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# Drug treatment for patients with tuberculosis in the National Tuberculosis Programme

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**Drug treatment for the patient with TB is major issue in any National TB Programme. The right choice of regimens in the Chemotherapy contribute a great deal to the outcome or the end result of the treatment. In Nepal it took many years to choose the right regimens for the drug treatment of TB. The present approved regimens have been tested throughout many countries of the world and found to have high case rates, low relapses and very cost effective. Drug treatment is the only effective method to control tuberculosis.**

*Key Words: Tuberculosis. Chemotherapy. Steptomycin. Paramino salicylic acid (Isoniazid. Observed Treatment Short Course Rifampicin, Ethambutol. Pyrazinamide. Thiacetazone. National TB Programme*

## INTRODUCTION

Tuberculosis is one of the most significant disease in the world today, causing more deaths than any other single infectious disease. Every year approximately eight million people develop the disease and nearly three million die from it.[1] In Nepal also tuberculosis is major public health problem affecting the young and productive age group. 60% of the adult population is estimated to be infected by the disease. Every year 22,000 new infectious case arise and 16,500 die from TB.[2] Tuberculosis has become enormous problem and the most effective control method is drug treatment of infectious cases.

Plenty of food, fresh air and sunshine in sanatoria built in the hillsides used to be only ways to treat tuberculosis. Collapse therapy, including crush of the phrenic nerve, artificial pneumothorax and thoracoplasty lung resection, were practiced for some time. Drug treatment is effective because of its direct destructive action on tubercle bacilli, leading to progressive sterilisation of tuberculosis lesions. To achieve total bacillary destruction and avoid relapse, drug treatment must be continued for many months.

Drug treatment for TB started after streptomycin was discovered in the 1940's. Sputum conversion together with clinical and radiological improvement occurred after 2-3 months of streptomycin treatment in patients with pulmonary tuberculosis. These goods responses, however ,did not last long, and the disease soon recurred as resistance to streptomycin quickly developed. It was then found that combined drug treatment with streptomycin plus paramino salicylic acid (PAS)

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prevented emergence of strains resistant to either of the two drugs and response to streptomycin plus PAS treatment was better than to single drug treatment.[3] The introduction of isoniazid (H) and its use in combination with streptomycin and PAS in the treatment of pulmonary tuberculosis further confirmed the inadequacy of monotherapy, and led to the development of uniformly successful primary chemotherapy regimens. From the 1950s, standard chemotherapy contained streptomycin plus isoniazid plus PAS and was given for a minimum of 18 months to 2 years. PAS could be replaced by ethambutol (E) or thiacetazone (TH) according to their acceptability and availability. Adverse reactions were comman and patients tended to stop treatment prematurely or iregularly particularly when they became symptom free. Therefore failure of drug treatment and multiple drug resistance occured. In the early 1960s the TB research Centre in Madras, demonstrated that ambulatory treatment was highly effective and did not expose close family contact to additional risk of infection[4]. Sanatorium treatment become less important. Later fully supervised intermittent drug treatment was introduced.[5]

## BASIC PRINCIPLES OF DRUG TREATMENT [6]

**Several basic principles must be followed in treatment of patients with TB.**

- The drug regimen selected must be one that a controlled trial has shown to be effective, that is practiced in use, and that is acceptable to the patient. Discussion with the patient will facilitate selection of the most appropriate from among the standard drug regimens available.
- Treatment should always be supervised, at least for the first 2 months. Directly Observed Treatment, short course (DOTS) is the most effective strategy for ensuring that patients are cured of their disease. Rifampicin particularly should never be given unsupervised.
- The patient must know and accept that the exact dose of each drug must be taken as prescribed. If he has any doubts, he should discuss then with the docter and not stop treatment of his own accord.
- Treatment must on no account be interrupted. The drugs are to be taken with the utmost regularity daily or as prescribed. Frequent or prolonged interruption in treatment leads to failure of treatment. Misusing one drug on one or two days, however, constitutes an occasional interruption which, if it is exceptional, may have no serious consequences.
- Treatment must be taken for the prescribed duration and months. Even if symptoms disappears soon after the start of drug treatment and sputum becomes negative after 2 or 3 months, the drugs must still be taken for the full prescribed duration. This must be stressed repeatedly to patients during treatment, especially after the third month of drug treatment.
- Only the standard drug regimens described in the national TB manual must be prescribed. Drug regimens tailored to suit individual patients or hapazard modifications that deviate from the technical recommendation are not authorized.
- The prescribed medicines must be supplied to every patient free of charge, to ensure that treatment will not be interrupted because the patient cannot buy the necessary drugs.
- The convenience of the patients is more important to the success of drug treatment than the convenience of the staff of the health centre. The treatment should be available as close to the patient's home as possible.
- Health education of the patients should not be an activity limited in time and independent of treatment. It must be systematic, repeated and integrated with all activities. Its aim to ensure the patient's full

and whole hearted cooperation in bringing his treatment to a successful conclusion.

### Who should be treated for TB? [7]

- Persons with acid fast organisms seen by sputum smear microscopy.
- If cultures for mycobacteria are available, persons with positive cultures should be treated.
- Persons with radiographic findings consistent active TB but who have at least three negative sputum smears or cultures.
- Persons with clinical or microbiological evidence of extrapulmonary TB.

### Aim of Drug treatment [8]

- To cure patient's with minimum interference with their living in as short a period of time as possible.
- To prevent death from active disease or its late effect.
- To avoid relapse.
- To prevent emergence of acquired drug resistance.
- To protect the community from infection.

### Mechanism of Drug treatment

Antituberculosis drugs vary in their bactericidal action, sterilizing action and their ability to prevent emergence of drug resistance.

Isoniazid (H) is a very potent bactericidal drug and kills some 90% of the bacillary population in a patients lesion during the first few days of drug treatment. Its action is not influenced by change of pH but takes place after the organisms have been exposed to the drug for 24 hours. It also is very effective in preventing the emergence of drug resistance.

Rifampicin (R) is another potent bactericidal drug, which has strong sterilizing activity and can kill the intermittently metabolizing bacilli after a short exposure to the drug. It is very effective in preventing emergence of drug resistance.

Pyrazinamide (Z) is very important sterilizing drug, and can kill the bacilli that are well protected in an acid medium in the macrophages.

Streptomycin (S) and Ethambutol (E) are less potentially bactericidal drugs and with slightly less ability to prevent emergence of drug resistance to isoniazid and rifampicin. They may have some role to play in treating patient's with pre-treatment resistant organisms.

Thiacetazone (T) is less potent in bactericidal ability and less effective in preventing emergence of drug resistance, so thiacetazone can be used in the continuation treatment after an initial intensive phase when available resources do not allow the use of ethambutol. The incidence of adverse effects to thiacetazone increases considerably if the patient also has HIV infection.

The sterilizing potency and efficacy of regimens containing isoniazid, rifampicin and pyrazinamide are measured by the sputum conversion rate at the end of the second month after starting treatment and relapse rates after stopping the treatment. Short course regimens containing these drugs can achieve over 90% sputum conversion in two months of treatment, and a more than 90% cure rate with a relapse rate less than 5%. A further advantages of regimens containing these drugs is that patients experience fewer adverse reactions to drugs and comply with their treatment.

### Cost effectiveness

As public health budgets become more stretched, it is becoming increasingly necessary to make comparisons such as these to determine which health interventions provide the best value for money. With so many pressing public health needs, it is more and more difficult to argue that "no cost is too great to pay to save one human life".

International organizations such as the WHO and World Bank have been wrestling with issue such as these and produced a background document on the burden of the diseases; the World Development Report 1993: Investing in Health, published by the World

Bank in July 1993, in view of limited public health spending and a limit less burden of preventable deaths and illnesses in the world, the report attempts to determine which diseases justify the most urgent attention.

To assess the cost effectiveness, the cost of preventing or treating a disease are related to the number of healthy years gained by the intervention. The formula is more complex for some diseases, since treating an infectious disease may also have benefits in preventing further infectious. For example, when an infectious TB patients is treated, this also prevents the infection of dozens of other people.

One of the findings of the report is that TB is the most cost effective disease to control in adults over the age of 15 years. This supports what research experts have been saying recently that for a relatively small amount of money, nearly 15 millions deaths from TB could be prevented in the next 10 years.

Studies in Malawi, Mozambique and Tanzania show that, if the additional TB cases by treating an infectious patients are considered, the cost is as low as $20 and never more than $ 100 for every life saved. This translates into as little as 90 cents for each year saved.

The National Tuberculosis Programme (NTP) of Nepal has adopted 3 categories for treatment of TB as recommended by WHO. The nationally approved regimen for infectious cases is 2RHEZ+6HE. A similar regimen (2SHRZ+6HT) has been tried in East Africa and the cohort has shown high cure rates (79%) and very low relapse rates. Results of treatment in 41,726 new smear positive patients enrolled on short course chemotherapy in IUATLD assisted National tuberculosis Programmes in Tanzania, Malawi, Mozambique and Nicaragua 1983-1988 are shown in the accompanying table. Thiacetazone is now being replaced by ethambutol in most countries because of the increased risk of adverse reactions to patients with HIV.

Table: Outcome of treatment in patients with short course chemotherapy.

| | Percentage of Patients | | | | |
|---|---|---|---|---|---|
| Country | Cured | Positive | Died | Absconded | Trans out |
| Tanzania | 77 | 2 | 7 | 10 | 4 |
| Malawi | 87 | 1 | 7 | 2 | 2 |
| Mozambiqu | 78 | 1 | 2 | 11 | 8 |
| Nicaragua | 78 | 2 | 3 | 13 | 5 |
| Total | 79 | 2 | 6 | 9 | 4 |

## Treatment Categories in the Nepal NTP

**Category I:-2 HRZE/6HE:** Contains rifampicin, isonazid, pyrazinamide and ethambutol for two months and followed by isoniazid and ethambutol for six months. This category is given to all the new infectious cases and severely ill pulmonary sputum negative cases. Streptomycin is replaced by ethambutol in the intensive phase because HIV is increasingly in prevalence in this region. Rifampicin is not included in the continuation phase because according to WHO guidelines every dose of rifampicin has to be directly supervised. This would be extremely difficult to achieve in Nepal.

**Category II:-2** SHRZE/1HRZE/5HRE Contains streptomycin for 2 months with rifampicin, isoniazid, pyrazinamid and ethambutol for 3 months, and then followed by rifampicin, isoniazid and ethambutol for 6 months. This regimen is given to failure and relapse cases who are smear positive.

**Category III:-**2HRZ/6HE Contains rifampicin, isoniazid, pyrazinamide for 2 months and followed by isoniazed and ethambutol for 6 months. This regimen is given to smear negative pulmonary TB and extra pulmonary cases.

In the past, patients have had unsupervised treatment. As a result many patients defaulted from treatment before they were cured, or took the medicines irregularly, and developed resistant TB. The new NTP policy is to have Directly Observed Treatment Short Course

(DOTS), with a health worker, community leader or family member responsible for ensuring that patient takes the medicine properly. If DOTS is implemented nationally, the national target of 85% cure rate will be achieved, the prevalence of multidrug resistant TB will fall, and the problem of TB will be reduced.

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