Treatment
20. **What were the main landmarks in the development of tuberculosis treatment?**

*K. Toman*¹

1. The discovery, in 1940, of the bacteriostatic effect of sulfonamides in guinea-pigs infected with tubercle bacilli. For the first time, it was demonstrated that a chemotherapeutic agent – a derivative of dapsone, known as promin (glucosulfone sodium) – was capable of stopping the progress of otherwise fatal tuberculosis in guinea-pigs (¹). However, the effect of dapsone and other sulfone derivatives on tuberculosis in humans was disappointing, although these compounds were found to be effective in the treatment of leprosy, and dapsone remains a basic antileprosy drug (²).

2. In 1944, streptomycin – an antibiotic newly isolated by Waksman from the soil organism *Streptomyces griseus* – showed a striking therapeutic effect on experimental tuberculosis in guinea-pigs. Soon afterwards, it was used for the first time in human patients (³, ⁴) (see “What is the therapeutic effect and what is the toxicity of antituberculosis drugs?”, page 110).

3. In 1949, it was discovered that *p*-aminosalicylic acid (PAS) prevented the emergence of drug resistance if given in combination with streptomycin. Since then, the administration of two or more drugs in combination has been recognized to be essential for adequate tuberculosis treatment.

4. The discovery, in 1952, of the antituberculosis activity of isoniazid – a chemical compound synthesized 40 years earlier. Since its introduction, isoniazid has been an important component of all primary drug regimens because it is highly effective, of relatively low toxicity, and inexpensive.

5. The startling results, in 1956, of trials in Madras (now Chennai) demonstrating that ambulatory, domiciliary treatment was highly effective without increasing the risk of infection for family contacts (see “What were the main findings of the Madras study comparing home and sanatorium treatment?”, page 173). These findings prompted a radical departure from the traditional sanatorium treatment and opened new prospects for nationwide treatment programmes in developing countries.

¹ Deceased.
6. The consistent finding that a substantial proportion of patients do not take medications as prescribed, even with extensive health education (5, 6). This finding, together with the risk of emergence and spread of drug-resistant tuberculosis, eventually led to the recognition of direct observation of tuberculosis treatment as the standard of care (7–9).

7. The demonstration, in 1964, that intermittent regimens can be as effective as daily regimens, thereby offering the advantage of convenient, directly observed treatment (see “What is intermittent treatment and what is the scientific basis for intermittency?”, page 130, and “What are the advantages of direct observation of treatment?”, page 183).

8. The discovery in the late 1960s of rifampicin as perhaps the most effective medication for tuberculosis (10). Rifampicin is a broad-spectrum antibiotic used predominantly for the treatment of tuberculosis. Use of rifampicin led to the emergence of modern and effective short-course regimens.

9. Monumental work done by the British Medical Research Council and partners around the world led to the development of standard short-course chemotherapeutic regimens (11, 12). The studies established a number of key points that provided the framework for the development of modern treatment. These points include the following:
   - Regimens of 6 and 8 months’ duration are extremely effective in achieving a high cure rate with a low relapse rate.
   - Rifampicin-containing regimens allow effective short-course treatment even of patients with smear-positive cavitary disease.
   - For 6- and 8-month regimens, both rifampicin and pyrazinamide are necessary, but pyrazinamide is required only for the initial phase of treatment (13).
   - Relapses with short-course treatment generally occur within the first year and relapses that occur following multidrug therapy are usually caused by organisms that retain their original susceptibility.
   - Multiple drugs can be given with minimal toxicity.

10. Studies in the 1980s that evaluated regimens with a treatment duration of less than 6 months demonstrated high relapse rates (11–40%) in patients with sputum smear-positive pulmonary tuberculosis (14).

11. Standardized and simplified regimens using fully intermittent, directly observed 6-month treatment (15, 16) have been shown to be effective on a mass basis.

References

**21. How does tuberculosis treatment work?**

*K. Toman*¹

Before the discovery of antituberculosis drugs, tuberculosis treatment consisted of attempts to strengthen the patient’s resistance to the disease. This included altering local and general host factors through traditional measures such as the avoidance of physical and mental strain, prolonged bedrest, a rich diet, artificial pneumothorax, and thoracoplasty.

Nowadays, host factors (see “What is the role of host factors in the pathogenesis, prevention, and treatment of tuberculosis?”, page 106) are considered to be less relevant for cure, and the action of drugs on the tubercle bacillus has assumed overwhelming importance. In other words, treatment is strictly antimicrobial.

The goal of tuberculosis treatment is to ensure relapse-free cure while preventing the emergence of drug resistance. The effect of treatment should therefore be judged not by the anatomical healing of lesions but by their sterilization, or at least by the elimination of bacilli from the sputum. *Mycobacterium tuberculosis* is a slow-growing aerobic organism that can remain dormant for a prolonged period. Consequently, prolonged treatment with multiple drugs is required to ensure relapse-free cure and to prevent the emergence of resistance. The effect of treatment is determined mainly by bacteriological, environmental (anatomical and biochemical), and pharmacological factors.

**Bacteriological factors**

*The numerical factor*

The number of tubercle bacilli varies widely with the type of lesion. According to data on lung specimens resected from untreated patients (¹), the number of bacilli in a medium-sized cavity communicating with the bronchi is about $10^8$ (100 million), whereas, in an encapsulated nodular lesion of the same size with no bronchial communication, the number can be as low as $10^2$ (100). (The numbers are also rather low in extrapulmonary lesions of the skin, lymph glands, meninges, and bones.) The larger the bacterial population, the higher is the probability that resistant mutant strains are

¹ Deceased.
The metabolic factor

Drugs kill organisms that metabolize actively and multiply continuously, but in each bacterial population there are bacilli with a very low metabolic rate. Some are inhibited owing to a low pH; others are dormant most of the time and grow – if at all – only during short periods. These organisms remain unaffected by most drugs; only rifampicin or pyrazinamide may attack them effectively under certain conditions. They survive even in the presence of such potent drugs as isoniazid and streptomycin and despite their susceptibility to these drugs. These organisms are also called “persisters”. This phenomenon explains to some extent why not all bacilli are killed during treatment, and why drug-susceptible bacilli are coughed up for some time thereafter. Relapse with drug-susceptible organisms after the end of treatment or endogenous reactivation may be due to bacilli that have persisted for a long time in a dormant state in residual lesions.

Environmental factors

The anatomical factor

The type of tissue harbouring tubercle bacilli may affect drug action because not all drugs are able to penetrate into all tissues and cells or permeate biological membranes, including the normal blood–brain barrier. Isoniazid, rifampicin, and pyrazinamide readily cross biological membranes, whereas streptomycin fails to enter many cells and is much less effective against intracellular than extracellular bacilli (2, 3). In humans, bacilli – particularly those in cavitary lesions – are mostly extracellular (4).

Biochemical factors

Environmental pH and partial oxygen pressure (pO₂) are important biochemical factors that influence the antimicrobial effect of a drug. At a neutral pH, as in cavity walls, all the bactericidal antituberculosis drugs are highly effective; streptomycin, however, is at its most active in a slightly alkaline (extracellular) environment, whereas pyrazinamide acts largely in an acidic medium such as that found inside cells. Little is known about the factors causing dormancy in bacilli, but it is suggested that dormant organisms survive within cells or in necrotic areas of old encapsulated lesions that do not communicate with a bronchus. There the pH is usually on the acidic side and the pO₂ is decreased. That the pO₂ is an important factor is shown by the small numbers of bacilli found in closed extrapulmonary lesions.
Pharmacological factors

Dosage

Drugs must be given in doses large enough to produce an inhibitory concentration at the sites where bacilli are found, but it is not necessary to keep this concentration at a constant level. In fact, studies on the role of dosage and serum levels of isoniazid (4) showed that it was the peak level that was important for the response to the drug. Thus, 400 mg of isoniazid given once daily was therapeutically superior to the same dose divided into two parts and administered at 12-hour intervals (4).

Combinations of drugs

Regimens should contain a combination of three or more drugs, particularly in the initial phase of treatment (see “What is the purpose of the initial intensive phase of two-phase treatment?”, page 122). In patients whose lesions contain large numbers of bacilli, the regimen should include at least two drugs to which the bacilli are susceptible, otherwise treatment failure due to the emergence of drug resistance is the likely consequence (see “How does drug resistance develop?”, page 193, and “Why does treatment fail and what can be done to avoid poor treatment outcome?”, page 185). In the early days of treatment, patients were given one drug; if that failed, further drugs were successively substituted or added, one at a time, with the result that these people eventually became chronic patients with organisms resistant to all the drugs they had received. Thus, treatment of tuberculosis disease should never be attempted with a single drug, nor should a single drug be added to a failing regimen.

The “lag period” factor

In vitro experiments have shown that, when tubercle bacilli are exposed to a drug for a short time (6–24 hours) and, after careful removal of the drug, are transferred to a drug-free medium, the surviving bacilli start to grow again after an interval of several days. This interval is called the “lag period”, and varies with the type and concentration of the drug and with the length of exposure. (Regarding the lag period after pulsed exposure to various drugs, see “What is intermittent treatment and what is the scientific basis for intermittency?”, page 130). All tuberculosis drugs have been tested for their ability to produce a lag period, in order to determine whether they are suitable for intermittent regimens. However, certain drugs are incapable of inducing this phenomenon, and the bacilli start to grow again immediately after removal of the drug. Such drugs seem to have only a bacteriostatic effect and are not suitable for intermittent use.

References


22. What is the role of host factors in the pathogenesis, prevention, and treatment of tuberculosis?

*M. Iademarco*¹ & *M. Reichler*²

There is a constant, lifelong interplay between the environment, health status, and genetics. For tuberculosis, important host factors in this dynamic process include age, nutritional status, emotional and physical stress, concurrent disease, social circumstances, access to health care, and possibly host genotype (including sex).

In the pre-chemotherapy era, treatment of tuberculosis was necessarily directed toward strengthening the host’s resistance (1, 2). Special diets and rest were believed to improve the patient’s immune response. By imposing strict bed-rest and using collapse techniques such as artificial pneumothorax, pneumoperitoneum, thoracoplasty, and plombage, clinicians attempted to restrict disease progression and promote healing. With the advent of chemotherapy, these methods have mostly become forgotten history. In addition, many scientific advances have extended our understanding of the biological principles governing the human immune response to tuberculosis.

An individual’s health status may be the most important single determinant of risk of progression to tuberculosis disease. Table 25 shows the incidence of disease in persons with a positive tuberculin test followed prospectively. Table 26 shows the relative risk of developing disease among persons with selected clinical conditions. Adult males are at an increased risk of developing tuberculosis, which may reflect a combination of biological and social causes (3). Stress and nutrition may also be important influences on the clinical course of the disease (4, 5).

Physical and chemical properties of the upper and lower respiratory tree form the first line of defence against inhaled mycobacteria. If these fail and the mycobacteria reach the alveoli, macrophages are the next line of defence. If the macrophages fail to kill the mycobacteria, the bacilli multiply intracellularly. The ensuing infection may result in dissemination of viable organisms via the bloodstream, which results in the recruitment of lymphocytes, repeated antigen presentation, the elaboration of lymphokines, and subsequent tubercle formation. Although an antibody response is seen

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Table 25

*Incidence of tuberculosis disease in persons with a positive tuberculin test, by selected risk factors*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Tuberculosis cases/1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent tuberculosis infection</td>
<td></td>
</tr>
<tr>
<td>infection &lt;1 year past</td>
<td>12.9</td>
</tr>
<tr>
<td>infection 1–7 years past</td>
<td>1.6</td>
</tr>
<tr>
<td>Tuberculosis infection &gt;2 years past</td>
<td>0.7</td>
</tr>
<tr>
<td>HIV infection</td>
<td>35.0–162</td>
</tr>
<tr>
<td>Injection drug use</td>
<td></td>
</tr>
<tr>
<td>HIV-seropositive</td>
<td>76.0</td>
</tr>
<tr>
<td>HIV-seronegative or unknown</td>
<td>10.0</td>
</tr>
<tr>
<td>Silicosis</td>
<td>68</td>
</tr>
<tr>
<td>Radiographic findings consistent with old tuberculosis</td>
<td>2.0–13.6</td>
</tr>
<tr>
<td>Weight deviation from standard</td>
<td></td>
</tr>
<tr>
<td>underweight by 15% or more</td>
<td>2.6</td>
</tr>
<tr>
<td>underweight by 10–14%</td>
<td>2.0</td>
</tr>
<tr>
<td>underweight by 5–9%</td>
<td>2.2</td>
</tr>
<tr>
<td>within 5% of standard</td>
<td>1.1</td>
</tr>
<tr>
<td>overweight by 5% or more</td>
<td>0.7</td>
</tr>
</tbody>
</table>

a Source: reference 8, reprinted with permission.

Table 26

*Relative risk of developing active tuberculosis, by selected clinical conditions*

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid organ transplantation:</td>
<td></td>
</tr>
<tr>
<td>renal</td>
<td>37</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
</tr>
<tr>
<td>Jejunoileal bypass</td>
<td>27–63</td>
</tr>
<tr>
<td>Solid organ transplantation:</td>
<td></td>
</tr>
<tr>
<td>cardiac</td>
<td>20–74</td>
</tr>
<tr>
<td>Carcinoma of head or neck</td>
<td>16</td>
</tr>
<tr>
<td>Chronic renal failure/haemodialysis</td>
<td>10.0–25.3</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>2–5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.0–4.1</td>
</tr>
</tbody>
</table>

a Relative to control population; independent of known exposure to tuberculosis and tuberculin test status.

b Source: reference 8, reprinted with permission.
in tuberculosis (6), the T-lymphocyte-mediated response is probably the most important immunological determinant of the patient’s ability to resist progression from tuberculosis infection to disease (7).

Two acquired immune processes act to contain tuberculosis infection. In the first, macrophages that have been activated by lymphokines kill intracellular organisms. In the second, cytolytic T-cells destroy macrophages infected with *Mycobacterium tuberculosis*. This latter mechanism is a delayed-type hypersensitivity reaction and is also responsible for the host response to the intradermal injection of a purified protein derivative of *M. tuberculosis* in an infected person. The balance between organism growth and host response over time dictates whether the infection progresses to clinical illness (9).

HIV infection has demonstrated the critical role played by host defences in preventing progression from tuberculosis infection to tuberculosis disease. The susceptibility of HIV-infected patients to tuberculosis and the clinical presentation of the disease closely follows their immune status. Early in the course of HIV infection, patients tend to have cavity formation and positive sputum smears, related in large part to the effort of their own immune systems to contain the infection, which results in destruction of lung parenchyma and pooling of large numbers of bacilli in the cavities thus created. As HIV infection progresses and CD4 cells are depleted, the host immune response becomes less effective, cavity formation and hence sputum smear positivity are less common, and disseminated forms of tuberculosis are more common. HIV infection increases both the risk and the pace of progression from tuberculosis infection to disease; among hospitalized AIDS patients, the median incubation time from exposure to smear-positive tuberculosis and development of tuberculosis disease was found to be 12 weeks (10).

Epidemiological evidence suggests that there may be a genetic component to the host immune response to tuberculosis. A 1978 study among monozygotic and dizygotic twins provided the first strong evidence that susceptibility to tuberculosis may be inherited (11). A number of candidate susceptibility genes have been recently identified. These include the genes coding for natural-resistance-associated protein-1, interferon-gamma receptor, vitamin D receptor, and human leukocyte antigen (HLA) DQB1 (11–16). HLA genotype has also been associated with an increased risk of progression to severe tuberculosis disease and with failure to respond to antituberculosis treatment (14).

These observations regarding the host immune response provide the foundation for renewed efforts to develop innovative approaches to tuberculosis diagnosis, treatment, and eventually, vaccination.

**References**


23. What is the therapeutic effect and what is the toxicity of antituberculosis drugs?¹

_T. Frieden² & M. Espinal³_

It is difficult to determine and measure the efficacy or toxicity of a particular drug, since antituberculosis drugs are almost invariably administered in combination regimens of several drugs. However, if two or more drugs are taken simultaneously, synergistic as well as antagonistic interactions may occur between the drugs and the host, generally making it impossible to say what is due to what. Although valuable knowledge has been gained from experimental work, there is still no suitable in vitro or animal model from which information can be unequivocally applied to humans.

**Isoniazid**

Isoniazid is the hydrazide of isonicotinic acid – a chemical compound first synthesized in Prague in 1912. However, its effectiveness in treating tuberculosis was demonstrated only in 1952. Since then, it has ranked among the most powerful antituberculosis agents. Isoniazid is effective only against the tubercle bacillus, not against other bacteria. It penetrates rapidly into all tissues and lesions, and its activity is not influenced by the pH of the environment. Because of its potency, infrequent toxicity, small bulk, and low cost, isoniazid is widely used in the treatment of tuberculosis. It is also used in preventive treatment to reduce the risk of progression from tuberculosis infection to disease (see “What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?”, page 220).

Isoniazid is administered orally, the dosage for daily regimens being 5 (range 4–6) mg/kg, i.e. usually 300 mg. In thrice-weekly regimens the dosage is 10 (8–12) mg/kg, i.e. about 450–600 mg given in a single dose for patients weighing 40–60 kg, and in twice weekly regimens the dose is 15 (13–17) mg/kg. The drug should not be given in divided doses: it has been shown that a high peak concentration in the serum is more important than a continuously inhibitory level (1).

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¹ Based on the chapter in the previous edition by K Toman.
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³ Medical Officer, Communicable Diseases, Stop TB, World Health Organization, Geneva, Switzerland.
The time during which an adequate isoniazid level is maintained in the tissues and body fluids depends also on the rate of inactivation of the drug. It is metabolized mainly by acetylation, at a rate that varies from one individual to another but is consistent in the same individual. The rate of inactivation is determined mainly by genetic factors, and patients can generally be divided into two groups: slow and rapid inactivators (acetylators) of isoniazid.

**Adverse reactions**

The most common toxic manifestation of isoniazid treatment is peripheral neuropathy. Tuberculosis patients infected with HIV are at higher risk of peripheral neuropathy. The earliest symptom is paraesthesia, followed by pricking pain and burning sensation in the feet and later in the hands. If untreated, the symptoms worsen and cause distress to the patient. The frequency of neuropathy increases with the dose. The condition is more common in slow inactivators, patients with diabetes or uraemia, malnourished patients, and daily users of alcohol.

Isoniazid neurotoxicity can be prevented by pyridoxine (vitamin B6) in rather small doses (10 mg/day). Pyridoxine also has a therapeutic effect on isoniazid-induced neurotoxicity, but high doses – though effective – may reduce the bactericidal activity of isoniazid (2). Some patients complain of light-headedness, lethargy, and fatigue, particularly with the higher intermittent doses. These effects generally subside with time and reassurance.

Isoniazid can also give rise to hepatotoxicity, most frequently in adults above 35 years of age, particularly when other potentially hepatotoxic agents are administered. Isoniazid-induced hepatotoxicity is reversible if the drug is stopped early. However, it can be fatal (3, 4). Infrequently, toxic psychosis and generalized epileptic convulsions may occur in both slow and rapid inactivators.

Isoniazid increases the serum concentrations of phenytoin and carbamazepine. Its absorption is impaired by antacids containing aluminium hydroxide.

**Rifampicin**

Rifampicin, a semisynthetic antibiotic first synthesized in 1965, is highly active against tubercle bacilli. In vitro and in vivo studies have demonstrated the exceptional bactericidal effect of rifampicin and its suitability for intermittent use (5–7). Since nontoxic oral doses produce a serum concentration about 100 times as high as levels that inhibit growth of *Mycobacterium tuberculosis*, rifampicin raised hopes from the outset that it would reduce the duration of treatment (8). In wild strains of the bacillus, the proportion of rifampicin-resistant mutants (1 : 10⁸) was found to be substantially lower than that of isoniazid-resistant mutants (1 : 10⁶).

Rifampicin is a key component of modern tuberculosis treatment and is the single most important drug in short-course treatment. It is given orally and the usual dose is 10 (range 8–12) mg/kg (maximum 600 mg), three or two times weekly. It
should preferably be given at least 30 minutes before the patient eats, since absorption is reduced when the drug is taken with food.

**Adverse reactions**

Rifampicin is well tolerated by most patients at the currently recommended dosages. Unlike other drugs, rifampicin produces some adverse reactions more frequently with intermittent than with daily regimens. Moreover, the risk of adverse effects increases with the interval between doses: thus toxicity is high if treatment is taken only once a week.

With currently recommended regimens, reactions are uncommon and generally minor. Rarely, serious hepatotoxicity, generally with a cholestatic pattern, may occur. Rifampicin causes orange-red discoloration of body secretions such as urine, faeces, tears, and sweat, and may result in permanent discoloration of soft contact lenses.

Reactions most frequently observed with intermittent regimens are as follows:

- A cutaneous syndrome consisting of flushing and/or pruritus, with or without rash, involving particularly the face and scalp, often with redness and watering of the eyes.
- An abdominal syndrome consisting of pain and nausea, sometimes accompanied by vomiting or, less commonly, diarrhoea.
- A “flu” syndrome consisting of attacks of fever, chills, malaise, headache, and bone pains.
- A respiratory syndrome (uncommon) characterized by shortness of breath, rarely associated with collapse and shock.
- Purpura and other rare reactions, such as acute haemolytic anaemia, shock, and renal damage with or without impaired kidney function or failure.
- Elevated serum levels of transaminase (quite common but transient, even when treatment is continued), and hepatotoxicity.

The first four of these syndromes typically begin 2–3 hours after the single, morning dose of rifampicin. Many patients exhibit more than one syndrome simultaneously. Cutaneous syndromes usually start during the first month, and gastrointestinal symptoms are spread over the first 6 months. The “flu” syndrome, observed only with intermittent regimens, generally begins in the third to fifth month of treatment (5).

**Management of adverse reactions to rifampicin (9–11)**

About half of the patients who experience adverse reactions require no major modification of their regimens. The cutaneous syndrome is often self-limiting and requires symptomatic treatment only. It is rarely necessary to change the regimen, unless other adverse effects, such as generalized hypersensitivity reactions, occur simultaneously. The abdominal syndrome requires only symptomatic treatment provided that it occurs alone. If the patient has been taking the drug on an empty stomach – as is recommended – reactions can usually be stopped by giving the drug during a small meal.
The “flu” syndrome, which is usually mild, requires no change of treatment; it is probably of an immunological nature. If it persists, a change to daily administration may be necessary.

Caution is required in patients with the respiratory syndrome, because shock may develop, with a sudden fall in the systolic blood pressure and anuria. Such cases require immediate hospital care. If shock is followed by renal failure (rare), rifampicin must be stopped and never given again. This also applies if haemolytic anaemia develops.

In summary, adverse reactions to rifampicin – when not self-limiting – can usually be controlled by reducing either the dosage or the interval between doses, e.g. from three times weekly to daily. These measures generally stop the episodes or render them so minor or infrequent that they are no longer of concern (see “What are the most common adverse drug events to first-line antituberculosis drugs, and what is the procedure for reintroduction of drugs?” on page 152).

If purpura occurs, rifampicin is stopped and not given again, even in a small test dose. The platelet count then returns to normal within a few days.

Asymptomatic rises in serum transaminase levels are common in patients receiving rifampicin and generally resolve spontaneously. Rarely, patients develop overt hepatitis. When a patient develops treatment-induced hepatotoxicity, all potentially hepatotoxic drugs should be stopped until clinical and biochemical hepatitis resolves. Non-hepatotoxic drugs, including streptomycin, ethambutol, and fluoroquinolones (except ciprofloxacin, which is excreted by the liver) can be used if necessary. After hepatitis resolves, the antituberculosis drugs can be reintroduced in a phased manner.

Rifampicin accelerates the hepatic cytochrome p450 pathway and reduces the serum levels of many drugs, including antifungal agents, corticosteroids, warfarin, and oral hypoglycaemic agents. Rifampicin also reduces the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors used to treat HIV (12). This interaction may lead to rapid development of resistance in HIV strains to the protease inhibitors. Rifampicin reduces the effectiveness of oral contraceptives (13) and patients should be advised to use non-hormonal contraception during, and for one month after, treatment with rifampicin-containing regimens.

Newer rifamycin derivatives related to rifampicin have been developed. Rifabutin has similar activity against\textit{Mycobacterium tuberculosis}, but it has a longer half-life than rifampicin and less effect on the pharmacokinetics of some antiretroviral drugs (14).

Rifapentene is a rifamycin derivative with a long half-life and has similar activity against\textit{M. tuberculosis} (15). Studies are under way to evaluate its effectiveness. Mycobacterial strains that are resistant to rifampicin are usually, but not always, resistant to rifabutin and rifapentene.

**Pyrazinamide**

Pyrazinamide has been shown to have a sterilizing effect inside macrophages where organisms grow slowly because of the acid pH of the environment. Thus, pyrazinamide...
Pyrazinamide is able to kill tubercle bacilli that cannot otherwise be attacked effectively by other currently available drugs.

Because it reduces the required duration of treatment, pyrazinamide is an integral component of short-course treatment. It is given orally, and the usual daily dose is 25 (range 20–30) mg/kg. In intermittent regimens, the dosage is 35 (30–40) mg/kg three times a week or 50 (40–60) mg/kg twice weekly.

**Adverse reactions**

At currently recommended doses, pyrazinamide rarely causes serious toxicity, but hepatotoxicity can occur at high dosages. Joint pain is a common adverse effect, occurring more commonly with daily than with intermittent pyrazinamide-containing regimens. Arthralgia can be successfully managed with acetylsalicylic acid or other analgesic, anti-inflammatory agents, and does not require withdrawal of the drug. Classic gout is rarely seen; if it develops it can be treated with colchicine. Serum concentrations of uric acid are often elevated in patients receiving pyrazinamide; asymptomatic increase in serum uric acid does not require any treatment.

Severe hepatotoxicity has been observed when regimens containing rifampicin and pyrazinamide are used (16).

Hypersensitivity, including fever, rash, and other cutaneous reactions, may occasionally occur.

**Ethambutol**

Ethambutol is a synthetic compound unrelated to other antituberculosis drugs. It is effective against *M. tuberculosis* and some other mycobacteria, e.g. *M. kansasii*, but it is ineffective against other bacteria or fungi. Ethambutol is mainly bacteriostatic.

Ethambutol is given orally and the usual dose is 15 (range 15–20) mg/kg daily, 30 (25–35) mg/kg three times weekly, and 45 (40–50) mg/kg twice weekly.

**Adverse reactions**

Ethambutol may produce retrobulbar neuritis, characterized by impairment of vision, with a reduction in visual acuity, red–green blindness, blurring, central scotomas, and peripheral field defects. Ocular toxicity seems to be dose-dependent and occurs only rarely if no more than 15 mg/kg is given daily (17, 18). Patients receiving ethambutol should be warned that an ocular examination should be undertaken if visual symptoms occur. Vision usually returns to normal within a few weeks if the drug is stopped, but the optic nerve may be permanently damaged if ethambutol is continued. Ethambutol should generally not be given to young children who cannot reliably report or be tested for impaired visual acuity.

Because it degrades rapidly in tropical climates, ethambutol must be manufactured and stored in such a way as to prevent absorption of moisture.
Streptomycin

Isolated by Waksman from a soil organism in 1943, streptomycin is now used in the form of streptomycin sulfate and is dispensed as a dry powder in vials. It is administered by intramuscular injection. The usual dose is 0.75–1 g (12–18 mg/kg), daily, two or three times a week, given in a single injection. In older patients and patients weighing less than 35 kg, a dose of 0.5 g is equally effective and less toxic.

The serum concentration of streptomycin reaches maximum 1 hour after administration, and remains above inhibitory levels for many hours.

Streptomycin does not penetrate cell walls or normal biological membranes, such as the meninges or the pleura, unless inflammatory changes have taken place (see also “How does tuberculosis treatment work?”, page 102). The drug is excreted almost entirely via the kidneys and, in patients with impaired renal function, may therefore accumulate and cause increased toxicity.

Adverse reactions

Apart from hypersensitivity reactions such as fever and rash (see also “What are the most common adverse drug events to first-line antituberculosis drugs, and what is the procedure for reintroduction of drugs?”, page 152), the main toxic effect of streptomycin is vestibular damage and potential ototoxicity. The risk increases with dose and age (over 40 years). Toxicity is manifested as vertigo and ataxia, tinnitus, and loss of hearing. The simplest way of demonstrating ataxia is to ask the patient to walk along a straight line with closed eyes. If the patient walks more unsteadily than with open eyes, ataxia is present. If a patient complains of dizziness and the drug is stopped or the dosage reduced, the dizziness may disappear. If treatment continues, vestibular damage and hearing loss may worsen and may become permanent; this risk is particularly high in patients with impaired renal function. Renal damage may also occur, particularly in patients with pre-existing renal disease, although it is often fully reversible if streptomycin is discontinued promptly.

Transient and minor adverse effects, such as circumoral numbness and tingling, may occur soon after injection.

Streptomycin is contraindicated in pregnant women because of the risk of impairing development of the eighth cranial nerve of the fetus. Streptomycin also potentiates neuromuscular blocking agents used during anaesthesia and should be avoided in patients with myasthenia gravis.

As with all injecting procedures, sterile needles should be used and subsequently disposed of safely.

Thioacetazone

The efficacy and toxicity of thioacetazone are discussed in detail elsewhere (see “What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?”, page 159). Thioacetazone is
given orally at the usual dose of 2.5 mg/kg daily; it is not effective when given inter-
mittently. Thioacetazone administered as a single dose of 150 mg has about the same
toxicity as PAS. Its adverse effects include rash, jaundice, and reversible bone-marrow
suppression. Cutaneous reactions appear to be more serious than with other drugs,
and exfoliative dermatitis or Stevens–Johnson syndrome may occur if the drug is not
stopped. Most of the serious adverse reactions have been observed within the first 4–6
weeks of treatment.

Thioacetazone was investigated in a large, controlled, double-blind, toxicity trial
(see “What are the merits of thioacetazone as a companion drug to isoniazid, and what
is the efficacy of the regimen of isoniazid plus thioacetazone?”, page 159). It was poorly
tolerated by the Chinese population of Singapore and Hong Kong Special Adminis-
trative Region of China, but was well tolerated in East African countries.

In HIV-positive individuals, the risk of major, potentially fatal cutaneous reactions
caused by thioacetazone is unacceptably high (19). Thioacetazone should therefore
never be used in patients who may be HIV-positive or in areas where HIV infection
is common.

**Reserve drugs (20)**

Reserve drugs include aminoglycosides (kanamycin, amikacin), polypeptides (capre-
omycin), thioamides (ethionamide and protionamide), fluoroquinolones (e.g.
ofloxacin and ciprofloxacin), cycloserine, and PAS (20). They can be classified as
follows (21, 22):

— drugs with bactericidal activity: aminoglycosides, capreomycin, and thioamides
— drugs with low bactericidal activity: fluoroquinolones
— drugs with bacteriostatic effect: cycloserine and PAS.

**Kanamycin and amikacin**

Kanamycin and amikacin are bactericidal agents of the aminoglycoside class; their
efficacy and adverse reactions are similar to those of streptomycin. The usual dose is
0.75–1 g (12–18 mg/kg) in a single injection.

**Adverse reactions**

Intramuscular administration of these drugs is much more painful than streptomycin
or capreomycin. Local measures (warm soaks, massage) provide some relief. Cross-
resistance between kanamycin and amikacin appears to be complete. Vertigo, ototox-
icity, and deafness may occur. Nephrotoxicity may also occur but is reversible. In
patients with impaired renal function, the daily dose should be reduced and/or the
intervals between doses increased to avoid accumulation of these drugs. In addition,
the renal function of such patients should be monitored regularly during use of the
drugs. Amikacin and kanamycin should not be used in pregnant women except as a
last resort.
Capreomycin

Capreomycin is a bactericidal agent of the polypeptide class and is obtained from *Streptomyces capreolus*. Its bactericidal effect is valuable in patients with bacilli resistant to streptomycin, kanamycin, and amikacin: there is no cross-resistance with the aminoglycosides. The usual dose is 0.75–1 g (12–18 mg/kg) in a single injection.

**Adverse reactions**

Adverse effects are similar to those of streptomycin, namely mainly tinnitus and vertigo, but possibly with a lesser risk of deafness. Kidney damage may occur. Hypokalaemia, hypocalcaemia, and hypomagnesaemia have also been reported. Eosinophilia and rash are not uncommon and generalized cutaneous reactions and hepatitis may occur rarely. There may be pain and swelling at injection sites if the drug is not given by deep intramuscular injection. Capreomycin should if possible be avoided in patients with impaired hearing or renal function. Serum urea and electrolytes should be monitored during treatment. This drug should also not be used in pregnant women except as a last resort.

Ethionamide (or protionamide)

Ethionamide and protionamide are bactericidal agents from the thioamide class. Although ethionamide is chemically related to isoniazid and pyrazinamide (all are derivatives of isonicotinic acid), there is little cross-resistance among these drugs. The chemical structure of ethionamide resembles that of thioacetazone, with which there is frequent and partial cross-resistance (bacilli resistant to thioacetazone are often susceptible to thioamides, but the reverse is seldom the case). Before the rifampicin era, ethionamide (or protionamide) was a basic component of the re-treatment regimen for tuberculosis patients with bacilli resistant to isoniazid and streptomycin. The maximum optimum daily dosage of ethionamide is 15–20 mg/kg, i.e. 0.5–1 g daily depending upon body weight and patient tolerance. For patients who are receiving directly observed treatment and are unable to tolerate a single dose, a daily dose of 750 mg can be administered as 500 mg under direct observation and 250 mg self-administered later in the day.

**Adverse reactions**

Ethionamide is one of the most unpleasant of all antituberculosis drugs for patients to take. The principal adverse effects are gastrointestinal – anorexia, salivation, nausea, metallic taste, abdominal pain, and diarrhoea. The drug can cause hypothyroidism, especially when given in combination with PAS, as well as hypoglycaemia in diabetic patients which, although rare, can be dangerous. Some adverse effects result from the action of the drug on the central nervous system, and are difficult to control. Hepatitis has also been reported. Patients with diabetes, liver disease, alcoholism, or psychiatric illness should be very carefully monitored if given this drug. An important factor
that can influence tolerance of ethionamide is patients’ determination not to give up treatment, but that requires strong support and persuasion by clinical and nursing staff, as well as sound organization. Effective organization is essential in order to provide convenient therapeutic and social services to patients under re-treatment, many of whom may have serious social problems. Ethionamide may be teratogenic and should not be used in pregnancy.

Other rare adverse effects include gynaecomastia, menstrual disturbance, impotence, acne, headache, and peripheral neuropathy.

**Fluoroquinolones**

Both ofloxacin and ciprofloxacin have a bactericidal effect in vitro against *M. tuberculosis*; newer fluoroquinolones may be more active. Although these drugs have not been studied extensively in controlled clinical trials, evidence suggests that ofloxacin and ciprofloxacin have roughly the same therapeutic efficacy. There is no cross-resistance with other antituberculosis agents, but there is complete cross-resistance between ofloxacin and ciprofloxacin (and between the other fluoroquinolones such as levofloxacin, which is the L-isomer – active moiety – of ofloxacin). The usual daily dose of ofloxacin is 7.5–15 mg/kg (maximum 800 mg); ciprofloxacin has been used at a daily dose of 1000–1500 mg. Levofloxacin is more active and less toxic, but is currently more expensive. Fluoroquinolones, when used together with other antituberculosis drugs, are moderately effective for the treatment of multidrug-resistant tuberculosis (23, 24). They are also useful if standard tuberculosis drugs are not tolerated, as in patients with severe liver disease.

**Adverse reactions**

Adverse reactions are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous system symptoms (such as dizziness, headache, mood changes, and rarely, convulsions). A caffeine-like effect is not uncommon. Very rarely, spontaneous rupture of the Achilles tendon may occur. These drugs should not be used in pregnant women or growing children because they may impair growth and cause damage to growing cartilage. Because of drug interaction, patients taking fluoroquinolones should avoid antacids, iron, zinc, sucralfate, and didanosine (DDI).

**Cycloserine (or terizidone)**

Cycloserine, a structural analogue of the amino acid d-alanine, has a relatively weak antituberculosis effect. Terizidone is a combination of two molecules of cycloserine. Cycloserine is used only in reserve regimens. It is given orally in doses of 0.5–1 g daily, divided into two or three doses, although a dose of 1 g per day is rarely tolerated. Cross-resistance to any of the other antituberculosis drugs has not been reported; however, drug susceptibility testing of cycloserine may be unreliable. Cycloserine was
valuable in preventing resistance to ethionamide in the re-treatment regimens (ethionamide, cycloserine, and pyrazinamide or kanamycin) that were used before the rifampicin era. Nowadays, its value lies primarily in preventing resistance to other reserve drugs.

**Adverse reactions**

The main toxic effects concern the central nervous system. Cycloserine may cause headaches, confusion, depression, seizures, and changes of behaviour, and may sometimes even provoke suicide. Very rarely there may be a generalized hypersensitivity reaction or hepatitis. Monitoring for central nervous system reactions is therefore essential when cycloserine is prescribed. To prevent minor adverse reactions such as insomnia, administration of small doses of a tranquillizer is sometimes recommended, and pyridoxine may reduce central nervous system effects. Health care workers in charge of treatment of inpatients, as well as the families of outpatients, should be warned to report immediately any undue depression or personality change. Cycloserine (and terizidone) should be avoided in patients with a history of epilepsy, mental illness, or alcoholism, and should be used very cautiously in patients with renal failure. Cycloserine and terizidone must be stored carefully.

**p-Aminosalicylic acid**

*p*-Aminosalicylic acid (PAS) was designed by Lehmann and first used in 1944. The usual dose for adults is 10–12 g orally per day in two or three doses; lower doses, e.g. 6–8 g, may be effective (25). As PAS is rapidly excreted, it must be administered in high doses, several times a day, in order to maintain the required high blood levels. It is bacteriostatic and prevents the emergence of isoniazid-resistant organisms when used in combination with isoniazid. This drug is now being used in reserve regimens to treat multidrug-resistant tuberculosis.

PAS is supplied in the form of tablets, powder, or granules, but some preparations do not keep well in tropical conditions. Other disadvantages are the large size of the sachets, the large number of tablets to be taken, and the unpleasant taste. Potassium salts and enteric-coated preparations may be better tolerated, although they are currently more expensive.

**Adverse reactions**

Apart from hypersensitivity reactions, such as fever, rash, and pruritus, the main adverse effects of PAS are gastrointestinal. Anorexia, nausea, vomiting, and abdominal discomfort are more common than diarrhoea. The side-effects may be lessened by administering the drug after food or with milk. The reported frequency varies with the country and the observer. However, patients can often be persuaded to put up with adverse effects, and in only 1–2% of cases is it necessary to stop the drug.
Gastrointestinal disturbances can be reduced by taking PAS with or immediately after food. Hepatitis and jaundice are rare complications, in which case the drug must be stopped. Hypothyroidism may occur with long-term administration, but reverses when the drug is stopped. Hypokalaemia may occur. The sodium salt form of PAS can result in sodium overload and this form of the drug should be used with caution in patients for whom restricted sodium intake is indicated. In the old tablet preparation of PAS, an excipient (bentonite) impaired the absorption of rifampicin. The new preparation, however, in the form of granules, does not interfere with rifampicin absorption, may be slightly better tolerated, and can be given twice (as opposed to three or four times) a day without loss of efficacy.

References

TREATMENT

24. What is the purpose of the initial intensive phase of two-phase treatment?

*K. Toman*¹

There is ample experimental and clinical evidence that the initial administration of more than one drug, particularly a three- or four-drug regimen, greatly improves the efficacy of treatment. Early work by Mitchison (1), Canetti (2), and others in the 1960s showed that at least two drugs given concurrently were required for the treatment of active tuberculosis; field trials had shown that monotherapy led to high treatment failure and relapse rates. This led to the concept that multidrug treatment would be required to eradicate the tubercle bacilli in patients with active disease.

The notion that an intensive phase of treatment with multiple drugs, followed by a continuation phase with fewer drugs, could be implemented and have a successful outcome gained acceptance. However, not every combination of two or three drugs will have this effect. At least two bactericidal drugs, such as isoniazid and streptomycin or isoniazid and rifampicin, are required in the initial phase. Pyrazinamide given in the initial intensive phase allows a reduction in treatment duration from 9 to 6 months. Ethambutol is of benefit when initial drug resistance may be present or if the burden of organisms is high (see “How effective is tuberculosis treatment and what are the needs for the future?” page 253).

The multiplication of susceptible organisms stops during the first days of effective treatment (1, 2), and the total number of bacilli in the sputum decreases rapidly, especially within the first 2 weeks (3). The experimental findings from laboratory and controlled studies are summarized below.

- It is crucial for the outcome of treatment, especially in patients harbouring large bacterial populations, to put a rapid stop to bacterial multiplication and ensure that drug-susceptible bacilli are killed as soon as possible (“early kill”), for the following reasons:

  — To prevent early deterioration and death in the first weeks of treatment.
  — If the bacterial population is rapidly reduced from, say, $10^8$ (a number commonly found in lung cavities) to $10^3$, there is little probability that new resistant mutants will appear, even after seven generations of uninhibited multiplication.

¹ Deceased.
Thus the emergence of new resistant mutants can be minimized or stopped by an initial phase of intensive treatment.

— There is good in vitro evidence that, the more rapid the antibacterial effect, the less likely is the emergence of persisters (4). The risk of relapse is thus reduced.

- Appropriate multidrug combinations always contain two drugs capable of destroying single-drug-resistant mutants that pre-exist in wild strains. Thus a three- or four-drug regimen will safely prevent these organisms from multiplying. Such multiplication may be particularly dangerous in the early treatment phase because an appreciable number of drug-resistant mutants may be present at the start of treatment. In one million tubercle bacilli (of a wild strain), about 10–50 isoniazid-resistant mutants and about 1–5 streptomycin-resistant mutants may be found. Thus, in a population of $10^8$ (a number commonly found in lung cavities), some 5000 isoniazid-resistant and several hundred streptomycin-resistant mutants could be present at the outset (see “How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?”, page 203). If these are allowed to multiply, resistance to two drugs can develop rapidly (5).

- In patients with initial resistance to a single drug (except rifampicin) the chances of a favourable response to treatment are almost unimpaired if an initial period of treatment with three or four drugs is provided (see “What are the possible consequences of inaccurate drug-susceptibility testing?” , page 213). Patients who will benefit from a fourth drug and an intensive initial phase are mainly those who harbour large numbers of tubercle bacilli, i.e. those who are usually positive by direct smear microscopy.

References

25. **What are the current recommendations for standard regimens?**

*A. Harries*

The aims of treatment regimens are to: cure the patient, prevent death from active disease or its late effects, prevent the emergence and spread of drug-resistant organisms, minimize relapse, and protect the community from continued transmission of infection.

All treatment regimens have two phases – an initial intensive phase and a continuation phase (1, 2).

**Initial intensive phase**

The initial intensive phase of treatment is designed to kill actively growing and semi-dormant bacilli. This means a shorter duration of infectiousness, usually with rapid smear conversion (80–90%) after 2–3 months of treatment. The initial phase of rifampicin-containing regimens should always be directly observed in order to ensure adherence. That phase usually involves between three and five drugs. If initial resistance rates are high, use of a three-drug regimen carries the risk of selecting drug-resistant mutants, especially in patients with high bacillary loads, i.e. with smear-positive pulmonary tuberculosis. Use of a four-drug regimen reduces the risk both of drug resistance developing and of failures and relapses. If a patient defaults on treatment after the initial intensive phase, relapse is less likely.

**Continuation phase**

The continuation phase eliminates most residual bacilli and reduces failures and relapses. At the start of the continuation phase, numbers of bacilli are low and there is less chance of selecting drug-resistant mutants: fewer drugs are therefore needed.

**Standard tuberculosis treatment regimens**

Treatment regimens recommended by WHO (1) are shown in Table 27. Standard codes are used for tuberculosis treatment regimens: each tuberculosis drug is represented by a standard abbreviation and each regimen has two phases. The number

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1 Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.
### Table 27

**Recommended treatment regimens for different diagnostic categories**

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Tuberculosis patients</th>
<th>Tuberculosis treatment&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Initial phase</strong></td>
</tr>
<tr>
<td>I</td>
<td>New smear-positive cases; new smear-negative pulmonary TB with extensive</td>
<td>2 HRZE&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>parenchymal involvement; severe concomitant HIV disease or severe forms of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>extrapulmonary TB</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Previously treated sputum smear-positive PTB:</td>
<td>2 HRZES / 1 HRZE</td>
</tr>
<tr>
<td></td>
<td>– relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– treatment after interruption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– treatment failure&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5 HRE</td>
</tr>
<tr>
<td>III</td>
<td>New smear-negative pulmonary TB (other than in Category I) and less severe forms of</td>
<td>2 HRZE&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>extrapulmonary TB</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Chronic and MDR-TB cases (still sputum-positive after supervised retreatment)</td>
<td>Specially designed standardized or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>individualized regimens are</td>
</tr>
<tr>
<td></td>
<td></td>
<td>suggested for this diagnostic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>category.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Source: reference 1.

<sup>b</sup> H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters indicates the number of months of treatment.

<sup>c</sup> Direct observation of treatment intake is required for the initial phase in smear-positive cases, and always in treatment that includes rifampicin.

<sup>d</sup> Streptomycin may be used instead of ethambutol. In meningitis, ethambutol should always be replaced by streptomycin.

<sup>e</sup> Whenever possible, drug sensitivity is recommended before category II treatment is prescribed in failure cases. In patients with proven MDR-TB, it is recommended that Category IV regimens are used.

<sup>f</sup> Contacts of patients with culture proven MDR-TB should be considered for early culture and sensitivity testing.

<sup>g</sup> Ethambutol in the initial phase may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients who are known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

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before a phase is the duration of that phase in months. A subscript number (e.g. 3) after a letter or letters in parentheses is the number of doses of that drug or drugs per week. If there is no subscript number, treatment with that drug is on a daily basis. The use of parentheses indicates that the drugs are formulated in fixed-dose combination; this formulation is recommended whenever possible. An alternative drug (or drugs) appears as a letter (or letters) in square brackets.
**Examples**

- **2(HRZE)/6(HE)**
  The initial phase is 2HRZE. The duration of the phase is 2 months. Drug treatment is daily (there is no subscript number after the letters) with isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) in a fixed-dose combination. The continuation phase is 6HE. The duration of the phase is 6 months. Drug treatment is daily with isoniazid (H) and ethambutol (E) in a fixed-dose combination.

- **2(HRZ)3E3/4(HR)3**
  In the initial phase treatment is three times a week (as indicated by the subscript number after the letters) with isoniazid (H), rifampicin (R) and pyrazinamide (Z) in a fixed-dose combination, plus ethambutol (E). The duration of the phase is 2 months. In the continuation phase treatment is three times a week (subscript number after the letters) with isoniazid (H) and rifampicin (R) in a fixed-dose combination. The duration of the phase is 4 months.

**New cases of tuberculosis**

Treatment regimens consist of an initial (intensive) phase lasting 2 months and a continuation phase usually lasting 4–6 months. During the initial phase, usually involving four drugs, there is rapid killing of tubercle bacilli and infectious patients become non-infectious within a few weeks. Symptoms improve, and many patients become asymptomatic after 4–8 weeks; most patients with sputum smear-positive pulmonary tuberculosis become smear-negative within 2 months. Pyrazinamide is given during the initial phase and has its maximum sterilizing effect within this time. No further benefit is obtained from continuing pyrazinamide for longer in patients with drug-susceptible bacilli, and the drug is therefore not used in the continuation phase. In the continuation phase, two drugs are generally used.

Patients with smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis harbour fewer bacilli in their lesions, so there is less chance of selecting drug-resistant mutants. Short-course treatment regimens with three drugs during the initial phase and two in the continuation phase are of proven efficacy and are recommended by WHO.

Some countries still use a 12-month regimen, particularly in patients with smear-negative pulmonary or extrapulmonary tuberculosis (2) (isoniazid and thioacetazone, supplemented with streptomycin and ethambutol for 2 months in the initial phase). A 12-month period of treatment is required because the regimen contains neither of the drugs (rifampicin and pyrazinamide) that sterilize the tuberculous lesions. The regimen therefore relies on semi-dormant bacilli becoming metabolically active during the treatment period and susceptible to the killing effects of isoniazid. Under routine conditions in nearly all countries the cure rates with this regimen are low, and WHO therefore does not recommend it. In addition, thioacetazone has serious
toxicity, particularly in patients infected with HIV, and should be replaced by ethambutol. However, this type of regimen may need to be used while the DOTS strategy package is being expanded to cover an entire country or area.

**Re-treatment cases**

Previously treated tuberculosis patients are more likely than new patients to harbour and excrete bacilli resistant to at least isoniazid. The re-treatment regimen consists of five drugs initially, with at least three in the continuation phase. In the initial phase the patient should receive at least two drugs that are still effective to reduce the risk of selecting further resistant bacilli.

**WHO-recommended treatment regimens**

WHO-recommended treatment regimens are shown in Table 27. There are several possible regimens, depending on a country’s budget, health coverage by primary health care facilities, capacity for direct observation, and qualifications of staff at peripheral health level. For each patient, the regimen recommended depends on the patient treatment category (see “What are the diagnostic categories and what is the rationale for these categories?”, page 128).

**References**

26. What are the diagnostic categories and what is the rationale for these categories?

A. Harries¹

There are four different diagnostic categories of treatment (see “What are the current recommendations for standard regimens?”, page 124). Patients are categorized according to priority for treatment, with priorities being based on cure of the patient, prevention of death, prevention of drug resistance, and reduction of transmission in the community. The highest priority is given to patients with new smear-positive pulmonary tuberculosis and other serious forms of the disease. If 100% of new smear-positive tuberculosis cases were detected and cured, the prevalence of tuberculosis would fall very rapidly (see “Can tuberculosis be controlled?”, page 301).

Category I
Includes patients with:

- New smear-positive pulmonary tuberculosis, because they are highly infectious and at high risk of death without treatment, and because treatment failure means risk of the spread of drug-resistant organisms to the community. Cure of a high proportion of new smear-positive patients would have the greatest impact on the control of tuberculosis.
- New patients with severe forms of extrapulmonary tuberculosis such as miliary disease, pericardial disease, meningitis, and spinal disease with spinal cord involvement. Although not infectious, these patients are at high risk of death unless treated with effective drug combinations.
- New patients with severe and extensive smear-negative pulmonary tuberculosis; patients with concomitant HIV diseases are at particularly high risk of death.

Category II
Includes patients previously treated for tuberculosis who have developed smear-positive pulmonary tuberculosis; includes patients with relapse, treatment failures, and patients who previously defaulted from treatment. These patients are given multidrug regimens because they are highly infectious and are more likely to have

¹ Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.
drug-resistant organisms that can spread to the community unless they are effectively treated. The entire course of treatment in such patients should be directly observed; patients who were treated previously are at much higher risk of default. For many patients, this represents their last real chance for cure.

**Category III**
Includes patients with smear-negative pulmonary tuberculosis and less serious forms of extrapulmonary tuberculosis such as pleural effusion and lymphadenopathy. These patients are much less infectious than those with smear-positive pulmonary tuberculosis, and there is less risk of development of drug resistance or of death. However, cases of HIV-infected smear-negative pulmonary tuberculosis may be at greater risk of death compared with HIV-infected smear-positive pulmonary tuberculosis cases because the former are more immunocompromised. HIV-infected patients may also be more prone to acquiring drug-resistant disease. Moreover, smear-negative patients may contribute to the spread of tuberculosis in the community. For these reasons, and because the HIV status in most tuberculosis cases is unknown, WHO now recommends that these patients receive the same regimen at Category I, with four initial drugs.

**Category IV**
Category IV is comprised of smear-positive pulmonary tuberculosis cases who have completed a fully supervised re-treatment regimen, and those who have multidrug-resistant tuberculosis (with resistance to isoniazid and rifampicin documented in a competent laboratory). Treatment of such patients is lengthy, costly, difficult for both patients and staff, and often unsuccessful. Highest priority must always be given to prevention of such cases by effective, directly observed primary treatment regimens. Where resources and expertise permit, treatment of such individual cases is sometimes attempted on humanitarian grounds (see “What reserve regimens are available and what is their place in tuberculosis control programmes?”, page 215). In settings where multidrug-resistant tuberculosis is common and many patients are immunocompromised, Category IV treatment may be necessary for rapid control of multidrug-resistant tuberculosis.
27. What is intermittent treatment and what is the scientific basis for intermittency?¹

T. Frieden²

Intermittent regimens are those in which the individual drugs are given at intervals of more than one day, e.g. three times a week.

Originally it was believed that anti-tuberculosis drugs needed to be given every day to maintain drug concentrations continuously at inhibitory levels. However, in vitro studies and animal experiments have demonstrated that certain drugs are also effective when the drug concentration drops temporarily below that level, and indeed even after the drug has disappeared completely from the lesion (1) or the medium (2).

In vitro experiments have demonstrated that, after a culture of *Mycobacterium tuberculosis* is exposed to certain drugs for some time, it takes several days (the “lag period”) before new growth occurs. Table 28 shows the lag period for growth of *M. tuberculosis* after exposure to different drugs for varying times.

There was no lag after exposure to thioacetazone for 24 hours or even 96 hours. Immediately the thioacetazone was removed from the culture medium, growth started again, suggesting that this drug is unsuitable for intermittent treatment; this was confirmed by animal experiments.

For each bactericidal drug there was a maximum lag period (last column) that seems to indicate the practical limit beyond which the interval between two doses should not be extended. Animal studies (4) have shown conclusively that the longer the chosen interval between doses, the higher the doses need to be for most of the drugs, with the exception of rifampicin. Thus, for high doses of isoniazid, a 3-day interval proved to be the optimum; extension of the interval to 8 days gave significantly worse results.

A series of experiments in an animal model (3) demonstrated that intermittent dosing actually increased the efficacy of treatment with isoniazid, rifampicin, and pyrazinamide (Figure 11).

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¹ Based on the chapter in the previous edition by K. Toman.
² Medical Officer, Stop TB Unit, Who Regional Office for South-East Asia, New Delhi, India.
Table 28

**Lag in growth of Mycobacterium tuberculosis after temporary exposure to drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (mg/litre)</th>
<th>Lag (days) after exposure for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 hours</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.2</td>
<td>2–3</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>50</td>
<td>5–40 b</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>5</td>
<td>8–10</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

* Source: reference 2 and 3.

b Depending on the pH of the medium.

**Figure 11**

**Mean root indices of disease related to interval between doses in guinea-pigs treated with isoniazid, ethambutol, or rifampicin**

* Source: reference 3, reprinted with permission.

**Standard intermittent regimens**

Although experimental findings cannot be mechanically transferred to humans, these results were promising enough to be explored in clinical studies. The first such randomized controlled clinical trial was undertaken at the Tuberculosis Research Centre, Chennai, India (5).
A standard oral regimen of isoniazid plus PAS twice daily was compared with a twice-weekly regimen of 1 g of streptomycin given by intramuscular injection plus 14 mg/kg body weight of isoniazid, given orally in a single dose. The oral regimen was dispensed for self-administration. For the intermittent regimens, patients attended the clinic twice a week at intervals of 3–4 days. Treatment was fully supervised, i.e. each patient first took isoniazid tablets in the presence of the staff (who verified that the tablets had actually been swallowed), and then received the injection of streptomycin. The results at 12 months are shown in Table 29.

The intermittent regimen was highly successful and perhaps slightly more effective than the daily regimen. The potency of intermittent treatment is all the more striking as most of the patients admitted to the study had extensive, bilateral cavitary disease with sputum heavily positive by direct smear. This feature was common to all the studies in Chennai (formerly Madras) in which the patients had severe disease. The relapse rates in a 2-year period were 8% for the twice-weekly regimen and 12% for the daily regimen; after 4 years, they were 12% and 15% respectively. In 4 out of 5 patients who relapsed on the intermittent regimen, the bacilli were susceptible to both isoniazid and streptomycin. This suggests that, had there been an intensive phase at the start of treatment, the susceptible bacilli would probably have been eliminated.

In another study, also undertaken in outpatients in Chennai, the possibility of increasing the interval between doses to one week was investigated. Four intermittent regimens were studied concurrently but, for the sake of simplicity, only two are described here.

The twice-weekly streptomycin plus isoniazid (S2H2) regimen was compared with streptomycin plus isoniazid given once weekly (S1H1). The dosage was the same for both regimens: 1.0 g or 0.75 g of streptomycin plus 15 mg/kg of isoniazid. The effect of a lower dose (0.75 g) of streptomycin was studied because it seemed likely this would be suffi-
cient and better tolerated, particularly by debilitated or elderly patients, than the usual dose of 1 g. The results of 12 months of treatment are summarized in Table 30.

The twice-weekly regimen again proved to be highly successful; the once-weekly regimen was considerably less effective. Nevertheless, it was impressive that, despite severe disease, 71% of patients on the once-weekly regimen achieved bacteriological quiescence (6).

The reasons for the inferiority of the once-weekly regimen were examined, and the findings were both interesting and important. In this analysis, patients were grouped according to the rate of inactivation of isoniazid and the dosage of streptomycin. Table 31 shows that the efficacy of the twice-weekly regimen was influenced neither by the

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients with quiescent disease at 1 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid inactivation rate</td>
</tr>
<tr>
<td></td>
<td>slow</td>
</tr>
<tr>
<td>$S_2H_2$ (twice weekly)</td>
<td>91</td>
</tr>
<tr>
<td>$S_1H_1$ (once weekly)</td>
<td>82</td>
</tr>
</tbody>
</table>

inactivation rate of isoniazid nor by a 25% reduction in the streptomycin dosage. In contrast, the once-weekly regimen was clearly affected by the rate of isoniazid inactivation and, to a lesser extent, also by the reduction in the streptomycin dosage. The twice-weekly regimen was thus shown to be robust and effective, even without an initial intensive phase.

The isoniazid inactivation rate also influenced the response to other once-weekly regimens investigated concurrently. With currently available medications, intermittency reaches its practical limit of effectiveness when the interval between doses is extended to one week.

The following conclusions may be drawn from the experience gained with intermittent treatment without rifampicin.

- Twice-weekly regimens containing isoniazid in high dosage (14–15 mg/kg) and streptomycin (0.75–1 g) are highly effective, whether given from the outset or after an initial intensive phase of treatment. Their efficacy in slow and rapid inactivators of isoniazid is similar. These regimens can be highly effective in patients with extensive disease and in populations with a high frequency of rapid inactivators.
- A once-weekly regimen of isoniazid (15 mg/kg) and streptomycin (1 g), after 4 weeks’ initial daily therapy with isoniazid and streptomycin, approached the efficacy of the twice-weekly regimen; however, unlike the latter, it was substantially inferior in rapid inactivators and therefore cannot be recommended.

**Short-course intermittent regimens**

The development of rifampicin and pyrazinamide prompted studies of intermittent short-course regimens. At first, investigators studied regimens with a daily intensive phase followed by an intermittent continuation phase. The risk of relapse is the key indicator of the effectiveness of a regimen. Many regimens achieve nearly 100% cure; relapse should be less than 5%. A series of studies has demonstrated that intermittent treatment following a daily intensive phase – which may be as short as two weeks – is highly effective, provided that treatment observation is ensured (Table 32).

Fully intermittent treatment has also been found to be highly effective (Table 33). The fully oral regimen of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin, has been studied in daily, partially intermittent, and fully intermittent regimens. Fully intermittent regimens, which make treatment observation more convenient and feasible for health workers and patients, achieve high levels of treatment success with low relapse rates (16). Such regimens have now been widely used, with good results. A twice-weekly, 6-month, rifampicin-containing regimen following 2 weeks of daily treatment has also been shown to be highly effective (17). However, a single missed dose will result in once-weekly treatment, which is less effective and potentially more toxic because of immunologically mediated adverse effects. Adverse reactions to rifampicin are more frequent in once-weekly treatment.
The World Health Organization Collaborating Centre for Tuberculosis Chemotherapy, Prague, reported excellent results (99–100% efficacy) in a study of which an important feature was the flexibility of the treatment organization. Each patient could choose to receive treatment at the most convenient place, such as a chest clinic, physician’s office, factory dispensary, health centre, or a hospital on the
way to work. If necessary, an outreach worker could visit the patient’s home. The area was partly rural and had adequate transport facilities.

The success of the study was due largely to the excellent cooperation of the patients, which was achieved by adapting treatment services to their convenience. This was greatly facilitated by the intermittent treatment regimen. Although the treatment of

<table>
<thead>
<tr>
<th>Country or area</th>
<th>Year of study</th>
<th>Regimen*</th>
<th>No. of patients assessed for relapse</th>
<th>Relapse in 2-year follow-up (%)</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kongb</td>
<td>1974</td>
<td>4H₃R₂Z₃S₃/2H₂Z₂S₂</td>
<td>71</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4H₃R₂Z₃S₃/4H₂Z₂S₂</td>
<td>83</td>
<td>1</td>
<td></td>
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<tr>
<td>South Africa</td>
<td>1975</td>
<td>6H₂R₂Z₂S₂</td>
<td>279</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Hong Kongb</td>
<td>1977</td>
<td>6H₂R₂Z₂E₂S₃</td>
<td>152</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6H₂R₂Z₂S₂</td>
<td>151</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6H₂R₂E₂S₂</td>
<td>166</td>
<td>8</td>
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<tr>
<td></td>
<td></td>
<td>6H₂R₂Z₂E₂</td>
<td>160</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hong Kongb</td>
<td>1979</td>
<td>2H₂R₂Z₂S₂/4H₂R₂S₂</td>
<td>220</td>
<td>3</td>
<td>20</td>
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<td></td>
<td>2H₂R₂Z₂S₂</td>
<td>205</td>
<td>5</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/2H₂R₂S₂</td>
<td>208</td>
<td>3</td>
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<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/4H₂R₂Z₂S₂</td>
<td>199</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Madras, India</td>
<td>1980</td>
<td>2H₂R₂Z₂S₂/4H₂R₂S₂</td>
<td>111</td>
<td>2</td>
<td>21</td>
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<td>2H₂R₂Z₂S₂/4H₂R₂S₁</td>
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<td>5</td>
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<tr>
<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/4R₂H₂</td>
<td>101</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/4R₂H₁</td>
<td>116</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/4H₂S₂</td>
<td>151</td>
<td>3</td>
<td></td>
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<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/4H₂R₂S₂</td>
<td>108</td>
<td>3</td>
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<td></td>
<td>2H₂R₂Z₂S₂/4H₂R₂S₁</td>
<td>117</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2H₂R₂Z₂S₂/4R₂H₂</td>
<td>102</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Canary Islandsd</td>
<td>1990</td>
<td>2H₂R₂Z₂(E₂)/4H₂R₂</td>
<td>80</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Madras, India</td>
<td>1990</td>
<td>2H₂R₂Z₂E₂/4H₂R₂</td>
<td>273</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Haiti</td>
<td>1990</td>
<td>2H₂R₂Z₂E₂/4H₂R₁</td>
<td>129 (HIV-infected)</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2H₂R₂Z₂E₂/4H₂R₁</td>
<td>211 (HIV-uninfected)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>1991</td>
<td>2H₂R₂Z₂S₂/4H₂R₃</td>
<td>300</td>
<td>3</td>
<td>24</td>
</tr>
</tbody>
</table>

* H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week.

b Now Hong Kong Special Administrative Region of China.

c Now Chennai.

d Ethambutol given only to patients with prior history of default.
tuberculosis in the former Czechoslovakia was almost entirely the responsibility of a rather extensive network of specialized inpatient and outpatient tuberculosis services, the participation of non-specialized health services was of great importance. Moreover, the study demonstrated how general health services can become increasingly involved in the management of tuberculosis patients, and are capable of taking over this responsibility from the specialized services.

References


28. **What is the dosage of drugs in daily and intermittent regimens?**

*H. Rieder*¹

Table 34 shows the current dosage of anti-tuberculosis drugs as indicated by WHO (¹), based on mg/kg body weight. However, WHO (²) and IUATLD (³) do not recommend the use of twice-weekly intermittent treatment because missing one of the doses results in insufficient treatment and a higher risk of toxicity.

In practice, however, it has proved useful to use dosages based on weight ranges to facilitate the prescription of drugs in terms of number of tablets. The weight of

Table 34  
**Dosages for anti-tuberculosis drugs in mg/kg body weight**ᵃ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily treatment</th>
<th>Treatment three times a week</th>
<th>Treatment twice a weekᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 (4–6)</td>
<td>10 (8–12)</td>
<td>15 (13–17)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 (8–12)</td>
<td>10 (8–12)</td>
<td>10 (8–12)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 (20–30)</td>
<td>35 (30–40)</td>
<td>50 (40–60)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 (12–18)</td>
<td>15 (12–18)</td>
<td>15 (12–18)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 (13–17)</td>
<td>30 (25–35)</td>
<td>45 (40–50)</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>2.5 (2–3)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ᵃ Source: references 1, 2.
ᵇ Not recommended by WHO and IUATLD because missing a dose results in insufficient treatment and higher risk of toxicity.

¹ Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.
tuberculosis patients differs in different countries as shown in Figure 12. Weight ranges – shown by the vertical dotted lines – as recommended by the IUATLD (2) may thus need adaptation by countries to ensure that the largest possible proportion of patients receive the correct dosage.

Alternatively, a single dosage appropriate for most patients can be used, as in the India Revised Tuberculosis Programme (4). Children and patients with very low body weight receive individually adjusted dosages, and patients with high body weight are given extra pills. This permits the use of prepacked treatment boxes, which facilitates drug management.

References


Figure 12

Distribution of body weight among sputum smear-positive patients in Kenya, Nepal, and Senegal

* Source: reference 3.
Each drug is needed in the minimum concentration that can inhibit growth of *Mycobacterium tuberculosis*. This concentration is called the minimum inhibitory concentration (MIC) of the drug and is determined in vitro by testing numerous wild strains to determine the MIC at which the growth of most of these is inhibited. Because it is an in vitro system, the technique affects the result. Thus, MIC values differ when determined on egg-based, broth, or agar media.

The highest dosage that does not lead too frequently to toxic reactions is determined in vivo. If the maximum concentration that can be achieved in serum without causing toxic reactions is lower than the MIC in vitro, the drug cannot be used. If the maximum serum concentration that can be achieved is far above the MIC, the therapeutic margin is large; if it is only slightly above the MIC, that margin is narrow.

A third important element – in addition to the MIC and the maximum serum concentration – is the length of time during which the serum level of the drug remains above the MIC. This is determined by the half-life of the drug. The serum level of each drug needs to remain above the MIC for a certain minimum time in order to exert its action on *M. tuberculosis*. This minimum time varies from one drug to the next.

More important than the MIC is the minimum bactericidal concentration (MBC) – the concentration at which the organism is killed by the drug. The MBC is always higher than the MIC and the MBC-to-MIC ratio is different for different drugs.

The maximum tolerable dosage of a drug, and thus the maximum serum concentration, is determined in clinical practice; the actual therapeutic effect of the drug is established in controlled clinical trials. The challenge is to determine the lowest dosage (to reduce the frequency of toxic reactions) that results in a serum concentration above the MIC (or better the MBC).

For example, a trial in East Africa studied whether increasing the dosage of isoniazid from 300 mg to 450 mg in combination with thioacetazone improved the efficacy of the regimen (1). It did not. Moreover, although isoniazid-attributable toxicity did

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1 Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.
not differ for the two dosages in this study, information obtained elsewhere indicates that isoniazid toxicity increases with increasing dosages. The optimum daily dosage of isoniazid was determined to be 300 mg. The optimum dosage of streptomycin was also determined (2): for long-term treatment, 0.75 g of streptomycin proved to be as effective as 1.0 g. The lower dosage was equally potent in preventing emergence of resistance to isoniazid and ensuring sputum conversion, but caused vestibular damage less frequently. This type of evaluation – finding a balance between toxicity and maximum therapeutic range – has been done for all anti-tuberculosis drugs and forms the rational basis for the current dosage recommendations.

A summary of the relation between MIC and the maximum serum concentration for the six essential anti-tuberculosis drugs shows that the therapeutic range is large for isoniazid and rifampicin, and smaller for the others (Figure 13) (3–8).

References

30. **What is the optimum duration of treatment?**

*T. Santha*

Short-course regimens achieve smear and culture conversion within 2–3 months in most patients. Many regimens achieve a favourable response, as defined by culture negativity at the end of treatment, of 97–100%. The challenge, however, has been to identify practical regimens that have low (<5%) relapse rates.

**Sputum-positive pulmonary tuberculosis**

Several studies have shown that a 6-month regimen containing rifampicin throughout and pyrazinamide in the intensive phase is highly effective in the treatment of sputum-positive tuberculosis (Table 35).

These regimens are nearly 100% effective at the end of treatment in patients with initially drug-susceptible organisms; the relapse rate over a 2-year follow-up period was 0–7%.

East African studies have shown that, if rifampicin is given only in the intensive phase, the regimen should be implemented for 8 months (Table 36): 6-month regimens with a continuation phase that does not contain rifampicin have a relapse rate of 7–18%, whereas 8-month regimens have relapse rates of 0–7%. A similar relapse rate (5%) has been reported with daily isoniazid and ethambutol for 6 months in the continuation phase (12).

In the initial studies, drugs were given daily throughout or at least during the initial intensive phase at least. Studies conducted at the Tuberculosis Research Centre, Madras (now Chennai), and in Hong Kong (now Hong Kong SAR) (3) have shown that fully intermittent regimens are equally effective, with near 100% efficacy at the end of treatment, followed by a relapse rate of 2–7%, and that the reduction in adverse reactions is significant (Table 37).

As indicated from the studies summarized here, treatment of newly diagnosed smear-positive patients should be daily or intermittent for 6–8 months; treatment for 8 months is required if rifampicin is not used in the continuation phase of treatment (5). The intensive phase should last for at least 2 months.

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1 Based on the chapter in the previous edition by K Toman.
2 Deputy Director, Tuberculosis Research Center, Chennai, India.
Smear-negative pulmonary tuberculosis

The optimum duration of treatment for smear-negative patients was investigated in a study in Hong Kong. Patients with five smears negative for acid-fast bacilli and X-rays suggestive of tuberculosis were treated for 2 or 4 months with an HRZS regimen (Table 38). Relapse rates were higher with 2–3 months of treatment and the study
### Table 37

**Intermittent short-course chemotherapy**

<table>
<thead>
<tr>
<th>Country or area</th>
<th>Year of study</th>
<th>Regimen&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Duration of treatment (months)</th>
<th>No. of patients assessed</th>
<th>Relapse rate after 2 years (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1974</td>
<td>4H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;/2H&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>6</td>
<td>71</td>
<td>6</td>
<td>5, 6</td>
</tr>
<tr>
<td>Kong&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>2H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;/4H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>6</td>
<td>220</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Madras&lt;sup&gt;d&lt;/sup&gt;, India</td>
<td>1980</td>
<td>2H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;/4H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>6</td>
<td>111</td>
<td>2</td>
<td>15, 16</td>
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<td>101</td>
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<td>6</td>
<td>108</td>
<td>3</td>
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<td>6</td>
<td>519</td>
<td>7</td>
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<sup>a</sup> Source: reference 3.
<sup>b</sup> H = isoniazid, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.
<sup>c</sup> Now Hong Kong SAR.
<sup>d</sup> Now Chennai.

### Table 38

**Duration of treatment for initially smear-negative pulmonary tuberculosis in Hong Kong**

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Initial culture status</th>
<th>Regimen&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Duration of treatment (months)</th>
<th>No. of patients assessed</th>
<th>Relapse rate after 2 years (%)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>1976</td>
<td>Negative</td>
<td>No treatment</td>
<td>–</td>
<td>176</td>
<td>40</td>
<td>17–19</td>
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<tr>
<td></td>
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<td>2HRZS</td>
<td>2</td>
<td>165</td>
<td>4</td>
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<tr>
<td></td>
<td></td>
<td>3HRZS</td>
<td>3</td>
<td>162</td>
<td>2</td>
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<td>3PHS/H&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>12</td>
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<td>2HRZS</td>
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<td>72</td>
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<td></td>
<td>3HRZS</td>
<td>3</td>
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<td></td>
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<td>68</td>
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<td>Negative</td>
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<td>364</td>
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<td>20</td>
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<td></td>
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<td>3</td>
<td>345</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>4</td>
<td>325</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>4HRZS</td>
<td>4</td>
<td>157</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>4</td>
<td>136</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6H&lt;sub&gt;j&lt;/sub&gt;R&lt;sub&gt;j&lt;/sub&gt;Z&lt;sub&gt;j&lt;/sub&gt;S&lt;sub&gt;j&lt;/sub&gt;</td>
<td>6</td>
<td>166</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Source: references 18–20.
<sup>b</sup> Now Hong Kong SAR.
<sup>c</sup> H = isoniazid, P = protonamide, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.
concluded that smear-negative patients require at least 4 months of treatment. However, for consistency and a margin of safety, WHO recommends 6-month regimens for smear-negative pulmonary tuberculosis.

Results of further shortening the duration of treatment

Two groups of investigators in France and India, in search of a shorter duration of treatment for pulmonary tuberculosis, tried daily regimens of 3 months’ duration (90 doses of HRZS) (Table 39). A regimen of HRZS given daily for 3 months in India achieved almost 100% culture conversion at 3 months, but 20% of patients had bacteriologically confirmed relapse (23). When fewer doses were given over a longer period – three times weekly for 2 months (27 doses) followed by twice weekly for 4 months (36 doses), making a total of 63 doses in 6 months – relapse rates were 4–6%. Thus, it is the period over which the drugs are given that is important, rather than the number of doses (15, 16).

Similarly, 4-month regimens studied in Singapore also had high relapse rates (8–16%) (7–9). Two 5-month regimens (2HRZS/3HZS and 3HRZS/2H2Z2S2) tried in Madras were effective and had low relapse rates (4–5%). However, this is the only study that investigated 5-month regimens and acceptable results were achieved only by using streptomycin for the entire 5 months of treatment.

Thus, there is at present no practical regimen of less than 6 months’ duration that has given acceptable results in smear-positive tuberculosis.

**Table 39**

Shorter duration of treatment for smear-positive pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Country or area</th>
<th>Year of study</th>
<th>Regimen a</th>
<th>Duration of treatment (months)</th>
<th>No. of patients assessed</th>
<th>Relapse rate after 2 years (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore</td>
<td>1973</td>
<td>2HRZS/2HRZ</td>
<td>4</td>
<td>79</td>
<td>11</td>
<td>7–9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2HRZS/2HR</td>
<td>4</td>
<td>77</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>1976</td>
<td>2HRZS/2HRZ</td>
<td>4</td>
<td>104</td>
<td>16</td>
<td>21, 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2HRZS/2HR</td>
<td>4</td>
<td>104</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Madras b</td>
<td>1977</td>
<td>3HRZS</td>
<td>3</td>
<td>200</td>
<td>20</td>
<td>23, 24</td>
</tr>
<tr>
<td>India</td>
<td>1974</td>
<td>2HRZS/3H2Z2S2</td>
<td>5</td>
<td>129</td>
<td>4</td>
<td>25, 26</td>
</tr>
<tr>
<td></td>
<td>1977</td>
<td>3HRZS/2H2Z2S2</td>
<td>5</td>
<td>187</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

a H = isoniazid, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.

b Now Chennai.
What is the optimum duration of standard, non-rifampicin-containing treatment?

There are situations in which rifampicin is either unavailable or rifampicin and pyrazinamide cannot be given to a patient. Before rifampicin and pyrazinamide became available, patients were treated for prolonged periods. For patients with initially sputum smear-positive tuberculosis, practically all effective regimens achieve bacteriological quiescence within 6 months of the start of treatment. However, relapse occurs in about a quarter of patients treated with streptomycin, isoniazid, and thioacetazone daily for 6 months (Table 40).

On the other hand, there is satisfactory evidence that more than 18 months of good treatment produces little, if any, additional benefit in terms of treatment success or prevention of relapse (6).

In studies in East Africa, addition of an initial supplement of streptomycin to the basic regimen of thioacetazone plus isoniazid daily for 8 weeks yielded a success rate of 96%; emergence of resistance was rare among patients who failed treatment. Two weeks of initial intensive treatment resulted in a failure rate of 10%, all with organisms resistant to isoniazid. Bacteriological response in patients who received an initial streptomycin supplement for 4 weeks was only slightly (2%) less favourable than in patients given the supplement for 8 weeks (Table 41).

The investigators concluded that it was desirable to supplement the daily thioacetazone–isoniazid regimen with streptomycin, preferably for the first 8 weeks of treatment; if this could not be achieved, the aim should be to give the streptomycin supplement for the first 4 weeks.

Other studies, in Madras and Singapore, showed that adding 2 weeks of initial

| Table 40
Duration of treatment when rifampicin is not used |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Country or area</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>East Africa</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Madras, India</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> H = isoniazid, P = protonamide, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.

<sup>b</sup> Now Chennai.
The intensive phase did not add any further benefit to the overall results of the regimens (31, 32). A study in Czechoslovakia (33) investigated the role of three drugs during the intensive phase in a fully intermittent regimen and found there was no advantage in extending the phase to 13 weeks (98% and 99%, respectively). Thus the optimum duration of intensive phase in a conventional long-term treatment is 8 weeks.

References


### Table 41

**Response to treatment with streptomycin plus isoniazid and thioacetazone (STH) daily for 2, 4, or 8 weeks, followed by isoniazid plus thioacetazone in the continuation phase: assessment at 1 year**

<table>
<thead>
<tr>
<th>Country or area</th>
<th>Duration of initial phase (STH)</th>
<th>No. of patients treated</th>
<th>Percentage of patients showing:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>favourable bacteriological response</td>
</tr>
<tr>
<td>East Africa</td>
<td>8 weeks</td>
<td>162</td>
<td>96</td>
</tr>
<tr>
<td>Africa</td>
<td>4 weeks</td>
<td>159</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>161</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Noneb</td>
<td>147</td>
<td>88</td>
</tr>
</tbody>
</table>

* Source: reference 1.
* Thioacetazone plus isoniazid, without initial supplement.


23. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and


31. **What are the most common adverse drug events to first-line tuberculosis drugs, and what is the procedure for reintroduction of drugs?**

_A. Harries_¹

### Isoniazid (1–3)

**Adverse effects**
- Skin rash.
- Sleepiness and lethargy.
- Peripheral neuropathy (paraesthesia, numbness and limb pain).
- Hepatitis.

**Rare adverse effects**
- Convulsions, pellagra, arthralgia, anaemia, lupoid reactions.

**Management**
- For skin reactions – see below.
- For lethargy – reassurance.
- For peripheral neuropathy – this may be prevented by giving vitamin B6 (pyridoxine), 10 mg daily, or vitamin B complex. For established peripheral neuropathy, pyridoxine should be given at a larger dose of 50–75 mg daily.
- For hepatitis – see below.

### Rifampicin

**Adverse effects**
- Gastrointestinal reactions (abdominal pain, nausea, vomiting).
- Hepatitis.
- Generalized cutaneous reactions.
- Thrombocytopenic purpura.
- On intermittent dosage, “flu syndrome”.

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¹ Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.
Rare adverse effects

- Osteomalacia, pseudomembranous colitis, pseudoadrenal crisis, acute renal failure, shock, haemolytic anaemia.

Rifampicin may cause gastrointestinal symptoms such as anorexia, nausea, abdominal pain, and vomiting. These symptoms occur soon after administration and can last several hours. In contrast, the “flu syndrome” consists of fever, chills, malaise, headache, and bone pains.

Rifampicin is a powerful enzyme inducer and may therefore reduce serum concentrations of other drugs that the patient is taking. This is of particular importance in women taking oral contraceptives. Patients should be warned that rifampicin colours all body secretions (urine, tears, semen, and sweat) red or orange.

Management

- For gastrointestinal reactions, the patient should be reassured. If gastrointestinal intolerance is severe enough to risk interruption of treatment, suspension of rifampicin for 3 or 4 doses, use of medications that provide symptomatic relief (e.g. metoclopramide to counteract vomiting), or, as a last resort, giving rifampicin with small amounts of food may allow continued use of the drug in almost all patients (1). Although concomitant ingestion of food reduces absorption of rifampicin slightly, this is far preferable to complete discontinuation of rifampicin.
- For hepatitis and skin reactions – see below.
- For adverse effects such thrombocytopenic purpura, shock, acute renal failure, or haemolytic anaemia the drug must be immediately withdrawn and never used again.
- For the “flu syndrome”, changing from intermittent to daily rifampicin administration can stop the reaction.

Pyrazinamide

Adverse effects

- Arthralgia.
- Hepatitis.

Rare adverse effects

- Gastrointestinal reactions, cutaneous reactions, sideroblastic anaemia.

Pyrazinamide may cause arthralgia by inhibiting renal tubular excretion of uric acid, and high concentrations of uric acid can lead to gout. Severe hepatotoxicity has been observed when regimens containing rifampicin and pyrazinamide are used for latent tuberculosis infection.
Management

- For joint involvement, simple treatment with analgesics usually minimizes symptoms. Indomethacin may be used for more severe joint involvement. If frank gout occurs, treatment with colchicine is required. Arthralgia is much less common with thrice-weekly treatment. Asymptomatic elevation of serum uric acid levels is expected and does not require either a change in medication or administration of other medications.
- For hepatitis – see below.

Ethambutol

Adverse effects

- The main adverse effect is retrobulbar neuritis.

Rare adverse effects

- Generalized cutaneous reactions, arthralgia, peripheral neuropathy, and – very rarely – hepatitis.

Note: Ethambutol may produce impairment of vision – red–green colour blindness, blurring, and decrease in visual acuity. However, the toxicity is dose dependent and occurs rarely when 15 mg/kg body weight is given daily or 25 mg/kg body weight is given three times a week.

Management

- It is good practice to carry out a basic examination of visual acuity before starting treatment with ethambutol. All patients should be warned that an ocular examination should be undertaken if visual symptoms occur. Impaired vision usually returns to normal within a few weeks of stopping the drug. Some programmes conduct monthly tests for red–green colour blindness (e.g. Ishihara tests), although the utility of this has not been demonstrated.

Streptomycin

Minor adverse effects

- Pain, rash, induration at injection site.
- Numbness around the mouth and tingling soon after the injection.

Major adverse effects

- Cutaneous hypersensitivity.
- Vestibular and auditory nerve damage to the patient and, in a pregnant woman, also to the fetus.
- Renal damage.
Management

- For minor adverse effects the patient can be reassured.
- For cutaneous hypersensitivity – see below.
- For vestibular, auditory, and renal damage, the risk increases with dose and age. The dose should not exceed 15–20 mg/kg and should be reduced in patients aged 45 years or more. Damage to the vestibular and auditory system usually occurs in the first 2 months and is manifested by ringing in the ears, giddiness, ataxia, and/or deafness. The condition is reversible if the drug dosage is reduced or the drug is stopped. Intermittent dosages (e.g. three times a week) are less likely to cause serious toxicity.

Thioacetazone

Common adverse effects

- Skin rash, sometimes with mucosal involvement.

Rare adverse effects

- Acute hepatic failure, agranulocytosis. Exfoliative dermatitis, which may be fatal, is more common in HIV-infected individuals.

Management

- If a rash or other sign of hypersensitivity develops, all treatment should be withdrawn and thioacetazone should not be used again. It can be replaced by ethambutol after the symptoms disappear. Because of the much higher frequency of toxicity in HIV-infected individuals, thioacetazone should not be used in patients suspected of being infected with HIV or in areas with high prevalence of HIV infection (see “What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?”, page 159). For management of cutaneous sensitivity see below.

Cutaneous and generalized hypersensitivity reactions to TB drugs

Skin reactions

Itching with no rash or with a mild rash

If the patient (not receiving thiacetazone, see above) complains of itching without a rash or itching with a mild rash, symptomatic treatment with antihistamines may be tried and tuberculosis treatment continued. However, the patient must be monitored with each subsequent dose of antituberculosis drugs.

Itching with a moderate/severe rash

If a moderate or severe rash develops, all treatment should be stopped.
Management of severe rash

If the rash is severe, or if there is evidence of mucosal involvement, hypotension, or severe illness, corticosteroid treatment should be instituted. Oral prednisolone, 40–60 mg, should be given daily until there is a response; the dose should then be reduced gradually in the following days according to the patient’s response. Tuberculosis treatment should be withheld until the reaction has completely subsided.

Reintroduction of antituberculosis drugs

Once the reaction has subsided, drugs can be reintroduced according to the schedule below.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug, dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isoniazid 50 mg</td>
</tr>
<tr>
<td>2</td>
<td>Isoniazid 300 mg</td>
</tr>
<tr>
<td>3</td>
<td>Rifampicin–isoniazid (RH) (half tablet)</td>
</tr>
<tr>
<td>4</td>
<td>Rifampicin–isoniazid (RH) (one tablet)</td>
</tr>
<tr>
<td>5</td>
<td>Rifampicin–isoniazid (RH) (full dose)</td>
</tr>
<tr>
<td>6</td>
<td>Day 5 regimen + pyrazinamide (half tablet)</td>
</tr>
<tr>
<td>7</td>
<td>Day 5 regimen + pyrazinamide (one tablet)</td>
</tr>
<tr>
<td>8</td>
<td>Day 5 regimen + pyrazinamide (full dose)</td>
</tr>
<tr>
<td>9</td>
<td>Day 8 regimen + ethambutol (half tablet)</td>
</tr>
<tr>
<td>10</td>
<td>Day 8 regimen + ethambutol (one tablet)</td>
</tr>
<tr>
<td>11</td>
<td>Day 8 regimen + ethambutol (full dose)</td>
</tr>
<tr>
<td>12</td>
<td>Full dose of Rifampicin–isoniazid + pyrazinamide + ethambutol</td>
</tr>
</tbody>
</table>

Isoniazid and rifampicin are the least likely to cause a reaction and should be reintroduced first. The drugs at the bottom of the table are more likely to cause a reaction. If the initial cutaneous reaction was severe, smaller initial challenge doses should be given. If the patient is restarted on an adequate tuberculosis treatment regimen (e.g. isoniazid, rifampicin, and pyrazinamide), re-challenging with the implicated drug (e.g. streptomycin) is not advisable.

Drug-induced hepatitis

Features that indicate the need to stop medication

Transient, asymptomatic increases in serum liver transaminases occur during the early weeks of treatment. There is no need to interrupt or change treatment unless there is anorexia, malaise, vomiting, or clinically evident jaundice. Clinical features of concern include protracted vomiting, mental changes, and signs of bleeding – all of which suggest impending acute liver failure and require immediate discontinuation of antituberculosis medications.
**Management of jaundice and other severe features**

If jaundice or any of the clinical features suggestive of acute liver failure develop, all drugs must be stopped until the jaundice or hepatic symptoms have resolved and the liver enzymes have returned to baseline levels. If liver enzymes cannot be measured, it is advisable to wait 2 weeks after the jaundice has disappeared before starting tuberculosis treatment. Other causes of hepatitis must be sought.

**Reintroduction of antituberculosis drugs**

Once hepatitis has resolved, the same drug regimen can be reintroduced, either gradually or all at once. However, if hepatitis has been life-threatening and was not of viral origin, it is probably safer to use the regimen of streptomycin, isoniazid, and ethambutol.

**Symptom-based approach to the management of drug reactions**

*Minor adverse effects not requiring stoppage of treatment*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Drug</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain, nausea</td>
<td>Related to rifampicin</td>
<td>Reassure the patient</td>
</tr>
<tr>
<td>Burning of the feet</td>
<td>Related to isoniazid</td>
<td>Continue isoniazid, and give pyridoxine 50–75 mg daily; large doses of pyridoxine may interfere with the action of isoniazid</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Related to isoniazid peripheral neuropathy</td>
<td>Reassure patient</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>Related to isoniazid</td>
<td>Reassure patient; give drugs with less water; give drugs over a longer period of time (e.g. 20 minutes); give drugs with a small amount of food; If these measures fail, provide antiemetic if appropriate</td>
</tr>
<tr>
<td>Joint pains</td>
<td>Related to pyrazinamide</td>
<td>Continue pyrazinamide; use aspirin or non-steroidal anti-inflammatory drug; use intermittent directly observed treatment, if possible</td>
</tr>
<tr>
<td>Red urine</td>
<td>Related to rifampicin</td>
<td>Reassure the patient</td>
</tr>
<tr>
<td>Women on rifampicin</td>
<td>Rifampicin may reduce the effectiveness of oral contraceptive pills</td>
<td>Alternative method of contraception should be provided</td>
</tr>
</tbody>
</table>
**Major adverse effects requiring stoppage of treatment**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Drug</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of hearing</td>
<td>Related to streptomycin</td>
<td>Auroscopy to rule out wax. Stop streptomycin if no other explanation; use ethambutol instead</td>
</tr>
<tr>
<td>Dizziness</td>
<td>If true vertigo and nystagmus, related to streptomycin</td>
<td>Stop streptomycin. If just dizziness with no nystagmus, try dose reduction for one week; if there is no improvement stop streptomycin and use ethambutol instead</td>
</tr>
<tr>
<td>Generalized reactions</td>
<td>May be due to rifampicin, pyrazinamide, and/or streptomycin</td>
<td>Stop all medication; use different combination of drugs</td>
</tr>
<tr>
<td>including shock, purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>May be due to drug-induced hepatitis</td>
<td>Stop all antituberculosis drugs until jaundice resolves and liver enzymes revert to baseline levels (see text)</td>
</tr>
<tr>
<td>Moderate–severe skin rash</td>
<td>Related to all tuberculosis drugs</td>
<td>Stop tuberculosis drugs (see text)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>Related to ethambutol</td>
<td>Visual examination. Stop ethambutol</td>
</tr>
<tr>
<td>Vomiting/confusion</td>
<td>Suspect drug-induced hepatitis</td>
<td>Urgent liver enzyme tests. If liver enzymes tests unavailable, stop tuberculosis drugs and observe</td>
</tr>
</tbody>
</table>

**References**

32. What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?\(^1\)

H. Rieder\(^2\)

Thioacetazone is one of the oldest known antituberculosis drugs. When it was introduced in the late 1940s, there was good evidence of its efficacy, but the relatively high dosages used in those days meant that adverse effects and toxicity were frequent. Thus, with the advent of isoniazid a few years later, thioacetazone was quickly forgotten.

In the early 1960s, thioacetazone was reinvestigated as a companion drug to isoniazid. The intention was to find an alternative to \(p\)-aminosalicylic acid (PAS) that would prevent the development of resistance to isoniazid equally well and be less bulky (as well as less expensive). Many pilot studies were conducted to establish the optimum dosage of both drugs. The result was the introduction of a regimen containing 150 mg of thioacetazone and 300 mg of isoniazid, given in one dose daily, which proved to be as effective as the PAS–isoniazid combination.

Thioacetazone plus isoniazid with an initial supplement of streptomycin

Several trials investigated the influence of a three-drug initial phase on the thioacetazone–isoniazid regimen. An initial supplement of streptomycin improved the results, with 4 and 8 weeks of streptomycin giving almost the same results.

In many low-income countries, thioacetazone-containing regimens have been used widely because they offer the following advantages:

- They are convenient for patients because only one tablet a day is required.
- They are the least expensive efficacious treatment regimen.
- The tablets have a long shelf life. Thioacetazone is stable even in tropical climates.

Effectiveness of thioacetazone with isoniazid in routine practice

The results obtained in a trial in Kenya were compared with those in a group of patients treated by the routine tuberculosis service (1) and provided valuable information. Both groups received the same regimen, i.e. three drugs (300 mg of isoniazid,

\(^1\) Based on the chapter in the previous edition by K Toman.
\(^2\) Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.
150 mg of thioacetazone, and 1 g of streptomycin) daily for 2 months, followed by two
drugs (150 mg of thioacetazone plus 300 mg of isoniazid, in a single tablet) daily for
10 months. Bacteriological quiescence was achieved in 96% of patients in the Kenyan
study at 12 months, compared with only 76% in the “routine” group (1). Analysis of
the records showed clearly that the results were dependent upon the regularity and
duration of treatment after the initial intensive phase. Patients who took treatment
irregularly or stopped their treatment early did poorly; those who took treatment reg-
ularly and continued for the full year did well. There was considerably more irregu-
larity in the group of routinely treated patients than in the trial group. Irregularity of
treatment in the continuation phase may nullify the benefits of an initial intensive
phase. As long as a high level of regularity cannot be ensured, even first-rate regimens
will produce inadequate results.

Thioacetazone plus isoniazid in the continuation phase following
rifampicin-containing intensive phase

A regimen consisting of 2 months of isoniazid, rifampicin, pyrazinamide and strep-
tomycin, followed by 6 months of thioacetazone plus isoniazid (2HRZS/6HT) was
investigated in East Africa (2). Results are summarized in Table 42.

This became the main treatment regimen for sputum smear-positive patients
without a history of prior treatment in many national tuberculosis programmes with
limited resources. Its advantages are:

- It is the least expensive short-course regimen, with high efficacy in patients with
  fully susceptible organisms.
- Directly observed treatment can be organized during the intensive phase, with a
  self-administered continuation phase. The probability of selecting rifampicin-
  resistant mutants is low, even in the presence of initial isoniazid resistance.
- In a patient for whom the above regimen fails, the possibility of cure with a re-
  treatment regimen based solely on first-line drugs is preserved, as the patient will

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pretreatment strain susceptibility to isoniazid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>0/81</td>
</tr>
<tr>
<td>Relapse</td>
<td>0/81</td>
</tr>
</tbody>
</table>

* Source: reference 2.
always receive at least two drugs (rifampicin and ethambutol) to which the organism is likely to be susceptible.

**Thioacetazone and HIV infection**

Cutaneous reactions are among the most important adverse side-effects of thioacetazone. A cutaneous reaction may present first as itching; this may be followed by a rash that may then quickly develop further into toxic epidermal necrolysis, with a case-fatality of 20–30%. An elegant study in Kenya demonstrated the causal relationship between adverse cutaneous reactions, thioacetazone, and HIV infection (3). The association is so strong and the harmful effects so serious that there is universal agreement that patients known or suspected to have HIV infection should never be given thioacetazone. Furthermore, patients receiving thioacetazone who develop any form of cutaneous reaction should be promptly taken off the drug and never receive it again.

Because tuberculosis patients in most settings where HIV and tuberculosis are common are not routinely offered HIV testing, and their HIV status is therefore unknown, thioacetazone should not be used in areas where prevalence of HIV infection is high.

The closest alternative regimen uses ethambutol and isoniazid in the continuation phase, for the same duration; it is well tolerated and has a similar high efficacy (4). Its drawback, in addition to the higher cost and the shorter shelf-life of ethambutol, is that, for patients with true treatment failure, the standard WHO-recommended re-treatment regimen may be less effective because ethambutol resistance may have emerged. This may increase the risk of rifampicin resistance, particularly in patients with HIV infection (5).

**References**

33. **How does management of extrapulmonary tuberculosis differ from that of pulmonary tuberculosis?**

*R. Balasubramanian,¹ R. Rajeswari¹ & T. Santha¹*

**Challenges in diagnosis**

The treatment of extrapulmonary tuberculosis differs from that of pulmonary tuberculosis in several ways. This is largely because of the difficulty of diagnosis, which often leads to empirical treatment without pathological or bacteriological confirmation. However, diagnosis made only on clinical grounds leads to over-diagnosis and unnecessary treatment of a large number of patients (1). In developing countries, the problems of diagnosis are compounded by a lack of diagnostic resources. Tuberculosis may not be considered at all in the differential diagnosis, resulting in delay or deprivation of treatment (2). Extrapulmonary forms of tuberculosis occur in all age groups, adding to diagnostic and treatment difficulties.

**Treatment and management of extrapulmonary tuberculosis**

Extrapulmonary tuberculosis is usually paucibacillary, and any treatment regimen effective in pulmonary tuberculosis is likely to be effective in the treatment of extrapulmonary tuberculosis as well. For the purposes of treatment, extrapulmonary tuberculosis can be classified into severe and non-severe forms. Severe forms include meningeal tuberculosis, spinal tuberculosis, neuro-tuberculosis, abdominal tuberculosis, bilateral pleural effusion, pericardial effusion, and bone and joint tuberculosis involving more than one site. Extrapulmonary tuberculosis of other sites is classified as non-severe.

There are few reports of the use of short-course chemotherapy in the treatment of extrapulmonary tuberculosis (3). The difficulty of defining a clear-cut “end-point” for assessing the efficacy of treatment of extrapulmonary tuberculosis has led to varying durations of treatment, and there have been relatively few controlled clinical trials (4). The principles involved in the diagnosis and management of extrapulmonary tuberculosis have therefore evolved mainly from experience gained in randomized controlled clinical trials on pulmonary tuberculosis. However, studies on extrapulmonary tuberculosis (tuberculosis of the spine, tuberculous lymphadenitis, abdominal tuber-

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closus, and brain tuberculoma) have clearly established the efficacy of short-course treatment (6–9 months) in both children and adults (5), with the overall favourable response varying from 87% to 99% (Table 43). Intermittent regimens have been shown to be as effective as daily regimens.

For the severe forms, it is preferable to treat with four drugs in the initial intensive phase and, if required, the total duration of treatment can be extended to 9 months, especially in tuberculous meningitis and neuro-tuberculosis. Steroids should be given in case of tuberculous meningitis with neurological impairment, massive pleural effusion, or tuberculous pericarditis. Lymph nodes can enlarge, persist, and become superinfected with bacteria in the course of tuberculosis treatment. Generally, no modification or prolongation of the tuberculosis treatment regimen is indicated.

Even though treatment gives good results in most forms of extrapulmonary tuberculosis, there are a few exceptions, such as meningitis and spinal tuberculosis (Pott’s disease), in which the outcome depends on early diagnosis. In tuberculous meningitis, even with short-course treatment the outcome is related to the stage of the disease at the time treatment is started; only a minority of patients with severe disease recover completely (11). Predictors of poor outcome are younger age and advanced stage; neurological sequelae are directly related to the stage of the disease and the duration of symptoms before admission. Similarly, in patients with spinal tuberculosis, the time taken for neurological recovery is not related to the type of treatment regimen but appears to be influenced by factors such as initial motor power, presence or absence of bed sore, and duration of kyphosis (11).

The long-term efficacy of short-course treatment regimens of 6–12 months’ duration in various forms of extrapulmonary tuberculosis has been studied (5). Patients were followed up systematically for 5–10 years. Relapse rates during long-term follow-up were less than 4% in all studies reviewed, demonstrating the adequacy of short-course treatment regimens for extrapulmonary tuberculosis.

**Role of surgery**

The introduction of short-course treatment for extrapulmonary tuberculosis has made surgery less important. It may be required for diagnosis (biopsy) and management of complications such as tuberculosis empyema and chronic constriction or destroyed kidney or lung with recurrent infections. The roles of surgery and drug treatment in the management of patients with tuberculosis of the spine were investigated in trials by the British Medical Research Council (12). It was concluded that operative procedures were generally unnecessary; ambulatory short-course treatment regimens were highly effective, and surgery was indicated only in patients aged less than 15 years and having an initial angle of kyphosis more than 30° (13). When surgery is indicated, anterior and posterior fusion are recommended to reduce kyphosis and improve function of the spine (14).
Table 43
Efficacy of treatment regimens in different forms of extrapulmonary tuberculosis

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment regimen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration (months)</th>
<th>No. of patients</th>
<th>Follow-up period (months)</th>
<th>Overall favourable response (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal tuberculosis</td>
<td>6HR + modified Hong Kong surgery</td>
<td>6</td>
<td>78</td>
<td>120</td>
<td>90</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6HR</td>
<td>6</td>
<td>78</td>
<td>120</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9HR</td>
<td>9</td>
<td>79</td>
<td>120</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Pott’s disease</td>
<td>Radical surgery + 2HERS/7H&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9</td>
<td>20</td>
<td>60</td>
<td>90</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2HERS/7H&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9</td>
<td>11</td>
<td>60</td>
<td>73</td>
<td></td>
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<tr>
<td>Tuberculous lymphadenitis</td>
<td>2H&lt;sub&gt;3&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;Z&lt;sub&gt;3&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;/4H&lt;sub&gt;3&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6</td>
<td>168</td>
<td>36</td>
<td>97</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal tuberculosis</td>
<td>2HRZ/4HR</td>
<td>6</td>
<td>85</td>
<td>60</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>EHS/HE</td>
<td>12</td>
<td>93</td>
<td>60</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Brain tuberculoma</td>
<td>3HRZ/3H&lt;sub&gt;3&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9</td>
<td>47</td>
<td>24</td>
<td>89</td>
<td>10</td>
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<td></td>
<td>3H&lt;sub&gt;3&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;Z&lt;sub&gt;3&lt;/sub&gt;/6H&lt;sub&gt;3&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9</td>
<td>44</td>
<td>24</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week.
References

34. How does treatment of tuberculosis differ in patients with pregnancy, liver disease, or renal disease?

A. Harries

Treatment in pregnant women (1, 2)

The four basic antituberculosis drugs – isoniazid, rifampicin, pyrazinamide, and ethambutol – are not teratogenic and are safe to use in pregnant women. Streptomycin and other aminoglycosides are potentially ototoxic to the fetus, and therefore should not be used in pregnancy: ethambutol can be used instead. p-Aminosalicylic acid has been used safely.

Ethionamide and prothionamide are teratogenic and can induce premature labour, and should not be used in pregnancy. Fluoroquinolones are teratogenic in laboratory animals.

Active tuberculosis in pregnancy must be treated because the disease will do more harm than the drugs. It is important that pregnant women understand that successful treatment of tuberculosis with one of the recommended standard regimens is important for a successful outcome of the pregnancy.

Treatment in a breastfeeding woman and her baby

A woman who is breastfeeding and has tuberculosis should receive a full course of tuberculosis treatment. All the antituberculosis drugs are compatible with breastfeeding, and a woman taking them can safely continue to breastfeed her baby. The mother and baby should stay together and the baby should continue to breastfeed in the usual way. However, the concentrations of the drugs in breast milk are insufficient to prevent or treat tuberculosis in infants.

In children, tuberculosis is most severe in those under the age of 6 years and, in particular, in those aged 3 years and under. A child who is in close contact with people who have tuberculosis should be brought to a health unit to be evaluated for symptoms of the disease. Children who have no symptoms should receive preventive treatment for latent tuberculosis infection regardless of whether they have been vaccinated with BCG. Preventive treatment consists of administration of isoniazid (5 mg/kg body weight) daily for 6–9 months.

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If a tuberculin skin test is available, it should be administered after 3 months:

- If the induration from the tuberculin test is less than 6 mm in diameter, preventive treatment should be stopped and the child should be vaccinated with BCG (if this has not been done previously).
- If the induration is 6 mm or more in diameter, preventive treatment with isoniazid should continue for another 3–6 months.

**Treatment in patients with liver disorders (1–4)**

Patients with the following conditions can receive the usual short-course treatment regimens:

**Established chronic liver disease**

Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of 8 months. If there is concern about the extent of liver damage, e.g. the patient has ascites with evidence of portal hypertension, an alternative regimen is streptomycin plus isoniazid plus ethambutol in the initial phase, followed by isoniazid and ethambutol in the continuation phase, for a total treatment duration of 12 months. Patients with established chronic liver disease should not receive pyrazinamide. Recommended regimens are therefore 2HRES/6HE, 2HRE/6HE, or 2HSE/10HE.

**Acute hepatitis**

It is uncommon for a patient to contract tuberculosis and acute viral hepatitis at the same time. However, it is not uncommon for patients to develop acute viral hepatitis during the course of tuberculosis treatment; in many settings, it is a common cause of jaundice during treatment (5). In some cases, it is possible to defer tuberculosis treatment until the hepatitis has resolved; in others it may be necessary to continue to treat tuberculosis. In the latter case, a combination of streptomycin and ethambutol for a maximum of 3 months is the safest option until the hepatitis has resolved. The patient can then receive the continuation phase of treatment with isoniazid and rifampicin for 6 months (6HR). In cases of extensive tuberculosis, a fluoroquinolone such as ofloxacin can be considered in conjunction with streptomycin and ethambutol as an interim non-hepatotoxic regimen, that is generally well tolerated.

**Treatment of patients with renal failure (3, 4)**

Isoniazid, rifampicin, and pyrazinamide can be given in normal dosage to patients with renal failure because these drugs are either almost entirely eliminated by biliary excretion or are metabolized into non-toxic compounds. In severe renal failure, patients receiving isoniazid should also receive pyridoxine to prevent peripheral neuropathy; pyrazinamide can compound the hyperuricaemia that occurs in renal failure.
Ethionamide and protionamide are also excreted almost entirely by non-renal routes, and can be given in the normal dosage in renal failure.

Streptomycin and ethambutol are excreted by the kidney. In the presence of renal failure, doses of both drugs must be reduced. Where facilities are available to monitor renal function, dosage can be adjusted appropriately. Thioacetazone is excreted partially in urine, but the margin between therapeutic and toxic dose is so narrow that patients with renal failure should not receive this drug. The safest regimen for patients with renal failure is 2HRZ/4HR.

References
35. How does treatment of tuberculosis differ in persons infected with HIV?

A. Harries

Treatment categories and treatment regimens

In general, tuberculosis treatment is the same for HIV-infected as for HIV-negative tuberculosis patients, with the exception of the use of thioacetazone. Thioacetazone is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected individuals (1). Ethambutol should therefore be used instead of thioacetazone in patients known or suspected to have HIV infection (see “What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?” page 159).

Some countries may not have the resources to substitute ethambutol for thioacetazone. Where the use of thioacetazone cannot be avoided, it is essential to warn patients about the risk of severe skin reactions. Patients must be advised to stop thioacetazone immediately if a skin reaction occurs and report to the nearest health facility.

Streptomycin remains a useful drug provided that adequate sterilization and safe disposal of syringes and needles can be ensured. Some countries with a high prevalence of HIV infection may not be able to ensure adequate sterilization of syringes and needles and should therefore not use streptomycin.

Response of tuberculosis patients infected with HIV to tuberculosis treatment

Response in patients who complete treatment

Patients who complete treatment show the same clinical, radiographic, and microbiological response to short-course treatment whether they are HIV-infected or HIV-negative (2, 3).

Case-fatality

HIV-infected patients have a much higher mortality during and after tuberculosis treatment compared with HIV-negative patients (2, 3). In sub-Saharan Africa, approx-

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imately 30% of HIV-positive, smear-positive tuberculosis patients die within 12 months of starting treatment, and about 25% of those who complete treatment die during the following 12 months. In the pre-HIV era, smear-negative pulmonary tuberculosis was a disease with a good treatment outcome. Evidence is slowly accumulating that in some areas HIV-infected, smear-negative pulmonary tuberculosis patients may have a worse prognosis than HIV-positive patients with smear-positive pulmonary tuberculosis. The larger number of deaths in HIV-infected tuberculosis patients during and after treatment is due partly to tuberculosis itself but largely to other HIV-related problems.

Case-fatality is lower in HIV-infected tuberculosis patients treated with short-course regimens than in those treated with standard 12-month regimens that do not include rifampicin (4, 5). This is partly because short-course treatment is more effective, but may also be related to the fact that rifampicin has broad-spectrum antibacterial activity as well as antituberculosis activity. Rifampicin may thus reduce deaths due to HIV-related bacterial infections during tuberculosis treatment. Adjunctive treatments given with antituberculosis drugs may reduce case-fatality rates.

There is evidence that direct observation of treatment is even more important for HIV-infected tuberculosis patients. In a multivariate analysis, Alpert et al. (6) found that self-administration of treatment was associated with higher case-fatality rates among HIV-infected tuberculosis patients, even when all other factors were controlled for. Similarly, Alwood et al. (7) found a case-fatality rate of 15% in HIV-infected tuberculosis patients treated with direct observation of treatment, compared with 43% in patients who received similar treatment regimens under self-administration.

Relapse

The tuberculosis relapse rate is low in HIV-infected tuberculosis patients who complete a full rifampicin-containing short-course treatment regimen. Extending the duration of the treatment regimen from 6 to 12 months in such patients further reduces the frequency of relapse (8). However, this difference is marginal and, given the expense, toxicity, and difficulty of longer treatment, most programmes treat HIV-infected patients for 6, or at most 9, months. The relapse rate is higher in HIV-infected than in HIV-negative tuberculosis patients treated with the standard regimen or a short-course regimen that uses ethambutol and isoniazid during the continuation phase (9–11).

TB treatment and antiretroviral therapy

Antiretroviral (ARV) drugs are increasingly available to persons living with HIV/AIDS, many of whom also have latent tuberculosis infection or active tuberculosis disease. Effectively given, ARVs lead to a gradual increase in host immunity, which in principle should reduce the risk of progression from latent tuberculosis infection to active tuberculosis disease. Paradoxically, ARVs can sometimes lead to the development of active TB in HIV-positive persons with latent infection, this development
being part of the immune reconstitution syndrome. Of the currently licensed ARV drugs, most protease inhibitors and non-nucleoside reverse transcriptase inhibitors interact with rifampicin and therefore should not be taken with rifampicin-based regimens, although they may be able to be given safely with rifabutin (12–15).

The optimal ARV regimens for use with anti-TB treatment and the best time to start ARV therapy in patients with TB have still to be worked out. Among patients on treatment for tuberculosis who are begun on ARVs, there can be paradoxical worsening of symptoms, presumably related to improved inflammatory response (16–17).

It is likely that ARV therapy will reduce HIV-related morbidity and mortality during and after anti-TB treatment, and may also reduce the risk of recurrent TB in HIV-positive persons who have successfully completed anti-TB treatment.

References

36. **What were the main findings of the Madras study comparing home and sanatorium treatment?**

*K. Toman*

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**Objectives of the trial**

The study was designed to assess the relative merits of home and sanatorium treatment. It focused on the effect of physical activity, diet, and accommodation on the outcome of treatment in terms of radiographic and bacteriological response. Of particular interest was the problem of infectivity of patients treated at home, i.e. the frequency of disease in close family contacts.

**Study design**

Persons living in Madras (now Chennai), up to about 8 km from the Tuberculosis Chemotherapy Centre (now the Tuberculosis Research Centre), who were more than 12 years of age, had a sputum smear and/or culture positive for tubercle bacilli, and had received no previous tuberculosis treatment (or for not longer than 2 weeks), were eligible. Most patients had far-advanced cavitary disease. Those with tuberculosis resistant to isoniazid or p-aminosalicylic acid (PAS), or with serious concomitant disease such as leprosy or diabetes, or in need of emergency medical action, or known to be pregnant were excluded. Almost all the patients lived in the poorest section of Madras.

**Drug regimen**

Every patient received isoniazid and PAS (sodium salt), the standard treatment at the time of the trial in the late 1950s.

**Home regimen**

Patients allocated to home treatment were asked to take their drugs at home and were expected to attend the Centre once a week to collect a week’s supply of drugs. In addition, each patient was visited by a health visitor and on certain occasions a “surprise” pill count was done, and a specimen of urine was collected to test whether the patient

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1 Deceased.
was taking the medicine as prescribed. Patients’ families received a free supply of milk powder monthly.

**Sanatorium treatment**

Patients allocated to treatment in a sanatorium were admitted to the main sanatorium in Madras, which was well staffed and had complete diagnostic and nursing facilities. Every patient was seen weekly by the medical staff of the centre, by a health visitor, and by a social worker.

**Physical activity**

Patients admitted to the sanatorium remained in bed (with bed-pan facilities) for 3–4 months. After that period they were allowed to be up for 2, and later for 4, hours daily. After 6 months, those considered to be sufficiently fit were permitted to go home once a month, but had to return the same evening.

Patients allocated to home treatment were advised to take rest and to return gradually to their previous physical activity or work only when medically fit. However, most of them were ambulatory much of the time. Female patients generally had to continue their usual work at home, and many male patients returned to work well before they could be considered fit; some refused to stop work at all. Those who had no regular jobs often went for long walks.

At least once a week the home patients had to travel to the Centre – a distance of up to 8 km each way – usually on foot because they were poor.

Most male patients were craftsmen, unskilled labourers, domestic servants, or street vendors, and they usually had to work very long hours in tropical conditions.

**Diet**

The patients in the sanatorium received a rich diet in terms of calories, fats, proteins (including animal proteins), minerals, and vitamins (1). The diet of home patients was inferior: for example, only 8% of them had a daily intake of 30 g or more animal protein, whereas all sanatorium patients had at least that much. The difference in the diet is magnified by the fact that the home patients had much less rest and soon resumed their previous activities.

**Accommodation**

Whereas sanatorium patients were treated in clean, well-ventilated wards, most home patients lived in overcrowded conditions with a floor space of less than 4.5 m² per person.

**Allocation of treatment**

Allocation was based on random numbers. For every patient eligible for the study, a sealed envelope was opened, and the random number on a slip of paper inside it was
decoded by the Centre's statistical unit (see “What are the principles and requirements of a controlled clinical trial?”, page 285).

Neither the Centre’s staff (medical and non-medical) nor anyone else had prior knowledge of the treatment that any patient was to receive.

Despite the randomization, by chance the patients treated at home – especially females – were at a certain disadvantage with respect to the severity of the disease, i.e. they had greater cavitation, lung involvement, and bacterial content of sputum.

Results and conclusions

Clinical response

There were three deaths from tuberculosis – two were patients treated in the sanatorium and one had been treated at home. (One death not due to tuberculosis, the result of electrocution at work, occurred in a home patient.)

The sanatorium patients gained more weight than those treated at home.

Radiological response

Radiological progress in terms of reduced cavity size or cavity closure was similar in both groups. When patients with corresponding pretreatment lesions were compared, progress in the two series showed even greater similarity.

Bacteriological response

There was rapid bacteriological progress in both groups (Table 44, Figure 14). Sputum positivity declined at almost the same rate in home and sanatorium patients. At 4 months, about 90% had achieved sputum conversion, i.e. multiple specimens examined monthly were negative on culture. Although some individual changes occurred

<table>
<thead>
<tr>
<th>Months</th>
<th>Percentage of home patients</th>
<th>Percentage of sanatorium patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
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<td>95</td>
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<tr>
<td>12</td>
<td>90</td>
<td>92</td>
</tr>
</tbody>
</table>

a Source: reference 2.
later, the high level of sputum conversion was maintained until the end of 12 months of treatment.

**Quiescence of disease and relapses**

The assessment of quiescence of the disease was based on very stringent criteria, i.e. 7–9 cultures examined during the last 3 months had all to be negative. In 75 (92%) of 81 sanatorium patients and 71 (86%) of 82 home patients, the disease was classified as quiescent (Table 45) (2).

The frequency of bacteriological relapse was studied in 126 patients whose disease was quiescent at the end of one year of treatment (3). Thus, 69 sanatorium patients and 57 home patients were followed up for up to 5 years (Table 46). During that observation period, 11 relapses occurred: 7 (10%) in the sanatorium patients and 4 (7%) in the home patients. The small differences observed at one year (see preceding paragraph) were clearly levelling out. Of the 11 patients who relapsed, eight did so in the first year of follow-up.
Risk to family contacts

The close family contacts of the patients admitted to the study were carefully followed for 5 years. The main study of the attack rate (4, 5) was undertaken in families whose only infectious member was the index case. In this way a comparison could be made between the “sanatorium” family contacts (whose infectious index was isolated for a year in sanatorium) and the “home” contacts (who remained exposed to their index cases, living in the same household throughout the treatment). In addition, both contact groups were equally exposed to the risks of the general urban environment of Madras.

All contacts who had radiographic lesions suggesting tuberculosis were excluded; the rest were subdivided into tuberculin non- reactors and reactors (0–4 mm and ≥5 mm induration, respectively, to 5 TU of tuberculin given intradermally).
As Table 47 shows, the frequency of disease in the non-reactor group was almost equal in the home contacts and in the sanatorium contacts. (Among the reactors—a less homogeneous group than the non-reactors—the frequency of disease was higher in the sanatorium contacts.)

Another important finding was that most of the contacts who developed disease during the first year of observation did so within the first 3 months, irrespective of whether the index case was treated at home or in a sanatorium. This was a strong indication that these contacts were probably already infected with Mycobacterium tuberculosis when first examined, i.e. it is very likely that they had already been infected before the index case was discovered and treated.

**Cooperation of the patients**

In spite of a very active welfare service for the patients and their families, 12 of the sanatorium patients discharged themselves from treatment, four being readmitted later. Only one of the patients treated at home was lost through self-discharge.

With regard to the regularity of drug intake, sanatorium patients occasionally, or during certain periods, also failed to ingest the prescribed medicines. This may be because sanatorium supervision was not always sufficient to ensure that every patient actually took every dose.

**Social problems**

A careful social record was kept for each family. Major problems arose in eight families of home patients and in 20 families of sanatorium patients. The difficulties were usually more serious in the latter and often resulted in disruption of the family.
Summary

In a controlled clinical trial, the effect of treatment was compared in two groups of patients – one group treated under good conditions in a sanatorium, the other under poor conditions at home.

The results in the sanatorium patients, despite good accommodation, nursing care, rich diet, and prolonged bed rest, were not superior to those in patients treated in overcrowded homes, who had a poor diet, much less rest, and often very long working hours. Radiographic changes, such as the reduction of cavity size and cavity closure, were very similar in both groups, particularly when patients with similar pretreatment lesions were compared. The proportion and speed of sputum conversion to negativity were similar in the two groups. After about 4 months, around 90% of the home and sanatorium patients produced multiple specimens that were all negative by culture, and this level was maintained throughout the remainder of the treatment year.

Results for quiescence of the disease at 1 year and relapses in the subsequent 4 years showed few, if any, differences between home and sanatorium patients. Thus, sanatorium treatment did not increase the likelihood of cure or reduce the likelihood of relapse. This study used conventional treatment; short-course treatment makes ambulatory management of tuberculosis patients particularly practical.

The risk to close family contacts was studied for 5 years. There was no difference in the incidence of disease between the contacts of patients treated at home and those of sanatorium patients, and exposure to the index case under effective treatment appeared to present no major risk to contacts. Thus domiciliary treatment did not entail any special danger that might have been prevented by sanatorium treatment.

The study indicated that the major risk to contacts lay in exposure to the infectious index case before diagnosis and the start of treatment. At that point, all the harm the index case could do to family contacts had already been done, so that subsequent isolation in a sanatorium was of little benefit.

The disadvantage of sanatorium treatment is the sacrifice it demands from patients: it is difficult to keep a patient in the sanatorium, separated from family for a long time and maintaining sanatorium discipline. A further social disadvantage is the disruptive effect on family life. Indeed, in this study, 12 patients discharged themselves from treatment (though four were later readmitted), compared with one self-discharge from treatment among home patients.

In addition, the study showed that treatment in a sanatorium is no safeguard against irregularity of drug taking unless the patient is seen to swallow every dose.

This study brought about the dramatic switch from institutional to ambulatory treatment as a general policy (see “What were the main landmarks in the development of tuberculosis treatment?”, page 99, and “When should tuberculosis patients be hospitalised, and how infectious are tuberculosis patients while on treatment?”, page 274).
References


37. How frequently do patients stop taking treatment prematurely?

J. Sbarbaro

The failure to take medications as prescribed is a universal and perplexing phenomenon that must always be taken into consideration in any efforts to treat patients or control disease in a community. The powerful and negative impact on public health programmes of deeply ingrained cultural and personal beliefs has been clearly demonstrated in the failure of patients to complete prophylaxis programmes for leprosy, filariasis, and rheumatic fever (1). Many studies have shown that one out of every three patients will prematurely stop taking their medication (2). Similar default rates have been documented among patients being treated for tuberculosis (1, 3–5). Unfortunately this behaviour is not limited to the ambulatory patient or to the home setting – measurements of drug serum levels and urine metabolites have repeatedly shown that even patients being treated in a hospital will hide and throw away medication delivered to them at the bedside (3).

Medication default rates as high as 65% have been documented for a broad spectrum of disease conditions, from hypertension and diabetes to arthritis, asthma, and congestive heart failure. These latter diseases confirm that even the presence of serious symptoms does not ensure patient adherence to a medication regimen. The disappearance of symptoms, however, leads to a further increase in the rate of medication default. Severity of illness, duration of illness, functional impairment, and the number of concurrent diseases do not influence compliance with medical recommendations.

Numerous efforts to pinpoint markers or characteristics that could distinguish compliant from non-compliant patients have been unsuccessful. Studies have found that age, sex, ethnicity, racial origin, socioeconomic status, educational level, marital status, cultural background, and religious belief are of no help in identifying who is or will be compliant with treatment. Unannounced home visits and pill counts have established that regular attendance at clinic does not ensure that patients are actually taking their medication. Intense educational efforts and even reliance on close family members, such as mothers, to ensure the ingestion of medication have proved equally ineffectual.

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Nevertheless, many health workers remain convinced that they can distinguish the reliable from the unreliable patient, especially if they have known the patient over a long period of time. Again and again, however, studies have demonstrated that even these professionals are unable to predict their patients’ compliance any better than by chance variation (3).

Not unexpectedly, even good adherence to treatment deteriorates over the weeks and months. The expense of treatment, in terms of both time and money, is a further deterrent to patient compliance. Complicated regimens are associated with even higher default rates.

Treatment interruption can be reduced by a well functioning tuberculosis programme (6) that reduces the barriers to treatment compliance (see “Why does treatment fail and what can be done to avoid poor treatment outcome?”, page 185). Preventing irregularity is the main reason to adopt direct observation of treatment, one of the key elements of the DOTS strategy.

References
38. **What are the advantages of direct observation of treatment?**

*J. Sbarbaro*¹

Even when innovative efforts to improve tuberculosis control services result in increased patient satisfaction and willingness to cooperate, non-adherence to medication recommendations continues to be a serious problem. Effective treatment of tuberculosis requires multiple drugs to be taken over a prolonged period by patients whose symptoms rapidly disappear, resulting in a renewed sense of well-being – factors that contribute to patient non-adherence to treatment. Tuberculosis control programmes that are committed to the health of their patients must therefore address and overcome this universal trait of non-adherence throughout the full course of treatment.

The main advantage of directly observed treatment is that treatment is carried out entirely under programme supervision. Only when a second person *directly observes* a patient swallowing the given medication can there be certainty that the patient is actually receiving the prescribed treatment regimen. No concealed irregularity can occur, as it can in self-administered regimens. The treatment observer ensures that medicines are taken at the correct intervals and in the correct dosages – and with that certainty come benefits both for the patient and for the community. Perhaps the most immediately apparent is the high cure rate associated with assured completion of treatment. Equally important is the dramatic reduction in the development of drug resistance, because direct observation eliminates the patient’s ability to intentionally or unintentionally discontinue one or more drugs, with the subsequent emergence of drug-resistant organisms (see “How does drug resistance develop?” page 193). Moreover, because there is close and continuing contact between the patient and the health worker, adverse effects and treatment complications can be quickly identified and addressed, especially during the critical initial phase of treatment. In addition, the frequency of contact with the treatment provider reduces the time between treatment interruption and action to retrieve the patient, from more than a month in self-administered treatment to just a day in directly observed treatment. Confirmed

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¹ Based on the chapter in the previous edition by K Toman.

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adherence to treatment further reduces the spread of infection in the community and thereby the burden of disease and development of new cases of tuberculosis.

Multiple analyses have demonstrated that the higher personnel and programme expenditures associated with directly observed treatment are more than offset by the savings in the costs of re-treatment, the costs of treating drug resistance and the costs associated with the treatment of the new cases of tuberculosis (many with drug resistance) which arise if treatment is not directly observed (1–3). Patients who are reluctant to continue treatment are immediately identified, allowing the community to develop alternative plans for their care. It is essential that health workers ensure that each patient actually ingests the drugs provided. The patient should therefore be given a glass of water or tea to help swallowing. It is also good practice to talk to the patient for several minutes after the medicines have been taken; this strengthens the bond between patient and provider and also ensures that the tablets have actually been swallowed. Directly observed treatment means that every dose is administered under direct observation, and convenience to the patient is essential for success.

References
39. Why does treatment fail and what can be done to avoid poor treatment outcome?¹

_F. Luelmo²_

Tuberculosis patients have an excellent chance of being cured, especially if they have not received antituberculosis drugs in the past and are not infected with HIV. Short-course treatment regimens can achieve more than 95% cure in previously untreated patients. In practice, however, this success rate is rarely achieved. The main reasons for failure are premature cessation of treatment (default) and irregularity in taking drugs, prescription of inadequate regimens, drug resistance, delay in starting treatment, death from AIDS, and drug toxicity.

**Early interruption of treatment and irregularity of drug intake**

By far the most important causes of poor treatment outcome are early interruption of treatment and irregularity of drug intake. These are most commonly the result of:

— poor access to health facilities (geographical, economic, limited or inconvenient hours, unfriendly service providers) and the resulting loss of income for the patient;
— irregular supply of drugs, leading to monotherapy and loss of confidence in the health facility;
— poor patient orientation regarding the duration of treatment; and
— the inevitable tendency of patients to forget drug intake and to stop treatment when they are feeling better (see “How frequently do patients stop taking treatment prematurely?”, page 181).

A variable proportion of patients have associated problems such as alcohol and drug dependence, which interfere with treatment adherence and require special strategies adapted to each patient (1).

**Inadequate regimens**

Inadequate regimens, which are more commonly prescribed in private clinical practice (2), increase the risk of treatment failure and relapse. Only treatment regimens

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that have proved successful in controlled clinical trials and are appropriate to the operational conditions – in terms of the combination of drugs, dosage, periodicity and length of application – should be used (3).

**Drug resistance**

In most settings, drug resistance is not the most important cause of treatment failure. For example, even in a poorly performing programme with a 10% rate of primary multidrug resistance, inability to cure patients most commonly arose from default among patients without multidrug-resistant tuberculosis (4). In settings that have recently improved the management of tuberculosis, drug resistance can be an important cause of failure and death, particularly when the strains are resistant to the two main bactericidal drugs isoniazid and rifampicin (multidrug-resistant strains). Drug resistance develops as a result of inadequate or irregular regimens and is a consequence of poorly organized programmes (see “What are the causes of drug-resistant tuberculosis?” , page 207). Multidrug resistant strains can be transmitted in the community or in closed environments and replace susceptible strains, making first-line regimens inadequate for achieving high cure rates.

**Diagnostic delay**

Delay in diagnosis and initiation of treatment increases the severity of disease and the risk of death. Delays are usually due to poor access to health care and barriers to care (such as wage loss, costs of consultation, diagnostic tests and treatment, and the need for multiple visits by the patient), lack of information on or of recognition of symptoms, lack of awareness of availability of services, and delayed diagnostic response of the health system (laboratory results, medical decision, etc.).

**AIDS**

Infection with HIV increases the probability of patients dying during treatment, often from causes other than tuberculosis (see “How does treatment of tuberculosis differ in persons infected with HIV?” , page 169). Prognosis depends on the degree of immunosuppression. Associated diseases in patients with AIDS, as well as antiretroviral treatment, may complicate tuberculosis treatment, and the deterioration and poor prognosis associated with HIV infection may reduce the patient’s motivation to continue tuberculosis treatment, leading to irregularity and default. Good coordination between the providers of tuberculosis care and HIV/AIDS care is required to address tuberculosis as one of a number of HIV-related diseases that complicate the course of HIV infection.

**Drug toxicity**

Drug toxicity can result in treatment failure and sometimes death if adequate care is not provided promptly. Changes in treatment necessitated by toxicity can prolong the
duration of treatment, especially in older patients. An episode of hepatitis or hypersensitivity can also complicate management of tuberculosis.

**Preventing poor outcomes of treatment**

Unsuccessful treatment may be reduced by:

- Decentralization of treatment to local health facilities and to the community, through health staff or trained and supervised community volunteers, as close to the patient's home or workplace as possible and at convenient times. The patient should be given the opportunity to choose who will directly observe treatment, and where. It is the responsibility of the health system to facilitate the patients' access to treatment; to educate patients regarding the duration of treatment and what to do should they change address; also to ensure that patients are found rapidly and brought back to the health facility if they do not attend for treatment. A system must be maintained to transfer patients from diagnostic to treatment facilities, from hospitals to outpatient care, and from one geographical area to another, and to monitor their arrival and the outcome of treatment.

- Regular supply of good-quality drugs, free of charge to the patient, with sufficient reserve stocks. Packages containing the drugs for the entire treatment of a particular patient prevent use of drugs for other patients in case of stock-out, which would result in interruption of treatment.

- Direct observation of drug intake to ensure that the patient takes all the drugs, to increase contact between patients and the health system, and to reduce the time from treatment interruption to recovery actions (see “What are the advantages of direct observation of treatment?”, page 183).

- Use of adequate standard regimens, including by private sector providers. Treatment regimens should start with four drugs in new patients (or three drugs in smear-negative pulmonary and non-severe extrapulmonary tuberculosis) and with at least five drugs in previously treated patients. Governments should choose national standardized treatment regimens based on efficacy data and operational experience, and ensure that they are used by both public and private providers, and that the regimens are followed and achieve the expected outcomes (see “How can the emergence of drug resistance be prevented?”, page 209).

- Use of fixed-dose combinations, which ensure that the patient takes “all or none” of the drugs, facilitates prescription and improves patient acceptance.

- Reduction of diagnostic delay through community information regarding symptoms, improved access to care, efficient procedures for collection and reporting of smear results, and case detection among patients with respiratory symptoms who attend health facilities for any reason.

- Prevention of HIV infection, and early diagnosis and adequate management of HIV-infected tuberculosis patients (5).
Thus, the key to treatment success is to be found in the organization of the delivery and adequate administration of treatment (6). Even the best available regimen will have a low success rate if treatment services are not focused on facilitating patient access to care and ensuring regular drug intake.

References

An essential element of effective tuberculosis control is a reliable supply of good-quality drugs provided to patients free of charge. Fixed-dose combinations (FDCs), incorporating two or more antituberculosis drugs into one tablet in fixed proportions, have been used since the late 1980s and are registered in more than 40 countries (1). Combinations of isoniazid and thioacetazone have long been used, and a combination of isoniazid and ethambutol is also commonly used. For short-course treatment, the two most common FDC preparations are isoniazid, rifampicin, and pyrazinamide, used in the intensive phase of treatment, and isoniazid and rifampicin, often used in the continuation phase. A four-drug FDC containing isoniazid, rifampicin, pyrazinamide, and ethambutol is being used increasingly (2); the WHO Model List of Essential Drugs includes FDCs in specific formulations.

Potential advantages of FDCs include the following (2–4):

- Drug resistance may be less likely to emerge since multiple drugs are incorporated into the FDC (5–7). The use of FDCs prevents treatment of tuberculosis with a single drug (monotherapy). Further, if treatment is interrupted (through default or because of inadequate drug supply), all drugs will be stopped, which should prevent resistant organisms being selected.
- The use of FDCs involves fewer products and will result in more accurate prescribing practices by clinicians. This might be especially helpful for clinicians less familiar with national tuberculosis treatment guidelines. Moreover, because the amount of each drug in an FDC is invariable, there may be fewer dosage errors.
- Procurement, management, and distribution of drugs are simplified by the use of FDCs. Fewer tablets need to be ordered and managed, and distribution and storage at the local level may be easier. Thus, the use of FDCs may result in increased efficiency.

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A treatment regimen using FDCs is simpler for the patient (fewer tablets), and may result in increased adherence to treatment (8, 9).

Rifampicin is often used to treat other infections and is sold without prescription in many countries. The use of rifampicin in FDCs may reduce inappropriate use of the drug for other infections, thus preserving its effectiveness for treating tuberculosis.

Nevertheless, the use of FDCs guarantees neither that a patient will ingest the correct number of tablets, nor that a patient will complete treatment. Effective case management is still essential, including directly observed treatment within the DOTS strategy (2, 3).

Potential disadvantages of FDCs include (2–4):

- Bioavailability (the amount of an ingested drug absorbed into the blood) of rifampicin may decrease when it is combined with other drugs in the FDC (10–13). Use of FDCs, particularly in three- and four-drug combinations, could therefore result in lower plasma levels of rifampicin, with consequent treatment failures, relapses, and/or emergence of rifampicin-resistant strains of *Mycobacterium tuberculosis* (14). However, if FDCs are produced according to good manufacturing practices (GMP), they will be equivalent to administration of the constituent drugs as single-drug preparations (15–17). Only FDCs for which bioavailability studies have been undertaken in human subjects should be used (7, 18). Demonstrated bioavailability should be a requirement for national registration (17, 19). However, although there may be proven bioavailability during the approval or tender process, there is often no systematic mechanism to ensure that all subsequent batches of FDCs also have adequate bioavailability. The regulatory structure required to adequately monitor GMP and ensure bioavailability standards for FDCs (either imported or domestically manufactured) is inadequate in most countries of the world (20). In addition, few laboratories in the world have been officially certified to perform bioavailability testing (21).

- The optimal operational efficiency from using FDCs may not be achieved because the doses required for treatment are not the same for all patients. Adjustments for weight are often necessary: the WHO-recommended dosage forms for FDCs allow for easy adjustment of dosage by weight. Adverse effects may also necessitate changes in the dosage. Hence, any tuberculosis control programme using FDCs must also supply single drugs to be used by tuberculosis specialists in particular circumstances.

- There are a number of different formulations of FDCs, involving different drug combinations and different dosages; confusion and incorrect dosing may arise if a country uses more than one FDC formulation. The formulations recommended by WHO and IUATLD should be the only ones used in a country. The national tuberculosis programme should attempt to have the registration of other formulations withdrawn by the national drug regulatory authority.
There is a theoretical risk that the availability of three- and four-drug FDCs over the counter, as may happen in many countries, would result in more widespread inappropriate use of tuberculosis drugs. In some areas, FDCs have been promoted as an alternative to effective tuberculosis control, potentially with adverse effects for the programme. Taking fewer than the recommended number of FDC tablets may expose bacilli to sub-inhibitory concentration of multiple drugs. In a study that compared patients treated with self-administered FDC with patients given single-drug preparations under direct observation, relapse rates were higher in the group using self-administered FDC (22).

When three- or four-drug FDCs are used in the intensive phase of treatment, a different two-drug FDC is used in the continuation phase. Patient and physician confusion and error may occur.

Small local manufacturers may not be able to produce FDCs, particularly four-drug FDCs, which may reduce competition and raise prices unless there is international procurement of drugs. A country that uses FDCs will need to provide additional training in drug procurement, treatment recommendations, and patient and provider education (3).

Although there are potential advantages to using FDCs, the benefits may be difficult to demonstrate given existing operational, programmatic and regulatory constraints. FDCs are likely to become more widely used, particularly in countries that import antituberculosis drugs, which suggests that measuring their impact is imperative. Each country must carefully weigh the advantages, disadvantages, and appropriate role of FDCs within its programme.

References


41. How does drug resistance develop?

K. Toman

Thanks to clinical and laboratory observations and to comprehensive experimental studies, much is known about how drug resistance develops, its clinical and epidemiological significance, and how it can be prevented or controlled.

The phenomenon of resistance was detected soon after the introduction of streptomycin for the treatment of human tuberculosis. When the drug was given alone, a striking improvement in the patient’s symptoms was observed at first, together with a rapid decrease in the number of bacilli in the sputum. Usually, the number of bacilli soon rose again and the patient’s condition deteriorated. Bacilli isolated from the sputum of patients who had received streptomycin alone for a few months were drug-resistant, i.e. the bacilli, instead of being killed, continued to grow in vitro in the presence of high concentrations of the drug.

A simple experiment soon provided an explanation (1). Sputum from patients who had never received any streptomycin was inoculated on media containing various concentrations of the drug. In many of the cultures, a few colonies appeared in media containing an inhibitory concentration of streptomycin (5–10 μg/ml). It was obvious that some of the bacilli present in the bacterial population must have been resistant to streptomycin, although they had never been in contact with the drug before. It was also observed that, the larger a bacterial population, the higher was the probability that resistant cells (mutants) were present.

Furthermore, it was noticed that, during the treatment of patients with streptomycin alone, the proportion of resistant bacilli rapidly increased. After 12 weeks of treatment, the number of colonies in media containing 100 or 1000 μg/ml of streptomycin approached the number of colonies in the control media without streptomycin.

This experience showed that large bacterial populations contain a minute proportion of organisms that are barely susceptible, if at all, to a particular drug, even before administration of that drug. The susceptible bacteria are killed by the drug, the few resistant organisms survive and multiply, and their non-susceptible descendants,
generation by generation, replace the susceptible organisms. Clinically relevant drug 
resistance is thus the result of a selective process.

In a patient infected with an initially isoniazid-resistant strain, treatment with iso-
niazid and rifampicin alone during the intensive phase may allow the selective growth 
of the few organisms that have or that may develop resistance to rifampicin. Thus, 
treatment with a single effective drug alone may cause a patient’s strain to become 
increasingly drug-resistant, as illustrated Figure 15.

Figure 15
*Treatment that is effectively monotherapy in a patient whose isolate was initially 
resistant to isoniazid (H) and susceptible to rifampicin (R)*

Inappropriate treatment with only two drugs (H and R) led to the development of 
resistance to rifampicin, followed by clinical deterioration. Inappropriate addition of 
a single drug (pyrazinamide, Z) to a failing regimen led to the emergence of 
resistance to pyrazinamide.

Reference

1. Pyle MM. Relative numbers of resistant tubercle bacilli in sputa of patients before and during 
treatment with streptomycin. *Proceedings of the Staff Meetings of the Mayo Clinic*, 1947, 
42. Why are special precautions needed to protect rifampicin?

A. Vernon

Rifampicin must be protected because it is the key sterilizing drug in short-course treatment of tuberculosis (1). With rifampicin, treatment for drug-susceptible disease can be completed in 6–9 months, depending on companion drugs, with combined rates of failure and relapse of less than 5%. Without rifampicin, treatment must generally be given for at least 12 months to achieve low rates of failure and relapse. Resistance to rifampicin results in a substantial increase in the rate of failure and relapse when standard three- or four-drug regimens are used (2). In trials by the British Medical Research Council, initial resistance to rifampicin was associated with a failure rate of 45% during treatment; moreover, half of the remaining patients relapsed, giving an overall rate of unfavourable treatment outcome of 72% (3). This is in striking contrast to the experience of patients with initial resistance to isoniazid and/or streptomycin as shown in table 48.

When there is rifampicin resistance, the minimum required duration of tuberculosis treatment with a feasible regimen is 12–15 months. If resistance to isoniazid is also present (i.e. multidrug resistance), the duration of treatment necessary is likely to be at least 18–24 months.

Resistance to any tuberculosis drug (including rifampicin) is predictable if the drug is used alone. This was first described with streptomycin in 1947 as the “fall and rise” phenomenon (see “What is the ‘fall and rise’ phenomenon and the ‘sequential regimen’ mechanism?”, page 200). Such resistance can develop after relatively brief periods of single-drug treatment, especially in patients with large numbers of actively replicating bacilli (e.g. in patients with extensive active disease or with severe immunosuppression such as that caused by AIDS). Similar resistance would be expected if only one drug in a regimen were effective (because of pre-existing resistance to the other agents in the regimen). Development of resistance due to the addition of a single drug to a failing regimen has also been well described (4).

Most rifamycin resistance involves mutations in critical domains of the rpoB gene in Mycobacterium tuberculosis (5). Resistance to all rifamycins is mediated by this
common mechanism and, to date, it appears that resistance to any rifamycin implies resistance to all members of the class.

Isolated use of one drug is most common when that drug is freely available and can thus be prescribed by inexperienced practitioners or used in self-medication by patients. Rifampicin resistance has also rarely occurred in AIDS patients taking rifabutin as prophylaxis against *Mycobacterium avium intracellulare* (6). These problems can be prevented by:

— restricting availability of rifampicin and related drugs (rifabutin, rifapentine) to tuberculosis control programmes (as is done in some developing countries with well-functioning programmes) or to licensed or experienced practitioners (as is done in many developed and some developing countries); and/or

— making rifampicin available exclusively as a fixed-drug combination in products that include isoniazid, so that the rifampicin component cannot be administered alone (see “What are the advantages and disadvantages of fixed-dose combinations of tuberculosis drugs?” page 189) (7).

The consequences of restriction of rifamycins are minimal, because rifampicin and related drugs have few other indications for which they are the preferred drugs. Rifampicin is occasionally indicated for the treatment of some deep-seated staphylococcal infections, and in prevention of meningococcal disease. Rifabutin is a useful secondary drug for the prevention and treatment of AIDS-related disseminated *Mycobacterium avium intracellulare* infections. Rifamycins should remain available for these other indications.

**References**


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**Table 48**  
*Response of patients with initial resistance to rifampicin, with initial resistance to isoniazid and/or streptomycin only, or with no initial drug resistance*  

<table>
<thead>
<tr>
<th>Initial resistance</th>
<th>Failures during treatment</th>
<th>Relapses after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>assessed</td>
<td>failed</td>
</tr>
<tr>
<td>Rifampicinb</td>
<td>11</td>
<td>5 (55%)</td>
</tr>
<tr>
<td>Isoniazid and/or streptomycin</td>
<td>246</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>No resistance</td>
<td>1361</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Source: reference 3.

b One patient resistant to R alone, one to HR, and seven to HRS.


43. **What are the different types of drug resistance?**¹

*M. Espinal*²

Primary resistance is due to infection with a resistant strain, originating from a patient who has acquired resistance as a result of inadequate treatment. Thus the patient with primary resistance to a drug has never taken this drug in the past, but the original source of infection must have done so. Acquired resistance occurs when a patient is exposed to a single drug through failure of the programme to ensure adherence to treatment, or because of selective drug intake, irregular drug supply, poor drug quality, inappropriate prescription, or, rarely, erratic absorption of medications. The growth of bacilli susceptible to that drug is suppressed, but multiplication of resistant organisms continues.

In surveys of the frequency of primary resistance, as well as in clinical practice, it is difficult to determine whether resistance is primary, since the patients themselves may not know, or may deny, that they have had previous treatment for tuberculosis. It is therefore better to use the expression “drug resistance among new tuberculosis cases”. This is defined as the presence of resistant strains of *Mycobacterium tuberculosis* in patients who have never received tuberculosis drugs or have received them for less than 1 month.

The term “acquired drug resistance” implies that the patient initially had a drug-susceptible organism that developed resistance during the course of treatment. In practice, in most areas of the world where tuberculosis is common, reliable pretreatment drug susceptibility results are not available. Further, epidemiological evidence suggests that, in some contexts, most previously treated patients with drug resistance initially had primary drug resistance (1). Thus, unless pretreatment drug susceptibility testing results are available, drug resistance in previously treated patients should simply be described as such, i.e. “drug resistance in previously treated patients”.

A “natural” drug-resistant strain is a wild strain that is resistant to a particular drug without ever having been in contact with it: neither the patient with naturally resistant bacilli nor the source of infection has received treatment with that drug in the

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¹ Based on the chapter in the previous edition by K. Toman.
² Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
past. This type of drug resistance is of little practical importance. Wild strains rarely possess sufficient natural resistance to affect the response to standard treatment. An exception is thioacetazone, to which natural resistance may be common in some areas (2). Natural resistance to pyrazinamide is also a characteristic of *Mycobacterium bovis* (3).

**References**

Figure 16 illustrates, for isoniazid, the “fall and rise” phenomenon frequently observed in patients who are inadequately treated (1, 2).

The first pair of columns represents a bacterial population before the start of treatment. The patient’s sputum is positive by direct smear and the total number of bacilli is 100 million (10^8) or more, as is common in medium-sized cavities. A small proportion (perhaps several hundred bacilli) are mutants resistant to, say, isoniazid at concentrations usually found in cavities (see “How does drug resistance develop?,” page 193, and “How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?,” page 203).

After the start of treatment, the total number of bacilli decreases rapidly (second pair of columns). However, it is the drug-susceptible part of the population (white bars) that diminishes, whereas the resistant part (black bars) remains practically unaffected. In the second month (third pair of columns), the total number of bacilli has decreased further at the expense of the susceptible organisms.

In the subsequent period (fourth pair of columns), the total number of bacilli remains about the same; however, the structure of the population has changed fundamentally because the resistant mutants have gained the upper hand.

During the next period, the resistant bacilli, now with a biological advantage, rapidly outgrow the remaining drug-susceptible bacilli (fifth pair of columns). After about the fourth month (sixth pair of columns), the mutant organisms have completely replaced the susceptible organisms: the strain has become fully resistant, and the total number of bacilli is approaching the original number (seventh pair of columns).

Thus the sputum, containing enormous numbers of bacilli, was smear-positive at the beginning. After the start of treatment, the bacillary content of the sputum decreased markedly until it was close to the borderline of demonstrability by direct microscopy – marked in the figure by a horizontal line between 10^4 and 10^5. (To find about 10 acid-fast bacilli in about 100 oil-immersion fields, the number of bacilli per

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1 Based on the chapter in the previous edition by K. Toman.
2 Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
millilitre of sputum must be around 50 000, i.e. between $10^4$ and $10^5$. See Table 2 in the section “How reliable is smear microscopy?”, page 14.) Thereafter, the bacillary content dropped further: the sputum became negative by smear microscopy and positive only by culture – the “fall”. After a certain time, the bacillary content increased again, the sputum again being positive by direct smear – the “rise”. What occurs, in fact, is the “fall” of the susceptible bacilli and the “rise” of the resistant mutants of the strain.

The “fall and rise” phenomenon is prevented by the use of appropriate multidrug regimens in the treatment of tuberculosis. Treatment regimens consisting of four drugs during the initial phase and two during the continuation phase reduce the risk of selecting resistant bacilli. The main principle of multidrug regimens is that mutants resistant to drug A (e.g. rifampicin) are killed by drug B (e.g. isoniazid) and mutants resistant to drug B (isoniazid) are killed by drug A (rifampicin) (3).

The emergence of multidrug resistance as a result of several sequences of inappropriate treatment has been recently called the “sequential regimen” mechanism (4). It is postulated that resistance may arise because of treatment irregularity, without monotherapy. Selection of resistant mutants could take place after different regimens have been administered, during which several cycles of killing and regrowth of

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* Figure 16

The “fall and rise” phenomenon

<table>
<thead>
<tr>
<th>Number of bacilli per ml of sputum (logarithmic scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10^6</td>
</tr>
<tr>
<td>10^7</td>
</tr>
<tr>
<td>10^8</td>
</tr>
<tr>
<td>10^9</td>
</tr>
<tr>
<td>10^10</td>
</tr>
<tr>
<td>10^11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Start of treatment (isoniazid alone)</th>
<th>Weeks of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Isoniazid-susceptible organisms</td>
<td>Smear +</td>
</tr>
<tr>
<td>Isoniazid-resistant organisms</td>
<td></td>
</tr>
</tbody>
</table>

* Source: references 1, 2.
resistant organisms occur. Resistance could arise first to one of the drugs in the combination, followed by the development of resistance to the other drugs, to produce a multidrug-resistant strain.

References

45. **How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?**¹

*A. Pablos-Mendez²*

Genetic mutations that confer drug resistance occur spontaneously, and isolated resistant bacilli are present in wild strains, i.e. in normal bacterial populations that have never been exposed to tuberculosis drugs. This phenomenon was demonstrated soon after the discovery of streptomycin (1) and was later found to occur with other tuberculosis drugs (2–5) (see “How does drug resistance develop?”, page 193).

The demonstration of pre-existing resistant mutants is relatively easy. A wild strain of *Mycobacterium tuberculosis* is inoculated on media containing concentrations of, say, isoniazid, ranging from 0 to 5 μg/ml of medium. Abundant growth develops after about 14 days on the medium containing no isoniazid or as little as 0.05 μg/ml. The tubes containing higher concentrations of the drug remain clear initially, but some growth of colonies appears after about 3 weeks. Over the next few weeks the number of these colonies increases and can reach several hundred, depending on the drug concentration. Each colony, as a rule, originates from one resistant bacillus pre-existing in the original (wild) strain.

The frequency of drug-resistant mutants in a wild strain depends on the origin of the strain, the type and concentration of drug, and, to a large extent, the total number of bacilli. As shown in Table 49, the probability that mutants are present decreases substantially as the bacterial population diminishes. Thus, for example, in a population of one million (10⁶) tubercle bacilli, the number of mutants resistant to 0.05 μg/ml isoniazid ranges from 20,000 to 40,000; in a population of 100 (10²), the number of resistant organisms is proportionally smaller (only 0–4 at the same drug concentration). This quantitative or numerical dependence is a factor of great practical importance.

Thus, drug-resistant mutants will be present before treatment starts, especially in lesions that harbour large numbers of tubercle bacilli, e.g. in the pulmonary cavities of untreated patients. The number of bacilli commonly found inside cavities (about 2.5 cm in diameter) is of the order of 100 million (10⁸). As a rule of thumb, the average frequency of resistant mutants is ~1 in 10⁶ to isoniazid and ~1 in 10⁸ to rifampin.

¹ Based on the chapter in the previous edition by K. Toman.
² Associate Director, The Rockefeller Foundation, New York, NY, USA.
Doubly resistant mutants, expected in ~1 in $10^{14}$ bacilli, are extremely unlikely. The number of bacilli resistant to any drug is much lower during latency, in patients without cavitary lesions, and after the intensive phase of treatment.

Table 50 shows the estimated number of resistant mutants in two bacterial populations: one containing 100 million ($10^8$) and the other 100,000 ($10^5$) bacilli growing...
at drug concentrations such as are attained in cavities. The numbers in Table 50 acquire greater practical importance when applied to actual situations. For example, a patient with cavitary tuberculosis heavily positive by smear microscopy might be treated with isoniazid alone. As Table 50 shows, the number of isoniazid-resistant mutants present at the outset of treatment would be substantial. At an intra-cavitary isoniazid concentration as high as $1 \text{ mg/ml}$, there might be about 300 resistant organisms; at a concentration of $0.2 \text{ mg/ml}$, the number of resistant mutants might be of the order of 500, and at a very low concentration of $0.1 \text{ mg/ml}$, they might number 4000.

Thus, in large intra-cavitary populations there are appreciable numbers of drug-resistant bacilli that are capable of multiplying and that will not be affected by a single drug, e.g. isoniazid. This finding accounts for the frequent failures observed with monotherapy of patients with large numbers of bacilli in their sputum (see “What is the ‘fall and rise’ phenomenon and the ‘sequential regimen’ mechanism?”, page 200; “Why does treatment fail and what can be done to avoid poor treatment outcome?”, page 185).

However, when the patient is treated with two active drugs, e.g. isoniazid and streptomycin, the situation is quite different (see the lower part of Table 50). Mutants resistant to one drug are, as a rule, susceptible to the other, and vice versa. Only mutants
resistant to both drugs simultaneously are a cause for concern. As can be seen in the lower part of the table, such doubly resistant mutants are present, if at all, only when the drug concentration is exceptionally low. Fortunately, such situations are rare.

Another important finding was that, when the bacterial population diminishes from, say, $10^8$ to $10^5$, as usually happens after the start of effective treatment (see the final column of Table 50), there is little likelihood that any mutants resistant to only one drug are present and virtually no likelihood of the presence of doubly resistant mutants.

These findings indicated that treatment with two or more effective drugs would most probably destroy any existing resistant mutants. Proper drug treatment, particularly with an initial intensive phase, could so markedly reduce the total bacterial population that the risk of the emergence of new resistant mutants would become minimal. Thus, after an initial intensive phase, treatment could continue less aggressively, e.g. switching from four drugs to two drugs. This hypothesis was supported by experimental evidence in murine tuberculosis and has became the basis of the two-phase treatment regimens in use today.

References
Drug-resistant tuberculosis is a man-made problem. Human error is the principal factor associated with the generation of drug-resistant strains of *Mycobacterium tuberculosis* (1, 2). Resistance to tuberculosis drugs is the result of spontaneous, independent, chromosomal mutations; treatment regimens involving several drugs therefore prevent drug resistance (3). The development of drug resistance is almost always a consequence of inadequate drug therapy, which may in turn be due to physician error (health provider-related factors), lack of drug availability (management-related factors), or failure of the tuberculosis control programme to address patient adherence (4–7).

The most common cause of drug-resistant tuberculosis is undoubtedly the lack of a properly organized system to ensure effective treatment (i.e. national tuberculosis programmes), and particularly the lack of effectively implemented directly observed treatment. In addition, errors that can select resistant bacilli are the prescription of inadequate treatment (8, 9) and the addition of one extra drug in the case of a failing regimen, effectively resulting in monotherapy. Management errors include the lack of availability of a standardized therapeutic regimen; difficulty experienced by poor patients in obtaining all the drugs that they need; shortages of tuberculosis drugs; and use of drugs (or drug combinations) of unproven bioavailability.

A basic principle of tuberculosis control is that the health system, not the patient, is responsible and accountable for ensuring complete treatment of all patients who start treatment. The ethical and pragmatic argument for this position is that tuberculosis control in general – and prevention of drug-resistant tuberculosis particularly – is a public good. This public good benefits not only individuals (by curing their disease), but also the community at large, by preventing cases of tuberculosis and preventing the emergence of drug resistance. Thus, tuberculosis programmes must accept that adherence to self-administered medication is unpredictable, and that treatment observation accessible and acceptable to the patient and accountable to the health system must be provided to ensure cure (see "What are the advantages of direct obser-

1 Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
2 Medical officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.
vation of treatment?”, page 183). Put simply, if patients develop drug resistance because of incorrect ingestion of medication, this is the legal and ethical fault and responsibility of the treatment system for failing to organize treatment, including direct observation, effectively. A high rate of drug resistance is thus correctly seen as a symptom of poor programme performance in the past.

Once patients acquire resistance to a single drug, they become increasingly likely to acquire further resistance from poor treatment. Thus, strains of tubercle bacilli become sequentially resistant to other agents and may develop multidrug resistance (i.e. resistance to at least isoniazid and rifampicin).

The best way to prevent drug resistance is to ensure the provision of effective regimens of directly observed short-course treatment with first-line drugs for all newly diagnosed tuberculosis cases. This should be implemented within the framework of a well-structured tuberculosis control programme.

References
Drug resistance can be prevented by the use of appropriate treatment regimens, and by ensuring that these regimens are taken correctly.

An appropriate regimen always includes at least two drugs to which the patient’s organism is susceptible. Several additional considerations must be taken into account. Pyrazinamide is relatively ineffective in preventing the emergence of drug resistance to companion drugs \((1)\). Thus, treatment with a regimen of isoniazid and pyrazinamide may lead to the emergence of isoniazid-resistant (and, subsequently, pyrazinamide-resistant) organisms, even if the isolate was initially susceptible to both isoniazid and pyrazinamide. During the initial phase of treatment, when the bacterial load is high and organisms are multiplying rapidly, use of multiple drugs to which the patient’s organism is susceptible is particularly important. In the continuation phase of treatment, emergence of resistance is much less likely. Because of the essential role of rifampicin in the treatment of individual cases and control of disease in the community (see “Why are special precautions needed to protect rifampicin?” , page 195), appropriate regimens that minimize the risk of acquisition of resistance, particularly to rifampicin, should always be used.

Choice of an appropriate regimen should be made by national authorities based on international recommendations, scientific evidence from controlled clinical trials, and knowledge of the drug susceptibility pattern of the community in which treatment regimens are being organized.

Optimal regimens maximize chances of cure while minimizing complexity, toxicity, cost and risk of development of additional drug resistance. However, even an optimal regimen will have no value unless it is used correctly. An “ideal” regimen is of little use – and may be counterproductive – if it is not widely accepted and applied. Widespread use of appropriate standard regimens will greatly reduce the risk of drug resistance. For this purpose, many countries involve professional organizations (e.g. thoracic societies) and public health authorities in reaching a consensus on standard regimens that are recommended for all patients.

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1 Medical officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.
Correct use of a regimen means that the drugs are taken in the right dosages, at the right times, and for the right duration. High dosages increase toxicity without a commensurate increase in efficacy; low dosages may reduce efficacy and allow emergence of resistance. First-line drugs should be taken as a single dose. Splitting first-line drugs into several doses per day lowers the peak drug concentration and therefore reduces efficacy and may increase the risk of emergence of drug resistance (2, 3).

Fixed-dose combinations of tuberculosis drugs may prevent the emergence of drug resistance by ensuring that a single drug can never be taken in isolation (see “What are the advantages and disadvantages of fixed-dose combinations of antituberculosis drugs?”, page 189). However, taking fewer than the recommended number of tablets of a fixed-dose combination drug may expose a patient’s organisms to sub-inhibitory concentrations of multiple medications. In addition, there are potential problems with the bioavailability of fixed-dose combinations. Use of fixed-dose combinations has not been proved to reduce the risk of drug resistance.

The only means of ensuring the prevention of drug resistance is the use of direct observation of an appropriate treatment regimen. Properly implemented, direct observation ensures that drugs are taken at the right dosage, at the right intervals, and for the required duration. (See “What are the advantages of direct observation of treatment?”, page 183.)

Areas that have implemented directly observed, standardized treatment regimens have prevented the development of drug resistance, even in the context of high rates of HIV infection (4–6).

References

It is difficult to perform susceptibility testing accurately even when skilled personnel are available and laboratory facilities are of a high standard. In countries where skilled manpower and adequate facilities for such tests are scarce, accuracy is even more difficult to achieve.

Much has been learned about the reliability of drug susceptibility testing in the past decade. An international initiative led by WHO and the IUATLD has improved our knowledge of the performance of international and national reference laboratories, including many in resource-limited countries (1, 2). This initiative, known as the Supranational Reference Laboratory Network, was established to improve the quality of susceptibility testing of national reference laboratories and to validate data obtained in surveys carried out within the WHO/IUATLD Global Project on Drug Resistance Surveillance.

Five rounds of proficiency testing were carried out annually between 1994 and 1998 as part of this initiative. A coordinating laboratory sent reference strains of Mycobacterium tuberculosis to all participating supranational laboratories. The laboratories were asked to test the susceptibility pattern of the reference strains using their habitual methods and classify the cultures as resistant or susceptible. The results were compared with a “gold standard” that was derived from the judicial results (i.e. the majority). The strains were also redistributed by some supranational laboratories to several national reference laboratories (sub-networks) around the world.

Overall cumulative sensitivity for drug resistance was 95%, specificity 95%, and reproducibility 96% (3). In 1998, overall sensitivity for resistance to isoniazid and rifampicin was 100% and overall specificity was 99% and 100%, respectively. However, three supranational laboratories and some national reference laboratories produced results that were below the standard (lower specificity), suggesting that misclassification of susceptible strains as resistant is still an issue of concern, even in highly qualified laboratories and in the context of carefully performed proficiency testing. (Proficiency testing overestimates laboratory accuracy when compared with routine

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1 Based on the chapter in the previous edition by K. Toman.
2 Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
practice, since laboratories generally give special attention to panels of samples analysed for proficiency testing.)

While the improvement of susceptibility testing has been remarkable, it is important to highlight that the WHO/IUATLD initiative applies to surveillance and not to clinical practice. Surveys are carried out every 3–5 years. Information for clinical action on the basis of susceptibility tests in resource-limited settings is still very scarce. Additional limitations are the difficulty and unreliability of testing susceptibility to reserve drugs. Furthermore, there is usually only one national reference laboratory in each resource-limited country. It is clear that only on very limited occasions would these laboratories be able to cope with susceptibility testing for clinical purposes. Finally, it is worth keeping in mind that clinical action based on unreliable susceptibility testing can be harmful to the patient (see “What are the possible consequences of inaccurate drug-susceptibility testing?” page 213). Thus, is often wise to limit the use of susceptibility testing to patients who fail standard short-course treatment under directly observed treatment, as the risk of drug resistance is higher in these patients.

Newer culture techniques using liquid media give more rapid results, but may increase the risk of cross-contamination of cultures in the laboratory and are generally expensive. In the future, it is possible that molecular or rapid growth-based techniques will be able to identify patients with rifampicin resistance – those whom standardized regimens would be unlikely to cure. At present, however, such techniques identify less than 80% of rifampicin-resistant isolates and are costly and unproven.

References

The possible consequences of inaccurate susceptibility testing include:

— misclassification of strains;
— unnecessary changes of treatment;
— use of reserve drugs; leading to:
  more toxicity
  less chance of cure
  more difficult management
  the need for hospitalization
  more laboratory work
  more staff needed
  higher costs.

Resistant strains may be misclassified as susceptible, and vice versa. If susceptible strains are reported as resistant, regimens may be changed unnecessarily and reserve drugs, if available, may be introduced. However, such drugs are usually more toxic, less effective, and more costly than the drugs used for primary treatment (1). In a review of 14 studies that included sputum cultures of more than 100 patients, false-positive cultures were identified in 13 (93%) of them (2). False-positive cultures may occur because of contamination of clinical devices, clerical errors, and laboratory cross-contamination. Of the 236 patients with false-positive cultures reported in sufficient detail, 158 (67%) were treated, some of whom experienced toxicity from treatment, as well as unnecessary hospitalization, tests, and contact investigations. Clearly, laboratory mistakes are not rare but they are infrequently recognized by laboratory and clinical personnel.

The management of ambulatory patients receiving reserve drugs may be difficult. Such patients often have to be hospitalized for a long time, which is many times more expensive than domiciliary treatment and risks the spread of tuberculosis in hospital. More staff will be needed, in particular for the additional laboratory work required

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1 Based on the chapter in the previous edition by K. Toman.
2 Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
(repeated tests of kidney and liver function, blood examinations, and close bacteriological follow-up), and this will add to the cost of hospital treatment. Thus, there may be a heavy drain on resources allocated to therapeutic services, merely as a consequence of inaccurate susceptibility tests.

It cannot be emphasized too often that, whatever the stage of development of a country’s laboratory services, no laboratory should embark on drug susceptibility testing and re-treatment with reserve drugs as long as there are deficiencies in case detection and primary treatment. In such cases, resources should be used to improve the treatment, with standard treatment, of persons in whom tuberculosis has been newly diagnosed. That is still the most effective way of avoiding the development of drug resistance – a man-made problem.

References
50. **What reserve regimens are available and what is their place in tuberculosis control programmes?**

*M. Espinal*

Reserve regimens are used for patients with multidrug-resistant tuberculosis (see “How does drug resistance develop?” page 193). Since such resistance is the result of inadequate treatment, the need for re-treatment with reserve regimens is avoidable. Before the various reserve regimens are reviewed, some principles of the management of re-treatment will be discussed. Without an organizational framework such as the one suggested in the DOTS strategy (See “What is DOTS?” page 241), and without knowledge of the operational requirements of treatment with reserve regimens, there is little chance of success. This has been shown even in high-resource settings where lack of an effective organizational framework allowed a rapid increase in both tuberculosis and drug resistance (1).

The provision of reserve regimens may prove to be an intolerable drain on resources, particularly in countries with limited financial resources, health facilities, and staff, in which annual government expenditure on health may be less than US$ 1 per head. It would be irrational for any country to divert resources to re-treatment with reserve regimens as long as a large proportion of new infectious cases remain untreated or ineffectively treated and short-course treatment with first-line drugs has not reached its full therapeutic potential (2). A large requirement for reserve drugs reflects inadequately managed short-course treatment. The vicious cycle shown in Figure 17 can occur all too easily.

**Management of re-treatment**

The treatment of patients whose organisms are resistant to the standard drugs or who do not tolerate those drugs presents many difficulties. These difficulties are caused by the drugs themselves and, to a great extent, by the attitudes of the health staff.

With few exceptions, reserve drugs are not highly effective. They often produce toxic reactions that are not only unpleasant but also sometimes dangerous. This may necessitate reducing the dosage, with the result that efficacy is reduced. Moreover,

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1 Based on the chapter in the previous edition by K. Toman.
2 Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
reserve drugs are expensive and several are unstable in tropical climates. Intermittent dosing is generally not possible, and several reserve drugs may have to be taken several times a day, further complicating their administration.

A significant proportion of patients with drug-resistant disease belong to groups whose cooperation is not easy to achieve, including those who are alcohol- or drug-dependent, prisoners, and homeless people. Special efforts are needed to persuade such patients to complete the long and arduous treatment regimen. Many authorities therefore recommend that treatment with reserve drugs should be started in hospital to facilitate close observation for toxic effects and the supervision of regularity. Only after tolerance of the drug regimen has been ascertained, and a patient’s cooperation has been secured, is ambulatory treatment given. However, patients often dislike hospital discipline and not infrequently discharge themselves from the hospital. Considerable efforts are then required to persuade a patient not to stop the treatment, which, with all its discomforts, is usually the only means of preventing the patient’s death. If the health staff are convinced of this, they can sometimes induce a patient to cooperate, but this will mean that every dose of pills must be swallowed under the direct observation of a dedicated health worker.

Because of the highly specialized biochemical and microbiological follow-up examinations needed, it is evident that the organization of re-treatment with reserve drugs demands special measures. These are a heavy drain on skilled staff time, hospital beds, and financial resources. Data on the cost of treating a patient with multidrug-resistant tuberculosis in a resource-poor setting are scarce, but the full cost of treating such a patient in the United States of America has been estimated at up to US$ 100 000 (3). Encouraging evidence is emerging on the use of reserve regimens under carefully selected programme conditions (4). In resource-poor settings, it may be possible to greatly limit the use of hospitalization; this has many advantages both for the patient and for the health care system. WHO and several partners are testing a new strategy for managing cases of multidrug-resistant tuberculosis in low- and middle-income
countries, using reserve drugs within the DOTS strategy and maximizing ambulatory treatment. The aim is to assess the feasibility and cost-effectiveness of using such drugs under the overall supervision of national tuberculosis programmes (5). This initiative is not appropriate for settings where effective tuberculosis control, i.e. DOTS, is not in place.

Re-treatment regimens for patients with organisms resistant to the standard drugs

Certain principles must be followed in designing a reserve regimen. The drugs should not have been used before: in many cases, prescribing a drug that has been used before offers no advantage. The initial regimen should include at least three drugs to which the bacilli are likely to be fully susceptible. Drugs should not be kept in reserve: the most likely effective regimen should be prescribed. If drug susceptibility testing is not available and resources are limited, standard re-treatment regimens with reserve drugs can be used (6). It is important to take into account the regimens the patient has received previously, whether they were fully administered under direct observation, and for how long. Even if susceptibility testing is unavailable, every effort should be made to obtain an accurate susceptibility testing profile of patients failing a standard regimen with first-line drugs, particularly if the treatment was actually given under direct observation.

If susceptibility results are not available, at least three drugs never before used for the patient, such as an aminoglycoside, ethionamide, and ofloxacin, should be used, as well as an injectable antibiotic such as capreomycin, amikacin, or kanamycin. Any reserve regimen should be given daily and directly observed. Bacteriological results (smear and, if possible, culture) should also be monitored. Pyrazinamide and ethambutol could be added as the fourth and fifth drugs of choice (even if used previously, because of the low probability of resistance). Another option is to replace ethambutol by cycloserine (or p-aminosalicylic acid). An intensive phase of 3–6 months should be followed by a continuation phase of 15–18 months with two or three of the most active and best-tolerated drugs.

If susceptibility test results are available, designing a regimen will depend on a number of factors, such as the drugs to which the strain of *Mycobacterium tuberculosis* is resistant. WHO recommends 3–4 oral drugs plus 1 injectable drug to which the isolate is susceptible for 3–6 months, and then at least 3 effective oral drugs for 15–18 more months. Examples of potentially useful reserve regimens are given in Table 51; all are daily regimens (6). There is some evidence that a longer duration of aminoglycoside treatment is associated with a higher success rate (7).

Dosages and adverse effects of reserve drugs are discussed elsewhere (see “What is the therapeutic effect and what is the toxicity of antituberculosis drugs?”, page 110).

The response of patients with multidrug-resistant strains to second-line drugs is variable. A 56% cure rate that increased to 85% after the addition of surgery was
reported in patients with chronic disease (8). It appears that multidrug-resistant tuberculosis patients without a history of prior treatment respond better to treatment than similar patients who have been treated previously. Indeed, several series of patients without previous treatment courses reported cure rates of 75–96% (9–11). These series, however, are from high-income countries or have been obtained with extensive clinical, laboratory, and programme support, and used tailored treatment regimens. Data at programmatic level are needed from resource-limited countries (12). The challenge for many resource-limited settings would be the countrywide implementation of tailored regimens with reserve regimens.

References

TREATMENT


51. **What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?**  
*M.E. Villarino\(^1\)

WHO recommends (1, 2) that tuberculosis programmes provide treatment for latent tuberculosis infection (LTBI) – also called preventive treatment – for:

- **Children under 5 years of age who are household contacts of smear-positive patients**  
  Infants and young children with latent *Mycobacterium tuberculosis* infection are at high risk of rapidly developing disease. Infants 2 years of age or younger are at particularly high risk of developing life-threatening tuberculous meningitis or miliary tuberculosis (3).

- **Persons infected with both HIV and *M. tuberculosis***  
  The annual risk among HIV infected, tuberculin-positive persons of developing tuberculosis (estimated to be 6–16%) is much higher than that of HIV-uninfected, tuberculin-positive persons, whose lifetime risk of developing tuberculosis is estimated to be no greater than 10%. When tuberculosis develops in an HIV-infected person, the course of immunosuppression in that person is accelerated; the treatment outcome depends both on the person’s degree of immunosuppression and on the use of appropriate tuberculosis treatment given under direct observation (4).

For persons in either of these high-risk categories, LTBI treatment can potentially reduce the risk of developing active tuberculosis, increase life expectancy, and reduce overall medical costs. However, this intervention strategy may not substantially reduce tuberculosis morbidity in the larger communities in which these persons reside (see “What is the epidemiological impact of treatment of latent tuberculosis infection?”, page 226). LTBI treatment programmes are costly, difficult to implement on a large scale, and carry a risk of drug toxicity. In addition, unless active tuberculosis is ruled out, patients with unrecognized active disease who are treated for LTBI may be harmed because they may develop drug resistance as a result of exposure to a drug regimen that is inadequate for treatment of tuberculosis.

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\(^1\) Chief, Diagnostic and Therapeutic Studies Section, Research and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.
Before a decision is made to incorporate LTBI treatment into a tuberculosis control programme, the following factors must be considered since they limit its application and effectiveness:

— hepatotoxicity (increases with age; is potentiated by other drugs, especially alcohol; is very rare in young children);
— non-adherence (a major factor in limiting effectiveness);
— drug resistance (LTBI regimens may be ineffective for drug-resistant infections);
— operational problems in implementation (need for tuberculin skin testing, for voluntary HIV counselling and testing programmes, etc.);
— the difficulty and cost of excluding tuberculosis and the risk of creating drug resistance if such exclusion is not effective; and
— the costs per se.

In many industrialized countries where incidence of tuberculosis has fallen to record low levels, it is believed that most new cases of tuberculosis disease occur in persons who were infected in the remote past, contained their infection, and then subsequently developed tuberculosis. Although efficient detection and treatment of persons with active tuberculosis remain the highest priority activities for all tuberculosis control programmes, these measures alone will not prevent the new cases that arise from the pool of individuals infected a long time ago. In low-prevalence countries, therefore, the treatment of persons with LTBI who are at high risk of developing active disease is an important component of tuberculosis control.

A regimen of isoniazid for 6–12 months has been the mainstay of treatment for LTBI for more than 30 years. However, the acceptability of isoniazid for LTBI has been limited by the poor patient adherence that results from the relatively long duration of treatment required, and by concerns about toxicity. Consequently, there has been interest in the development of shorter regimens as alternatives to isoniazid for the treatment of LTBI. In recent years, several studies of “short-course” treatment of LTBI have been undertaken in persons infected with HIV (5).

The identification of persons with LTBI is a prerequisite for a treatment programme, and guidelines for administering and interpreting the tuberculin skin test are therefore required. The tuberculin test is indicated only for persons at highest risk of tuberculosis and is discouraged for those at low risk. Persons at increased risk of tuberculosis include those who have had recent infection with M. tuberculosis and those who have clinical conditions associated with an increased risk of progression from LTBI to active tuberculosis (5). Except in community surveys of risk of infection, the tuberculin test should be given only to persons who, if found to be tuberculin-positive, would receive treatment for LTBI. Thus, except in some community surveys, a decision to administer a tuberculin test is a decision to treat if LTBI is found, irrespective of the age of the person tested.

Many clinical guidelines use a rating system to grade the strength of the recommendation (A, B, or C) and the quality of evidence supporting the recommendation.
(I, II, or III), as shown in Table 52. Four regimens are recommended for the treatment of adults with LTBI. For children, the only recommended treatment continues to be a 6–12-month regimen with isoniazid alone.

Prospective, randomized trials in HIV-negative persons indicate that preventive treatment with isoniazid for 12 months is more effective than 6 months’ treatment. However, a daily isoniazid regimen for 9 months is recommended in many countries – in subgroup analyses of several trials, the maximum beneficial effect of isoniazid was achieved by 9 months’ treatment, with minimal additional benefit gained by extending treatment to 12 months (6). When compared with placebo, both 6-month and 12-month regimens are effective in HIV-positive patients; however, these regimens have not been compared with each other in randomized trials. Although a 9-month regimen of isoniazid is preferred for the treatment of LTBI, a 6-month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations, treatment for 6 months rather than 9 months may provide a more favourable outcome from the standpoint of cost-effectiveness; based on local conditions, tuberculosis programmes or providers may opt for a 6-month rather than a 9-month course of isoniazid. Both the 9- and 6-month isoniazid regimens may be given intermittently (i.e. twice weekly).

A 2-month daily regimen of rifampicin and pyrazinamide is recommended on the basis of the results of a prospective randomized trial of LTBI treatment in HIV-infected persons. The trial showed the 2-month regimen to be similar in safety and efficacy to a 12-month regimen of isoniazid (7). However, severe hepatotoxicity has been observed when regimens containing rifampicin and pyrazinamide have been used for LTBI (8). Twice-weekly rifampicin and pyrazinamide for 2 or 3 months may

Table 52
Rating system for grading the strength of the treatment recommendation

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Rating(^a) (evidence(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HIV–</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>B (II)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>B (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>B (II)</td>
</tr>
<tr>
<td>Rifampicin + pyrazinamide</td>
<td>2 months</td>
<td>Daily</td>
<td>B (II)</td>
</tr>
<tr>
<td></td>
<td>2–3 months</td>
<td>Twice weekly</td>
<td>C (II)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>4 months</td>
<td>Daily</td>
<td>B (II)</td>
</tr>
</tbody>
</table>

\(^a\) A: preferred, B: acceptable alternative, C: offered when A and B cannot be given.

\(^b\) I: randomized clinical trial data, II: data from clinical trials that are not randomized or were conducted in other populations, III: expert opinion.
be considered when alternative regimens cannot be given. This intermittent regimen should be administered as directly observed treatment. Some experts recommend that the 2-month regimen of daily rifampicin and pyrazinamide also be given under direct observation, which can consist of five observed and two self-administered doses each week. When rifampicin cannot be used (e.g. in HIV-infected persons receiving protease inhibitors), rifabutin may be substituted (9). Rifampicin given daily for 4 months is recommended on the basis of the efficacy of such a regimen in a prospective randomized trial of tuberculin-positive persons with silicosis and a non-randomized trial in persons exposed to isoniazid-resistant tuberculosis (10, 11). This option may be especially useful for patients who cannot tolerate isoniazid or pyrazinamide.

Before treatment of LTBI is started, active tuberculosis must be ruled out by clinical history, physical examination, chest X-ray, and, when indicated, bacteriological studies. The WHO-recommended protocol for evaluation and treatment of childhood contacts of active tuberculosis is summarized in Table 53 (12).

<table>
<thead>
<tr>
<th>If:</th>
<th>And:</th>
<th>Then:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The child has symptoms of tuberculosis</td>
<td>A physician determines that the child has tuberculosis</td>
<td>A full course of tuberculosis treatment should be given</td>
</tr>
<tr>
<td>The child does not have symptoms of tuberculosis</td>
<td>A tuberculin test is not available</td>
<td>The child should receive treatment for LTBI</td>
</tr>
<tr>
<td>The child does not have symptoms of tuberculosis</td>
<td>A tuberculin test is available</td>
<td>The child should receive 3 months of treatment for LTBI and a tuberculin test should then be done</td>
</tr>
</tbody>
</table>

If: 

The child’s induration to the tuberculin test is positive  
Continue treatment of LTBI for a full course (i.e. 6–12 months of 5mg/kg of isoniazid)

The child’s induration to the tuberculin test is negative  
Stop the preventive treatment and give BCG vaccination (if there has been no previous vaccination)
tacts of smear-positive patients, a chest X-ray should be done to rule out active tuberculosis before the start of treatment in at least all HIV-infected persons. All HIV-infected persons who have cough, fever, or other symptoms compatible with tuberculosis should be subjected to careful evaluation, including bacteriological studies, before LTBI treatment is started. Children who have symptoms that are potentially compatible with tuberculosis (e.g. fever, cough, failure to thrive) must also undergo an X-ray before the start of treatment. Ideally, this should apply to all children but, if X-ray is unavailable, LTBI treatment may be given unless a child is symptomatic. For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 months is the recommended regimen for LTBI. A chest X-ray to evaluate the possibility of active tuberculosis should be undertaken in pregnant women (with appropriate shielding precautions) when required, even during the first trimester of pregnancy. For women at risk of progression from LTBI to disease, especially those who are HIV-infected or who have probably been recently infected with M. tuberculosis, start of treatment should not be delayed on the basis of pregnancy alone, even during the first trimester. When the risk for active tuberculosis is lower, some experts recommend waiting until after delivery to start treatment for LTBI.

Baseline laboratory testing is not routinely indicated for all patients at the start of LTBI treatment. Patients whose initial evaluation suggests a liver disorder should have baseline liver function tests of serum AST (SGOT) or ALT (SGPT) and of bilirubin. Baseline testing is also indicated for patients with HIV infection, women who are pregnant or in the immediate postpartum period (i.e. within 3 months of delivery), persons with a history of or risk factors for chronic liver disease, and persons who consume alcohol regularly. It is not routinely indicated in older persons. Active hepatitis and severe liver disease are relative contraindications to treatment. Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver enzymes are abnormal and for others with a risk of hepatic disease. Patients should be educated about the adverse effects associated with LTBI treatment and advised to stop treatment and promptly seek medical evaluation if these occur. They should be questioned about adverse effects and monitored for development of jaundice.

The significance of LTBI treatment in countries where tuberculosis incidence is high and growing, and where M. tuberculosis continues to be transmitted at high rates, has been questioned. Certainly, an LTBI treatment programme should not be a priority in the overall tuberculosis control strategy in such contexts. The primary strategy for controlling tuberculosis is to minimize the risk of transmission by early identification and complete treatment of patients who have active infectious tuberculosis. Selective LTBI treatment programmes may be feasible and affordable for some middle-income countries, but are always a lower priority than programmes of successful management of tuberculosis cases. In low-income countries with high tuberculosis prevalence, LTBI treatment programmes would have at most a secondary role in tuberculosis control. The use of LTBI treatment as a tuberculosis prevention strat-
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eye should be reserved for persons or groups with the highest risk of developing active tuberculosis. In countries experiencing an epidemic of HIV, treatment of LTBI can provide important benefits for the individual. Although such a strategy could theoretically reduce the incidence of tuberculosis and blunt the impact of HIV on tuberculosis epidemiology if widely applied, this would be difficult, if not impossible, to achieve under programme conditions. Even – or especially – in such settings, prompt identification and rapid, complete treatment of patients with smear-positive tuberculosis is the highest priority.

References

52. **What is the epidemiological impact of treatment of latent tuberculosis infection?**

*Z. Taylor*

Treatment of latent tuberculosis infection (LTBI) is an important component of tuberculosis control in the USA, but is rarely used outside North America other than for treatment of contacts of infectious cases. Until recently, isoniazid daily or twice weekly for 6–12 months was the only commonly recommended treatment regimen (1). This was based on the results of randomized, placebo-controlled trials that established the efficacy of isoniazid in preventing tuberculosis in persons with latent infection (2, 3). The average reduction in the development of active tuberculosis observed in these trials was 60% (2). In persons who took more than 80% of their prescribed medication for 12 months, the effectiveness of isoniazid approached 90% (2). Isoniazid taken for 6 months was effective, but treatment for 12 months was even more effective (3). More recent recommendations include a 2-month regimen of daily rifampicin and pyrazinamide and a 4-month regimen of rifampicin, as an alternative to 6–9 months of daily or twice-weekly isoniazid (4). The recommendations were based on controlled clinical trials that found equivalent protection using these regimens compared with isoniazid regimens (4).

Most of the reported clinical trials of LTBI treatment involved high-risk populations such as recent contacts, persons in high-risk congregate settings, persons with HIV infection, or persons with untreated, inactive tuberculosis (2, 3, 5, 6). The epidemiological impact of these treatment trials depended not only on the effectiveness of treatment, but also on the contribution of the treated groups to the incidence of tuberculosis in their communities. Three clinical trials, conducted in Greenland, Alaska, and Tunisia, attempted to measure the impact of LTBI treatment on the incidence of tuberculosis in a population. The trial in Greenland in 1956 involved 76 villages and 8081 participants (7). In each village, all eligible adults were given either isoniazid or placebo, with everyone in any given village receiving the same medication. Medication was administered twice weekly for two 13-week periods, with an intervening 13-week break. The trial in Alaska began in 1957 and involved 30 communities and 6064 participants (8). In this trial, households were randomized to receive either isoniazid or placebo. Finally, the Tunisian trial, which started in 1958,

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was conducted in a poor suburb of Tunis (2). Blocks of houses were randomized to receive either isoniazid or placebo; a total of 15,910 persons participated in the trial. The results of these trials are summarized in Table 54.

There is an obvious variation in the results of these trials, with a substantial effect in Alaska, a much smaller effect in Greenland, and the smallest effect in the Tunisian community study. The trials in Alaska and Greenland took place in small, isolated villages with populations that supported the interventions. In addition, effective tuberculosis control programmes were in place in both locations. In Greenland, 400–600 mg isoniazid was given twice weekly on consecutive days for 13 weeks, followed by 13 weeks without treatment, and then a further 13 weeks of twice-weekly isoniazid. This is not a standard dosage schedule and is possibly sub-optimal, which may explain the reduced effectiveness observed in this study. In the Tunisian study, there was evidence that adherence to medication was low in the study population.

In conclusion, the epidemiological impact of the treatment of LTBI may be a 31–59% reduction in active tuberculosis in a community where an effective tuberculosis control programme is in place. Table 54 provides the results of the community trials of preventive treatment with isoniazid, 1956–1958.

### Table 54

**Results of community trials of preventive treatment with isoniazid, 1956–1958**

<table>
<thead>
<tr>
<th>Trial/treatment group</th>
<th>No. of participants</th>
<th>Case rate per 1000 person-years</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Greenland villagers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3907</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>4147</td>
<td>9.8</td>
<td>31&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Alaskan villagers</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3017</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>3047</td>
<td>3.2</td>
<td>59&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Tunisian community</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8141</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>7769</td>
<td>2.3</td>
<td>26&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Source: references 2, 7, 8.

<sup>b</sup> P < 0.0001 by chi square statistic.

<sup>c</sup> Statistically insignificant.
losis control programme is in place and where the majority of active tuberculosis results from reactivation of latent infection. Theoretically, the reduction could be as much as 80–90% if all cases of active tuberculosis were the result of reactivation of latent infection, all persons with latent infection could be identified, and all persons with latent infection completed treatment. In practice, this combination of circumstances is rarely if ever to be found. Even in a low-incidence, resource-rich country like the USA, a significant proportion of active tuberculosis cases result from recent transmission of infection (10, 11) and completion of treatment for LTBI is often less than 50% (12, 13). The epidemiological impact of the treatment of LTBI is therefore likely to be more modest than the effect estimated by the studies in Alaska and Greenland. Further, the human and financial resources required to identify and treat persons with LTBI on a mass basis exceed the capacity of most tuberculosis control programmes. For well-funded, effective tuberculosis control programmes, treatment of LTBI in contacts, prisoners, persons with both HIV and LTBI, and other high-risk populations may be a viable option. The epidemiological impact will depend on the contribution of the risk group to tuberculosis incidence in the population, the proportion of the group identified treated, and the proportion of persons who complete treatment.

References


