

Directly observed therapy (DOT) for tuberculosis: why, when, how and if?

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Introductory article

Randomised controlled trial of self-supervised and directly observed treatment for tuberculosis

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Background. Tuberculosis is a major public health problem in South Africa, made worse by poor adherence to and frequent interruption of treatment. Direct observation (DO) of tuberculosis patients taking their drugs is supposed to improve treatment completion and outcome. We compared DO with self-supervision, in which patients on the same drug regimen are not observed taking their pills, to assess the effect of each on the success of tuberculosis treatment. **Methods.** We undertook an unblinded randomised controlled trial in two communities with large tuberculosis caseloads. The trial included 216 adults who started pulmonary tuberculosis treatment for the first time, or who had a second course of treatment (re-treatment patients). No changes to existing treatment delivery were made other than randomisation. Analysis was by intention to treat. Individual patient data from the two communities were combined. **Findings.** Treatment for tuberculosis was more successful among self-supervised patients (60% of patients) than among those on DO (54% of patients, difference between groups 6% (90% CI –5.1 to 17.0)). Re-treatment patients had significantly more successful outcomes if self-supervised (74% of patients) than on DO (42% of patients, difference between groups 32% (11% to 52%)). **Interpretation.** At high rates of treatment interruption, self-supervision achieved equivalent outcomes to clinic DO at lower cost. Self-supervision achieved better outcomes in re-treatment patients. Supportive patient–carer relations, rather than authoritarian surveillance implicit in DO, may improve treatment outcomes and help to control tuberculosis. (Lancet 1998;352:1340–3)

Directly observed therapy (DOT), and preferably short course chemotherapy (DOTS), is one of the five key elements in the WHO global tuberculosis control programme strategy and has been widely publicised as a “breakthrough” and strongly promoted globally by the WHO^{1,2} and others.³ The impetus for increasing DOT has largely been based on observational studies against historical controls, with little or no randomised data of “head to head” DOT versus self-administered therapy. The Introductory Article by Zwarenstein *et al* is the first randomised trial of DOT against self-administered therapy to compare adherence and outcome.⁴ After random assignment of patients to direct observation (DO) or self-treatment with weekly checks of drug collection and use, the outcome measures (with cure or completed treatment regarded as a successful outcome) were compared on an intention to treat basis. Data for the two sites combined showed treatment success, as defined, in 60% of self-supervised and 54% of DO patients. The 6% difference (90% CI –5.1 to 17) was

contained in the prespecified equivalence range of –20% to +20% and indicated zero rate difference. Male sex, unemployment, and “new” patient status showed no difference in treatment success. Women, employed patients, and patients whose income derived from family or social support were more successful with self-supervised treatment but, although the upper limit of the equivalence interval was exceeded, favouring self-supervision, the confidence interval included zero rate difference. Re-treatment patients, however, were significantly more successful with self-supervision than with DO (74% versus 42%; difference 32%, 90% CI 11 to 52), exceeding the 20% upper limit of equivalence and excluding zero difference. However, since only 60% completed treatment in the self-treatment arm and a smaller proportion in the DO arm, a null effect of DOT cannot be concluded. The equivalence of the two methods could, however, be due to a failure of DOT itself to improve outcome or of more widespread resource and structural problems resulting in difficulties

in supporting either type of care, since completion rates were lower than in studies of DOT in other developing countries.^{5,6}

Systematic Cochrane-style reviews of all strategies across five trials—including patient reminders, supervision by health care workers, and cash incentives—had previously shown all to have positive effects on adherence,⁷ so the paper by Zwarenstein *et al* is the first randomised trial of specific antituberculosis compliance promoting strategies not to show a positive benefit of intervention.

Compliance versus outcome

Compliance with drug treatment in tuberculosis was recognised as a problem in the 1950s.⁸ Controlled trials with drug compliance measured by metabolite checks have shown a significantly increasing trend to relapse with poor compliance.⁹ Where the interrelationships between regimen, compliance, and relapse have been examined, compliance was the major determinant of outcome ($p < 0.0001$), but with age also being important. Relapse rates ranged from 1.1% in 731 patients with good compliance, through 5.9% of 118 with moderate compliance, to 50% of 24 with poor compliance.¹⁰ Professor Fox's reviews of the practice of physicians and the compliance of patients^{11,12} drew attention to the two elements involved: poor patient compliance with treatment and the administration of treatment for an excessive length of time.

Studies in England and Wales from 1978/9,¹³ through the 1980s^{14,15} and in 1993¹⁶ have consistently shown that treatment is given for longer than required in either a majority or a significant minority of patients, which may encourage non-compliance in patients.

Range of treatment options

Short course chemotherapy is established as the "gold standard" treatment^{17–20} but there are a number of ways in which it can be given. Least satisfactory is unmonitored treatment where the patient is prescribed treatment without any subsequent form of assessment of compliance by a physician or nurse. Monitored self-medication is where the compliance with the regimen is intermittently, preferably randomly, assessed by urine tests/pill counts; DOT is where all tablets should be seen to be swallowed, and can either be given selectively to those thought likely to be, or proven to be, non-compliant, or given unselectively or "universally". Many programmes of DOT have incentives built in to aid

patient cooperation, and some in the USA have penal powers to deal with non-compliance.²¹

Development of the concept of directly observed therapy (DOT)

With the advent of chemotherapy in the 1950s it became clear that, not only was ambulatory treatment possible but, given the low availability of tuberculosis hospital beds in resource poor countries, it was the only realistic option. Wallace Fox in an analysis of a Medical Research Council study⁸ in Madras highlighted the problems of reaching high rates of treatment compliance in ambulatory patients. This led to the testing of DOT even in such a resource poor environment and demonstrated that "long term daily supervised administration can be organised under special circumstances, even in developing countries"²² and, in turn, led to supervised intermittent treatment.²³ Moves towards supervised treatment were also tried in Hong Kong²⁴ and London.^{25,26}

In the USA selective DOT programmes were introduced in the early 1960s²⁷ but only for the "unreliable or questionably reliable individual". Sbarbaro then expanded the twice weekly supervised programme²⁸ and, by the late 1970s, was advocating universally applied DOT.^{29,30} Intermittent DOT continued to be advised only for difficult patients^{31,32} and was routinely practised only in some centres.²¹ Only after the widespread system failures of New York and its consequences was DOT made the standard of care as a matter of Federal policy.³³ Since some physicians still felt that universal DOT was unnecessary where other approaches had proved effective, a compromise dictated that universal DOT was not required where "a qualitative evaluation of local treatment completion rates exceeded 90%".³³

In the UK selective DOT is advised for those thought likely or proved to be non-compliant.¹⁷ However, whilst accepting that the UK health care system differed from that of the USA, Morse also suggested in an editorial that universal DOT would become needed if rates of adult non-completion were greater than 10% as reported in 1988.¹⁵

Evidence for DOT

Evidence supporting the use of DOT has mainly come from observational/comparative studies, often against historical cohort outcomes, and from cost effectiveness analysis either of decision analysis or modelling types, some of which are summarised in tables 1 and 2, respectively. Many of the observational/comparative

Table 1 Studies on the outcome of directly observed therapy (DOT)

Reference	Type of study	Country	Factors in addition to DOT	Outcome/comments
21	Descriptive/comparative	USA	Sanction of involuntary admission; jail for default	>90% completion rate; sputum conversion twice self-administered
34	Observational	USA	—	Some support for DOT but less effective in foreign born residents
35	Observational	South Africa	Occupational setting (economic incentive of keeping job)	85% completed; of these, cure 96%, relapse 5.7%
36	Descriptive	Bangladesh	Community health workers; free drugs; written contract; patient pays incentive bonus	8 month regimen; 81–86% cure
37	Retrospective DOT vs self-administered	USA	—	8 month completion 52% vs 35% 12 month completion 70% vs 53%
38	Retrospective	China	—	New cases: relapse 3.3%, death 3.3%
39	Retrospective	USA	Multidisciplinary team	Re-treatment: relapse 5.6%, death 8.5%
40	Retrospective	USA	Patient transport provided	85% compliance, 66% completion
41	Descriptive	USA	Service and educational incentives	Primary drug resistance fell from 13% to 6.7%; relapse from 21% to 5.5%
				98% overall treatment completion index

Table 2 Cost effectiveness studies on directly observed therapy (DOT)

Reference	Study method	Outcome/conclusion
42	Modelled on published rates of therapy, relapse and acquired MDR-TB	Direct costs of DOT and self-administered equal DOT more expensive when patients' time costs included DOT less expensive outpatient costs
43	Decision analysis comparing 6 month DOT, self-administered fixed drug therapy and conventional therapy	DOT and fixed drug combinations more cost effective than conventional self-administered therapy Marginal cost benefit of DOT over fixed drug therapy
44	Modelling	DOT better than conventional but this was mainly due to removal of inpatient costs (conventional included initial 2 months inpatient treatment)
45	Economic modelling	Twice weekly DOT after 2 weeks initial inpatient treatment most cost effective strategy (largely due to inpatient costs)
46	Economic analysis	DOT 88% of cost of self-administered short course chemotherapy

studies have had additional programme elements which may have given the programme—including DOT—advantages over the previous programme with which it was being compared. These additional programme elements can be important and contribute to the success of the programme independently from the DOT element. A South African study⁴⁷ comparing the effectiveness of different types of DOT supervisor showed that treatment completion rates were better with community health workers (88%) or a voluntary lay person (85%) than with a clinic based health worker (79%), and also that the fall in case holding rates between 1991 and 1995 was less with community health workers (95% to 90%) and voluntary lay persons (88% to 84%) than with clinic based health workers (84% to 71%). A separate study, also in South Africa, showed that the introduction of dosage cards for DOT compliance increased the compliance from 62% to 88–93% after intervention.⁴⁸

Studies on the economic aspects of DOT are not without methodological criticism, often using historical or derived data on which the costs are modelled. A review of published cost effectiveness studies of tuberculosis treatment programmes⁴⁹ concluded that “those with fully ambulatory short course chemotherapy are currently the most cost effective option, although this depends on the costs of providing an effective community based service. Whilst DOT may be more effective than self-administration because of the reduced need for follow up and monitoring, more studies are needed, however, that include real outcome figures and household measures of cost. Effects should be measured in terms of actual outcome and not taken from the literature. Most of the studies reviewed did not consider the difficulties of introducing a theoretically cost effective change into a health service. Further work could consider measuring cost in terms of resources—for example, staff rather than only finances—and more work is needed on household perspectives”.

Dissenting voices: disentangling the DOT element from other programme aspects

Dissenters or sceptics who have labelled DOT as “supervised swallowing”⁵⁰ say that the success of DOT

programmes is derived from the substantial technical and financial investment in tuberculosis programmes that DOT represents, not the DOT element itself.⁵¹ They also say that the definition of DOT—or what is meant by it—varies and quote, for example, the Director General of the WHO² who defines DOTS as therapy where “tuberculosis patients must be observed swallowing each dose of their anti-tuberculosis medicine by a health worker or trained volunteer”, whereas others in the WHO Global Tuberculosis Control Programme state that it “includes drugs, reserve drug supply, sputum testing facilities with quality control, patient tracking systems and political commitment”. In a recent DOT study in Bangladesh³⁶ the DOT package included population screening, mobilisation of community health workers, comprehensive health education, free drugs, a national microscopy service, a written contract, and payment by the patient of an “incentive bonus” of five days wages. In Baltimore, USA, DOT also includes involuntary hospital admission and jail for patients who default from treatment.²¹ Further comment was also made by the sceptics that a major reason for the success of the Bangladesh study³⁶ was implementation by “an effective non-governmental organisation capable of securing technical and financial support from several donor agencies”.⁵²

Even in the USA there are dissenting analyses of the effectiveness of DOT.⁵³ This study estimated the DOT and treatment completion rates for the years 1990–4 for all tuberculosis treatment programmes in 25 cities or counties with 100 cases in any year between 1990 and 1993 anywhere in the USA. Three cohorts were formed: high treatment completion (>90%), intermediate completion (70–89%), and low completion (<70%). In 1990 the median 12 month treatment completion rate was 80% for the entire study population, with a median estimated DOT rate of 16.8%. By 1994 those rates had increased to 87% and 49%, respectively, with increases seen in all three completion rate cohorts. The authors conceded that DOT had had a marked impact in jurisdictions with historically low completion rates. They commented, however, that treatment completion rates of over 90% could be obtained with DOT proportions far lower than those proposed by advocates of universal DOT, even though they admitted entering the study with the prejudice that more DOT was automatically better.

Conclusions

The Introductory Article⁴ does not show any positive benefit from the DOT intervention in the first direct comparison directly against self-administered treatment. This does not mean that DOT is not effective as the problem could have been a weak programme. More work needs to be done to define what are the most effective programme elements to support DOT, which are most cost effective and useful in resource poor countries, with household or patient costs being weighted more heavily. The USA analysis⁵³ shows that, in areas with historically low completion rates, these are significantly improved; equally, high completion rates (>90%) can be achieved with only modest rates of DOT, and the cost benefits of further increasing the high completion rate in a good programme by a major increase in DOT may show this not to be a cost effective use of resources. The message may be that the investment that DOT requires improves a weak programme by improving not just completion rates but other programme elements, whereas universal or high

LEARNING POINTS

- * A randomised trial of directly observed versus self-supervised treatment showed self-supervised treatment performed superiorly, particularly in re-treatment patients.
- * Treatment completion rates were low with both interventions in this study.
- * Studies of intervention strategies to promote adherence to treatment had previously all shown positive effects.
- * Studies of the effectiveness of directly observed therapy (DOT) have been by observation/comparison or of cost effectiveness against historical controls and have not focused particularly on patient cost elements.
- * Sceptics of the universal DOT approach attribute its success to the additional programme resources/incentives or potential sanctions rather than to the DOT element itself.

rates of DOT may add little to a well organised and staffed programme achieving high completion rates already.

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