Pierre Chaulet

Tuberculosis: a six-month cure

Today the treatment of tuberculosis can be based on a course of chemotherapy that lasts only 6 months, giving patients the best chance of cure and affording the health personnel an exceptional opportunity to improve both their patients’ compliance with the treatment and the overall efficiency of their own activities.

The best strategy for prevention of tuberculosis is to cure patients who have it. During the last decade a quiet revolution has taken place in treatment methods: short-term chemotherapy regimens have gradually won general acceptance in national antituberculosis programmes, both in high-prevalence developing countries as different as Algeria, Brazil, and Singapore and in low-prevalence industrial countries. The reason for this is very simple: these regimens are highly effective and reliable, and enable us to attain the objective of cure with the minimum of constraints either for patients or for health personnel (1).

6 months supplemented by pyrazinamide for the first 2 months. With these three essential drugs, administered every day at the same time and in a single dosage, a final cure rate verging on 100% is obtained both in pulmonary tuberculosis and in extrapulmonary cases, irrespective of age. During the last 4 months of treatment the drugs can also be given, under the direct supervision of a health officer, three times or twice a week, with equally successful results.

In countries where the primary bacterial resistance rate is high, and especially for cases of lung tuberculosis, this basic regimen is supplemented for the first 2 months of treatment by a fourth drug, streptomycin, which has to be injected intramuscularly, or ethambutol, which is taken orally. The success rate this gives is almost as high for cases with bacilli initially resistant to isoniazid (3-15% of new cases of lung tuberculosis, depending on the country) as it is for the far more numerous cases in which the bacilli are initially susceptible. Moreover the success rate is maintained even when the drugs are administered three times a week throughout the course of treatment rather than every day, at dosages adjusted to body weight (Table 2).

Questions most commonly asked

Nowadays, which are the best chemotherapy regimens for tuberculosis?

All regimens use an association of several drugs chosen from among the six essential antituberculosis drugs (Table 1). The best therapeutic regimen is the one in which a combination of the two main drugs, isoniazid and rifampicin, is given daily for

The author is Professor and Head of the Matibef Tuberculosis and Lung Diseases Clinic, West Algiers University Hospital Centre, Béni-Messous, Algiers, Algeria.
### Table 1. Essential antituberculosis drugs and their dosage schedules

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common abbreviation</th>
<th>Daily</th>
<th>Intermittent</th>
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<tr>
<td></td>
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<td>mg/kg</td>
<td>maximum (mg)</td>
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<td>Isoniazid</td>
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<td>Pyrazinamide</td>
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<td>Ethambutol</td>
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<td>1200</td>
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<tr>
<td>Streptomycin</td>
<td>S</td>
<td>15</td>
<td>1000</td>
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<td></td>
<td></td>
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<tr>
<td>Thioacetazone*</td>
<td>T</td>
<td>4</td>
<td>150</td>
</tr>
</tbody>
</table>

Source: *Antituberculosis regimens of chemotherapy. Recommendations of the Committee on Treatment, International Union against Tuberculosis and Lung Diseases, December 1987.*

* 15 mg/kg after two months.
* 750 mg for patients over 45 years old.
* Always associated with isoniazid in the same tablet.

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**If there are not enough funds available to give all patients rifampicin for six months, is there an alternative solution?**

Indeed yes. In that case, the best regimens are those that include rifampicin at least for the first two months, but to achieve the same efficacy as 6-month regimens they must last a little longer: 8 months (Table 2).

These regimens comprise an initial 2-month phase during which four essential drugs, namely isoniazid, rifampicin, streptomycin, and pyrazinamide, are given every day, and a continuation phase during which the following drugs are given daily: isoniazid and thioacetazone for 6 months; or isoniazid and rifampicin for 2 months followed by isoniazid alone for 4 months; or isoniazid, streptomycin, and pyrazinamide twice a week for 6 months (1,2).

Under the conditions in which programmes are implemented, the combined failure and 3-year relapse rate with regimens lasting 6 and 8 months was always below 5% (0-4%) compared to 15-20% with the 12- and 18-month regimens that did not include rifampicin (3-5).

**What are the epidemiological, social, and economic consequences of introducing short regimens into national antituberculosis programmes?**
Table 2. Modern drug treatment regimens applicable in national antituberculosis programmes

<table>
<thead>
<tr>
<th>Duration</th>
<th>Treatment regimens*</th>
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| 6 months | 2RH then 4RH (or 4R₂H₂ or 4R₁H₀)  
2SRHZ then 4RH every day or thrice weekly  
2ERHZ then 4RH every day or thrice weekly |
| 8 months | 2SRHZ then 6TH  
2SRHZ then 2RH/4H  
2SRHZ then 6S₃H₂Z₂ |

* The drugs used in these regimens are conventionally represented by their usual abbreviations: R = rifampicin, H = isoniazid, Z = pyrazinamide, S = streptomycin, E = ethambutol, T = thiacetazone.

The number preceding a group of letters indicates the duration in months of the phase, initial or continuation, during which the drugs are administered every day in a single dosage.

The subscript number after a letter represents the number of weekly dosages of the drug.

As field experience in Algeria and the United Republic of Tanzania has shown, the general application of shorter regimens reduced the number of failures and relapses (i.e., patients requiring a second course of chemotherapy), the number of chronic patients with sputum containing resistant bacilli, the acquired bacterial resistance rate, and, consequently, the primary bacterial resistance rate (6-8). By their ease of administration, in a single daily dose, orally using a smaller volume than before, the shorter regimens facilitate treatment on an ambulatory and partially supervised basis. Where intramuscular injections of streptomycin are involved, they can be reserved for the first 8 weeks or replaced by ethambutol tablets. It must be emphasized in passing that, in countries where the AIDS epidemic is of concern and it is not possible to sterilize syringes in the basic health units, it is better to avoid streptomycin. Because of the intermittent drug administration, regimens that are both short and fully supervised can be applied in special situations—as, for instance, those in which patients live more than an hour’s journey from a health unit or are mentally ill or drug-addicted and not therefore capable of complying with instructions. By cutting down the total duration of the treatment, the short regimens reduce the costs incurred by the health services, the number of check-up visits, the number of trips the patient has to make, the number of days’ work lost, and the resulting loss of income.

In developing countries, the purchase of the drugs needed for short regimens uses up precious foreign exchange. Is it not better for them to keep to the old 12- or 18-month regimens, admittedly less effective but far less costly?

That is a problem facing health planners and decision-makers. There are two answers to it (9). The first relates to the cost of antituberculosis drugs: in real terms their prices have fallen considerably in the past 15 years, and the cost of the drugs needed for short (8-month) regimens is only between two and four times that of the drugs needed for the old regimens. Even in the poorer countries, relatively expensive drugs like rifampicin and pyrazinamide are being imported either to treat the failures from the old regimens or in response to pressure from influential social brackets. It is better for the patients and more economical to give two months of rifampicin and pyrazinamide (in association with other, cheaper drugs) to all recognized tuberculosis cases and treat them for 8 months than to be obliged, after treating them all for 12 months, to give 20% of them (failures or relapses, often with bacilli resistant to isoniazid) a further 12-month course of therapy that includes rifampicin.

The cost of antituberculosis drugs has to be compared with their benefits: are we sure that, even in the most destitute countries, precious foreign exchange is not being
spent on inessential or even useless medicines?

The second answer is that we must distinguish between the cost of drugs and the cost of treatment. Even if we take into account only the cost to the health services of treatment (cost of initial, in-treatment, and end-of-treatment consultations; bacteriological and X-ray examinations; and any intramuscular injections), we find that the cost of medicines represents only 30% of the cost of a fully ambulatory course of treatment. And as soon as there is a 1- or 2-month period of hospitalization (even under very basic conditions), the cost of drugs represents only 5% of the cost of treatment.

It is on the strength of these data that health planners and decision-makers should logically persuade those in charge of national antituberculosis programmes to adopt the shorter regimens and adapt their technical directives to the new realities. The 8-month regimen costs less than 7 inpatient days at $5 a day (the cost in certain African countries) or three chest X-rays at $10 each.

When you live in a low-income country how do you go about procuring the necessary antituberculosis drugs for an up-to-date national programme?

Again, there are two solutions. In emergencies, recourse can be had to international assistance projects supported by governments or nongovernmental organizations. But such extrabudgetary resources are not unlimited nor available indefinitely, so they are liable to make the implementation of the national programme dependent on the duration of the assistance project and to impose a choice of drug regimens ill-adapted to the national resources and health facilities. They have

the major disadvantage of reducing national self-reliance (9).

Hence the best solution is to find the needed resources under the regular budget of the health services, within the framework of an overall plan. By analysing the country’s total spending of foreign exchange on antituberculosis drugs (in both the public and the private sectors and in the social security system) and by comparing the prices actually paid with the prices for the same drugs bought through WHO, a source of potential savings can already be identified.

The second solution is to cut unnecessary expenditure such as the purchase of nonessential drugs, repeated monthly X-ray examinations, the initial hospitalization of all patients, and prolonged hospital stays lasting several months. The allocation of the available budgetary resources can then be organized differently.

For this solution to be fully successful, it is desirable whenever possible to centralize drug purchases at the national level and proceed by inviting bids from suppliers while establishing strict quality control for drugs purchased under their generic (international nonproprietary) names. The quantities of drugs to be purchased should be estimated in the light of the treatment regimens selected, the number of patients to be treated, and the competence of the health teams (9).

But you have just said that the shorter regimens are easy to apply. What difference does the competence of the health teams make?

Competence makes a difference at all levels (10). The health authorities must standardize the treatment regimens chosen and not have several standards or a double
one—e.g., a short regimen for the most severe and contagious cases and a long regimen for the others. The delivery of antituberculosis drugs to patients free of charge must be planned and organized; there can be no question of penalizing for their illness patients who are drawn from the poorer strata of society. Above all, it is important to get the right target and treat only tuberculosis patients. The precise definition of the categories of patients to be treated is the responsibility of those in charge at the highest level. In a country with a high prevalence of the disease, where the programme must be based on priority treatment of sources of infection, we know that the great majority of lung tuberculosis cases admitted for treatment should be sputum-smear positive, and ideally all patients should be tested to ensure that only the positive ones are admitted. If more than 15% of pulmonary cases are admitted for treatment without bacteriological testing, it means that there are errors of diagnosis on the positive side, a risk of inappropriate utilization of drugs in chronic patients who have already been treated, and finally waste of drugs (11).

At the periphery, where the patients live and where they are treated and supervised by the health teams, the success of short regimens depends on adherence by the physicians and nurses to the standard treatments defined in the national programme and on the patients’ compliance with the treatments prescribed (10).

Patients’ compliance with the treatment depends mainly on the competence and conscientiousness of the health teams. It can be absolute if the treatment is fully and carefully explained at the very start to the patient and his family, and if the treatment is fully supervised. But in the circumstances usual in developing countries, where 80% of the population is rural and most people live far away from the district centres, supplementary measures have to be taken. Arrangements have to be made for direct supervision of the treatment during the first 8 weeks at the dispensary or health centre, or at home, or at the district hospital (where possible, if the patient agrees). Arrangements then have to be made for regular monthly distribution of the drugs needed, in tightly closed containers to be kept by the patients. In addition there must be a system of “defaulter action”, in the form of a reminder letter or home visit, for patients who attend irregularly or fail to keep their appointments for more than a week. From the very first day a list must have been made of all the patient’s possible addresses, including those of family, parents, friends, and place of work.

Lastly, competence is needed in the country’s drug supply and distribution system (9). The pharmaceutical staff responsible for supplying the health services must be informed on international market conditions, on the progress achieved in dosage forms (e.g., a combination in fixed proportions of two or three essential antituberculosis drugs), so facilitating drug management and distribution, and on the quality control of imported antituberculosis drugs, single or combined, so as to ensure their bio-availability. The staff responsible for drug distribution within the country must also have technical standards to refer to and a secure stock at the intermediate level so that there is never any interruption in the supply of drugs to patients.

Clearly, then, short chemotherapy regimens are not in themselves a panacea: their potential effectiveness is attained only if a whole series of appropriate decisions is taken at the highest level and if all the planned activities are carried out at each of the levels concerned.
You say that hospitalization is necessary when possible and if the patient agrees. Could you define the role of the hospital?

Let us be clear on this point. Hospitalization is not, in itself, essential. What is needed is direct supervision of treatment for the first 8 weeks (either every day or 3 days a week) by a health worker. This supervision can be carried out by the staff of the health unit nearest to the patient’s home, provided the health worker is competent to distribute a few tablets, to give an intramuscular injection with sterile equipment (should it be needed), and to enter the treatment correctly in the patient’s record. However, the distance between the patient’s home and the nearest dispensary is sometimes too great for daily or thrice-weekly supervision; in these cases, hospitalization can be a solution to the problem of supervision, if the patient accepts it. There is no reason why a few beds in the district general hospital should not be used for this purpose. This is an exceptional solution for an exceptional situation, not a general rule. Hospitalization does not in itself guarantee good treatment; it is often imposed on patients without consulting them and even without ensuring supervision of treatment. Once again, the most important thing is to ensure that a good course of chemotherapy is fully supervised throughout the treatment, or at the very least for the first two months.

For results to be achieved in the community, the short regimens selected for the national tuberculosis programme must be applied through a health system that covers the population. The integration of tuberculosis treatment into primary health care will require appropriate support at district level, firstly to ensure that suspected cases of tuberculosis are continuously picked up at all the health units and infectious contacts identified by sputum smear tests at the district laboratories, and secondly to ensure that the drugs needed are available without interruption and that treatment is supervised.

Can effective treatment really reduce the extent of the tuberculosis problem?

It all depends on the percentage of patients receiving such treatment. We know that, untreated, a lung tuberculosis case remains contagious for 2 years on average. Short regimens reduce the contagiousness of a recognized case within a fortnight, and sputum cultures become negative by the second month in almost 95% of cases. When a country’s health services are successful in identifying and curing over two-thirds of the new sources of infection each year, we see a rapid decline in tuberculosis prevalence in that country. On the other hand, if the health services identify only 10% of the sources of infection, there is little or no decline in tuberculosis prevalence even if the cases recognized are cured.

In many developing countries the actual situation is not so clear-cut, but it is more serious. The health services do succeed in regularly identifying 30-50% of the new cases occurring in the community, particularly in the urban areas, but the treatment regimens are poor, either because they are not standardized or because they are ineffective, irregularly applied, needlessly long, or unsupervised—or for all those reasons at once. Consequently, the patients do not recover; they become chronic cases, expectorating bacilli that are often resistant and become increasingly so until the patients die, as they inevitably do in the absence of rational means of treatment. Those are the situations where the working methods must be urgently
reviewed so that every case identified becomes within 6 months a cured case.

After that it will remain to improve the performance of the health service in the identification of sources of infection through the development of an efficient primary health care system and a supervised network of laboratories for smear testing. But that is another story, and we must not be prevented from acting now to cure the patients identified.

References


Hospitalization versus ambulatory treatment

Routine hospitalization of tuberculous patients should not be a part of control programme operations. It prevents patients from leading a socially active life and creates practical and economic problems for them and their families, as well as for the control programme. The invariably limited inpatient capacity may hinder the expansion of case-finding activities. Nevertheless, if their clinical status requires it, tuberculosis patients should be admitted to hospital. They should be discharged as soon as they have improved sufficiently to continue treatment as outpatients.