

# Directly observed therapy for treating tuberculosis (Review)

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## This record should be cited as:

Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003343. DOI: 10.1002/14651858.CD003343.pub3.

**This version first published online:** 17 October 2007 in Issue 4, 2007.

**Date of most recent substantive amendment:** 13 August 2007

## ABSTRACT

### Background

For tuberculosis treatment, policies have been introduced to encourage adherence to treatment regimens. One such policy is directly observed therapy (DOT), which involves people directly observing patients taking their antituberculous drugs.

### Objectives

To compare DOT with self administration of treatment or different DOT options for people requiring treatment for clinically active tuberculosis or prevention of active disease.

### Search strategy

In May 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 2), MEDLINE, EMBASE, LILACS, and *mRCT*. We also checked article reference lists and contacted relevant researchers and organizations.

### Selection criteria

Randomized and quasi-randomized controlled trials comparing a health worker, family member, or community volunteer routinely observing people taking antituberculous drugs compared with routine self administration of treatment at home. We include people requiring treatment for clinically active tuberculosis or medication for preventing active disease.

### Data collection and analysis

Both authors independently assessed trial methodological quality and extracted data. Data were analysed using relative risks (RR) with 95% confidence intervals (CI) and the fixed-effect model when there was no statistically significant heterogeneity (chi square  $P > 0.1$ ). Trials of drug users were analysed separately.

### Main results

Eleven trials with 5609 participants met the inclusion criteria. No statistically significant difference was detected between DOT and self administration in terms of cure (RR 1.02, 95% CI 0.86 to 1.21, random-effects model; 1603 participants, 4 trials), with similar results for cure plus completion of treatment. When stratified by location, DOT provided at home compared with DOT provided at clinic suggests a possible small advantage with home-based DOT for cure (RR 1.10, 95% CI 1.02 to 1.18; 1365 participants, 3 trials). There was no significant difference detected in clinical outcomes between DOT at a clinic versus by a family member or community health worker (2 trials), or for DOT provided by a family member versus a community health worker (1326 participants, 1 trial). Two small trials of tuberculosis prophylaxis in intravenous drugs users found no statistically significant difference between DOT and self administration (199 participants, 1 trial) or a choice of location for DOT for completion of treatment (108 participants, 1 trial).

### Authors' conclusions

The results of randomized controlled trials conducted in low-, middle-, and high-income countries provide no assurance that DOT compared with self administration of treatment has any quantitatively important effect on cure or treatment completion in people receiving treatment for tuberculosis.

## PLAIN LANGUAGE SUMMARY

### **Directly observing people taking their tuberculosis drugs did not improve the cure rate compared with people without direct monitoring of treatment**

Tuberculosis is a very serious health problem with two million people dying each year, mostly in low-income countries. Effective drugs for tuberculosis have been available since the 1940s, but the problem still abounds. People with tuberculosis need to take the drugs for at least six months, but many do not complete their course of treatment. For this reason, services for people with tuberculosis often use different approaches to encourage people to complete their course of treatment. This review found no evidence that direct observation by health workers, family members, or community members of people taking their medication showed better cure rates than people having self-administered treatment. The intervention is expensive to implement, and there appears to be no sound reason to advocate its routine use until we better understand the situations in which it may be beneficial.

## BACKGROUND

### **Adherence in tuberculosis management**

Effective drugs for tuberculosis have been available since the 1940s, but two million people continue to die each year, mostly in low-income countries (Dye 1999; Netto 1999). People with tuberculosis require treatment for at least six to eight months. Many find it difficult to complete their course of treatment and this serves as a major constraint to eradicating the disease (Fox 1958; Addington 1979; Cuneo 1989). Poor adherence to treatment can lead to prolonged infectiousness, drug resistance, relapse of tuberculosis, or even death. Incomplete treatment thus poses a serious risk for the individual as well as the community.

There are three groups of people for whom adherence is important: people under evaluation for suspected tuberculosis (to ensure they complete the diagnostic regimen or start treatment); people receiving prophylaxis (preventive therapy), where antituberculous drugs are given to people exposed to tuberculosis or thought to be at particular risk; and people with diagnosed tuberculosis in whom completion of treatment helps ensure cure.

Adherence to a tuberculosis treatment programme requires accessible and appropriate health care. People need to be diagnosed correctly, provided with information about their disease and the need for completion of treatment, and supplied with appropriate outpatient drugs. But even where these services are available, people may not adhere to the intended regimen. Healthcare providers have responded by developing a variety of specific measures to improve adherence (Cuneo 1989; CDC 1993; Sbarbaro 1994). These interventions are aimed at influencing the behaviour of healthcare personnel, the organization of the service, or the behaviour of the person with suspected or confirmed tuberculosis. Originally we included all these interventions in one Cochrane Review, but this approach did not allow us to consider the particulars of each of the following interventions, and why in one set of circumstances it may be effective and another it may not. This Cochrane Review is one of several planned or in progress to evaluate each type of intervention:

- Directly observed therapy (DOT): an appointed agent (health worker, community volunteer, family member) directly monitors people swallowing their antituberculous drugs (this review).
- Staff motivation and supervision: training and management processes that aim to improve how providers care for people with tuberculosis.
- Reminder systems and late patient tracers in the diagnosis and management of tuberculosis: routinely reminding patients to keep an appointment and actions taken when patients fail to keep an appointment (Liu 2007).
- Education and counselling for promoting adherence to the treatment of active tuberculosis: provision of information or one-to-one or group counselling about tuberculosis and the need to attend for treatment (M'Imunya 2007).
- Incentives and reimbursements: money or cash in kind to reimburse expenses of attending services, or to improve the attractiveness of visiting the service.
- Contracts: written or verbal agreements to return for an appointment or course of treatment (Bosch-Capblanch 2007).
- Peer assistance: people from the same social group helping someone with tuberculosis return to the health service by prompting or accompanying them.

### **DOT**

DOT seeks to improve the adherence of people to tuberculosis treatment through health workers, family members, or community members directly observing them taking their antituberculous drugs. This approach was first adopted in studies in Madras, India, and Hong Kong as early as the 1960s (Bayer 1995), and a number of specialists now widely recommend DOT for the control of tuberculosis (Bass 1994; Maher 1997; Chaulk 1998; Enarson 2000). Indeed, Frieden and Sbarbaro state that it is essential and that it prevents relapse occurring and drug resistance developing (Frieden 2007).

The advantages of DOT are that people can be closely monitored and that there is a social process with peer pressure that may im-

prove adherence. On the other hand, the disadvantages associated with DOT are that it moves away from adherence models of communication with cooperation between patient and provider back to a traditional medical approach with the patient as the passive recipient of advice and treatment (Donovan 1992; Sumartojo 1993); resource implications for such a policy are substantial, particularly in low-income and middle-income countries where the case load is high; and it may make adherence worse if it is rigidly applied in an authoritarian setting or where people are expected to travel considerable distances to have their treatment supervised

### **Programmes that include DOT**

Over the years DOT has come to mean much more than the supervised swallowing of drugs, causing considerable confusion. In the USA, DOT programmes are complex and consist of several components including social support, housing, food tokens, and jail for recalcitrant people (ATS 1992; Volmink 2000b).

The World Health Organization (WHO) promotes another version of DOT called 'directly observed therapy, short course' (DOTS). This is a comprehensive tuberculosis management programme that focuses on low-income countries. DOTS is a five-element strategy for the control of tuberculosis that consists of political commitment, improved laboratory analysis, direct patient observation while swallowing each dose of medication, a drug supply that provides for the correct complete short course antituberculous drug combination for free, and a reporting system that documents the progress in curing the patient (WHO 1997).

The WHO believes that direct observation is a key element for the success of DOTS and has retained it in more recent definitions of the DOTS strategy, although their documentation has clearly taken into account criticisms of their blanket policy. For example, the WHO states that the third component of their expanded strategic framework is "standardized short-course chemotherapy to all cases of TB [tuberculosis] under proper case-management conditions including direct observation of treatment" (WHO 2002). The 2004 progress report mentions direct observation for "at least" the first two months of treatment (WHO 2004). Even so, how this is interpreted in countries varies, and direct observation by a health worker remains national policy in China, for example.

In contrast, we have previously suggested that the benefits associated with DOT programmes found in observational studies may be attributable to simultaneous inputs rather than direct observation specifically (Volmink 1997a). An informed debate is important because direct observation has considerable resource implications; it therefore important to determine how important this intervention is for improving adherence to tuberculosis treatment and ensuring cure. Since our initial Cochrane Review (Volmink 1997b), which documented the absence of randomized controlled trials of DOT, several trials have been conducted aimed at disaggregating the effects of this specific intervention from those of accompanying inputs, and they are included in this review update.

Not only is there a debate about whether DOT is effective, there is also a debate about who should provide this. This may be contingent practically on an individual's circumstances, but the specialists are divided in their recommendations: some consider family members can help, whereas others regard family observation as a "seductive but risky concept" (Frieden 2007). We therefore also summarize trials comparing DOT through different providers and settings.

## **OBJECTIVES**

To compare DOT with self administration of treatment or different DOT options for people requiring treatment for clinically active tuberculosis or prevention of active disease.

## **CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

### **Types of studies**

Randomized and quasi-randomized controlled trials.

### **Types of participants**

People requiring treatment for clinically active tuberculosis *or* medication for preventing active disease (prophylaxis or preventive therapy).

### **Types of intervention**

#### **Intervention**

Health worker, family member, or community volunteer routinely observes participants taking their antituberculous drugs.

#### **Control**

Routine self administration of treatment at home, with intermittent clinic visits for drugs with or without treatment adherence checks.

Where researchers explored different methods of implementing direct observation, the experimental method was allocated to the intervention group and the standard method to the control.

### **Types of outcome measures**

#### **Primary**

- Cure.
- Completion of treatment.
- Development of clinical tuberculosis (in trials of drug prophylaxis).

#### **Secondary**

Keeping outpatient appointments.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Infectious Diseases Group methods used in reviews.

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

### Databases

We searched the following databases using the search terms and strategy described in Table 01: Cochrane Infectious Diseases Group Specialized Register (May 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 2); MEDLINE (1966 to May 2007); EMBASE (1974 to May 2007); and LILACS (1982 to May 2007). We also searched the *metaRegister* of Controlled Trials (*mRCT*) using 'tuberculosis AND DOT\*' (May 2007).

### Researchers and organizations

For unpublished and ongoing trials, we contacted individual researchers working in the field and the following organizations: World Health Organization (1997 and 2004), the International Union Against Tuberculosis and Lung Disease (IUATLD) (1997), and the Centers for Disease Control and Prevention (1997).

### Reference lists

We also checked the reference lists of all studies identified by the above methods.

## METHODS OF THE REVIEW

### Trial selection

Both authors independently applied the inclusion criteria to all identified trials. We used the titles and abstracts of the identified citations to exclude trials that clearly did not meet the inclusion criteria. If either author judged that the trial might be eligible for inclusion, we obtained the full paper. We independently screened the full articles of selected trials to confirm eligibility and resolved any disagreements by discussion.

### Assessment of methodological quality

We independently evaluated the methodological quality of each trial, classifying the generation of allocation sequence and concealment of allocation as adequate, inadequate, or unclear according to Juni 2001. We classified blinding as adequate if steps were taken to ensure the people recording the main outcome of the study were blind to the assigned interventions and inadequate if this was not the case or if there was no mention of attempts to blind the observers. We assessed completeness of follow up as adequate if 90% or more, inadequate if less than 90%, or unclear if not mentioned.

### Data extraction

We independently extracted the data and checked whether authors had conducted an intention-to-treat analysis. Trialists were contacted to supply missing information and to clarify issues. We resolved discrepancies through discussion.

### Data analysis

We used Review Manager 4.2 to analyse the data, using relative risk (RR) with 95% confidence intervals (CI) to assess estimates of effect. We used the fixed-effect model when there was no statistically significant heterogeneity (chi square  $P > 0.1$ ).

## DESCRIPTION OF STUDIES

Eleven trials with 5609 participants met the inclusion criteria (*see* 'Characteristics of included studies'). Twelve studies that initially seemed to fit the inclusion criteria were eventually excluded from our review; reasons for these decisions are provided in the 'Characteristics of excluded studies'.

Eight of the 11 trials were conducted in low-income and middle-income countries and evaluated DOT for treating people with active tuberculosis: Pakistan (Walley 2001); South Africa (Zwarenstein 1998; Zwarenstein 2000); Tanzania (Lwilla 2003; Wandwalo 2004); Nepal (Newell 2006); Thailand (Kamolratanakul 1999); and Swaziland (Wright 2004). Three trials were in high-income countries: one in Australia (MacIntyre 2003); and two in the USA that examined prophylaxis in intravenous drug users (Chaisson 2001; Malotte 2001). Two trials were cluster randomized (Lwilla 2003; Newell 2006). One trial used a quasi-random method of allocation (MacIntyre 2003).

### Services for general populations

#### *DOT versus self administration of treatment*

Five trials compared DOT with self administration of treatment. There is some overlap of data in two of these trial reports, but we have taken this into account in the analyses: Zwarenstein 1998 combined data from two communities in which trials compared direct observation by nurses at clinics with self administration of treatment, while Zwarenstein 2000 described data from one of these trials that had three arms of direct observation by nurses, lay health workers, and self administration. Kamolratanakul 1999 allowed participants to choose between DOT by a health worker, community leader, or family member; most chose the latter. Walley 2001 compared DOT by a health worker or community health worker with DOT by a family member and with self administration of treatment. MacIntyre 2003 evaluated DOT by a family member.

#### *Alternative DOT delivery options*

A cluster-randomized trial from Tanzania (Lwilla 2003) compared a community health worker observing people at home with DOT at a health facility. Three trials compared DOT by a family member

with either DOT by a health worker at a health facility (Wandwalo 2004) or DOT by a community health worker (Wright 2004; Newell 2006).

### Services for intravenous drug users

Two trials from the USA evaluated DOT in drug users on prophylaxis for latent tuberculosis (Chaisson 2001; Malotte 2001). Malotte 2001 studied intravenous and crack cocaine users, and compared DOT by an outreach worker at a site chosen by the participant (with or without a US\$5 at each visit) with DOT at a community clinic with a US\$5 at each visit. Chaisson 2001 involved intravenous drug users, and studied DOT by an outreach nurse with self administration either with monthly peer support or monthly clinic visits.

### Outcomes

The numbers of people cured, cured and completed treatment, or completed treatment were the main outcomes assessed in the included trials.

### Adjustment for clustering

Both cluster trials adjusted for clustering appropriately: standard error of the coefficients for clustering on units corrected using the Huber-White-Sandwich method (Lwilla 2003); and, in Newell 2006, using the coefficient of variation between clusters.

## METHODOLOGICAL QUALITY

See Table 02 for a summary of the assessment.

### Generation of allocation sequence

Seven trials used adequate methods – computer-generated random sequences (Zwarenstein 1998; Zwarenstein 2000; Walley 2001; Chaisson 2001), a random-number table (Kamolratanakul 1999), coin tossing (Wandwalo 2004), and random draws of paper from a basket (Newell 2006). One trial used alternate allocation, an inadequate method (MacIntyre 2003). The remaining trial reports did not provide information (Malotte 2001; Lwilla 2003; Wright 2004).

### Allocation concealment

Four trials employed adequate methods for concealing allocation (Zwarenstein 1998; Zwarenstein 2000; Walley 2001; Malotte 2001). Allocation concealment was unclear in three trials (Chaisson 2001; Lwilla 2003; Wright 2004) and not used in the remaining trials (MacIntyre 2003; Kamolratanakul 1999; Wandwalo 2004; Newell 2006).

### Blinding

Outcome assessment was blind in only four trials (Walley 2001; MacIntyre 2003; Wright 2004; Newell 2006).

### Completeness of follow up

In two trials, more than 10% of participants were excluded from the analysis (Chaisson 2001; Lwilla 2003). A further four trials

did not provide sufficient information to assess this aspect of study quality (Zwarenstein 2000; Malotte 2001; Walley 2001; MacIntyre 2003). In the rest of the trials follow up was adequate.

## RESULTS

### (1) Services for general public

#### *DOT versus self administration of treatment*

Treatment outcomes were similar among participants in the DOT and self administration of treatment arms. There was no statistically significant difference between the interventions for the number of people cured (1603 participants, 4 trials, Analysis 01.01), cured or completed treatment (1603 participants, 4 trials, Analysis 01.02), or completed treatment (173 participants, 1 trial, Analysis 01.03). There was significant heterogeneity between the trials for cure (chi squared 8.41; df = 3), but the point estimate of the RR was close to one, and no difference was demonstrated with either fixed-effect or random-effects models (Analysis 01.01).

We explored whether different effect sizes were associated with home-based and clinic-based DOT. Effect size was similar in the two groups (Analyses 02.01 and .02). Home-based DOT was strongly influenced by the trial from Thailand (Kamolratanakul 1999), and there was a statistically significant improvement in cure, but the difference was small (RR 1.10, 95% CI 1.02 to 1.18; 1365 participants, 3 trials, Analysis 02.01).

#### *DOT: family member or community health worker versus at clinic*

Wandwalo 2004 found cure or treatment completion to be similar for those observed by a family member compared with a health worker (587 participants, 1 trial, Analysis 03.01). A cluster-randomized trial, Lwilla 2003, which evaluated DOT by a community health worker, found no difference for sputum conversion at two months (OR 0.62, 95% CI 0.23 to 1.71) or cure at the end of treatment (OR 1.58, 95% CI 0.32 to 7.88; trial authors adjusted for design effects).

#### *DOT: family member versus by a community health worker*

Wright 2004 found no statistically significant difference in the number of people cured or who completed treatment (1326 participants, Analysis 04.01). A cluster-randomized trial, Newell 2006, which compared community-based DOT by a community health worker or village health worker with family-based DOT, found no statistically significant difference in success rates (cure and treatment completion) (85% vs 89%; OR 0.67, 95% CI 0.41 to 1.10; trial authors adjusted for design effects).

### (2) Services for intravenous drug users

Chaisson 2001 found no statistically difference in the number of people who completed twice-weekly clinic-based DOT and those on daily self administration of treatment (199 participants, Analysis 05.01). For participants receiving prophylaxis, Malotte 2001

studied people receiving prophylaxis and found no statistically significant difference in the number who completed treatment between those allowed to choose their DOT location and those receiving DOT at a community clinic (108 participants, Analysis 06.01).

## DISCUSSION

Direct observation of people taking their antituberculous drugs is widely advocated and forms part of the World Health Organization's 'directly observed therapy, short course' (DOTS) strategy. While this strategy includes a number of useful components, the available evidence does not provide strong support for the routine adoption of direct observation in favour of self administration of treatment either for people with active tuberculosis or those with latent tuberculosis requiring prophylaxis. There is also no evidence that one form of direct observation is better than another: direct, randomized comparisons between clinic-based DOT and community-based DOT did not demonstrate a difference; and, within community-based DOT, comparisons between DOT provided by a family member versus a community health worker had similar outcomes.

Given the prevailing support for DOT-based programmes, these findings are important. We have previously suggested that the benefits associated with DOT programmes in observational studies may be attributable to simultaneous interventions rather than direct observation being the key adherence-promoting strategy (Volmink 2000b). A qualitative study notes that the implementation of DOT is in the process of shifting from being a rigid model involving observation of drug swallowing to one that includes an array of incentives and enablers for supporting the patient (Macq 2003). Within such a package of patient-centred interventions it remains to be established whether direct observation is necessary at all. Of interest in this regard are the findings of a cluster-randomized trial in a rural South Africa in which motivation and support from a lay health worker (with or without DOT) was shown to be more effective in ensuring treatment than a conventional DOT-based service (Clarke 2005). People with tuberculosis are often poor and encounter numerous barriers to treatment adherence. Strategies aimed at reducing social and health system barriers may therefore be preferable to coercive approaches that impact negatively on patient autonomy. The encouraging results of a recent trial in Senegal using a multifaceted approach to address these challenges, which also included a flexible approach to DOT, lend support to this notion (Thiam 2007). Further rigorous trials, in particular those testing interventions social and family barriers to adherence, are needed (Garner 2007).

One of the trials included in our review found a modest improvement with DOT for cure and treatment completion (Kamolratanakul 1999), and one may speculate about the reasons for

these findings. The Thai health system is relatively well resourced and has a tuberculosis control programme that is well organized. This is in contrast to the trials in South Africa (Zwarenstein 1998; Zwarenstein 2000) and Pakistan (Walley 2001) where the trials were conducted in areas with high disease burden, overcrowded tuberculosis clinics, and poorly motivated staff. On the other hand, DOT did not improve treatment completion rates in either Australia (MacIntyre 2003) or the USA (Chaisson 2001; Malotte 2001), both of which are low burden, highly resourced settings. A second reason one might posit is that cultural responses to supervision may vary with Thai people being more responsive to this approach. Finally, Kamolratanakul 1999 is so far the only trial to have allowed participants to choose their supervisor, and this patient-centred approach may also have influenced the effects.

Can adopting a DOT policy make adherence worse? The authors of the South African trial suggest an increasingly negative and demoralizing effect of direct observation on participants with tuberculosis (Zwarenstein 1998). This trial found that in participants with a first episode of tuberculosis, the outcomes were equivalent in DOT and self administration of treatment arms, while 'retreatment' participants who were assigned to DOT fared worse than those who self administered treatment. Given the small numbers of participants in the retreatment group, further research is warranted to confirm the findings.

Bias could have influenced the results in some of the trials. As outlined in the methodological quality assessment, the number of trials with adequate quality criteria was limited: four with adequate method for concealing treatment allocation; four with blinding of the outcome assessors; and two trials that excluded more than 10% of participants from the analysis. Nevertheless, these trials are not easy to implement and are a credit to the researchers who have worked hard to develop the evidence base for rational decision making.

## AUTHORS' CONCLUSIONS

### Implications for practice

Randomized controlled trials provide no assurance that the routine use of DOT in low- and middle-income countries improves cure or treatment completion in people with tuberculosis. There is also no rigorous evidence to support the use of DOT for prophylaxis in people with latent tuberculosis.

There appears to be no sound reason to advocate the allocation of resources to the routine use of DOT until we better understand the situations in which it may be beneficial. In the meantime, it could reasonably be argued that resources should be invested in interventions that have been shown to be effective for improving adherence, such as providing patient motivation and support, incentives, and defaulter action.



## Implications for research

The relation between DOT and treatment outcome is complex. Factors that determine its usefulness in various settings require further study. The extent to which the quality of interaction between patients and their observers influences outcome would be a particularly fruitful topic for future research. It will also be worth testing whether DOT efficacy differs in people receiving tuberculosis treatment for the first time compared with those requiring retreatment, and in men compared with women. Comparisons of DOT in relation to other strategies aimed at improving adherence should be determined.

## POTENTIAL CONFLICT OF INTEREST

None known.

## ACKNOWLEDGEMENTS

To the Global Health Council and the Department of Arts, Culture, Science and Technology of South Africa for supporting Jimmy Volmink in the preparation of the review in the period before the 2006 update. This document is an output from a project funded by the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

## SOURCES OF SUPPORT

### External sources of support

- Department for International Development UK

### Internal sources of support

- South African Medical Research Council SOUTH AFRICA
- Liverpool School of Tropical Medicine UK

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\* Indicates the major publication for the study

**TABLES****Characteristics of included studies**

<b>Study</b>	<b>Chaisson 2001</b>
Methods	Generation of allocation sequence: randomized, with factorial overlay; computer-generated random numbers Allocation concealment: not stated Blinding: none Completeness of follow up: 88%
Participants	Number: 300 randomized; 73% men; 85% unemployed; 27% with documented HIV infection Included: adult, intravenous drug users with positive tuberculin skin test (at least 10 mm induration or 5 mm if HIV positive); given isoniazid preventive therapy for 6 months Excluded: people with active tuberculosis
Interventions	(1) DOT twice weekly by outreach nurse at clinic or community location

### Characteristics of included studies (Continued)

	(2) Daily self administration of treatment, monthly peer counselling group meetings with lunch, and clinical assessments by a nurse; peer counsellor was a former injection user who had completed preventive therapy, and who was trained in counselling and supervised by a health educator (3) Daily self administration of treatment with monthly clinic assessment; factorial design with immediate or deferred US\$10 stipend at the end of each month; deferred payments credited each month and given when treatment completed or participant withdrew
Outcomes	(1) 6 months treatment completed, defined as 80% or more of treatments taken (observed for DOT group and 6 monthly visits plus reporting that at least 80% medication taken during a month for other groups) (2) Pill counts (3) Isoniazid metabolites in the urine (4) Electronically monitored bottle opening in a subset
Notes	Location: Baltimore City Health Department TB Clinic, USA Date: 1995-7 Duration of DOT duration not stated
Allocation concealment	B – Unclear

### Study **Kamolratanakul 1999**

Methods	Generation of allocation sequence: central block random allocation scheme prepared for each of 15 study sites; random-number table used Allocation concealment: none Blinding: no blinding of assessors Completeness of follow up: 100% (no losses)
Participants	Number: 837 randomized; 73% male Included: new smear positive adults (aged 15+)
Interventions	(1) Daily supervision: participants chose their supervisor from (a) health centre staff, (b) community members, or (c) family members; for (b) and (c) health workers visited homes twice monthly (first 2 months) or monthly for checking of treatment cards, pill counts, and urine tests (2) Self administration of treatment: 1 month drug supply given at diagnosis and after each follow-up visit; no treatment supervision between visits  All participants received the same drug regimen: isoniazid-rifampicin-pyrazinamide-ethambutol for 2 months and isoniazid-rifampicin for 4 months
Outcomes	(1) Cure rate (primary outcome): completed 6 months antituberculous therapy, with 2 negative sputum exams, 1 at end of treatment (2) Treatment completion: completed 6 months antituberculous therapy but less than 2 sputum exams (3) Sputum conversion rate: negative sputum at end of third month (4) Percentage defaults (5) Percentage transfers (6) Caseholding rate
Notes	Location: Thailand Date: 1996-7 Duration of DOT not stated Informed consent not obtained as participants were not told that they were participating in a study Choice of supervisor for DOT participants: 352 chose a family member; 34 chose a community member; and 24 chose health centre staff One participant in daily supervision arm excluded due to protocol violation so not strictly intention-to-treat
Allocation concealment	C – Inadequate

**Characteristics of included studies (Continued)**

<b>Study</b>	<b>Lwilla 2003</b>
Methods	Cluster-randomized controlled trial: 9 pairs of centres matched by type and size Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: none Completeness of follow up: 87% at 2 months and 69% at 7 months
Participants	Number: 18 clusters randomized; 522 participants; mean age 35; 60% male Included: new smear positive adults
Interventions	(1) Community-based DOT: daily observation by community health volunteer (site not stated) for intensive 2-month treatment period; health worker visited volunteer every 2 weeks and district co-ordinator visited volunteer monthly; at each visit participants' treatment card checked and drugs counted (2) Institution-based DOT: required to attend health facility daily for 2 months, and then monthly after this  Continuation phase of 6 months: both groups managed the same and expected to self administer treatment daily
Outcomes	(1) Sputum negative at 2 months (primary outcome) (2) Cure at 7 months (sputum negative at 2 months and at 5 to 7 months)
Notes	Location: Tanzania Date: 1999-2000 Duration of DOT not stated
Allocation concealment	B – Unclear

<b>Study</b>	<b>MacIntyre 2003</b>
Methods	Quasi-randomized controlled trial Generation of allocation sequence: alternate allocation Concealment of allocation: none Blinding: assessment of urinary isoniazid blinded Completeness of follow up: not stated
Participants	Number: 173 recruited, mostly foreign nationals; male 51%; mean age 41 (range 14 to 83) Included: new tuberculosis participants Excluded: multiple-drug resistant tuberculosis; relapsed tuberculosis; HIV-positive cases; and nontuberculous mycobacterial infections
Interventions	(1) Family-based DOT: daily observation by a nominated family member who received education and was expected to record participant compliance with pill taking; weekly phone calls from a nurse; nurse on call; nurse home visit every 2 weeks (2) Self administration of treatment: daily  Both groups had monthly visits to health facilities and standardized recording charts
Outcomes	Treatment completion measured by: (1) Percentage clinic attendances to collect drugs (2) Urinary isoniazid (6 random checks over months; all had to be > 0)
Notes	Location: Australia Date: 1998 to December 2000 Duration of DOT not stated
Allocation concealment	C – Inadequate

<b>Study</b>	<b>Malotte 2001</b>
Methods	Generation of allocation sequence: randomized, blocks of 18 Allocation concealment: sequentially numbered, opaque, sealed envelopes

**Characteristics of included studies (Continued)**

	Blinding: none Completeness of follow up: not stated
Participants	Number: 163 randomized; 82% male Included: active or recent injection or crack cocaine users screened for tuberculosis with positive tuberculin skin test (at least 10 mm induration or 5 mm if HIV positive) Excluded: people with active tuberculosis
Interventions	(1) DOT by outreach worker (location decided by participant) plus US\$5 at each visit (2) As (1) but no money (3) DOT at study community site plus US\$5  All participants received isoniazid 2 times a week for 6 months or 1 year (depending on HIV status)
Outcomes	(1) Percentage medication taken on time; excludes medication taken late (next day) (2) Completion of medication
Notes	Location: Long Beach, California, USA Date: 1994-7 Lost to follow up included prison or moved and were included in outcome (1) but excluded completely from outcome (2)
Allocation concealment	A – Adequate

**Study Newell 2006**

Methods	Cluster-randomized controlled trial Generation of allocation sequence: 5 randomly selected districts allocated to each arm; the name of each district was written on an individual paper and randomly drawn from a basket Allocation concealment: method not stated Blinding: laboratory technicians assessing the primary outcomes were blinded Completeness of follow up: 100% (no clusters or individuals lost)
Participants	Number: 10 districts with 907 people randomized; all smear positive; 67% male Included: people with tuberculosis (aged 15+); new smear-positive cases, diagnosed at health facilities in the study area; HIV-status not known
Interventions	(1) Community-based DOT: daily treatment supervised by a female community health worker (unpaid volunteer selected by the district health authority) or village health worker (community worker paid by government). Patients mainly visited at home, but occasionally patients met their supervisor at her home. Supervision was for the duration of treatment with drugs provided to the supervisor monthly. Tracing by the supervisor was undertaken for patients who discontinued treatment (2) Family-based DOT: daily supervision by a household member chosen by the participant with drugs provided to the supervisory weekly. Government workers traced those who discontinued treatment
Outcomes	(1) Treatment success: cure plus treatment completion [primary] (2) Treatment success compared with the World Health Organization target of 85% (3) Estimated case detection rate with the World Health Organization target of 70% (4) Compare the above rates in men and women
Notes	Location: hill and mountain districts of Nepal Date: 2002-3
Allocation concealment	C – Inadequate

**Study Walley 2001**

Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: opaque, sealed envelopes Blinding: assessors blinded
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## Characteristics of included studies (Continued)

	Completeness of follow up: not stated
Participants	Number: 497 randomized; 51.3% male Included: adults (aged 15+); new smear-positive cases
Interventions	(1) DOT by a health worker at a health facility that met “access criteria” or a community health worker at or near the participant’s home: access criteria were return journey from the participant’s home to facility < 2 km, < 2 h duration, and < 10 rupees, and for unmarried women an accompanying relative was available; participants had to attend a health facility or meet a community health worker 6 times per week for 2 months to take their drugs; thereafter they self administered drugs that the participants collected twice a month (2) DOT by a family member chosen by the participant (3) Self administration of drugs collected by participant fortnightly  All participants received isoniazid-rifampicin-pyrazinamide-ethambutol for 2 months and isoniazid-ethambutol for 6 months
Outcomes	(1) Cure: sputum negative at 7 or 8 months and on at least 1 previous occasion (2) Treatment completion: treatment completed, but smear results not available on at least 2 occasions before completion of treatment (3) Treatment failure (4) Death (5) Default (6) Transferred out
Notes	Location: Pakistan Date: 1996-8
Allocation concealment	A – Adequate

<b>Study</b>	<b>Wandwalo 2004</b>
Methods	Generation of allocation sequence: coin tossing in each of 5 clinics Allocation concealment: none Blinding: none Completeness of follow up: 100% (no losses)
Participants	Number: 587 randomized; 322 smear positive, 182 smear negative, and 83 extrapulmonary tuberculosis; 57% male Included: people with tuberculosis (aged 5+); new smear positive, smear negative, and extrapulmonary cases; HIV-status not known Excluded: previously treated for tuberculosis; severe illness; transferred from another clinic; previously enrolled in the study
Interventions	(1) Community-based DOT: daily treatment supervised at home by ‘guardian’ (usually a family member) during 2-month intensive period; supervisors trained to observe drug taking, encourage participants to complete treatment, keep records, collect drugs, and assess drug side effects; during first 2 months participants received ‘spot’ visits by health workers who conducted treatment card checks and pill counts; during first 2 months participants also requested to attend clinic every 2 weeks for clinical review and progress monitoring (2) Health facility-based DOT: daily supervision at clinic by health workers during the 2 month intensive period  Apart from the observation option participants received the same standardized management including drug therapy
Outcomes	(1) Treatment success: cure plus treatment completion (2) Cure: smear positive initially and negative at 7 or 8 months and on at least 1 previous occasion (3) Treatment completion: positive results initially, negative at 2 months and no results at end of treatment; or smear negative initially and received treatment on clinical grounds; or those who completed full course of treatment but had no initial or end-of-treatment results (4) Death: from all causes



## Characteristics of included studies (Continued)

	(5) Treatment failure: participants who remained or became smear positive or 5 months or later (6) Default: failed to collect medication for > 2 consecutive months (7) Transferred out: transferred to a clinic in another area
Notes	Location: Dar es Salaam, Tanzania Date: 2001-3
Allocation concealment	C – Inadequate
<b>Study</b>	<b>Wright 2004</b>
Methods	Generation of allocation sequence: unclear; stratified into adults and children; then, within each group, randomized by type of tuberculosis (sputum positive, sputum negative, extrapulmonary, relapse) Allocation concealment: unclear; sealed, sequentially numbered envelopes not stated if opaque Blinding: assessors of sputum results blinded Completeness of follow up: 98%
Participants	Number: 1353 randomized; 55% male; most 15+ years Included: adults and children with smear positive or negative, extrapulmonary tuberculosis, or relapse of previously treated tuberculosis Excluded: died before discharge; or too ill to receive outpatient treatment; lived in area without treatment supporter; or referred in after treatment commenced
Interventions	(1) DOT by community health worker: participants visited for observation daily; community health worker trained to provide daily treatment supervision, record adherence on Treatment Support Card, remind participants who did not report for treatment, and notify diagnostic centre about those who defaulted treatment (2) DOT by family member: family member or carer chosen by participant trained to provide daily treatment supervision, record adherence on Treatment Support Card, and remind participants who did not report for treatment; participants also required to visit the community health worker weekly to check side effects and adherence and receive health education; defaulters reported to the diagnostic centre
Outcomes	(1) Cure or treatment completion: cure defined as smear negative at 6 months and on at least 1 previous occasion; treatment completion defined as treatment completed but smear results not available on at least 2 occasions before treatment completion (2) Death (3) Treatment failure: remained or became smear positive at > = 5 months (4) Default: failed to collect medication for > 2 consecutive months (5) Transferred out: formally transferred to another centre
Notes	Location: Swaziland Date: 2000-2
Allocation concealment	B – Unclear
<b>Study</b>	<b>Zwarenstein 1998</b>
Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: consecutively numbered, opaque, sealed envelopes in each of 5 clinics Blinding: none Completeness of follow up: 114/120 (95%) in 1 trial and 102/120 (85%) in other trial excluded from analysis
Participants	Number: 216 included in analysis; 62% male; 57% < 35 years Included: adults (aged 15+) with pulmonary tuberculosis; both new and retreatment cases Excluded: severe disease or multiple drug resistance; treatment at a non-study clinic for more than 2 weeks; need to be supervised at school or at the workplace; and leaving the area within a month
Interventions	(1) DOT by clinic nurses: participants asked to visit the clinic 5 days a week for 8 weeks (new participants) or for 12 weeks (retreatment participants); thereafter expected attendance was 3 days a week for the continuation phase; clinic visits restricted to normal working hours and adherence card signed and dated by a nurse at each visit and kept at the clinic

## Characteristics of included studies (Continued)

(2) Self administration of treatment: participants had to visit clinic once a week or send a relative to collect drugs; participants completed their own adherence card for every day of drug taking and a nurse recorded the weekly drug collection; adherence card handed to nurse at the weekly clinic visit

New cases received Rifater (combined rifampicin-isoniazid-pyrazinamide) for 8 weeks followed by Rifinah 4 (combined rifampicin-isoniazid) plus additional isoniazid for 18 weeks

Retreatment participants received Rifater plus ethambutol for 12 weeks and Rifinah plus rifampicin-ethambutol for 22 weeks

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Outcomes	(1) "Successful treatment" included those who were cured and those who completed treatment; "cured" applied to those who converted from a positive smear and/or culture to a negative smear and/or culture at the end of treatment (6 months for new participants and 8 months for retreatment participants); "treatment completed" referred to participants who (a) completed the full course of treatment but had no pretreatment or post-treatment bacteriological results; (b) had negative pretreatment results and had been treated on clinical grounds; or (c) had positive pretreatment results, negative results after 2 months and no post-treatment results (2) "Treatment failure" applied to participants with a positive smear or culture at the end of treatment (3) "Treatment interrupters" applied to participants who stopped taking treatment for 8 or more weeks during the treatment period (4) Transfer to another treatment facility (5) Death from tuberculosis or other causes while on treatment
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Notes	Location: 1 trial in each of 2 low-income communities near Cape Town, South Africa Date: 1994-5 Results combined 54 participants in 1 trial allocated to community supervision not reported in this paper Exclusions from analysis: trial 1 (6 cases of multiple drug resistance) and trial 2 (12 cases of multiple drug resistance and 6 not tuberculosis) Number of exclusions per arm of the 2 trials not given
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Allocation concealment	A – Adequate
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### Study **Zwarenstein 2000**

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Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: consecutively numbered, opaque, sealed envelopes Blinding: none Completeness of follow up: not stated
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Participants	Number: 174 randomized Included: new or retreatment participants aged 15+ who were sputum or culture positive
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Interventions	(1) DOT by clinic nurses (see Zwarenstein 1998) (2) Self administration (see Zwarenstein 1998) (3) DOT by lay health workers: participants took drugs at home of a lay health worker under supervision; if participant missed treatment for 1 day, a lay health worker visited participant's home and if necessary a member of the South African Tuberculosis Association (SANTA) also visited the participant
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Outcomes	As for Zwarenstein 1998
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Notes	Location: 4 clinics in a township near Cape Town, South Africa Date: 1994-5 18 participants excluded from analysis: 12 with multiple-drug resistant tuberculosis and 6 not tuberculosis
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Allocation concealment	A – Adequate
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DOT: directly observed therapy; HIV: human immunodeficiency virus

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## Characteristics of excluded studies

Study	Reason for exclusion
Batki 2001	Compared direct observation plus with methadone treatment for injecting drug users with routine tuberculosis treatment without methadone
Carroll 2004	Before-and-after study; no control group
Hwang 2004	Not randomized
Jasmer 2004	Different criteria for allocation to self administration or direct observation
Lewin 2004	An educational intervention was evaluated
Mathew 2002	Cohort study
Moulding 2001	Trial evaluating devices that monitor treatment using uranium along a strip of photographic film
Pungrassami 2002	2 publications reporting the same study; not randomly allocated
Sorete-Abore 2002	Cohort study
Tandon 2002	Described as a randomized trial, but the randomization led to very different numbers in the 2 groups; subsequently over 50 participants (out of a total of 379) crossed over from self treatment to direct observation and were excluded from the analysis; little detail for the rest of the study provided
Thiam 2007	Multifaceted intervention including directly observed therapy
Toyota 2003	Patients in hospital

## ADDITIONAL TABLES

**Table 01. Search strategies for databases**

Search set	CIDG SR <sup>^</sup>	CENTRAL	MEDLINE <sup>^^</sup>	EMBASE <sup>^^</sup>	LILACS <sup>^^</sup>
1	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis
2	DOT*	PATIENT COMPLIANCE	PATIENT COMPLIANCE	PATIENT COMPLIANCE	DOT*
3	directly observed therapy	PATIENT PARTICIPATION	PATIENT PARTICIPATION	PATIENT MONITORING	supervision
4	2 or 3	patient monitoring	MOTIVATION	DOT\$	2 or 3
5	1 and 4	MOTIVATION	DECISION SUPPORT TECHNIQUES	directly observed therapy	1 and 4
6	-	DECISION SUPPORT TECHNIQUES	DOT*	compliance	-
7	-	DOT*	directly observed therapy	motivation	-
8	-	directly observed therapy	compliance	patient\$	-
9	-	compliance	patient*	defaulter\$	-
10	-	defaulter*	defaulter*	adheren\$	-
11	-	adheren*	adheren*	supervis\$	-

**Table 01. Search strategies for databases** (Continued)

Search set	CIDG SR <sup>^</sup>	CENTRAL	MEDLINE <sup>^^</sup>	EMBASE <sup>^^</sup>	LILACS <sup>^^</sup>
12	-	supervision*	supervis*	2-11/or	-
13	-	2-12/or	2-12/or	1 and 12	-
14	-	1 and 13	1 and 13	Limit 13 to human	-
15	-	-	Limit 14 to human	-	-

<sup>^</sup>Cochrane Infectious Diseases Group Specialized Register

<sup>^^</sup>Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term

**Table 02. Methodological quality assessment<sup>^</sup>**

Trial	Randomization type	Sequence <sup>^^</sup>	Concealment <sup>^^</sup>	Blinding (assessors)	Completeness <sup>^^</sup>
Chaisson 2001	Individual	Adequate	Unclear	Inadequate	Inadequate
Kamolratanakul 1999	Individual	Adequate	Inadequate	Inadequate	Adequate
Lwilla 2003	Cluster	Unclear	Unclear	Inadequate	Inadequate
MacIntyre 2003	Individual	Inadequate	Inadequate	Adequate	Unclear
Malotte 2001	Individual	Unclear	Adequate	Inadequate	Unclear
Newell 2006	Cluster	Adequate	Inadequate	Adequate	Adequate
Walley 2001	Individual	Adequate	Adequate	Adequate	Unclear
Wandwalo 2004	Individual	Adequate	Inadequate	Inadequate	Adequate
Wright 2004	Individual	Unclear	Unclear	Adequate	Adequate
Zwarenstein 1998	Individual	Adequate	Adequate	Inadequate	Adequate
Zwartenstein 2000	Individual	Adequate	Adequate	Inadequate	Unclear

<sup>^</sup>Details of methods in the 'Characteristics of included studies';

<sup>^^</sup>Generation of allocation sequence, allocation concealment, and completeness of follow up

## ANALYSES

### Comparison 01. Direct observation versus self administration

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure	4	1603	Relative Risk (Random) 95% CI	1.02 [0.86, 1.21]
02 Cure or completion of treatment	4	1603	Relative Risk (Fixed) 95% CI	1.06 [1.00, 1.13]
03 Completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

### Comparison 02. Direct observation versus self administration: stratified by location of direct observation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure			Relative Risk (Fixed) 95% CI	Subtotals only
02 Cure or completion of treatment			Relative Risk (Fixed) 95% CI	Subtotals only

### Comparison 03. Direct observation: home versus clinic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure or completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

### Comparison 04. Home-based direct observation: family member versus community health worker

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure or completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

### Comparison 05. Intravenous drug users: direct observation versus self administration

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

### Comparison 06. Intravenous drug users: choose own location versus treatment centre

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antitubercular Agents [\*therapeutic use]; \*Directly Observed Therapy; Randomized Controlled Trials as Topic; Tuberculosis, Pulmonary [\*drug therapy]

### MeSH check words

Humans

## COVER SHEET

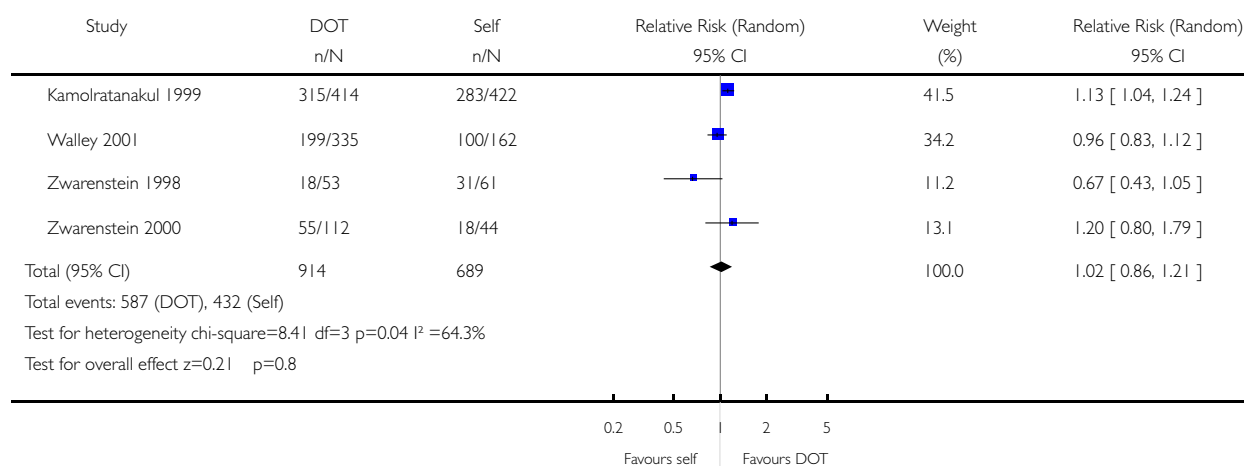
<b>Title</b>	Directly observed therapy for treating tuberculosis
<b>Authors</b>	Volmink J, Garner P
<b>Contribution of author(s)</b>	Jimmy Volmink initiated the review, wrote the protocol, applied the inclusion criteria, conducted the data extraction, and drafted the review. Paul Garner helped write the protocol, applied the inclusion criteria, constructed comparisons, and helped draft the review. Both authors remain actively involved in updating.
<b>Issue protocol first published</b>	2001/4
<b>Review first published</b>	2001/4
<b>Date of most recent amendment</b>	17 August 2007
<b>Date of most recent SUBSTANTIVE amendment</b>	13 August 2007
<b>What's New</b>	<p>2007, Issue 4: added Newell 2006, with no change to the conclusions; added references to new tuberculosis adherence reviews in the 'Background' section and reworded objectives to clarify that the review encompasses comparisons between different types of directly observed therapy.</p> <p>2006, Issue 2 (Volmink 2006): Lwilla 2003, MacIntyre 2003, Wandwalo 2004, and Wright 2004 added; no change to the conclusions.</p> <p>2003, Issue 1 (Volmink 2003): Chaisson 2001 and Malotte 2001 added; no change to the conclusions.</p> <p>2001, Issue 4 (Volmink 2001): first version of this review on directly observed therapy.</p> <p>2000, Issue 4 (Volmink 2000a): original review split into a series of Cochrane Reviews, each focusing on particular intervention promotion strategies, such as directly observed therapy in this review.</p> <p>1997, Issue 2: review first published as 'Interventions for promoting adherence to tuberculosis management'.</p>
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	Information not supplied by author
<b>Date authors' conclusions section amended</b>	Information not supplied by author
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**DOI** 10.1002/14651858.CD003343.pub3  
**Cochrane Library number** CD003343  
**Editorial group** Cochrane Infectious Diseases Group  
**Editorial group code** HM-INFECTN

**GRAPHS AND OTHER TABLES**

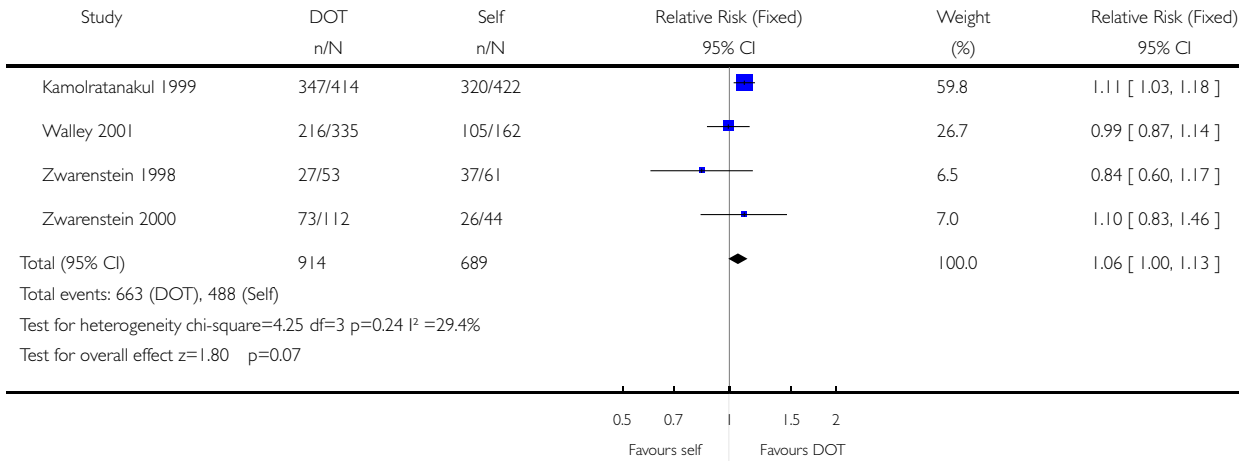
**Analysis 01.01. Comparison 01 Direct observation versus self administration, Outcome 01 Cure**

Review: Directly observed therapy for treating tuberculosis  
 Comparison: 01 Direct observation versus self administration  
 Outcome: 01 Cure



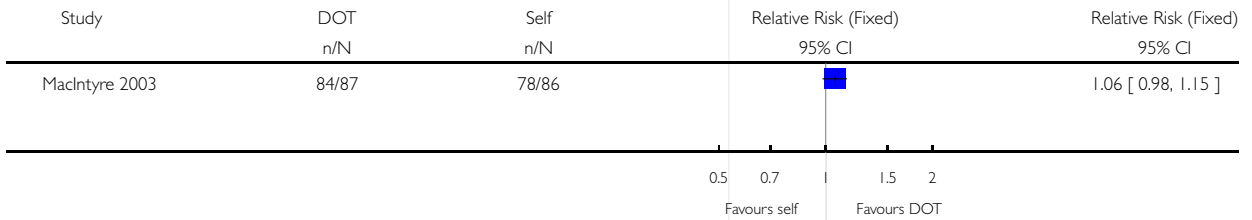
**Analysis 01.02. Comparison 01 Direct observation versus self administration, Outcome 02 Cure or completion of treatment**

Review: Directly observed therapy for treating tuberculosis  
 Comparison: 01 Direct observation versus self administration  
 Outcome: 02 Cure or completion of treatment



**Analysis 01.03. Comparison 01 Direct observation versus self administration, Outcome 03 Completion of treatment**

Review: Directly observed therapy for treating tuberculosis  
 Comparison: 01 Direct observation versus self administration  
 Outcome: 03 Completion of treatment



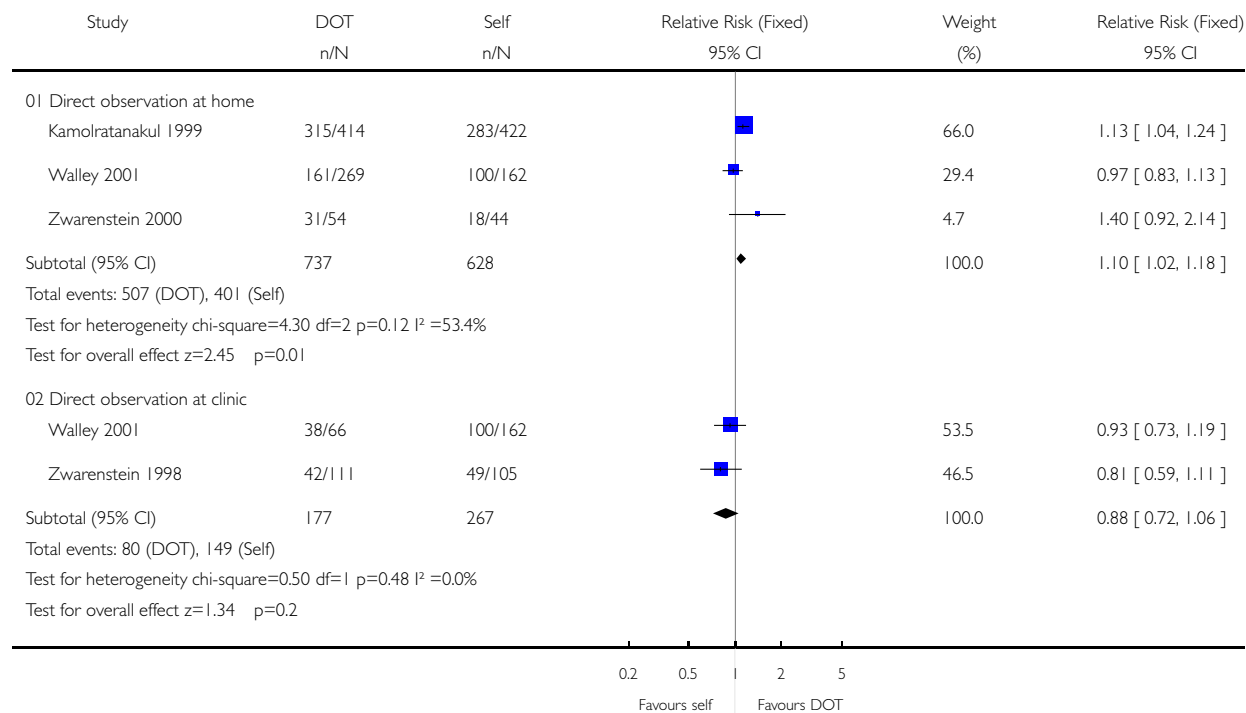


**Analysis 02.01. Comparison 02 Direct observation versus self administration: stratified by location of direct observation, Outcome 01 Cure**

Review: Directly observed therapy for treating tuberculosis

Comparison: 02 Direct observation versus self administration: stratified by location of direct observation

Outcome: 01 Cure

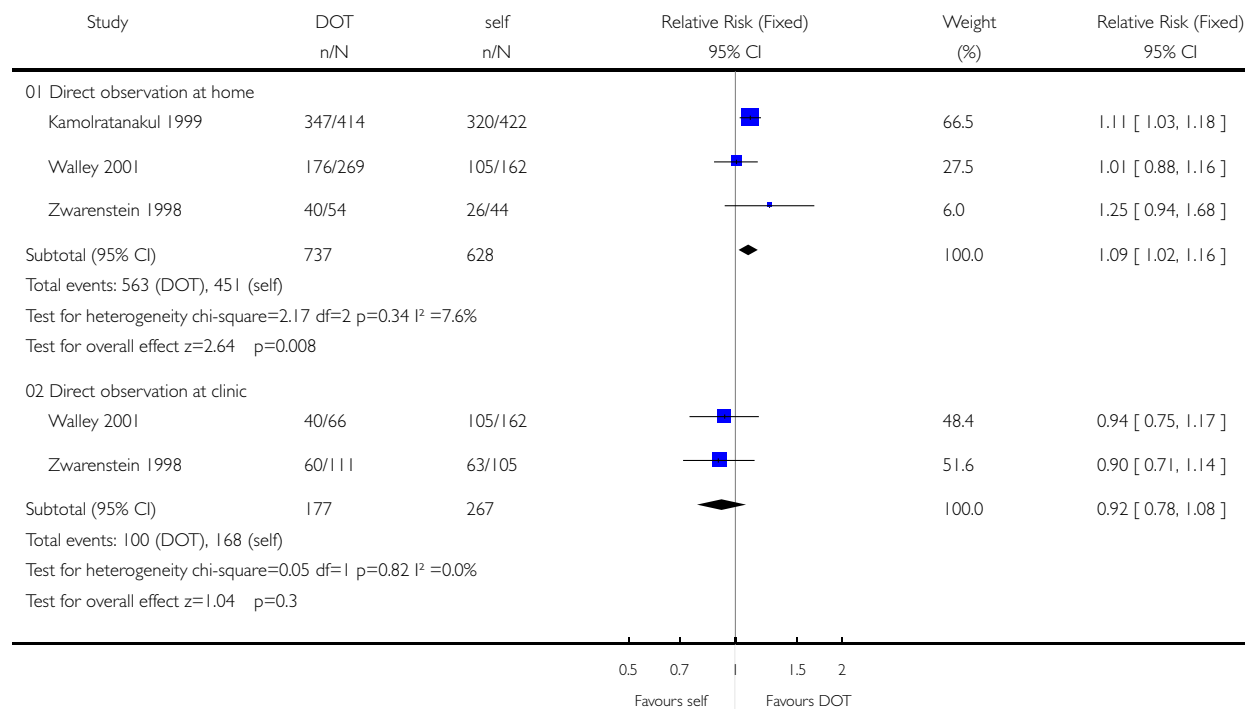


**Analysis 02.02. Comparison 02 Direct observation versus self administration: stratified by location of direct observation, Outcome 02 Cure or completion of treatment**

Review: Directly observed therapy for treating tuberculosis

Comparison: 02 Direct observation versus self administration: stratified by location of direct observation

Outcome: 02 Cure or completion of treatment

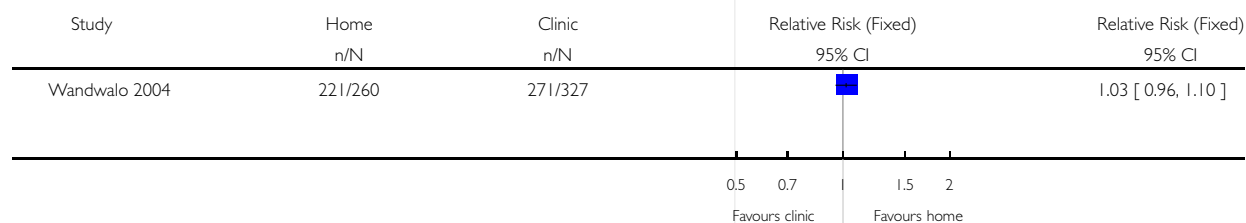


**Analysis 03.01. Comparison 03 Direct observation: home versus clinic, Outcome 01 Cure or completion of treatment**

Review: Directly observed therapy for treating tuberculosis

Comparison: 03 Direct observation: home versus clinic

Outcome: 01 Cure or completion of treatment

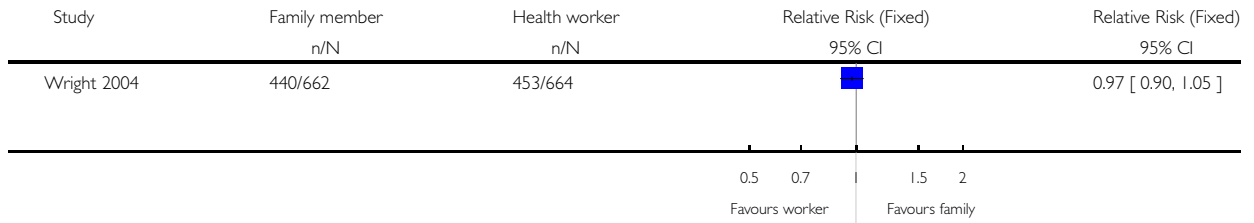


**Analysis 04.01. Comparison 04 Home-based direct observation: family member versus community health worker, Outcome 01 Cure or completion of treatment**

Review: Directly observed therapy for treating tuberculosis

Comparison: 04 Home-based direct observation: family member versus community health worker

Outcome: 01 Cure or completion of treatment



**Analysis 05.01. Comparison 05 Intravenous drug users: direct observation versus self administration, Outcome 01 Completion of treatment**

Review: Directly observed therapy for treating tuberculosis

Comparison: 05 Intravenous drug users: direct observation versus self administration

Outcome: 01 Completion of treatment



**Analysis 06.01. Comparison 06 Intravenous drug users: choose own location versus treatment centre, Outcome 01 Completion of treatment**

Review: Directly observed therapy for treating tuberculosis

Comparison: 06 Intravenous drug users: choose own location versus treatment centre

Outcome: 01 Completion of treatment

