December 2016 – SUPPORT Summary of a systematic review

Is directly observed therapy effective for treating tuberculosis?

Successful tuberculosis treatment depends on adherence to treatment schedules, which people often find difficult. Directly observed therapy (DOT) requires a health worker, family or community member to witness the physical drug intake, and has been widely promoted as a means to improve adherence to treatment.

Key messages

➔ **In treatment of active tuberculosis in the general population**

- DOT probably leads to little or no difference to whether patients are cured, and/or whether they complete treatment
- DOT delivered at *home* probably leads to a small increase in cure rates and/or treatment completion compared to *self-administration*
- DOT delivered at *clinics* probably leads to little or no difference in cure rates or treatment completion compared to *self-administration*
- DOT delivered at *clinics* probably leads to little or no difference in cure rates or treatment completion compared to DOT delivered at *home*
- DOT delivered at *home by a health worker* probably leads to little or no increase in cure rates or treatment completion compared to DOT delivered at *home by a family member*

➔ **In prophylaxis of tuberculosis in intravenous drug users**

- DOT probably leads to little or no difference in treatment completion compared to *self-administration*
- DOT at a *chosen location* probably leads to little or no difference in treatment completion compared to DOT at a *treatment centre*

Who is this summary for?

People making decisions concerning delivery of anti-tuberculosis treatment

! This summary includes:

- **Key findings** from research based on a systematic review
- **Considerations about the relevance of this research** for low-income countries

X Not included:

- Recommendations
- Additional evidence not included in the systematic review
- Detailed descriptions of interventions or their implementation

This summary is based on the following systematic review:

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.

What is a systematic review?

A summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise the relevant research, and to collect and analyse data from the included studies

SUPPORT was an international project to support the use of policy relevant reviews and trials to inform decisions about maternal and child health in low- and middle-income countries, funded by the European Commission (FP6) and the Canadian Institutes of Health Research.

Glossary of terms used in this report: www.supportsummaries.org/glossary-of-terms

Background references on this topic: See back page

Background

Tuberculosis is an infectious disease that continues to be a major public health problem, particularly in low- and middle-income countries. Effective drugs to prevent or cure tuberculosis are available but successful treatment depends on good adherence to treatment schedules. Individuals receiving treatment often find adherence difficult. Directly observed therapy (DOT) requires a health worker, family or community member to witness the physical drug intake in a health centre or in a patient's home. DOT has been widely promoted as a means to improve adherence to treatment and is at the core of the DOTS programme promoted by the World Health Organization. There is little strong evidence, however, for its effectiveness.

How this summary was prepared

After searching widely for systematic reviews that can help inform decisions about health systems, we have selected ones that provide information that is relevant to low-income countries. The methods used to assess the reliability of the review and to make judgements about its relevance are described here: www.supportsummaries.org/how-support-summaries-are-prepared/

Knowing what's not known is important

A reliable review might not find any studies from low-income countries or might not find any well-designed studies. Although that is disappointing, it is important to know what is not known as well as what is known.

A lack of evidence does not mean a lack of effects. It means the effects are uncertain. When there is a lack of evidence, consideration should be given to monitoring and evaluating the effects of the intervention, if it is used.

About the systematic review underlying this summary

Review objective: 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.

Types of	What the review authors searched for	What the review authors found
Study designs & Interventions	Studies evaluating health workers, family members, or community volunteers routinely observing participants taking anti-tuberculosis drugs	11 randomised trials and quasi-randomised trials with a combined total of 5,609 participants
Participants	People requiring treatment for clinically active tuberculosis *or* medication for preventing active disease (prophylaxis or preventive therapy)	9 studies on the general population (treatment of active tuberculosis) with a combined total of 5,302 participants and 2 studies on intravenous drug users (prophylaxis) with a combined total of 307 participants
Settings	No restrictions	8 studies set in low- and middle-income countries: Pakistan (1), South Africa (2), Tanzania (2), Nepal (1), Swaziland (1), Thailand (1) 3 studies set in high-income countries: Australia (1), United States of America (USA) (2 studies including intravenous drug users)
Outcomes	Cure; Completion of treatment; Development of clinical tuberculosis (in trials of drug prophylaxis); Keeping outpatient appointments	Cure (4 studies), Cure or completion of treatment (6), and Completion of treatment (3). Some studies reported multiple outcomes.
Date of most recent search: August 2007		
Limitations: This is a well-conducted systematic review with only minor limitations.		

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

Summary of findings

The review identified 11 trials, including 9 on the delivery of anti-tuberculosis treatment to members of the general population, and 2 on prophylactic treatment of intravenous drug users. Eight studies were conducted in low- and middle-income countries; both the studies of intravenous drug users were conducted in the USA. Data on the cure of tuberculosis and completion of treatment were identified; no data were found on the development of clinical tuberculosis and keeping outpatient appointments.

1) Treatment of active tuberculosis – general population

Included studies compared DOT with self-administration and compared alternative DOT delivery options.

➔ **DOT probably leads to little or no difference in cure rates, and/or completion of treatment. The certainty of this evidence is moderate.**

➔ **DOT delivered at *home* probably leads to a small increase in cure rates and/or treatment completion compared to *self-administration.* The certainty of this evidence is moderate.**

➔ **DOT delivered at *clinics* may lead to a small decrease in cure rates or treatment completion compared to *self-administration.* The certainty of this evidence is low.**

➔ **DOT delivered at *clinics* probably leads to little or no increase in cure rates or treatment completion compared to DOT delivered at *home.* The certainty of this evidence is moderate.**

➔ **DOT delivered at *home by a health worker* probably leads to little or no increase in cure rates or treatment completion compared to DOT delivered at *home by a family member.* The certainty of this evidence is moderate.**

About the certainty of the evidence (GRADE) *

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This is sometimes referred to as 'quality of evidence' or 'confidence in the estimate'.

† Substantially different = a large enough difference that it might affect a decision

See last page for more information.

DOT versus self-administration and DOT in various locations and through different channels

People General population (treatment of active tuberculosis)
Settings Low-and middle-income countries, Australia
Intervention Self-administration, DOT in various locations and through different channels
Comparison DOT, DOT in various locations and through different channels

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Without DOT or with other type of DOT	**With DOT**		
Cure	Self-administration 63 per 100	DOT 64 per 100	RR 1.02 (0.86 to 1.21)	⊕⊕⊕◯ Moderate
	Difference: 1 more cured per 100 people receiving TB treatment (Margin of error: 9 fewer to 13 more)			
	Self-administration 64 per 100	DOT (at home) 70 per 100	RR 1.10 (1.02 to 1.18)	⊕⊕⊕◯ Moderate
	Difference: 6 more cured per 100 people receiving TB treatment (Margin of error: 1 to 11 more)			
	Self-administration 56 Per 100	DOT (at clinic) 49 per 100	RR 0.88 (0.72 to 1.06)	⊕⊕◯◯ Low
	Difference: 7 fewer cured per 100 people receiving TB treatment (Margin of error: 16 fewer to 3 more)			
Cure or completion of treatment	Self-administration 71 per 100	DOT 75 per 100	RR 1.06 (1.00 to 1.13)	⊕⊕⊕◯ Moderate
	Difference: 4 more cured or completed treatment per 100 people receiving TB treatment (Margin of error: 0 to 9 more)			
	Self-administration 72 per 100	DOT (at home) 78 per 100	RR 1.09 (1.02 to 1.16)	⊕⊕⊕◯ Moderate
	Difference: 6 more cured or completed treatment per 100 people receiving TB treatment (Margin of error: 1 to 11 more)			
	Self-administration 63 per 100	DOT (at clinic) 58 per 100	RR 0.92 (0.78 to 1.08)	⊕⊕⊕◯ Moderate
	Difference: 5 fewer cured or completed treatment per 100 people receiving TB treatment (Margin of error: 14 fewer to 5 more)			
	DOT (at clinic) 83 per 100	DOT (at home) 85 per 100	RR 1.03 (0.96 to 1.10)	⊕⊕⊕◯ Moderate

	Difference: 2 more cured or completed treatment per 100 people receiving TB treatment (Margin of error: 3 fewer to 8 more)			
	DOT (at home, health worker) 68 per 100	DOT (at home, family member) 66 per 100	RR 0.97 (0.90 to 1.05)	⊕⊕⊕◯ Moderate
	Difference: 2 fewer cured or completed treatment per 100 people receiving TB treatment (Margin of error: 7 fewer to 4 more)			
Completion of treatment	Self-administration 91 per 100	DOT 96 per 100	RR 1.06 (0.98 to 1.15)	⊕⊕⊕◯ Moderate
	Difference: 5 more completed treatment per 100 people receiving TB treatment (Margin of error: 2 fewer to 9 more)			

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The risk WITHOUT the intervention is based on DOTS or one DOTS option. The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is based on the overall relative effect (and its 95% confidence interval).

2) Prophylaxis of tuberculosis - intravenous drug users

Included studies compared DOT with self-administration, and compared alternative DOT delivery options.

➔ ***DOT* probably leads to little or no increase in treatment completion compared to *self-administration.* The certainty of this evidence is moderate.**

➔ **DOT at a *location chosen by the patient* may lead to slightly lower treatment completion compared to DOT at a *treatment centre.* The certainty of this evidence is low.**

DOT versus self-administration and DOT in various locations

People Intravenous drug users (IVDs)
Settings USA
Intervention Self-administration, DOT in community clinic
Comparison DOT, DOT at chosen location

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Without DOT or with other type of DOT	**With DOT**		
Completion of treatment	Self-administration 79 per 100	DOT 81 per 100	RR 1.02 (0.89 to 1.18)	⊕⊕⊕◯ Moderate
	Difference: 2 more completed treatment per 100 IVD users receiving TB prophylaxis (Margin of error: 9 fewer to 14 more)			
	Treatment centre 60 per 100	Chosen location 53 per 100	RR 0.88 (0.63 to 1.23)	⊕⊕◯◯ Low
	Difference: 7 fewer completed treatment per 100 IVD users receiving TB prophylaxis (Margin of error: 22 fewer to 14 more)			

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The risk WITHOUT the intervention is based on DOTS or one DOTS option. The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is based on the overall relative effect (and its 95% confidence interval).

Relevance of the review for low-income countries

➔ Findings	▷ Interpretation*
APPLICABILITY	
➔ **Eight of the 9 studies focusing on the treatment of active tuberculosis among members of the general population were conducted in low- and middle-income countries.** ➔ **The study investigating prophylaxis for intravenous drug users was conducted in the USA.**	▷ *The findings are of direct relevance to low-income countries.* ▷ *The heterogeneity between the findings from studies conducted in different country settings suggests as-yet unidentified confounders (for example, local habits and cultural characteristics)* ▷ *The findings from the two studies that investigated prophylaxis for intravenous drug users may be transferable to low-income country settings but the delivery process and support structures for local population may differ from those of the original study settings*
EQUITY	
➔ **The review did not include information on equity.**	▷ *DOT frequently involves costs (financial, time, productivity) for patients. Self-treatment might avoid these costs, potentially rendering adherence to anti-tuberculosis treatment schedules more feasible in poor populations.*
ECONOMIC CONSIDERATIONS	
➔ **The review did not provide data related to economic considerations.**	▷ *DOT is costly for health services. Available evidence suggests that DOT leads to little or no differences in cure rates or completion of treatment. Compared to other forms of administration, such resources could be invested in interventions of proven effectiveness in order to improve adherence.*
MONITORING & EVALUATION	
➔ **The review did not find evidence of the effects of DOT on development of clinical tuberculosis (for those receiving prophylaxis) or on keeping outpatient appointments.**	▷ *There needs to be a clear identification of the contexts in which DOT is beneficial (e.g. specific health systems and cultural characteristics).* ▷ *The effects of DOT on the development of clinical tuberculosis (for those receiving prophylaxis) and on keeping outpatient appointments requires further research.*

*Judgements made by the authors of this summary, not necessarily those of the review authors, based on the findings of the review and consultation with researchers and policymakers in low-income countries. For additional details about how these judgements were made see: www.supportsummaries.org/methods

Additional information

Related literature

Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. *Lancet* 1995;**345**(8964):1545–8.

Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. *JAMA* 1998;**279**(12):943–8.

Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tuberculosis: the importance of direct observation. *Bulletin of the World Health Organization* 2007;**85**(5):407–9.

Garner P, Smith H, Munro S, Volmink J. Promoting adherence to tuberculosis treatment. *Bulletin of the World Health Organization* 2007;**85**(5):404–9.

Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. *Lancet* 2000;**355**(9212):1345–50.

Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. *BMJ* 2008;336(7642):484–7.

Kangovi S, Mukherjee J, Bohmer R, Fitzmaurice G. A classification and meta-analysis of community-based directly observed therapy programs for tuberculosis treatment in developing countries. *Journal of Community Health* 2009;34(6):506–13.

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Conflict of interest

None declared. For details, see: www.supportsummaries.org/coi

Acknowledgements

This summary has been peer reviewed by: Gabriel Rada, Paul Garner, Simon Goudie, and Hanna Bergman.

This review 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.

The summary should be cited as

Steinmann P. Is directly observed therapy effective for treating tuberculosis? A SUPPORT Summary of a systematic review. December 2016. www.supportsummaries.org

About certainty of the evidence (GRADE)

The "certainty of the evidence" is an assessment of how good an indication the research provides of the likely effect; i.e. the likelihood that the effect will be substantially different from what the research found. By "substantially different" we mean a large enough difference that it might affect a decision. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the study design (randomised trials versus observational studies), factors that reduce the certainty (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and factors that increase the certainty (a large effect, a dose response relationship, and plausible confounding). For each outcome, the certainty of the evidence is rated as high, moderate, low or very low using the definitions on page 3.

For more information about GRADE:
www.supportsummaries.org/grade

SUPPORT collaborators:

The Cochrane Effective Practice and Organisation of Care Group (EPOC) is part of the Cochrane Collaboration. The Norwegian EPOC satellite supports the production of Cochrane reviews relevant to health systems in low- and middle-income countries .
www.epocoslo.cochrane.org

The Evidence-Informed Policy Network (EVIPNet) is an initiative to promote the use of health research in policymaking in low- and middle-income countries. www.evipnet.org

The Alliance for Health Policy and Systems Research (HPSR) is an international collaboration that promotes the generation and use of health policy and systems research in low- and middle-income countries.
www.who.int/alliance-hpsr

Norad, the Norwegian Agency for Development Cooperation, supports the Norwegian EPOC satellite and the production of SUPPORT Summaries.
www.norad.no

The Effective Health Care Research Consortium is an international partnership that prepares Cochrane reviews relevant to low-income countries. www.evidence4health.org

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