

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Direct Observational Therapy for the Treatment of Tuberculosis: Clinical Evidence and Guidelines

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Research Questions

1. What is the clinical evidence regarding the provision of direct observational therapy for the treatment of tuberculosis?
2. What are the evidence-based guidelines regarding the use of direct observational therapy for the treatment of tuberculosis?

Key Findings

Eight systematic reviews (seven with meta-analyses), five randomized controlled trials and eight non-randomized studies were identified regarding the provision of direct observation therapy for treatment of tuberculosis. Additionally, eight evidence-based guidelines were identified regarding the use of direct observational therapy for the treatment of tuberculosis.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were tuberculosis and directly observed therapy. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, any types of clinical trials or observational studies, and guidelines. The search was also limited to English language documents published between Jan 1, 2015 and Apr 28, 2020. Internet links were provided, where available.

This report is a component of a larger CADTH Condition Level Review on TB. A condition level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH's Condition Level Review of TB, please visit the project page (<https://www.cadth.ca/tuberculosis>).

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People receiving pharmaceutical treatment for tuberculosis infection
Intervention	Direct observational therapy (i.e., patient is observed while taking a dose of pharmaceutical treatment to ensure treatment adherence)
Comparator	Q1. Direct observational therapy conducted by an alternative provider (e.g., public health nurse, other health care professionals, tuberculosis community leaders, students, laypeople) Video observed therapy Self-administered therapy Q2. Not applicable
Outcomes	Q1. Differences in treatment adherence between different methods of direct observational therapy Q2. Recommendations regarding how to administer directly observed therapy, such as who should administer it or the method of administration
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies and evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Eight systematic reviews (seven with meta-analyses^{1-6,8})¹⁻⁸, five randomized controlled trials⁹⁻¹³ and eight non-randomized studies¹⁴⁻²¹ were identified regarding the provision of direct observational therapy for treatment of tuberculosis. Additionally, eight evidence-based guidelines²²⁻²⁹ were identified regarding the use of direct observational therapy for the treatment of tuberculosis. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Eight systematic reviews (seven with meta-analyses^{1-6,8})¹⁻⁸, five randomized controlled trials⁹⁻¹³ and eight non-randomized studies¹⁴⁻²¹ were identified regarding the provision of direct observation therapy (DOT) for treatment of tuberculosis (TB). Detailed study characteristics can be found in Table 2.

Of the eight systematic reviews identified¹⁻⁸, five of these studies^{1,2,4,6,7} compared DOT to self-administered therapy (SAT), with all the authors having different conclusions as to whether DOT was more effective than SAT in treatment success and adherence rates for TB. Additionally, two of the identified systematic reviews^{5,8} assessed community-based-direct observed therapy (CB-DOT) compared to clinic-based DOT and found that CB-DOT led to higher treatment completion rates compared to clinic-based DOT. Moreover, one of the identified systematic reviews⁴ compared whether DOT by a healthcare facility (or health care provider) had higher treatment success rates compared to home-based DOT and concluded there was no statistically significant differences in treatment success rates among groups.

Various DOT therapies were examined among the identified randomized controlled trials⁹⁻¹³ including facility based-DOT, in-person DOT, wireless observed therapy (WOT), video observed therapy (VOT) and family-based DOT. Overall, the authors of these studies⁹⁻¹³ had different conclusions whether DOT was more effective in terms of treatment completion, compliance and adherence compared to another type of DOT or SAT.

Similarly, the identified non-randomized studies¹⁴⁻²¹ compared various types of DOT to SAT or other forms of DOT in terms of treatment success, treatment completion, adherence or loss to follow-up. Notably, the studies^{14,16} comparing DOT to SAT had differing results and conclusions as to whether DOT was more effective than SAT for TB treatment. Like the identified systematic reviews^{5,8} comparing CB-DOT with clinic-based DOT, the authors of one non-randomized study²⁰ concluded that treatment completion and success rates were higher in the CB-DOT group compared to clinic-based DOT. Moreover, the authors of another study¹⁶ noted there was no statistically significant differences in treatment success rates among the home visit DOT group and the modified DOT group. While authors of another study¹⁵ concluded that treatment completion was higher in the group receiving DOT from rural health care providers compared to those receiving DOT from community healthcare workers.

Eight non-randomized studies¹⁴⁻²¹ were identified regarding the provision of direct observation therapy for treatment of tuberculosis. Relevant recommendations have been summarized in Table 3.

Table 2: Characteristics of Included Studies

Last Name of First Author (year)	Population (N = # of participants)	Intervention	Comparator	Related Outcomes	Conclusions
Systematic Reviews and Meta-Analyses					
Mackay (2019) ¹	Adults N = 1,603 for included RCT studies N = 1,626 for included observational studies	DOT	SAT	<ul style="list-style-type: none"> - Loss to follow-up - Treatment failure - Cure - Treatment completed - All-cause mortality 	<ul style="list-style-type: none"> - Magnitude of the difference between DOT and SAT for all outcomes was small and not statically significant.
Alipanah (2018) ²	Not specified	<ol style="list-style-type: none"> 1. DOT 2. DOT provided by healthcare providers 3. DOT in community 4. DOT 5. DOT 	<ol style="list-style-type: none"> 1. SAT 2. DOT provided by family members 3. DOT in clinic 4. Medication monitors 5. VOT 	<ul style="list-style-type: none"> - Treatment success - Treatment adherence - Treatment failure - Loss to follow-up 	<ul style="list-style-type: none"> - DOT had lower rates of treatment success, and adherence compared to SAT - DOR by family members had lowers rate of adherence compared to DOT by healthcare providers. - DOT in community had higher treatment success, lower treatment failure and

Last Name of First Author (year)	Population (N = # of participants)	Intervention	Comparator	Related Outcomes	Conclusions
					loss to follow-up compared to DOT in clinics. - DOT was comparable with VOT
Kibret (2017) ³	Patients with MDR-TB N = 5,047 from 14 included observational studies	DOT-Plus	Standardized treatment regimens	- Treatment success/completion - Incomplete treatment	- Patients enrolled in standardized treatment regimens had higher incomplete treatment rates. - Treatment success was higher for DOT-Plus
Yin (2016) ⁴	Patients with MDR-TB N = 7,466 from 31 included studies	1. DOT 2. DOT by healthcare provider 3. DOT in healthcare facility	1. SAT 2. DOT by family members and private providers 3. Home-based DOT	- Treatment success	- Treatment success rates higher in DOT compared to SAT - No statistically significant differences among DOT in healthcare facility, at home or private providers - No statistically significant differences among DOT facility-based compared with DOT home-based.
Zhang (2016) ⁵	Patients with pulmonary TB N = 12,839 from eight RCTs and 12 NRS	CB-DOT	Clinic-based DOT	- Treatment success - Completed treatment - Reduced death	- Pooled results of all studies indicated that CB-DOT improved treatment outcomes
Karumbi (2015) ⁶	Patients with active TB N = 5,662 included from 11 RCTs	1. DOT 2. DOT	1. SAT 2. Another form of DOT (different provider or setting)	- TB cure - Treatment completion	- Treatment completion was similar among DOT and SAT groups - No difference in cure or treatment completion among DOT at home (by family members or community health workers) compared to DOT at health facility
Sharma (2015) ⁷	No abstract	DOT	SAT	No abstract available	
Wright (2015) ⁸	Patients with TB N = not specified Eight studies included	CB-DOT	Clinic DOT	- Treatment success - Loss to follow-up	- CB-DOT was more effective than clinic DOT for treatment success - No difference between groups for loss to follow-up -

Last Name of First Author (year)	Population (N = # of participants)	Intervention	Comparator	Related Outcomes	Conclusions
Randomized Controlled Trials					
Al Sahafi (2019) ⁹	Patients with TB	Facility-based DOTS	Community mobile outreach DOTS	<ul style="list-style-type: none"> - Default rate - Mean compliance scores 	<ul style="list-style-type: none"> - Overall default rate among mobile outreach DOTS was 3% versus 22% for facility-based DOTS - A significant difference was found in the mean compliance scores favoring community mobile outreach
Browne (2019) ¹⁰	Patients with drug-susceptible TB N = 61	WOT	In person-DOT	<ul style="list-style-type: none"> - PDA of WOT - Prescribed doses of WOT (versus DOT) - AE 	<ul style="list-style-type: none"> - WOT confirmed 93% of prescribed doses compared to 63% for DOT - WOT was non-inferior to DOT - AEs were < 10%
Guo (2019) ¹¹	Adults patients with confirmed pulmonary TB N = 810	VDOT	DOT	<ul style="list-style-type: none"> - Treatment result/completion - Treatment adherence 	<ul style="list-style-type: none"> - Both groups had high treatment completion rates
Dave (2016) ¹²	Children with TB N = 624	Family-based DOT	Provider-based DOT (usual-care)	<ul style="list-style-type: none"> - Treatment success rates 	<ul style="list-style-type: none"> - Treatment success rates were similar among groups - Family-based DOT is non-inferior to provider-based DOT
Ricks (2015) ¹³	Substance users with TB N=94	DOT administer by public health personal	DOT administered by previous substance-using outreach worker	<ul style="list-style-type: none"> - Treatment completion - Adherence 	<ul style="list-style-type: none"> - Significantly higher rates of non-completion and non-adherence from DOT-public health group - DOT administered by outreach workers had improved treatment completion and adherence.
Non-Randomized Studies					
Bhatt (2020) ¹⁴	New diagnosed adult patients with pulmonary TB N=191	Intermittent DOTS	Daily SAT	<ul style="list-style-type: none"> - Treatment success - Default - Treatment failure - Relapse 	Outcomes did not significantly differ between groups
Prasad (2020) ¹⁵	Patients with TB	DOTS from RHCPs	DOT with CHWs	<ul style="list-style-type: none"> - Treatment completion 	<ul style="list-style-type: none"> - Successful treatment completion was higher in

Last Name of First Author (year)	Population (N = # of participants)	Intervention	Comparator	Related Outcomes	Conclusions
	N = 72			- Unsuccessful outcomes	the RHCP group although the difference was not statistically significant - Unsuccessful outcomes were similar in both groups
Onwubiko (2019) ¹⁶	Adults who are homeless with LTBI N = 274	DOT	SAT	- Treatment completion (OR)	- The odds of completing LTBI treatment on DOT was 40% higher than SAT
Jinbo (2017) ¹⁷	Patients with LTBI N=179	DOT	No-DOT	- Treatment completion rate	- Treatment completion rate was higher in the DOT group (94.6%) compared to no-DOT (73%).
Tanvejsilo (2017) ¹⁸	Patients with pulmonary TB	Home visit-DOT	Modified-DOT	- Treatment success rate	- There were no statistically significant differences in treatment success rates between groups.
Chuch (2016) ¹⁷	Patients with TB N= 390	VDOT	DOT	- Adherence - Treatment completion	- Treatment adherence was higher in the VDOT group (95%) compared to DOT (91%) - Treatment completion was comparable among groups
Dobler (2015) ²⁰	Patients with confirmed TB N=1,768	CB-DOT	Clinic-DOT	- Treatment completion - Treatment success	- Treatment completion and success rates were higher in the CB-DOT group compared to clinic-DOT
Snidal (2015) ²¹	Patients with TB N = 142	DOTS	Control groups (not specified)	- Cure rates - Lost to follow-up	- DOTS group had a lower lost to follow-up rate than control groups - DOTS had a higher cure rate than control groups

AE = adverse events; CB-DOT = community-based DOT; CHW = community health workers; DOT = direct observed therapy; DOTS = directly observed treatment short course; LTBI = latent TB infection; MDR-TB = multi-drug resistance TB; OR = odds ratio; PDA = positive detection accuracy; NRS = non-randomized studies; RCT = randomized controlled trials; RHCP = rural healthcare providers; SAT= self-administered therapy; TB = tuberculosis; VOT = video observed therapy; WOT = wirelessly observed therapy

Table 3: Recommendations of Included Evidence-Based Guidelines

Recommendations
BHIVA²²
<ul style="list-style-type: none"> • “We recommend individualised, enhanced patient-centred care plans for all patients, some of which may include directly observed therapy (DOT) and video observed therapy (VOT). (GPP)” (Page 11) • “We recommend against the routine use of DOT and VOT in patients with active TB (GRADE 1B) but recommend these in MDR-TB cases. (GPP)” (Page 11)
WHO²³
<ul style="list-style-type: none"> • “Community- or home-based DOT is recommended over health facility-based DOT or unsupervised treatment (conditional recommendation, moderate certainty in the evidence).” • “DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment (conditional recommendation, very low certainty in the evidence).” • “Video-observed treatment (VOT) may replace DOT when the video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients (conditional recommendation, very low certainty in the evidence).”
ATS/CDC/ISDA²⁴
<ul style="list-style-type: none"> • “We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis (conditional recommendation; low certainty in the evidence).” (Page 856)
ATS/CDC/ISDA²⁵
<ul style="list-style-type: none"> • We suggest using DOT rather than SAT for routine treatment of patients with all forms of TB (conditional recommendation/low confidence in the effects) (Page 966)
NICE²⁶
<p>Quality Statement 5</p> <ul style="list-style-type: none"> • “People with active tuberculosis (TB) from under-served groups are offered directly observed therapy”
ECDC²⁷
<ul style="list-style-type: none"> • “Compliance to lengthy TB treatment could be promoted by support from family and friends (inconsistent evidence) or healthcare workers (moderate evidence). In addition, hospitalization and a strict DOT policy could be facilitators for compliance if the approach was patient-centered and culturally sensitive. However, in some cases patients saw hospitalization as a threat and DOT as paternalistic (conflicting evidence). Cultural-sensitivity and appropriate care increased access and adherence to treatment (moderate evidence)” (Page 18)
NICE²⁸
<ul style="list-style-type: none"> • “The TB case managers should work with the person diagnosed with TB to develop a health and social care plan, and support them to complete therapy successfully” (Page 56) • “Offer directly observed therapy as part of enhanced case management in people who: <ul style="list-style-type: none"> ○ do not adhere to treatment (or have not in the past) ○ have been treated previously for TB ○ have a history of homelessness, drug or alcohol misuse ○ are currently in prison, or have been in the past 5 years ○ have a major psychiatric, memory or cognitive disorder ○ are in denial of the TB diagnosis ○ have multidrug-resistant TB ○ request directly observed therapy after discussion with the clinical team ○ are too ill to administer the treatment themselves” (Page 57)
Singapore Ministry of Health²⁹
<ul style="list-style-type: none"> • “Directly observed therapy (DOT) should be the standard of care for all infectious tuberculosis cases. Tuberculosis patients who are assessed to have difficulty adhering to treatment or who pose greater public risk of transmission,

Recommendations

e.g. sputum-smear positive or working in institutional settings or settings with susceptible populations, or those at risk of or diagnosed with drug-resistant tuberculosis, are high priority for DOT” (Page 7)

- *“Multidrug-resistant tuberculosis (MDR-TB) patients should be treated under strict programme conditions by physicians experienced in MDR-TB management. Directly observed therapy (DOT) should be utilized for the entire treatment duration.” (Page 8)*

ATS = American Thoracic Society; BHIVA = British HIV Association; CDC = Centre for Disease Prevention and Control; ECDC = European Centre for Disease Prevention and Control; IDSA = Infectious Disease Society of America; NICE = National Institute for Health and Care Excellence

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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See: Sections Directly observed therapy; Page 11 and 38

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See: Table 1, PICO question 2; Page 966

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See: Quality Statement 5; Page 18

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See: *Facilitators; Page 18 and Appendix 3, Page 29*

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See: *Recommendations 1.7.1.2 and 1.7.1.3; Page 56 and 57*

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See: *Recommendations 37 and 44*

Appendix — Further Information

Previous CADTH Reports

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Systematic Reviews and Meta-analyses

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