addition to findings from clinical trials, evidence from animal experiments at the Pasteur Institute in Paris¹¹, from *in vivo* and *in vitro* laboratory work by Dickinson and Mitchison in London¹² and from studies in East Africa on early bactericidal activity¹³ have provided valuable data on the activity of antituberculosis drugs. On the basis of these findings, Mitchison suggested the existence of four types of bacterial populations in a patient with TB, according to their anatomical locations and degree of metabolic activity¹⁴. The first is a population of actively growing bacilli present in liquefied caseous material of the tuberculous lesion and the lining of the walls of pulmonary cavities. This is by far the largest fraction of the total bacterial population and contributes to the entire bulk of the bacilli excreted in the sputum. These bacilli are killed by isoniazid, and to a lesser extent by rifampicin and streptomycin.

The second population consists of slow-growing bacilli situated within macrophages in an acid milieu; pyrazinamide is the only drug that acts on this population, and probably rifampicin, to a lesser extent. The third population consists of small number of bacilli present extracellularly in solid caseous lesions and exhibit brief spurts of growth; rifampicin is the only drug that acts rapidly and kills these bacilli during their brief periods of activity. Besides these three populations of bacilli there probably exists a fourth population of dormant bacilli that is beyond the reach of any drug. All these populations of bacilli exist in the lesions and therefore it is necessary to give at least 3 drugs, isoniazid, rifampicin and pyrazinamide, and possibly streptomycin as well to cover the spectrum of all the bacillary populations, to ensure sterilization of the lesions.

Drug combinations in short course chemotherapy

Short-course chemotherapy has been the standard of care for treating TB for the last 30 years. The choice of the individual drugs in the treatment regimen in short-course chemotherapy is crucial. Bactericidal and sterilizing activities of the individual drugs have to be considered. Evidence of bactericidal activity can be obtained from laboratory studies on the effects of the drugs on cultures of tubercle bacilli *in vitro*, efficacy of the drugs in experimental TB in laboratory animals and the speed of sputum conversion in patients undergoing treatment and the magnitude of the fall in the bacterial content of sputum within a short period of initiation of treatment¹⁵. The sterilizing activity of the drugs is assessed from the proportion of patients who have bacteriological relapse after stopping treatment. The bactericidal activity of antituberculosis drugs as assessed in *in vitro* and animal experiments is shown in Table I.

Current short-course regimens use an initial intensive phase (usually 2 months) of multiple drugs to rapidly reduce the number of organisms present; this is followed by a longer continuation phase of fewer drugs that have the ability to kill (sterilize) the more slowly growing organisms. From studies done in human treatment trials, the rate of killing appears to be fastest during the initial several days of treatment¹³. Thus, the first phase of antituberculosis

Table I. Bactericidal activity of first line antituberculosis drugs in *in vitro* studies and in animal experiments

Drug	Bactericidal activity		
	<i>In vitro</i>	In mouse	In guinea pig
Isoniazid	2+	2+	2+
Rifampicin	2+	2+	2+
Streptomycin	3+	1+**	2+
Pyrazinamide	2+*	2+**	0**

*pH 5.2-5.6

** Drugs given in dosage considerably higher than that used in man

0, no activity

1+, 2+, 3+ (indicate increasing degrees of bacterial activity)

Source: Ref. 15

treatment focuses on rapid killing of organisms and is referred to as the phase of bactericidal activity. The measure of bactericidal activity of a treatment regimen is the proportion of patients who become sputum culture negative after two months of treatment. Fig. 1 summarises the bactericidal activity of different antituberculosis drugs assessed by the proportion of patients who become sputum culture negative after two months of treatment, in patients with bacteriologically positive pulmonary TB treated in clinical trials in Madras¹⁶, East Africa¹⁷ and Hong Kong¹⁸. Isoniazid alone produced sputum culture conversion in 44 per cent of patients, reflecting its high bactericidal potential. The addition of a bacteriostatic drug thioacetazone, or PAS or ethambutol to isoniazid did not result in any significant increase in culture negativity. Even the addition of a bactericidal drug streptomycin to isoniazid only resulted in a marginal increase to 49 per cent. In contrast, the addition of pyrazinamide or rifampicin contributes significantly to the bactericidal activity and are therefore suitable for short-course chemotherapy.

In contrast, it takes a much longer time to kill the more slowly growing organisms or persistors, and the goal of this phase of treatment is to kill all the remaining viable bacilli or reach a point of sterilization; thus, the second phase of treatment is referred to as the phase of sterilizing activity. The measure of the sterilizing activity of a regimen is reflected by the relapse rate after successful treatment.

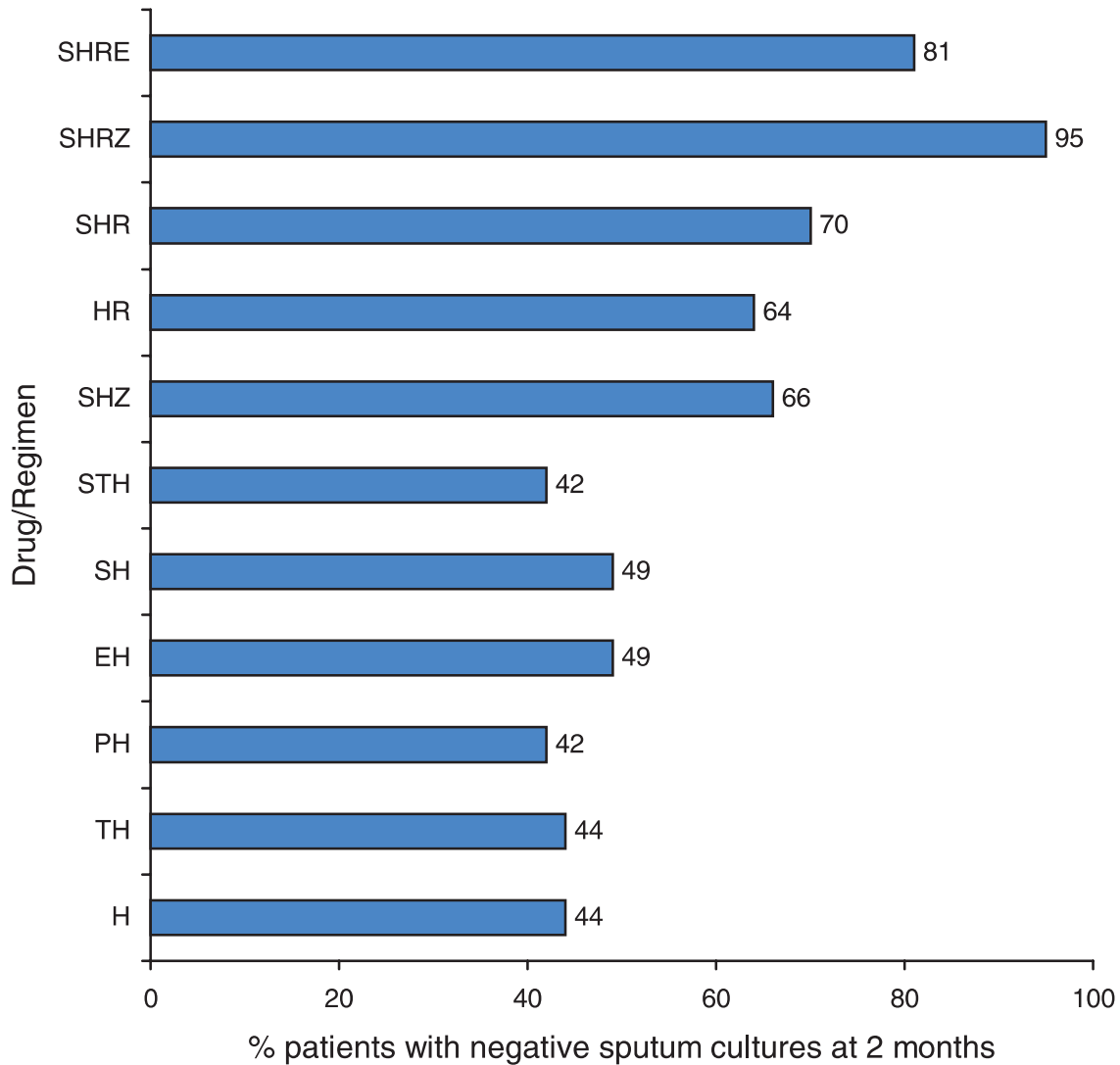


Fig.1. Bactericidal activity of different antituberculosis drugs assessed by the proportion of patients who become sputum culture negative after two months of treatment, in patients with bacteriologically positive pulmonary tuberculosis treated in clinical trials in Madras, East Africa and Hong Kong.

H, isoniazid; T, thioacetazone; P, para-aminosalicylic acid (PAS); E, ethambutol; S, streptomycin; Z, pyrazinamide; R, rifampicin
Source: Refs.16-18.

Of these two phases, it is the sterilizing activity of a regimen that is more important because it determines the duration of treatment; the better the sterilizing activity of a regimen, shorter the duration of treatment. In contrast, the early bactericidal activity of an antituberculosis regimen is less important overall except it probably provides an indication of how long a patient remains infectious. Fig.2 illustrates the sterilizing activities of different drug combinations in clinical trials for the treatment of patients with bacteriologically positive pulmonary TB

in East Africa^{10,19} and Hong Kong^{18,20}. The addition of thioacetazone to streptomycin-isoniazid combination did not contribute to the sterilizing activity with the relapse rate continuing to be high, *viz.*, 22 per cent. Pyrazinamide, on the other hand made a significant contribution and reduced the relapse rate from 29 to 8 per cent. It is also seen that the sterilizing activity of ethambutol is inferior to that of pyrazinamide. The low rate of relapses with the 6-month isoniazid-rifampicin and the 6-month isoniazid-rifampicin-streptomycin regimens are

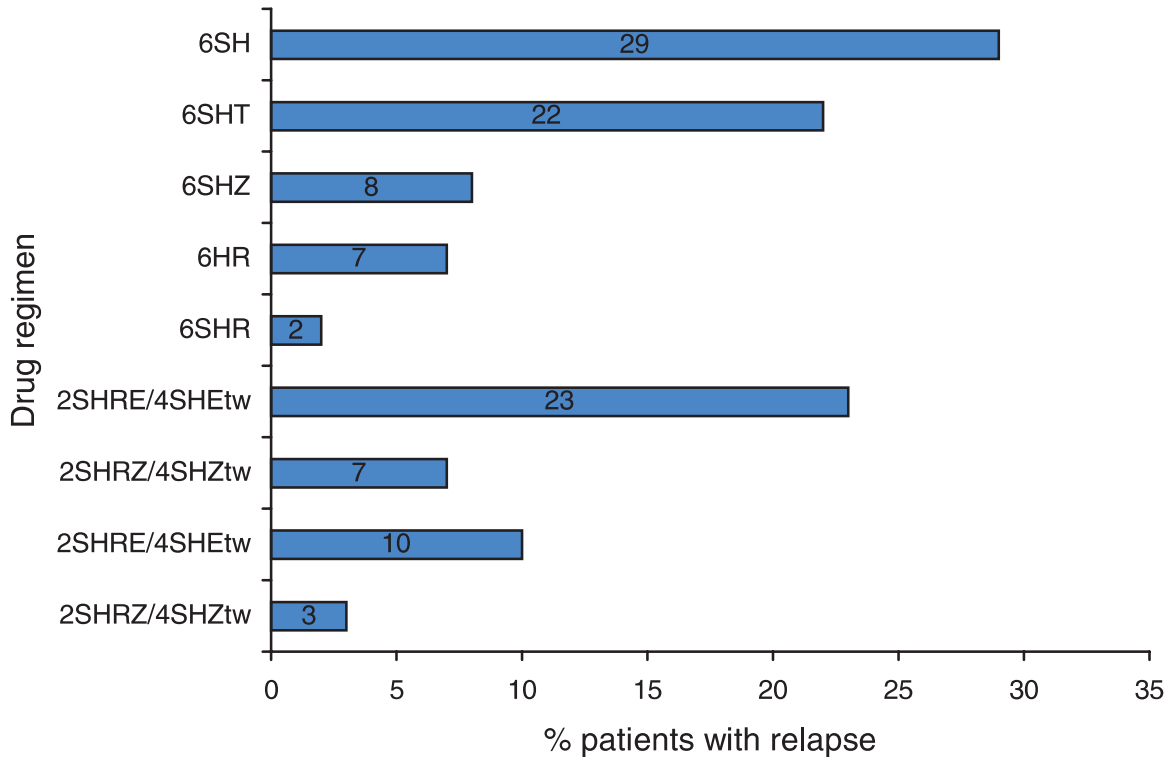


Fig.2. Relapse rates of different drug combinations in clinical trials for the treatment of patients with bacteriologically positive pulmonary tuberculosis East Africa and Hong Kong.

S, streptomycin; H, isoniazid; T, thioacetazone; Z, pyrazinamide; R, rifampicin; E, ethambutol; tw, indicates treatment given twice-weekly

Numbers preceding drug regimens indicates number of months of treatment

Source: Refs.10, 18-20.

reflective of the substantial and significant contribution of rifampicin in achieving sterilisation.

Intermittent treatment regimens

The efficacy of intermittent treatment (*i.e.*, treatment given twice or thrice-weekly rather than daily) was established fairly early in the history of the chemotherapy of TB. Intermittent treatment is based on the lag effects exhibited by cultures of *M. tuberculosis* after being exposed to pulses of bactericidal antituberculosis drugs such as isoniazid and rifampicin, but not to a bacteriostatic drug such as thioacetazone, and in experimental tuberculosis in guinea pigs²¹⁻²³. A randomized clinical trial by the TRC, Chennai, showed that streptomycin plus isoniazid twice a week for 12 months was as effective in providing a bacteriological cure as PAS and isoniazid given daily for 12 months in patients with sputum positive pulmonary TB^{24,25}. A BMRC study

in Hong Kong showed that streptomycin, isoniazid and pyrazinamide given for 9 months either daily, or thrice-weekly or twice-weekly were all equally efficacious²⁶. Subsequently another study from the same site showed that 6 months of a thrice-weekly, 4-drug regimen was very effective so long as isoniazid, rifampicin and pyrazinamide were included in the regimen; substituting ethambutol for pyrazinamide however increased the relapse rate to an unacceptably high level²⁷ (Table II).

A large randomized clinical trial in Chennai by the TRC²⁸ compared either thrice-weekly or twice-weekly 4-drug regimens (isoniazid, rifampicin, pyrazinamide and streptomycin) for the first two months followed by either twice-weekly or once-weekly 3-drug or 2-drug combinations for the next 4 months. The second month sputum culture negativity ranged from 86 to 89 per cent and the relapse rates were 3 per cent for the thrice-weekly initial phase

Table II. Rates of relapse after treatment in patients treated with daily and intermittent regimens in Hong Kong

Study	Regimen	Patients	% relapse
Hong Kong Chest Service/BMRC ²⁶	9 SHZ	65	5*
	9 SHZ thrice-weekly	65	6*
	9 SHZ twice-weekly	49	6*
Hong Kong Chest Service/BMRC ²⁷	6 HRZE	161	1**
	6 HRSZE thrice-weekly	150	1**
	6 HRSZ thrice-weekly	150	1**
	6 HRSE thrice-weekly	160	8**
	6 HRZE thrice-weekly	161	2**

BMRC, British Medical Research Councils

Superscript numerals represent reference numbers

Number preceding regimens indicates months of treatment

S, streptomycin; H, isoniazid; Z, pyrazinamide; R, rifampicin; E, ethambutol

* relapse rates at 30 months

** relapse rates at 12 months after

regimens and 6 per cent for the twice-weekly initial phase regimens, respectively.

The advantages of intermittent treatment are significant. While the efficacy is equal to that of daily treatment, intermittent regimens are less expensive, have fewer adverse drug reactions and most importantly, intermittent treatment facilitates directly observed therapy. Poor adherence to treatment by patients has been, and still is, the biggest bugbear for control of TB, as many patients discontinue treatment before completing the full course. So, the establishment of intermittent treatment was a major breakthrough in TB treatment.

Tuberculosis control

The treatment of patients with active TB is the cornerstone of any TB control programme. The World Health Organisation's (WHO) Global Tuberculosis Programme emphasises the importance of standardised treatment administered under direct observation as one of the important components of its global strategy to control TB. The 'directly observed treatment short course' (DOTS) strategy, is today recognised as the only means by which effective TB control could be

achieved. From the public health perspective the highest priority in a TB control programme is the identification and treatment of the infectious TB patient, *i.e.*, those patients with sputum smear-positive pulmonary TB. In settings of resource constraints it is necessary for rational resource allocation to prioritise TB treatment categories according to the cost-effectiveness of treatment of each category. The WHO has ranked TB patients from category I (highest priority) to category IV (lowest priority) and the treatment regimen for each category is shown in Table III²⁹. Disease categorisation is based on the severity of the disease judged by the patient's sputum smear status and or clinical condition and radiological extent of the disease, the site of the disease (pulmonary or extra-pulmonary) and whether or not the patient had received prior treatment for TB. Significant modifications in the WHO guidelines of 2003²⁹ from the previous guidelines of 1997³⁰ are (i) TB patients with concomitant HIV infection are included in category I; and (ii) the treatment for category III patients is the same as that for category I patients, *i.e.*, a 4-drug intensive phase followed by a 2-drug continuation phase. Member countries have the liberty to choose the regimens most appropriate for them.

Table III. WHO recommended treatment regimens for different disease categories

Disease Category	Tuberculosis patient definition	Treatment regimen	
		Initial phase (daily or three times weekly)	Continuation phase (daily or three times weekly)
I	New smear-positive New smear-negative with extensive parenchymal involvement New severe extra-pulmonary tuberculosis or severe concomitant HIV infection	2 HRZE*	4 HR or 6 HE daily
II	Previously treated sputum smear-positive pulmonary tuberculosis - relapse - treatment after interruption - treatment failure	2 HRZES/ 1 HRZE	5 HRE
III	New smear-negative pulmonary tuberculosis Extra-pulmonary tuberculosis	2 HRZE	4 HR or 6 HE daily
IV	Chronic and MDR tuberculosis	Specially designed standardized or individualized regimens	

H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomycin

* Streptomycin may be used instead of ethambutol. In meningeal TB ethambutol should be replaced by streptomycin.

MDR – multidrug resistant

Number preceding regimens indicates months of treatment

Source: Ref. 29

Revised National Tuberculosis Control Programme (RNTCP)

India has had a National Tuberculosis Control Programme functioning from the early 1960s. This programme was based on the research findings of the TRC and the National Tuberculosis Institute (NTI) in Bangalore. Though the programme was based on sound epidemiological and scientific principles, a comprehensive review of the programme in 1992

identified that it suffered from managerial weakness, inadequate funding, over-reliance on X-ray for diagnosis, non-standard treatment regimens, low rates of treatment completion and lack of systematic information on treatment outcomes³¹. Faced with these facts the Government of India has implemented a Revised National Tuberculosis Control Programme (RNTCP). This programme builds on the substantial infrastructure established by the previous programme. The RNTCP is based on the WHO's DOTS strategy

Table IV : Recommended treatment regimens for different disease categories under Revised National Tuberculosis Control Programme of India

Disease category	Tuberculosis patient definition	Treatment regimen	
		Initial phase	Continuation phase
I	New smear-positive New smear-negative with extensive parenchymal involvement New severe extra-pulmonary tuberculosis	2 HRZE thrice-weekly	4 HR thrice-weekly
II	Previously treated sputum smear-positive pulmonary tuberculosis - relapse - treatment after interruption - treatment failure	2 HRZES/ 1 HRZE thrice-weekly	5 HRE thrice-weekly
III	New smear-negative pulmonary tuberculosis Extra-pulmonary tuberculosis	2 HRZ thrice-weekly	4 HR thrice-weekly

H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomycin

Drug dosages in mg.: Thrice-weekly

Isoniazid 600

Rifampicin* 450

Ethambutol 1200

Pyrazinamide 1500

Streptomycin 750

* Rifampicin dosage 600 mg. For patients weighing 60 kg., or more

Source: Ref. 32

and consists of the following components: (i) diagnosis of pulmonary TB to be made primarily by sputum microscopy; (ii) treatment to be given under direct observation, at least during the intensive phase; (iii) regular drug supply to be ensured; (iv) the patient's progress to cure to be monitored by follow-up sputum tests; and (v) ensuring administrative and political commitment. Treatment is given thrice-weekly both during the intensive phase and the continuation phase³² (Table IV). Category I patients are those with newly diagnosed smear-positive pulmonary TB, or newly diagnosed smear-negative pulmonary TB who are clinically seriously ill or with extensive parenchymal lesions on the chest X-ray, or those with severe forms of extra-pulmonary TB. Category II patients are those with sputum smear-

positive pulmonary TB who have been treated for TB in the past, and who have now presented with a relapse, or treatment failure or have attended after a period of interrupted treatment. Category III patients consist of newly diagnosed sputum smear-negative pulmonary TB and those with non-serious forms of extra-pulmonary TB, viz., TB of the lymphnodes, skin or unilateral pleural effusion.

Category I patients receive a 6-month regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for two months followed by isoniazid and rifampicin thrice-weekly for four months (2HRZE thrice-weekly/4HR thrice-weekly). The patient's response to treatment is monitored with sputum smear examinations at 2 and 4 months and at

the end of treatment. If the second month sputum smear is positive the intensive phase is extended for one more month.

Category II patients receive an 8-month regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for three months with streptomycin for the first two months, followed by isoniazid, rifampicin and ethambutol thrice-weekly for five months (2SHRZE thrice-weekly/1HRZE thrice-weekly/5HRE thrice-weekly). As for category I patients, sputum smear examination is done at the end of the intensive phase, and if it is positive, the intensive phase is extended by one more month.

Category III patients receive a 6-month regimen similar to the category I regimen, but without ethambutol in the intensive phase (2HRZ thrice-weekly/4HR thrice-weekly).

During the intensive phase of treatment every dose is administered under direct observation, while during the continuation phase patients are asked to attend the treatment clinic once a week, when one dose of treatment is given under direct observation and the other two doses given to the patient for self-administration. A unique feature of the RNTCP is that all the medicines come in blister packs and each patient is allotted a box of medicines that contains drugs for the full duration of treatment, at treatment initiation. The drug box however will not be handed over to the patient, but maintained in the treatment clinic, and medicines from the box can be given only to the allocated patient. This helps instill confidence in the patient that he will never arrive at the treatment centre and find that there are no medicines. Patients who fail on category II regimen, some of whom are likely to have multidrug resistance (MDR) should be managed in specialised referral institutes.

How short is short-course chemotherapy?

In the last few years the fluoroquinolone group of drugs have added a new dimension to the chemotherapy of TB. Quinolones have considerable *in vitro* activity against *M. tuberculosis* and other mycobacteria³³, and they have been used as part of regimens to treat patients with MDR TB (TB caused

by *M. tuberculosis* that is resistant to isoniazid and rifampicin with or without resistance to other anti-TB drugs). There is limited data on the use of fluoroquinolones in the treatment of patients with drug-susceptible TB. A randomized trial first shed light on the role of ciprofloxacin in the treatment of drug-susceptible pulmonary TB³⁴. A regimen of isoniazid and rifampicin for 6 months plus ciprofloxacin for the first 4 months was compared with isoniazid and rifampicin for 6 months plus pyrazinamide for the first 4 months plus ethambutol for the first 2 months in HIV seropositive and negative pulmonary TB patients. The relapse rate 6 months after treatment was unacceptably high with the ciprofloxacin-containing regimen, indicating that ciprofloxacin added nothing to the sterilizing activity of isoniazid and rifampicin. However, a recent landmark clinical trial from the TRC, Chennai studied the role of ofloxacin in shortening the duration of treatment for TB³⁵.

One of the long-term goals for the control TB has been to shorten the duration of treatment while ensuring high rates of cure and low rates of relapse. Shorter treatment regimens would ease drug administration for both patients and providers. An effective, fully oral regimen of 3 or 4 months' duration would have significant practical advantages for TB control. In a previous randomized clinical trial by the TRC, Chennai, a 3-month regimen of daily streptomycin, isoniazid, rifampicin, and pyrazinamide resulted in a nearly 100 per cent favourable outcome at the end of treatment; yet 20 per cent of the patients relapsed in the subsequent 21 months³⁶. Based on that experience, as well as the results of *in vitro* studies demonstrating the bactericidal activity of ofloxacin³⁷, the TRC conducted a randomized clinical trial to assess the efficacy of 3-, 4-, and 5-month regimens using ofloxacin instead of ethambutol in the intensive phase for the treatment of patients with bacteriologically confirmed pulmonary TB³⁵. The results in patients followed up for 24 months after treatment showed that among patients with drug-susceptible bacilli treated with the 4- and 5-month regimens with a 3-month intensive phase of isoniazid, rifampicin, pyrazinamide and ofloxacin daily followed by

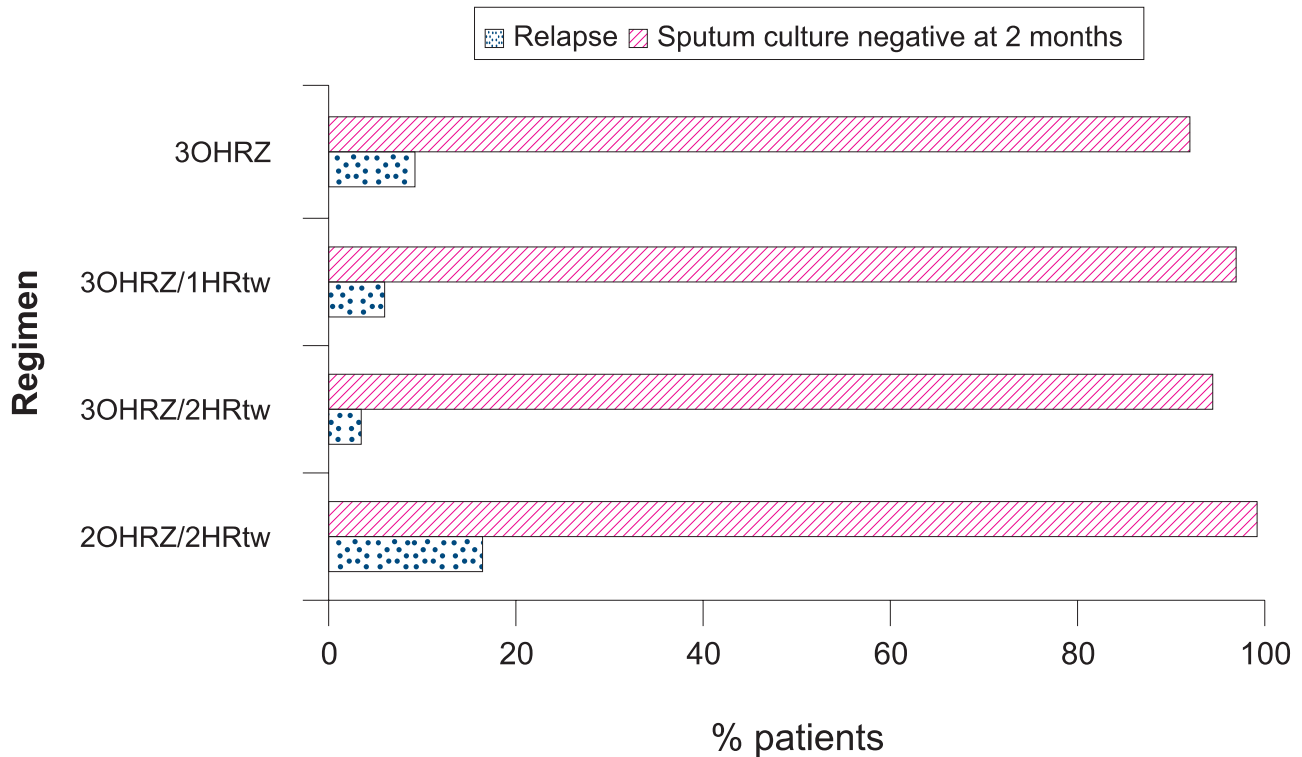


Fig.3. Results in bacteriologically positive pulmonary tuberculosis patients treated with ofloxacin-containing regimens of 3,4 and 5 months in Chennai, South India.

Regimens:

3OHRZ: ofloxacin, isoniazid, rifampicin and pyrazinamide daily for 3 months

3OHRZ/1HRtw: ofloxacin, isoniazid, rifampicin and pyrazinamide daily for 3 months followed by isoniazid and rifampicin twice-weekly for 1 month

3OHRZ/2HRtw: ofloxacin, isoniazid, rifampicin and pyrazinamide daily for 3 months followed by isoniazid and rifampicin twice-weekly for 2 month

2OHRZ/2HRtw: ofloxacin, isoniazid, rifampicin and pyrazinamide daily for 2 months followed by isoniazid and rifampicin twice-weekly for 2 month

Relapse rates are for 24 months after completing treatment.

Source: Ref. 35.

isoniazid and rifampicin twice-weekly for one or two months, only 4 and 2 per cent relapsed, respectively. The sputum culture conversion after 2 months of treatment was 92-97 per cent. (Fig.3). This study showed that it is feasible to shorten the duration of treatment for smear-positive pulmonary TB from the currently recommended 6 months to 4 months. With newer fluoroquinolones such as moxifloxacin and gatifloxacin that exhibit even more potent antimycobacterial activity, both bactericidal³⁸, and sterilizing^{39,40}, it should be possible in the near future to further reduce the duration of treatment for TB. Clinical trials using

moxifloxacin or gatifloxacin along with first line antituberculosis drugs are being planned at TRC.

Extra-pulmonary tuberculosis

Extra-pulmonary TB accounts for 10-15 per cent of all cases of TB. In general it is more difficult to diagnose than pulmonary disease, and often requires invasive procedures to obtain diagnostic specimens for histological or bacteriological confirmation. Because this form of TB is not considered to be of public health importance as the patients are not infectious and do not transmit the disease to others,

Table V. Recommended drug dosage of antituberculosis drugs for childhood tuberculosis

Drug	Recommended dosage (dose range) in mg/kg body weight	
	Daily	Thrice-weekly
Isoniazid	5 (4-6)	10 (8-12)
Rifampicin	10 (8-12)	10 (8-12)
Pyrazinamide	25 (20-30)	35 (30-40)
Streptomycin	15 (12-18)	15 (12-18)
Ethambutol	15 (15-20)	30 (20-35)
Thioacetazone	2.5	Not applicable

Source: Ref. 29

most guidelines for treatment intended for use in low-income countries have not addressed the treatment of this entity in any great detail.

However, the TRC, Chennai has conducted clinical trials in tuberculous lymphadenitis^{41,42}, tuberculous meningitis⁴³, spinal TB^{44,45}, abdominal TB⁴⁶, tuberculoma of the brain⁴⁷ and cutaneous TB (manuscript in preparation). A BMRC study investigated the efficacy of a 6-month regimen with or without prednisolone for treating patients with tuberculous pericarditis, in Transkei, South Africa⁴⁸. The evidence from all these trials indicate that extra-pulmonary TB can be effectively treated with short-course chemotherapy, often with fewer drugs than in the case of pulmonary TB. Except for meningitis, all other forms of extra-pulmonary TB can be successfully treated with 6-month regimens. The RNTCP recommends category III regimen for lymphnode TB, cutaneous TB and unilateral pleural effusion, and category I regimen for more severe forms of extra-pulmonary TB. Patients with tuberculous meningitis should be treated for at least nine months. Corticosteroids should be used concurrently, at least in the initial stages of treatment for meningitis, pericarditis and large pleural effusions.

Tuberculosis in children

The DOTS strategy is applicable to all patients with TB, including children. The recommended

regimens for the treatment of childhood tuberculosis are the same as for adults. The dosage of drugs is shown in Table V. However, there are important differences between children and adults that may affect drug choice and dosage, which need to be borne in mind. Recommended dosage is based on research in adults and yet metabolism of drugs varies with age. The effectiveness of an ethambutol-isoniazid continuation phase has never been studied in children, whereas rifampicin-isoniazid has proved efficacy. In children with tuberculous meningitis streptomycin should be used instead of ethambutol because ethambutol does not cross the blood-brain barrier. Corticosteroids should also be used. Given the choice, ethambutol should be avoided in young children, as it will not be possible to monitor visual problems, if they arise.

Child contacts of patients with infectious tuberculosis

Children who are close household contacts of sputum smear-positive pulmonary TB patients should be screened for TB. Those with a diagnosis of TB should be treated. Those who are well and aged five years or less should receive isoniazid prophylaxis (5 mg/kg daily) for three months. A tuberculin test should be done then, if available. If the test is negative BCG vaccination should be given; if the tuberculin test is positive, isoniazid prophylaxis should be continued for three more

Table VI. Regimens recommended by WHO for treatment of multidrug resistant tuberculosis (MDR TB)

Drug susceptibility profile of essential drugs:	Initial phase (6 months)	Continuation phase (12-18 months)
Not available	Kanamycin* Ethionamide Quinolone** Pyrazinamide/ Ethambutol	Ethionamide Quinolone Pyrazinamide/ Ethambutol
Resistant to Isoniazid and rifampicin	Streptomycin^ Ethionamide Quinolone Pyrazinamide/ Ethambutol	Ethionamide Quinolone Pyrazinamide/ Ethambutol
Resistant to all essential drugs	1 injectable + 1 quinolone + 2 of these 3 drugs: PAS, Ethionamide, Cycloserine	1 quinolone + 2 of these 3 drugs: PAS, Ethionamide, Cycloserine
Drug susceptibility profile of reserve drugs available	Individually tailored regimen according to susceptibility pattern	Individually tailored regimen according to susceptibility pattern

* Amikacin or capreomycin can also be used. However, since there is cross-resistance between kanamycin and amikacin, if either drug was used previously, or if resistance to them is suspected, capreomycin is the preferred choice.
** Ofloxacin or ciprofloxacin
^ If resistance to streptomycin is confirmed, replace with kanamycin, amikacin or capreomycin
Source: Ref. 29

months. If tuberculin test is not available, isoniazid prophylaxis should be continued for six months. Children who are well and above five years should be clinically followed up⁴⁹.

Multi-drug resistant tuberculosis (MDR TB)

The WHO declared TB as a global emergency in 1993. One of the reasons for this unprecedented declaration was an epidemic of MDR TB in the USA in the late 1980s and early 1990s, predominantly in HIV infected individuals housed in prisons and shelters for the homeless, conditions that facilitated rapid transmission of infection. Mortality was in the order of 80 per cent and the mean duration from diagnosis to death was 4-16 wk^{50,51}. Alarmed by this, the WHO conducted a worldwide survey on drug resistance that suggested that there were hotspots of MDR TB⁵². In India initial resistance to rifampicin and isoniazid ranged from 0.5 to 5.3 per cent⁵³.

The importance of MDR TB lies in its poor response to available therapeutic regimens. In HIV-negative patients with MDR TB, only 56-88 per cent show a consistent response to treatment and the risk

of failure is 80 times higher than in those with drug-susceptible strains⁵⁴. In a study on immunocompetent MDR TB patients, the mortality directly attributable to TB was 22 per cent⁵⁵ while the mortality in HIV infected patients has been reported to range from 75-90 per cent⁵⁶.

The management of MDR TB is a challenging problem. Treatment is less effective, more toxic and much more expensive compared to the treatment of patients with drug susceptible TB. Certain guidelines have to be borne in mind when confronted with suspected drug resistance. The first and foremost of these is to obtain from the patient an exhaustive and meticulous history of previous treatment for TB. Details such as the names of drugs, the dosage, when taken, for what duration and with what regularity are all important. All available prescriptions have to be scrutinised. Patients often do not know what drugs they had been prescribed. So indirect questions might be necessary, such as did the patient take any capsules which made the urine red, any medicines that caused joint pains *etc.*⁵⁷. The treatment regimen should include at least four drugs that the patient is known to be susceptible to, or has not previously received,

Table VII. Symptom-based approach to side effects of antituberculosis drugs:

Side-effects	Drugs(s) probably responsible	Management
<i>Minor:</i>		
Anorexia, nausea, abdominal pain	Pyrazinamide, Rifampicin	Continue anti-tuberculosis drugs Check drug doses Antacids, anti-emetics Give drugs with small meals or last thing at night
Itching, no rash	Pyrazinamide Rifampicin Isoniazid Streptomycin	Antihistamines
Joint pains	Pyrazinamide	Aspirin
Burning sensation in feet	Isoniazid	Pyridoxine 100 mg
<i>Major:</i>		
Giddiness or deafness	Streptomycin	Stop responsible drug(s) Stop streptomycin; use ethambutol
Jaundice, hepatitis	Pyrazinamide, Rifampicin, Isoniazid	Stop pyrazinamide, rifampicin, isoniazid; use streptomycin, ethambutol
Visual impairment	Ethambutol	Stop ethambutol
Pruritis, skin rash	Thioacetazone Pyrazinamide Rifampicin Isoniazid Streptomycin	Stop responsible drug
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin; never use again
'Flu syndrome'	Rifampicin	Stop rifampicin
Seizures	Isoniazid	Stop isoniazid

Source: Ref. 29

including an injectable agent and a fluoroquinolone in the initial phase, and at least three of the most active and best tolerated drugs in the continuation phase. Treatment should be given daily and directly observed. An initial phase of at least six months should be followed by a continuation phase of 12-18 months. Treatment should be continued till the sputum cultures remain negative for at least 12 months. Table VI lists the regimens recommended by the WHO for treatment of MDR TB²⁹.

While drug susceptibility testing may not be available in many resource-limited settings, all efforts should be made to obtain a reliable drug susceptibility profile of the patient's infecting organisms. It is wise to bear in mind that even in developed countries, there is much variation in results from different laboratories which perform drug susceptibility tests for *M. tuberculosis*. Out of more than 80 strains of *M. tuberculosis* typed as resistant to streptomycin,

isoniazid or PAS at the peripheral laboratory, only 27-49 per cent of the strains were confirmed to be resistant when retested at the reference laboratory⁵⁸. Incorrect susceptibility test results can lead to unnecessary changes of regimen, decreasing the chances of cure. Judicial clinical judgment often obviates the need for drug susceptibility testing. If drug susceptibility testing is considered essential, it should be done in a laboratory with established credentials.

An important dictum in the management of tuberculosis is never to substitute a single drug in a regimen that appears to be failing. Doing so may lead to the sequential development of resistance to the drug that is being introduced. Always two or more new drugs should be added to an existing regimen. Since most drugs used in the treatment of MDR TB have adverse effects, toxicity has to be carefully monitored. Sometimes drugs may need to be withdrawn either temporarily or permanently and alternate drugs substituted. Often adverse reactions can be managed with symptomatic treatment. The patient needs constant encouragement and motivation to cope with adverse reactions to drugs and to complete the full course of treatment. Ideally this should be done in hospital and so it is a good policy to hospitalise patients, at least initially, to facilitate close monitoring, both for toxicity and for treatment compliance.

The value of the older drugs in the treatment of MDR TB today has to be emphasised. Many young patients with MDR TB have not received PAS or thioacetazone in the past and these can be used with success in such patients. So also the value of high dose isoniazid (600 mg), in patients with documented isoniazid resistance. In our experience at TRC, Chennai, patients with MDR TB who have remained sputum positive for years together when treated with other drugs have converted to sputum negativity when switched on to 600 mg of isoniazid and PAS as a last resort.

The duration of therapy for MDR TB has not been clearly established. The duration that has been recommended in the USA is 18-24 months at least, or

for 24 months after sputum culture converts to negative⁵⁹. At the TRC, Chennai, MDR TB patients are treated for a minimum period of 18 months and for at least 12 months after sputum cultures become consistently negative.

Role of Surgery

In carefully selected patients surgery may have an important role to play in the management of MDR TB. A number of studies have demonstrated the value of resectional surgery in patients with predominantly unilateral disease, with adequate respiratory reserve and in whom chemotherapy alone had failed^{60,61}.

Adverse reactions to anti-tuberculosis treatment

The currently recommended antituberculosis regimens are usually well tolerated. However some patients may experience problems, usually due to the bulk of the drugs, a single day's dose consisting of 6-7 tablets. The patients have to be informed about the orange discolouration of the urine due to rifampicin, as this usually alarms patients if they are not told. They have to be reassured that this is not something unexpected or harmful.

Drug related adverse effects may be minor or major²⁹ (Table VII). In general, a patient who has minor adverse effects should be encouraged to continue the treatment with symptomatic measures such as antacids, antihistamines, antiemetics or analgesics, as indicated. If major adverse reactions occur, the regimen, or the offending drug, if identified, must be stopped. Further management depends on the nature of the adverse reaction, and may have to be done in a hospital.

Hepatic dysfunction:

Transient elevation of transaminase levels is relatively common during the course of antituberculosis treatment and does not warrant interruption of treatment. Drug-induced hepatitis accompanied by clinical jaundice necessitates withholding of all drugs and institution of supportive treatment. Once liver function returns to normal, antituberculosis drugs may be reintroduced. If

jaundice recurs, rifampicin, isoniazid and pyrazinamide should be withdrawn and the patient treated with streptomycin and ethambutol. During the course of jaundice, if antituberculosis treatment is considered essential, streptomycin and ethambutol should be used.

Renal impairment: Rifampicin induced renal impairment or failure is rare and is more common when rifampicin is given intermittently⁶². It is believed to be immune-mediated. Rifampicin should be stopped immediately and measures to support renal function, including haemodialysis, should be instituted. After renal function returns to normal tuberculosis treatment can be continued without rifampicin. Renal impairment may also occur with streptomycin. In the presence of pre-existing renal impairment rifampicin, isoniazid and pyrazinamide can be given in normal dosages. In the presence of severe renal failure dosage of isoniazid should be reduced to 200 mg with pyridoxine to avoid peripheral neuropathy. Streptomycin and ethambutol are the two main drugs that are cleared by the renal route. Extra care should be exercised if these drugs are to be used in the presence of renal impairment. Treatment should be planned in consultation with the nephrologist.

Acute thrombocytopaenia and 'shock syndrome': These are rare but life-threatening reactions that may be caused by rifampicin. Rifampicin should be immediately withdrawn from the treatment regimen and supportive measures instituted. Rifampicin should never be re-administered to such patients.

Flu syndrome: This is an immune mediated adverse reaction attributed to rifampicin, usually when the drug is administered in an intermittent rhythm and rarely during daily therapy. It is characterized by fever with or without chills, myalgia, headache and prostration, which characteristically come on after a defined time interval following rifampicin intake. It can be managed with antipyretics, but if the symptoms are severe, rifampicin should be withdrawn from the treatment regimen.

Treatment of TB in special situations

Pregnancy: All first line antituberculosis drugs, except streptomycin can be used in pregnancy. Pyridoxine is sometimes recommended for pregnant women receiving isoniazid. A pregnant woman should be advised that successful treatment of TB with the recommended regimens is important for successful outcome of pregnancy. Women patients should be advised to avoid pregnancy while on antituberculosis treatment. Rifampicin interacts with oral contraceptive medicines resulting in reduced protection against pregnancy. A woman on oral contraceptives can choose between two options while on treatment with a rifampicin-containing regimen; she can either take an oral contraceptive with a higher dose of oestrogen (50: g) or adopt another form of contraception till TB treatment is completed²⁹.

Breast feeding women with TB should receive a full course of antituberculosis treatment. All antituberculosis drugs are compatible with breast feeding. The only precaution that the mother should practice is not to cough onto her baby. The baby should receive prophylactic isoniazid for at least 3 months beyond the time the mother is considered to be non-infectious. BCG vaccination of the newborn should be postponed until the end of isoniazid prophylaxis²⁹.

Liver disorders: Isoniazid, rifampicin and pyrazinamide are all potentially hepatotoxic. Of the three, rifampicin is least likely to cause hepatocellular damage. Patients with the following conditions can receive the usual short-course chemotherapy regimens provided there is no clinical evidence of chronic liver disease - hepatitis virus carriage, past history of acute hepatitis, excessive alcohol consumption. However, in such patients hepatotoxic reactions to antituberculosis therapy may be more common and should therefore be anticipated. Patients with established hepatic disease should not receive pyrazinamide. Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total duration of 8 months. Alternate regimens are nine months of rifampicin and ethambutol, or 12 months of ethambutol and isoniazid with streptomycin for the first two months²⁹.

If a patient with TB develops concurrent acute hepatitis unrelated to TB or its treatment, and this may be very difficult to distinguish, sometimes it may be possible to defer TB treatment until the acute hepatitis has resolved. In other cases, when it is necessary to treat TB during acute hepatitis, the combination of ethambutol and streptomycin is the safest option. After the hepatitis resolves, the patient can then receive a continuation phase of six months of isoniazid and rifampicin. If the hepatitis has not resolved, ethambutol and streptomycin should be continued for 12 months²⁹.

Renal impairment: Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosages to patients with renal impairment or failure. Patients with severe renal failure should receive pyridoxine with isoniazid to prevent peripheral neuropathy²⁹.

Streptomycin and ethambutol are excreted by the kidneys. These drugs can be given in reduced doses if facilities are available for monitoring renal function. Thioacetazone is partially excreted in the urine; however, since the margin between a therapeutic dose and a toxic dose is too narrow, patients with renal failure should not receive this drug. The safest regimen for patients with renal failure is 6 months of isoniazid plus rifampicin with pyrazinamide for the first 2 months²⁹.

Tuberculosis with concomitant HIV infection: The HIV epidemic has had an adverse impact on the global epidemiology of TB with many parts of sub-Saharan Africa and the Far East bearing the brunt⁶³. TB case rates have increased many times in some countries solely attributed to HIV. It is estimated that there were 3.82-4.58 million HIV infected individuals in India as of December 2002⁶⁴, with a majority of them also infected with TB and thus being at greater risk of breaking down with TB disease. The prevalence of HIV seropositivity in TB patients varies widely across the country⁶⁵⁻⁶⁷. Current evidence suggests that anti-TB drug resistance in HIV-TB patients is not yet a matter of concern and the currently recommended 6-month

treatment for TB is expected to be as effective for HIV infected TB patients as for HIV negative ones⁶⁷. However, this has not been established in a clinical trial. Such a clinical trial is now in progress in TRC, Chennai and the interim results should be available in the near future. While TB patients with concomitant HIV infection may respond as well to standard antituberculosis treatment as those who are immunocompetent, deaths during treatment, partly due to HIV itself and partly due to other HIV related diseases, are more frequent in HIV infected patients, particularly in the advanced stages of immunodeficiency. It is also likely that relapses will be more in HIV-TB patients compared to TB patients without HIV. Answers to these questions are likely to become available from the TRC clinical trial. Thioacetazone is contraindicated in those who are HIV infected.

Highly active antiretroviral therapy (HAART) is now recognized as the optimum treatment for those in the later stages of HIV infection⁶⁸. Although HAART is now standard of care in the industrialised countries, very few HIV-infected people have access to HAART in places where the burden of HIV is greatest (sub-Saharan Africa and Asia). While HIV infection is now the biggest risk factor for TB infection progressing to disease, TB has also been shown to facilitate HIV replication and dissemination through the dysregulation of host cytokines, chemokines and their receptors⁶⁹. Thus the combination of antiretroviral treatment along with antituberculosis treatment can be expected to improve the outcome of patients with TB and HIV. While considering treatment regimens for such patients it has to be remembered that rifampicin cannot be used along with protease inhibitors. In treating patients with HIV related TB, the priority is to treat TB, especially smear-positive pulmonary TB. Possible options for antiretroviral therapy in TB patients include the following²⁹.

(i) Defer antiretroviral treatment till TB treatment is completed; (ii) Defer antiretroviral treatment until the end of the initial phase of treatment for TB and use ethambutol and isoniazid in the continuation phase; (iii) Treat TB with a rifampicin-containing regimen and use efavirenz

plus two nucleoside reverse transcriptase inhibitors (NRTI); and (iv) Treat TB with a rifampicin-containing regimen and use two NRTIs; then change to a maximally suppressive HAART regimen on completion of TB treatment.

Diabetes mellitus: Diabetes mellitus is a well-recognized risk factor for TB. Preliminary results from a clinical trial by the TRC, Chennai suggests that the category 1 regimen of RNTCP (2EHRZ thrice weekly/4HR thrice weekly) is sufficiently effective for treating newly diagnosed smear-positive pulmonary TB patients with concomitant Type 2 diabetes mellitus, provided good glycemic control is achieved (unpublished observation).

The present class of antituberculosis drugs was introduced more than 30 yr ago. With the global threat of TB in alliance with the HIV epidemic and the spectre of multidrug resistant disease, there is now a desperate need for new drugs to treat TB. Medicines are needed which can both withstand the test of resistance and ensure shorter treatment. New methods such as combinatorial chemistry and research breakthroughs such as the genome sequencing of *M. tuberculosis*⁷⁰ have opened up new avenues for the pursuit of novel compounds. Possible drug targets could be gene products involved in mycobacterial metabolism, persistence, transcription, cell wall synthesis and virulence⁷¹.

Even with these initiatives it may be many years before new drugs become available. The Global Alliance for TB Drug Development plans to have a new drug in production only by 2010⁷². In the interim, the window of opportunity offered by the discovery of the antituberculosis activity of the fluoroquinolones and the success of ofloxacin in a clinical trial in patients has to be exploited. Randomised clinical trials are being planned with the newer generation fluoroquinolones such as moxifloxacin and gatifloxacin to shorten treatment duration.

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