TUBERCULOSIS CONTROL
The DOTS Strategy
(Directly Observed Treatment Short-Course)

An annotated bibliography

Compiled by
The Global Tuberculosis Programme
and
The Regional Office
for South-East Asia

World Health Organization
Geneva
1997
## CONTENTS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>Case finding</td>
<td>3</td>
</tr>
<tr>
<td>Directly observed treatment</td>
<td>4</td>
</tr>
<tr>
<td>Short-course chemotherapy (including intermittent regimens)</td>
<td>9</td>
</tr>
<tr>
<td>Intermittent treatment</td>
<td>11</td>
</tr>
<tr>
<td>Treatment of HIV-infected TB patients</td>
<td>13</td>
</tr>
</tbody>
</table>
The WHO recommended strategy for TB control

INTRODUCTION

This bibliography is intended for the use of National Tuberculosis Programme (NTP) Managers and personnel working in TB control. The aim is to provide a selective overview of the main aspects of TB control, utilizing the scientific literature to explain the basis of the key components of the DOTS strategy. This list is not comprehensive, nor is it representative of all aspects of TB control. It is largely drawn from the scientific literature published in English. The bibliography includes representative examples of scientific papers based on country-level and regional information.

The bibliography will be updated each year and will be distributed to NTP Managers and Ministries of Health. It is available from the WHO Regional Offices and from WHO Headquarters.* We would appreciate receiving your comments and suggestions on improvements for future editions of this bibliography. Please address correspondence to:

Dr Thomas Frieden  
c/o South-East Asia Regional Office  
World Health House  
Indraprastha Estate  
Mahatma Gandhi Road  
New Delhi 110002  
India

tel: 91 11 331 7804  
fax: 91 11 332 7972  
email: friedenta.who.ernet.in

Dr Jacob Kumaresan  
Medical Officer  
Global Tuberculosis Programme  
World Health Organization  
20 avenue Appia  
1211 Geneva 27  
Switzerland

tel: 791 2385  
fax: 791 4199  
email: kumaresanja.who.ch

The bibliography will be useful as a source of reference material and guidelines. We hope that this information will reach all key personnel involved in TB control, particularly NTP Managers. It will also be useful for those who teach TB control in schools of public health, medical institutions and allied professional schools. We hope that this bibliography will provide answers to many of the questions which health workers may face in the course of their TB control activities.

Please note that this bibliography is available for reference purposes only.

* World Health Organization, 20 avenue Appia, 1211 Genève 27, Switzerland  
Attn: Documentalist, Global Tuberculosis Programme.
Case Finding


   Review of diagnostic accuracy of x-rays. Readings were discordant for 30% of x-rays read by different experts, and 21% of experts reading the same film at two separate times. Consistency of reading by highly experienced radiologists was only slightly better.


   Even with intensive case finding, 78% of all smear-positive cases were found to have major symptoms of tuberculosis. The authors noted that “even with the present extremely limited and inadequate facilities available for the diagnosis and treatment of the disease, over half of the sputum-positive persons ... have actually sought assistance at government medical institutions, motivated by their symptoms.” Improvement in diagnostic practices in primary care services, rather than case-finding in the community, is the best means to increase the effectiveness of case finding.


   Clear and comprehensive review of case finding and other aspects of tuberculosis. “Most new positive results are obtained from the first and second specimens.” “In new, untreated patients with prolonged chest symptoms and abnormal lung x-ray shadows, two consecutive smear examinations (e.g., of on-the-spot and overnight sputum) were practically equivalent to one culture examination.” X-ray failed to diagnose 10-15% of culture-positive patients, and diagnosed nearly 40% of patients as having TB who had negative cultures and likely did not have active TB. “Patients without symptoms are not an urgent matter of public health concern. Their prognosis is likely to be favourable and their infectiousness, if any, is slight.”

4. Shimao T. Tuberculosis case-finding. WHO/TB/82.131

   Even in countries with extensive, repeated programmes of mass miniature radiography (MMR), most new cases are detected by symptomatic visits to clinics, especially for smear-positive cases. Those at highest risk for TB are at highest risk for not participating in MMR.

"X-ray evidence of clinically active tuberculosis is very unreliable.... The patient himself will remain the focal point from which to start case-finding of tuberculosis. He will not "forget" his disease because the vast majority of serious forms of tuberculosis cause unpleasant symptoms..... Mass indiscriminate radiography will have no place in any future tuberculosis control programme.... Well-organized outpatient chemotherapy, especially if provided free of charge, will attract symptomatic cases from far and wide.... Mankind will only be freed of tuberculosis if a reasonable annual decrease in the risk of tuberculosis infection is achieved in all developing countries."


Two sputum specimens examined for AFB detect most positives on smear, "though three specimens might be optimal". Even if culture techniques improve considerably, they will not replace smear for diagnosis of tuberculosis.


"It will be appreciated that these irregularities have been detected in patients under intensive supervision. The great majority keep up the social side of the relationship with the clinic and attend regularly. Surprisingly, mere attendance at the clinic in no way means regularity in taking medicine."


Review of problems with self-administered treatment, particularly of drugs taken for long periods of time. Studies from the Tuberculosis Research Centre in India summarized: non-adherence was not related to side effects, dosage, or prior receipt of one year of supervised treatment. Nonadherence was as high with placebo as with active drug. Surprise home visits revealed a much greater degree of nonadherence than pill counts or urine tests. Excerp[ing the author's summary: "Every effort was made to obtain and keep the patient's cooperation and much time was spent during several interviews explaining both to the patient and to the family the seriousness of the disease and the necessity for a long course of chemotherapy. The infectious
nature of the disease and the radiographic lesion was demonstrated to the whole family. The patient was warned that he would feel much better after a few weeks of treatment and that he might be tempted to stop taking his medicine, but that to do so might have very serious consequences. Such instruction was repeated at every monthly examination, and at other visits to the clinic as well as in the patient's home, by the doctors, by the public health nurses, and by the health visitors. Further, an attempt was always made to get another member of the family to watch the patient swallow the [medicine]. The explanation was always given in simple language. Despite this approach, ensuring self-administration was a major problem.”


Review of transmission and epidemiology. Patients who are smear-positive are much (2-20 times) more infectious, and are also much more likely to die if untreated. Smear-positive patients are usually symptomatic, and most had promptly sought care. Periodic radiographic screening of the population cannot “diminish transmission to a noticeable extent.” An untreated patient may infect 5-10 patients/year, 10-20 per lifetime. Approximately 10% of infected patients develop disease, of whom about half are sputum positive. Therefore, even without treatment, tuberculosis rates are likely to decline slowly if social conditions are stable. Ensuring effective treatment can accelerate decline in the risk of infection two-to-three fold.


Despite difficult conditions in a refugee camp, supervised treatment was given, with a default rate of less than 10%.

"...Demonstrates the feasibility of successfully integrating a short-course therapy with a program design to allow high compliance under difficult field conditions.”


Review of compliance. Approximately one third of patients do not take medications regularly as prescribed, and perhaps one third of patients who do take medications make errors in self-administration. Noncompliance is not related to disease state, age, sex, race, marital status, severity of illness, educational level, adverse effects of medications, or patients' understanding of their disease. In one study of tuberculosis patients, 31% of a select patient group who had been pre-judged by the authors to be undoubtedly reliable took less than 70% of their prescribed medicine. Pill count, particularly if not done on surprise home visits, is an inaccurate means of measuring compliance.

Using directly observed, short-course chemotherapy, cure rates of 86-90% can be achieved. Cost per year of life saved with ambulatory short-course treatment was US$1. “Chemotherapy for smear-positive tuberculosis is thus cheaper than other cost-effective health interventions such as immunisation against measles and oral rehydration therapy.”


In 1978 DOT was implemented, and in 1986 short-course chemotherapy was introduced. Emphasis was placed on smear-positive cases. Prevalence of smear-positive tuberculosis in Beijing decreased from 127 per 100,000 in 1979 to 16 per 100,000 in 1990, a decrease of 17% annually. "Case finding itself is of no value and even harmful, in our experience, if a good treatment programme is not ensured for all new smear-positive cases discovered."


Default rates of patients on short-course therapy with DOT were <10% compared with 39% for patients not on DOT. DOT cost less than non-DOT: "We believe it is time for entirely intermittent directly observed treatment programs ... to be used for all patients.... By observing that every dose is taken, especially during the initial phase of treatment, when the burden of mycobacteria is highest and the risk of selecting for drug-resistant mutants is greatest, we will have fewer treatment failures and less acquired drug resistance.... A program of directly observed therapy cannot be implemented unless a well-organized infrastructure exists to support it.... Programs of directly observed therapy are not simple or easy to conduct. They require energetic administration, creativity, and flexibility.... We have found that patients from all segments of society, and their physicians, accept directly observed treatment when the issue of public accountability and public health requirements for documentation of treatment are properly explained. Since the costs are equal to or below those of the standard regimens, we believe that every patient with tuberculosis in this country should receive directly observed therapy."


"DOT should be considered for all patients because of the difficulty in
predicting which patients will adhere to a prescribed treatment regimen....If the percentage of patients who complete therapy within 12 months is <90% or unknown, the use of DOT should be expanded."


Community volunteers and health workers provided entirely intermittent short-course directly observed treatment (HRZE)2. 89% of patients completed treatment, and completion rates were the same for patients treated by community volunteers and those treated by health workers. Prior to programme implementation, only 18% of patients completed treatment.


Describes application of DOTS strategy in Nicaragua, including laboratory network with overall concordance of 98.2% between peripheral and central laboratories. The programme was able to achieve a reasonable degree of diagnostic accuracy as well as of patient cure despite being implemented during a war.


After application of universal DOT in one area of Texas in the United States, drug resistance and relapse rates decreased markedly. No resistance developed in patients on appropriate DOT.


Universal application of directly observed therapy since 1970 was associated with a steady decrease in cases, down to 4.7/100,000 in 1991, and a low rate of drug resistance.


Availability of free medication for short-course chemotherapy was associated with cure rates of only 40% and a rapid increase in drug resistance. Application of DOT doubled cure rates and was associated with a rapid decline in tuberculosis (>15% annually) and in drug resistance (75% in three years). Decreases were greatest in populations (such as children) where recent transmission of tuberculosis was previously common. The economic savings from DOT were far greater than the expense of the program. "New York City's experience demonstrates that tuberculosis can be controlled even in populations in which immunosuppression is
common and the prevalence of drug-resistant organisms is high."


In 1990, there were almost 3.8 million cases of tuberculosis reported, of which 49% were from South-East Asia. Notification rates are increasing in many areas of the world. If worldwide control of tuberculosis does not improve, 90 million new cases and 30 million deaths are expected in the decade 1990-1999. Effective tuberculosis control requires: 1) government commitment to an effective control program, 2) case detection through predominantly passive case finding, 3) administration of standardized short-course chemotherapy to at least all sputum smear-positive cases under proper case management conditions (i.e., supervised administration of drugs), 4) establishment and maintenance of a system of regular drug supply, and 5) establishment and maintenance of an effective monitoring system for program management and administration.


"By the early 1960s, those concerned with tuberculosis control in places as diverse as Hong Kong, Madras, and London had concluded that effective treatment requires direct supervision.... We believe that the weight of historical evidence and recent experience make the move to directly observed therapy as a standard of care crucial to the prevention of drug resistance."


The authors implemented a program of DOT using short-course chemotherapy, first to selected patients, then to virtually all patients in the city of Baltimore. Case rates declined much more rapidly than in the pre-DOT treatment period, and case rates declined significantly faster when virtually all patients received DOTS than when selected patients received it. Case rates declined more rapidly in cities without DOTS, even though Baltimore had a high rate of AIDS, and even after controlling for socioeconomic differences. "Since implementing community-based DOT, Baltimore's annual TB case rates dropped the most, both in absolute and relative terms, compared with the other major cities in this study....Directly observed therapy seems imperative among populations and within regions where the disease has become epidemic. Failure to resolve the age-old TB problem of treatment completion will prove costly in both economic and human terms."

Improved programme management, with fully supervised treatment during the intensive phase, was associated with a reduction in the proportion of patients with drug resistant tuberculosis.


200,000 smear-positive patients were diagnosed. New patients were treated with 2(HRZS) / 4(HR) / 2, retreatment cases with 2(HRZSE) / 6(HRE) / 3.

The cure rate for new patients was 90% and was 81% for previously treated patients. Failure rate in previously treated patients fell progressively from 18% to 6%.


Review of all published trials of interventions to improve adherence including educational sessions, counselling, reminders, pamphlets, written instructions. Improvements in adherence were at best short-term, moderate, and inconsistent. “Even the most effective interventions did not lead to substantial improvements in adherence. Most people have difficulty following self-administered medical treatments.”


Review of evidence for short-course treatment up to 1981. Six month regimens are only acceptable if pyrazinamide as well as isoniazid and rifampicin are used in the initial phase. Regimens of 2HRZS/4HR had relapse rates of 0-2%. Regimens of 2HRZE/4HR, 6HRZE, and 6(HRZE) / 3 had relapse rates of 1-2%. “The advantage of full supervision of every dose of medicament in ensuring that a very high level of success is achieved is obvious, as is the element of uncertainty introduced by depending on self-administered regimens, whatever their duration. It is paradoxical to insist on the importance of 100% success with primary chemotherapy and to use self-administered chemotherapy as a means of achieving it.”


Analysis of 12 controlled trials, showing that patients with resistance to isoniazid or streptomycin did well with six-month, 4-5 drug regimens, but that patients with initial resistance to rifampicin did poorly, with 8/11 (73%) having unfavourable outcomes.

Of five regimens studied, the one regimen which did not include pyrazinamide was not acceptable. Four regimens were all acceptable, with relapse rates <5%: 6(HRZSE)$_3$, 6(HRZS)$_3$, 6(HRZE)$_3$, 6HRZE. There was no difference in efficacy between the thrice weekly and the daily regimen.


Evaluated three six-month regimens and found all to be acceptable, with five year relapse rates of 2-3%. The regimens were: 2HRZS/4(HR)$_3$, 1HRZS/5(HR)$_3$, 2HRZ4(HR)$_3$. There were few patients with drug resistance in the series.


Trial of the "Denver Regimen," which is

$$0.5HRZS1.5(HRZS)_2/4.5(HR)_2$$
given to 125 patients with every dose directly observed. Only two patients (1.6%) relapsed.


Review of key trials up to 1987. First advance was East African/BMRC trials showing that 6HRS could achieve cure in >95% of patients. Second were trials, primarily from Hong Kong, showing that intermittent treatment is equivalent to daily treatment. Third were trials exploring role of various agents, showing that 2HRZS/6HT is effective, and that 2HRZ/4HR, either daily or intermittent, is effective. Fourth were trials showing that no regimen of less than six months duration was adequate for smear positive patients.


Three short-course regimens were evaluated: 3HRZS, 3HRZS/2(HSZ)$_3$, 3HZS/2(HSZ)$_2$. None of the regimens had acceptably low relapse rates, although the five month regimen of 3HRZS/2(HSZ)$_2$ had a relapse rate of 6.2%, but required three months of daily attendance, and streptomycin injections throughout.
No regimen of less than six months duration has been shown to be acceptable for smear-positive tuberculosis.


Controlled trial of 427 consecutive patients treated with fully supervised 2(HRZE)2/4(HR)2. Cure rates were 87% and 81% for HIV-uninfected and HIV-infected patients, respectively. The lower cure rate in HIV-infected patients was a result of deaths from non-TB-associated causes. Relapses occurred in 5% of HIV-infected patients and 3% of HIV-uninfected patients. Six of the 13 patients who relapsed had drug susceptibility testing performed; one of these patients had an isolate resistant to isoniazid and ethambutol. "Thrice-weekly, supervised, short-course therapy for tuberculosis was highly effective in patients with and without HIV infection. Intermittent therapy was extremely well tolerated."

**Intermittent Treatment**


*Early demonstration of the effectiveness of intermittent therapy, isoniazid and streptomycin given twice weekly.*


*Review of a series of animal studies on intermittent treatment. These studies showed that intermittent treatment with isoniazid, rifampicin, and ethambutol was associated with increased anti-tuberculosis activity, while intermittent treatment with thiacetzone, ethionamide, and streptomycin was associated with decreased activity.*


*Daily and intermittent treatment was equivalent in efficacy. There were slightly fewer adverse reactions in the patients receiving intermittent treatment. "The main*
The advantage of intermittent chemotherapy over daily chemotherapy is that it is practicable to administer it under full supervision and thereby eliminate concealed irregularity -- a major problem with self-administered daily regimens.


Daily and intermittent treatment regimens were compared. The frequency of severe and of mild adverse reactions was similar in the two groups, except that arthralgia was significantly less common in patients receiving intermittent treatment.


Twice and thrice weekly regimens were as effective as daily regimens. Six month regimens without rifampicin did not produce acceptable results.


Compared four fully intermittent, 6-month, directly observed regimens, and also evaluated use of a combination formulation. The regimens were 4(HRZS)2/2(HRZ)3, 4(HRZS)2/2(HR)3, 2(HRZS)2/2(HRS)2/2(HR)3, and 6(HRZ)3. Showed that in regimens containing rifampicin throughout, pyrazinamide does not have benefit if given beyond two months. Also found no difference in efficacy between combination tablets and separate tablets.

Among injection drug users, rates of tuberculin skin test positivity were similar among HIV-infected and HIV-uninfected patients. The rate of development of active disease was 24 times higher among HIV-infected patients (7.9 vs. 0.3 cases per 100 person-years of observation). The possibility that some of the active disease resulted from recent infection rather than reactivation of remote infection could not be excluded.


HIV-positive patients with positive sputum cultures were more likely than HIV-negative patients to have negative sputum smears (43% vs. 24%). In addition, HIV-positive patients who had positive smears had lower grades of positivity of these smears, had lower colony counts on culture, and their cultures took longer to become positive. The diagnosis of tuberculosis may be missed or delayed in patients with HIV.


191 HIV-infected patients with sputum smear-positive tuberculosis were randomized to receive either 2HTS/10HT or 2HRZ/7HR. Patients receiving thiacetazone were 10 times more likely to have adverse reactions (18.2 vs. 1.6 reactions per 100 person years). Patients who received the rifampicin-containing regimen were more likely to have negative cultures after two months of treatment (74% vs. 37%), and were 60% more likely to survive.


HIV infected patients who received directly observed, intermittent treatment were more likely to complete treatment than were HIV infected patients who received short-course chemotherapy without directly observed treatment (DOT). HIV infected patients who received DOT were also much more likely to survive (85% vs 57%, P=0.01). This improved survival was found in multivariate as well as univariate analysis.

247 consecutive HIV-infected patients with smear-positive pulmonary or clinically confirmed extrapulmonary tuberculosis were compared with 312 HIV-negative TB patients. Mortality during treatment was higher in HIV-infected patients (6% vs. 0.4%), and was even higher (10%) in HIV-infected patients with low (<200/μL) CD4+ lymphocyte counts.


Study of severity of AIDS and mortality among HIV-infected patients with and without TB. “Active tuberculosis was associated with an increased risk for death (odds ratio 2.17), even when controlling for age, intravenous drug use, previous opportunistic infection, baseline CD4+ count, and antiretroviral therapy.” TB may hasten the development of AIDS in HIV-infected persons.

47. Chum HJ, O’Brien RJ, Chonde TM, Graf P, Rieder HL. An epidemiological study of tuberculosis and HIV infection in Tanzania, 1991-


Tanzania has had a programme of directly observed treatment since 1982. Despite a high rate of HIV infection, which was present in one third of patients studied, there was no evidence for an increased rate of relapse among HIV-infected patients, and rates of drug resistance remained low.


HIV-infected patients with pulmonary tuberculosis were less likely to have positive sputum smears for AFB than were patients with TB who did not have HIV infection (54% vs 75%). Multivariate analysis of the factors associated with survival revealed that HIV-infected patients with higher CD4 cell counts, those who received DOT, those with drug-susceptible isolates, and those without a history of injection drug use lived longer.