INT J TUBERC LUNG DIS e-publication ahead of print 4 December 2012

http://dx.doi.org/10.5588/ijtld.12.0537

REVIEW ARTICLE

Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis

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SUMMARY

BACKGROUND: Scaling up treatment for multidrug-resistant tuberculosis is a global health priority. However, current treatment regimens are long and associated with side effects, and default rates are consequently high. This systematic review aimed to identify strategies for reducing treatment default.

METHODS: We conducted a systematic search up to May 2012 to identify studies describing interventions to support patients receiving treatment for multidrug-resistant tuberculosis (MDR-TB). The potential influence of study interventions were explored through subgroup analyses.

RESULTS: A total of 75 studies provided outcomes for 18 294 patients across 31 countries. Default rates ranged from 0.5% to 56%, with a pooled proportion of 14.8% (95%CI 12.4–17.4). Strategies identified to be associated with lower default rates included the engagement of community health workers as directly observed treatment (DOT) providers, the provision of DOT throughout treatment, smaller cohort sizes and the provision of patient education.

CONCLUSION: Current interventions to support adherence and retention are poorly described and based on weak evidence. This review was able to identify a number of promising, inexpensive interventions feasible for implementation and scale-up in MDR-TB programmes. The high default rates reported from many programmes underscore the pressing need to further refine and evaluate simple intervention packages to support patients.

KEY WORDS: default; retention; MDR-TB

THE MULTIDRUG-RESISTANT tuberculosis (MDR-TB) pandemic is rising in prevalence and global importance. There were an estimated 650 000 cases of MDR-TB cases worldwide in 2010, with <5% of all TB patients tested for multidrug resistance.[1] Historically, proportions of MDR-TB among TB cases have been highest in Eastern European countries, although in absolute numbers China and India now contribute 50% of all new MDR-TB cases.[2] Furthermore, in sub-Saharan Africa, the human immunodeficiency virus (HIV) epidemic and limited resources for comprehensive MDR-TB programmes have aided the spread of MDR-TB and the emergence of extensively drug-resistant TB (XDR-TB).[3] MDR-TB, defined as *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin, is more costly and complex to treat than fully susceptible disease, with treatment typically lasting at least 18 months. XDR-TB is defined as MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable agent.[2]

Current approaches to treating MDR-TB rely on lengthy treatment durations (typically a minimum of 20 months) using drugs associated with substantial toxicities, often resulting in high default rates. Other reported factors influencing treatment default include high costs of treatment for patients in settings where patients must pay,[4] indirect costs such as loss of wages,[5] increased poverty and sex discrimination,[6] dissatisfaction with health care worker attitudes,[7] limited knowledge and negative beliefs and attitudes to treatment,[8] challenges with drug procurement and sustained supply of second-line drugs, substance abuse and psychiatric disorders.[9]

Defaulting from treatment is of both medical and public health concern, as patients are at higher risk of mortality and morbidity, and may contribute to further spread of MDR-TB in the community.[10,11] A study in Peru found that half of defaulters had died within 3 years.[12] It is therefore important to identify effective methods to support patients throughout the duration of treatment. Current guidelines propose a range of potential interventions, such as psychosocial and economic support, but these are poorly supported by evidence.

This systematic review and meta-analysis aims to identify programmatic interventions that can improve adherence to and reduce default from MDR-TB treatment.

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Article submitted 11 July 2012. Final version accepted 15 August 2012.

METHODS

This review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses: guidance for reporting of systematic reviews and meta-analyses).[13]

Search strategy and selection criteria

We carried out the review in three parts. First, an initial selection was made of studies included in two previous systematic reviews of MDR-TB treatment outcomes[14,15] to identify relevant papers published between 1965 and December 2008 (the search dates for these reviews): 52 papers met the inclusion criteria and were included in the review. Second, to identify papers published after 2008, a new search was conducted to identify studies published between 1 December 2008 and 1 May 2012. Two databases were searched, Medline via OVID and EMBASE, using the highly sensitive search strategy (see Appendix A Table)* including the search terms drug resistance, TB and treatment outcomes both as free word and MeSH terms. No geographic restrictions were applied. Finally, we contacted experts in the field and hand-searched bibliographies of relevant articles.[16,17] A standardised web survey was developed (see Appendix A Figure) and sent to authors of included studies to gain further information on patient support strategies. All articles were screened by one reviewer (AT) and verified by a second reviewer (NF).

Eligibility criteria

We included studies published in English that reported final outcomes on treatment for cohorts of at least 10 adult culture-confirmed MDR-TB patients with access to second-line drugs and at least first-line drug susceptibility testing. Studies were excluded if they were conducted exclusively among children, provided only interim outcomes (defined as $\leqslant$12 months on treatment) to avoid bias towards a lower default rate, or studies reporting outcomes on fewer than 10 patients. Our outcome of interest was default, as adherence to treatment is far less commonly reported. If studies included outcomes for patients who had not yet completed treatment, these patients were excluded from the analysis. Studies conducted in the same location during the same time period were considered as potential duplicates; this was verified by contacting authors. Default was defined as treatment interruption for $\geqslant$2 consecutive months for any reason without medical approval.[2]

Data extraction and analysis

One reviewer (AT) extracted data on default from MDR-TB treatment programmes, and details of interventions used to improve retention in care. Data were entered into an Excel spreadsheet (Microsoft, Redwoods, WA, USA), and verified by a second reviewer (NF). Variables were classified into three broad categories: provision of treatment, counselling and incentives/enablers. Point estimates and 95% confidence intervals (CIs) for the proportion of people who defaulted from treatment are described. Raw proportions were stabilised by arcsine square-root transformation, and proportions were then pooled using a DerSimonian-Laird random effects model and the τ^2 statistic calculated as an estimate of between-study variance.[18,19] Sub-group analyses were carried out to determine the potential influence of various interventions, as well as the impact of geographic region (as defined by the World Health Organization [WHO][20]), economic classification (as defined by the World Bank[21]) and MDR-TB burden (as defined by the WHO).[22]

RESULTS

The search strategy identified 974 studies, of which 75 papers reporting outcomes on 78 different programmes were taken through for review (Figure 1).

Characteristics of studies included

Our review includes data from 18 294 patients; studies reported a range of patient cohort sizes from 13 to 1407 patients. Studies reported over a time period from 1982 to 2011, and took place across 31 countries, with the largest numbers originating from India, South Africa, South Korea, Peru, the United States and Russia (6–10 studies each); 23 studies originated from high-income countries, 32 from upper middle-income countries, 18 from lower middle-income countries and only 2 from low-income countries (Appendix B).[23–97]

Provision of treatment

The majority of the studies (58 studies, 13 826 patients) used individualised regimens, 17 (4289 patients) used a standardised regimen and 2 (139 patients) used a mixture of both. Directly observed treatment (DOT) was provided throughout the course of the treatment in 36 studies (7635 patients), 24 (6635 patients) provided partial DOT, and 10 (3352 patients) did not administer treatment under DOT. The DOT provider was a nurse in 21 studies (6012 patients), a community health worker (CHW) in 7 (916 patients), a family member in 2 (38 patients) and a mixture of providers in 17 (2345 patients). Location for DOT was in a facility (hospital or clinic) for 36 studies (9845 patients), at home for 3 (180 patients) and at a mix of facility and home for 20 (3830 patients). The study cohorts varied in size, with 40 studies reporting outcomes on cohorts of fewer than 100 patients,

*The Appendices are available in the online version of this article.

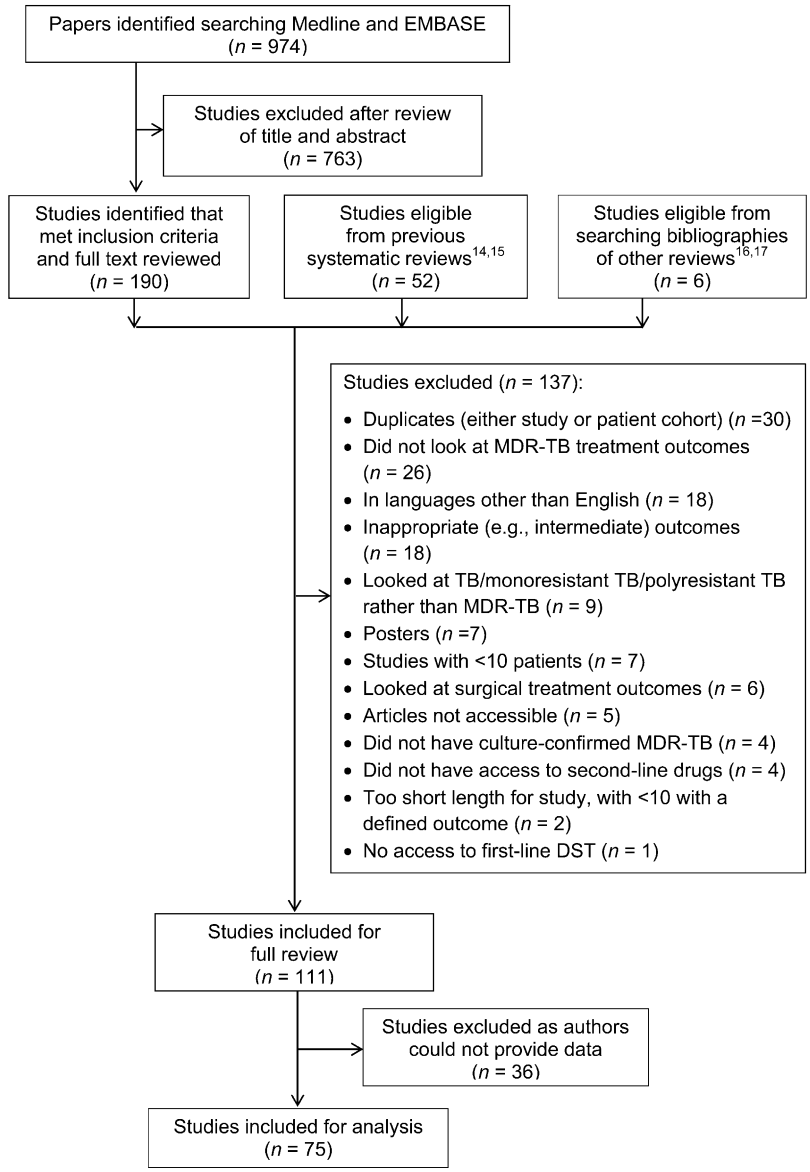

Figure 1 Study selection. MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing.

25 reporting outcomes on a cohort of 100–499 patients, 8 reporting outcomes on a cohort of 500–999 patients and 5 reporting outcomes on a cohort of over 1000 patients.

Counselling and education

Counselling was reported to have been provided throughout the course of treatment in 16 studies (2802 patients), through education, psychiatric care, group therapy or psychosocial support. The most common of these was psychosocial support, reported to be available in 13 studies (1989 patients). Patient education, with or without family involvement, was reported in 10 studies (1495 patients), group therapy in 3 (749 patients), provision of psychiatric care in 3 (1274 patients) and substance abuse specialist support was reported in 1 (38 patients).

Incentives/enablers

Incentives or enablers were reported to have been provided in 47 studies (9560 patients), most commonly in the form of nutrition support (28 studies, 5642 patients), followed by transport reimbursement (18 studies, 3662 patients) and accommodation (14 studies, 1915 patients).

Rates and determinants of treatment default

Default proportions ranged from 0.57% (95%CI [confidence interval] 0.52–4.91) to 55.6% (95%CI 51.55–59.62), with a median default of 13.8% (interquartile range [IQR] 5.6–20.5) and a pooled proportion of 14.8% (95%CI 12.4–17.4) patients defaulting from care (τ^2 0.12). The complete forest plot summarising default for each study is provided in Appendix C.

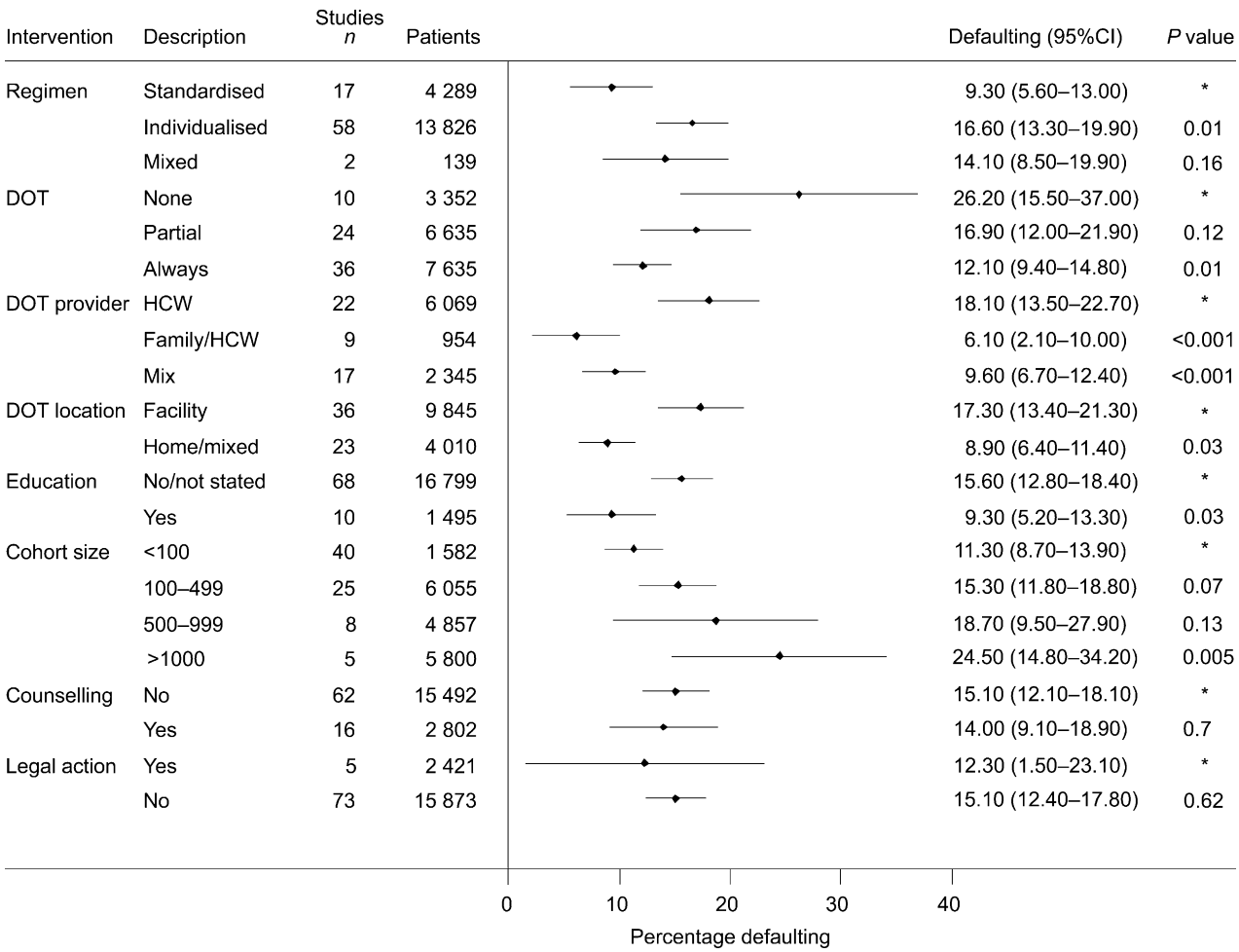

Figure 2 Summary of subgroup analysis of treatment and programme factors that may influence defaulting from treatment. CI = confidence interval; HCW = health care worker; DOT = directly observed treatment.

We undertook a range of subgroup analyses to identify factors that may influence treatment default. The full range of subgroup analyses are reported in Appendix D, and the most important and programmatically relevant of these are summarised in Figure 2.

There was a lower default rate when DOT was always provided compared to when no DOT was provided, and when the DOT provider was a CHW compared with a health care worker in a facility or nurse. Cohort size was also found to be influential, with lower default rates in smaller programmes. The use of a standardised regimen also appeared to result in lower default rates compared to individualised regimens. The provision of counselling did not appear to influence default, but provision of patient education did (Figure 2).

A broad range of incentives and enablers were assessed, but none were found to obviously reduce default from treatment, alone or in combination. The only potential difference was seen when comparing the delivery of a package of financial support, nutrition and transport reimbursement, which was associated with a lower default rate (9.7%, 95%CI 7.5–11.8), compared to studies that did not provide this combination of interventions (15.1%, 95%CI 12.5–17.7, $P = 0.002$).

Default rates were not found to be associated with study design, geographic region, economic classification or national drug-resistant TB rates. Finally, five studies used legal action to enforce adherence to treatment.[60,65,74,75,86] There was no difference between these studies (12.3%, 95%CI 1.5–23.1) and those that did not use legal action (15.1%, 95%CI 12.4–17.8, $P = 0.62$).

Comparison of the 10 studies with the lowest and highest default rates

To further explore drivers of default, we compared studies with the highest and lowest default rates. Among the studies with low default rates, three provided interim outcomes before the end of treatment: two reported outcomes after 12 months, resulting in default rates of 0.7% (95%CI 0.03–2.30)[62] and 1.27% (95%CI 1.13–10.62),[80] and a third calculated default after 17 months of treatment (proportion defaulting 1.69%, 95%CI 0.70–6.44).[68] However, when these studies were dropped from the overall analysis, the overall default rate remain unchanged (15.7%,

95%CI 13.0–18.5). In the group of studies with low default rates, a prospective cohort study based in Thailand used a comparative cohort design to assess the use of mobile phone reminders to improve adherence to treatment.[68] Both groups provided DOT at home by a family member throughout the standardised treatment regimen, and medication education provided by a pharmacist. Default rates for both groups were low, at 1.3% (95%CI 1.13–10.62). Only five of the 10 countries with the highest default rates are classified as lower middle-income countries, compared to 9/10 countries with the lowest default rates classified as either upper middle-income or high-income counties. Three of the studies from South Korea[52,57,59] with high default rates, and one from India[38] with low default rates, charged the patients for treatment.

Reporting quality

All studies were observational, and the majority were retrospective in design, which carried the risk of bias and confounding of results. The quality of reporting varied considerably. Prior treatment history was poorly reported, with the majority of the studies ($n = 60$) reporting mixed cohorts with variable proportions of newly treated patients and previously treated patients. While this may bias outcomes, it nevertheless reflects programmatic reality. Other important variables were inconsistently reported: 8 studies did not state whether or not DOT was administered, 18 studies did not state DOT location and 27 did not report DOT provider.

DISCUSSION

The WHO has established a goal of universal access to diagnosis and treatment of MDR- and XDR-TB by 2015.[22] However, even if this goal is achieved, there is a risk that much of this progress will be undone by high default rates with a concomitant risk of mortality, resistance amplification and ongoing community transmission. This review identified several relatively simple, inexpensive interventions that have the potential to reduce default: engagement of CHWs as DOT providers; provision of DOT throughout treatment; limiting cohort size through, for example, decentralisation of services; providing patient education; and a package of adherence interventions. The beneficial impact of these interventions reinforces the concept that the provision of treatment closer to the community level, and in a patient-centred manner, contributes to improved retention in care. Another notable finding is the association between larger programme size and increased default.

The finding that studies providing DOT through CHWs rather than nurses or health care workers in a facility appeared to reduce default may provide a way both to improve adherence and to rationalise health service use, thus freeing up health worker time for clinical tasks. Furthermore, the use of CHWs in a decentralised environment has been found to be affordable, without compromising treatment success rates.[98] The beneficial effects of DOT are unlikely to be the result of DOT alone, and include motivating and reassuring patients as to their treatment progress and early identification of side effects on a daily basis.[99] Health care workers in busy health care settings are likely to have less time to provide comprehensive patient support and take a narrow interpretation of DOT as simply watching patients take their medication. In addition, CHWs are generally quicker to train than nurses and clinicians, and have been demonstrated to improve adherence to treatment for other infectious diseases, such as HIV.[100]

The association between lower default rates and the use of standardised regimens may reflect a benefit in terms of simplifying treatment regimens and side-effect management, and allowing for a more consistent and reliable supply of drugs[101] (in one study, stock-outs were a cause of non-adherence to treatment[95]). It is important to note, however, that treatment outcomes tend to be better for patients on individualised regimens.[15] This highlights the difficult trade-off between simplicity and efficacy using currently available drugs, and suggests there might be a role for a choice of standardised regimens in patient management which could be tailored to an individual's results.

Studies that used a comprehensive package of adherence interventions (including financial support, transport reimbursement and nutrition) tended to have lower default rates. While such interventions have a cost, they may be less costly than the consequences of default. However, only a few studies reported using such interventions in combination. The use of an out-patient model of care may not only improve convenience to the patient, it has also been found to be more cost-effective than in-patient care,[4] allowing greater investment in patient support and packages of incentives and enablers. There is a need for further research focusing on the cost-effectiveness of interventions to improve patient retention.

The observation that default rates tended to increase with cohort size could be because smaller cohort study settings may be more likely to be able to provide better quality care, as there are a smaller number of patients to manage. Health facility factors may also help explain this association, but we were unable to extract information on staff to patient ratio, quality of staff training and waiting times. Nevertheless, this indicates the potential for decentralised care utilising CHWs as a way of scaling up MDR-TB treatment without increasing default rates.

Legal action to enforce adherence to treatment gave mixed results, but overall did not appear to reduce default or help retain patients in care. Consideration of such approaches must be balanced against the human rights implications, and the potential consequences

of discouraging other patients from coming forward for diagnosis and treatment are significant.[102]

Finally, the lack of association between default and geographic variation or economic status shows that similar levels of retention in care can be achieved in a range of settings.

Strengths and limitations

The studies included in this review are subject to a number of limitations. Most studies were retrospective, observational studies, which may result in reporting bias and unmeasured confounding. The wide range of study settings, patient populations and interventions resulted in a highly heterogeneous sample with wide variations in reported default rates, but this is reflective of programmatic variability. We used a random-effects model, which is more appropriate for meta-analyses in which heterogeneity is anticipated, and attempted to explore potential sources of variation through subgroup analyses. However, this was limited by the quality of reporting. For example, one paper did not report any interventions to support patient retention, but on contacting the author seven incentives/enablers were provided;[26] thus, the fact that 31 papers did not report using any incentives/enablers does not necessarily mean that this was not done. However, the author survey response was poor, with less than half of the study authors contacted (33/75 authors) responding. Given the fact that all studies were observational in design, there are likely to be unmeasured factors that contributed to explaining the variability between studies. The differing definitions of default between studies also may mean that the proportion of patients defaulting was classified differently, although the majority used the standard WHO definition, limiting this potential variation. Other key variables, such as DOT or type of nutritional intervention, were rarely explicitly defined. Only English language publications were included, resulting in the exclusion of 18 studies, which partly explains the lack of representation of studies from low- and middle-income settings (nine studies were from these regions); however, our review was broadly representative, capturing reports from 31 countries, less than a third of which were from high-income settings. Finally, the large number of subgroup analyses undertaken gives potential for spurious results. Nevertheless, the fact that this review was able to describe interventions from 78 studies including over 20 000 patients provides a solid starting point for future research.

While this review focused on interventions targeting patient reasons for treatment default, responsibility for ensuring treatment adherence must be shared by the health care system.[103] Treatment default may also result from disrespectful, uncaring treatment from the health care staff involved,[7] issues that are not systematically reported. An important area for future research would be to investigate the impact of interventions focusing on health care system improvement, for example the impact of intensive staff education on the default rates of patients in MDR-TB programmes.[104]

CONCLUSIONS

This review provides an overview of interventions used across a large number of studies and a wide range of settings, allowing a broad generalisability of these findings to MDR-TB treatment programmes. The confirmation of the beneficial effect of DOT provision and the findings of lower default through use of community health workers, standardised regimens and combinations of adherence interventions, provide evidence for the provision of patient-friendly DOT provision for MDR-TB management, particularly in the context of cost-effective decentralised care. These findings may also support a move away from the controversial and ineffective use of legal action to enforce adherence. Perhaps one of the most important findings of this review was our inability to identify any rigorous comparative studies to assess interventions to reduce default and improve retention in care. Only one prospective comparative cohort was identified, comprising just 38 MDR-TB patients. This contrasts starkly with HIV/AIDS (acquired immune-deficiency syndrome) care, for which over 90 randomised trials have been conducted to assess adherence support interventions.[105] Comparative prospective studies would greatly strengthen the evidence base to allow better decision making in practice and policy where resources are limited to achieve the goal of universal access to effective MDR-TB treatment.

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APPENDIX A: SYSTEMATIC REVIEW PROTOCOL

BACKGROUND

Multidrug-resistant tuberculosis (MDR-TB) is a growing global issue. Despite high default rates reported from TB programmes providing second-line drug treatment worldwide, a limited amount of research has been conducted on methods to improve adherence. Default is an important cause of the spread and amplification of drug-resistant TB (DR-TB).

OBJECTIVE

To assess strategies to support adherence and reduce default in DR-TB treatment.

METHODS

Search strategy

MeSH and free word searches using terms for TB, treatment outcomes and drug resistance according to a compound search strategy (Table)

Databases

- Medline via Ovid
- EMBASE via Ovid

Table Search strategy

#1	Search TB.mp.
#2	Search Multi$.mp.
#3	Search Drug$.mp.
#4	Search Multidrug.mp.
#5	Search Multi-drug.mp
#6	Search extensively drug resistant.mp.
#7	Search extensively drug-resistant.mp
#8	Search drug resistanc$.mp.
#9	Search #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	Search #1 and #9
#11	Search MDRTB.mp.
#12	Search MDR-TB.mp.
#13	Search MDR TB.mp.
#14	Search XDRTB.mp.
#15	Search XDR-TB.mp.
#16	Search XDR TB.mp.
#17	Search Tuberculosis, Multidrug-Resistant/ or Extensively Drug-Resistant Tuberculosis/ (MeSH)
#18	Search #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	Search #10 and #18
#20	Search cure.mp.
#21	Search default.mp.
#22	Search successful.mp.
#23	Search follow up.mp.
#24	Search completion.mp.
#25	Search outcome.mp.
#26	Search failure.mp.
#27	Search death.mp.
#28	Search complian$.mp.
#29	Search adherence.mp.
#30	Search #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31	Search #19 and #30
#32	Search limit 31 to yr="2008–Current"

Inclusion criteria

Types of studies

- Clinical trials
- Cohort
- Case control
- Case series ⩾10 patients

Types of participants

Inclusions

- Adults (aged >16 years) diagnosed with culture-confirmed MDR-TB

Exclusions

- Paediatric studies
- Follow-up of <12 months
- Default rates unavailable after contacting the study authors

Types of intervention

Any programmatic interventions enhancing treatment adherence rates and reducing default. Further information from studies reviewed in full will be obtained by sending an online standardised survey to the authors (Figure).

Types of outcome

- Proportion of patients defaulting from treatment

Data analysis

Point estimates and 95% confidence intervals will be calculated for the proportion of treatment defaulters and pooled using a DerSimonian-Laird random effects model. Sub-group analyses will be carried out to determine the potential influence of clinical and programme interventions. Information on the following will be extracted as potential determining retention in care:

- Economic development
- Geographical region
- DR-TB burden
- Regimen
- Cohort size
- Directly observed treatment (DOT) provider
- DOT location
- Home visits
- Counselling
- Nutrition support
- Free care
- Transport
- Accommodation
- Sick leave
- Financial support
- Reminder devices
- Defaulter tracing
- Location
- Study design
- Legal action

1. Please provide your name, study and date published.
2. Does your study provide directly observed therapy (DOT)?
   - ❑ Yes
   - ❑ Partial
   - ❑ No

   If your study provides DOT, who is the DOT provider?
   - ❑ Nurse
   - ❑ Community health worker (paid)
   - ❑ Community health worker (volunteer)
   - ❑ Family member
   - ❑ Other (please specify) _____
3. Where is DOT provided (if used)?
   - ❑ Hospital (as in-patient)
   - ❑ Hospital (as out-patient)
   - ❑ Clinic
   - ❑ Home
4. Is treatment free of charge?
   - ❑ Yes
   - ❑ No
   - ❑ Other (please specify) _____
5. Was there access to counselling?
   - ❑ Yes
   - ❑ At start only
   - ❑ Throughout
   - ❑ No
   - ❑ Other (please specify) _____
6. Were any incentives or enablers used? Please describe incentives/enablers if used. Examples below:
   - ❑ Yes
   - ❑ No
   - ❑ Management of adverse side effects
   - ❑ Nutritional support (free meals/food vouchers/food packages)
   - ❑ Transport reimbursement
   - ❑ Accommodation (hospital/other)
   - ❑ Income generation activities
   - ❑ Disability allowance
   - ❑ Sick leave
   - ❑ Reminder devices
   - ❑ Home visits
   - ❑ Other (please specify) _____
7. Are patients institutionalised for some or all of their treatment? If so, for how long?
   - ❑ Yes
   - ❑ No
   - ❑ Partial
   - ❑ Other (please specify) _____
8. If default information is available, what definition for default did you use?
   - ❑ WHO definition
   - ❑ Other (please specify) _____
9. Did you measure adherence to medication? If so, how?
   - ❑ Yes
   - ❑ No
   - ❑ Other (please specify) _____
10. Were any other measures taken to support adherence?

    _____
    _____
    _____
    _____

Figure Author survey

APPENDIX B: Characteristics of studies

Study	Years	Type of study	Country	Population size (MDR/ XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/ enablers provided	Legal action used	Default definition
Abbate et al.[23]	2002–2008	RC	Argentina	17 (all XDR-TB)	Individualised	Never	NA	1/week	NS	NA	Yes	Yes: throughout	Nutrtional support; accommodation; reminder devices; defaulter tracing	NS	WHO definition*
Anger et al.[24]	2000–2006	RC	USA	16 (10 XDR-TB)	Individualised	DOT (partial)	NS	NS	NS	Hospital	NS	NS	NS	NS	NS
Banerjee et al.[25]	1993–2006	RC	USA	540 (17 XDR-TB)	Individualised	DOT (partial)	NS	NS	NS	NS	NS	NS	NS	NS	NS
Bang et al.[26]	1992–2007	RC	Denmark	27	Individualised	DOT (partial)	Nurse; family member	NS	Mixed	Hospital (in-patient) Hospital (out-patient) Home	Yes	Yes: throughout	Nutritional support; transport reimbursement; accommodation; disability allowance; sick leave; home visits	NS	WHO definition*
Bartu[27]	2001–2004	RC	Czech Republic	45	Individualised	NS	NS	NS	NS	NS	NS	NS	NS	No	WHO definition*
Bashar et al.[28]	1987–1997	RC	USA	28	Individualised	DOT (partial) Started in 1992	NS	NS	NS	NS	NS	NS	NS	NS	NS
Bendayan et al.[29]	2000–2005	RC	Israel	132	Individualised	DOT (always)	Nurse; CHW	Daily (DOT)	Yes	Hospital (in-patient) Clinic Home	Yes	Yes (timing/ frequency not stated)	Nutritional support; transport reimbursement	NS	WHO definition*
Bonilla et al.[30]	1997–2007	RC	Peru	43 XDR-TB	Individualised	DOT (partial)	Nurse; CHW (volunteer)	Daily (DOT)	Mixed	Clinic Home	Yes	Yes: throughout	Nutritional support; transport reimbursement; accommodation; home visits; adherence measured by treatment card	NS	WHO definition*
Bonnet et al.[31]	2003–2005	PC	Georgia	68	Individualised	DOT (always)	NS	Monthly	NS	Hospital (in-patient) Clinic	Yes	Yes: throughout (education, social support)	Nutritional support; transport reimbursement; accommodation; home visits	No	WHO definition*
Brust et al.[32]	2008–2009	RC	South Africa	45	Standardised	DOT (always)	Nurse CHW Family member	Daily (DOT) monthly out-patient appt	Mixed	Hospital (in-patient 2–6 weeks) Home	Yes	Yes: throughout (education)	Transport reimbursement; home visits	NS	WHO definition*
Brust et al.[33]	2000–2003	RC	South Africa	1209	Standardised	DOT (partial)	Nurse	Daily (DOT) monthly out-patient appt	Yes	Hospital (in-patient 4–6 months)	Yes	Unknown	NS	NS	WHO definition*

APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/enablers provided	Legal action used	Default definition
Burgos et al.[34]	1982–2000	RC	USA	48	Individualised	DOT (always/partial) After 1994 always	Nurse CHW	Daily (DOT)	Yes	Hospital Clinic Home	Yes	Yes: throughout	Nutritional support; transport reimbursement; accommodation; home visits	No	WHO definition*
Chiang et al.[35]	1992–1996	RC	Taiwan (China)	299	Individualised	None	Nurse	Weekly	Yes	NS	NS	NS	NS	NS	WHO definition*
Cox et al.[36]	2003–2005	PC	Uzbekistan	87	Individualised ($n = 52$) Standardised ($n = 35$)	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (6 months) Clinic	Yes	Yes: start only (psychiatric support)	Accommodation; nutritional support (patients and family)	NS	WHO definition*
Datta et al.[37]	2003–2007	PC	India	52 (8 XDR-TB)	Individualised	DOT (timing unclear)	NS	NS	NS	NS	No	NS	NS	NS	NS
Dhingra et al.[38]	2002–2004	PC	India	27	Individualised	Never	NA	Monthly until sputum conversion 3 months	NA	NA	No	NS	Treatment of co-morbidities		Withdrawal from treatment for any reason
Escudero et al.[39]	1998–2000	PC	Spain	25	Individualised	DOT (partial)	Nurse	Monthly	Yes	Hospital	NS	Yes: throughout (psychological support)	Defaulter tracing	NS	WHO definition*
Farley et al.[40]	2000–2004	PC	South Africa	757	Standardised	DOT (partial)	NS	Daily (DOT) at start; monthly	NS	Hospital	Yes	Yes: At start only	No	No	WHO definition*
Ferrara et al.[41]	1995–1999	RC	Italy	126	Individualised	DOT (partial)	Nurse	NS	Yes	Hospital (in-patient); out-patients (rarely)	Yes	Yes: throughout	No	NS	WHO definition*
Ferrer et al.[42]	1994–2007	PC	Mexico/USA border	46	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Clinic Home	Yes	Yes: timing unclear	Nutritional support; home visits	NS	WHO definition*
Gammino et al.[43]	1996–2004	RC	Peru Estonia Philippines Latvia Russia	1146	Individualised	DOT (always)	NS	NS	NS	Peru and Philippines: ambulatory (throughout) Estonia, Latvia and Russia: hospitalised	NS	NS	NS	NS	Final treatment outcomes assigned by the respective TB programmes

APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/enablers provided	Legal action used	Default definition
Geerligs et al.[44]	1985–1998	RC	Netherlands	44	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (predominantly) Out-patient	NS	Yes: timing unclear (education and psychosocial support)	NS	No	Patient compliance: 'patients considered compliant with therapy if they reported on a regular basis to the out-patient clinic and took their medications regularly according to physician, family or specialised TB nurses.'
Gegia et al.[45]	2008	PC	Georgia	380 (49 XDR)	Individualised	DOT (always)	Daily (DOT)	NS	NS	Hospital (in-patient) Clinic	Yes	Yes: throughout (psychological care)	Nutritional support; transport reimbursement	NS	WHO definition*
Gelmanova et al.[46]	2006–2008	PC	Russia	38	Individualised	DOT (always)	Nurse Driver (no family/SAT allowed)	DOT (twice daily) Physician visits every 10 days	Yes	Hospital (in-patient) Clinic Home Anywhere patient wanted (home, sputnik car, market place for homeless)	Yes	Yes: throughout (psychologist, social worker, substance abuse specialist)	Accommodation; transport passes; nutritional support; monthly hygiene sets; clothing provision; cell phones provided to nurses; defaulter tracing; adherence measured by counting pills taken over prescribed	No	WHO definition*
He et al.[47]	2004–2008	RC	China	241	Standardised	DOT (partial)	CHW	NS	Yes	Clinic Home	Yes	NS	NS	NS	WHO definition*
Heller et al.[48†]	2001–2008	PC	South Africa	57	Individualised	DOT (partial)	HCW	3x/week	Yes	Hospital (in-patient) Clinic	Yes	Yes: throughout	Nutritional support; disability allowance	NS	WHO definition*
Hersi et al.[49]	1989–1998	RC	Canada	24	Individualised	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Isaakidis et al.[50]	2007–2011	PC	India	45 (culture-confirmed)	Individualised	DOT (always: initially tried SAT but rapidly changed to DOT)	CHW	DOT (twice daily) 1/week with physician in 1st month 1–2/month after	NS	Clinic (no more than 10 min from patient's home) Hospital if complicated	Yes	Yes: throughout (psychological, group therapy, social outings)	Nutritional support; transport reimbursement; accommodation; home visits; treatment of comorbidities; default tracing; adherence measure by pill count and timeline of consultations	NS	WHO definition*

APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/ enablers provided	Legal action used	Default definition
Jeon et al.[51]	2001–2005	RC	South Korea	158 (all XDR-TB)	Individualised	DOT partial (since 2005)	Nurse	Not stated	Yes	Hospital (in-patient)	Yes	No	NS	NS	WHO definition*
Jeon et al.[52]	2004	RC	South Korea	202	Individualised	DOT (partial)	Nurse	Not stated	Yes	Hospital	Partial	No	Defaulter tracing	NS	WHO definition*
Joseph et al.[53]	2006–2007	PC	India	38	Standardised	DOT (always)	Nurse CHW	Daily (DOT)	NS	Hospital (2–4 weeks) Clinic	Yes	Yes: throughout (education)	Transport reimbursement; home visits; adherence measured by treatment card	NS	WHO definition*
Karagoz et al.[54]	1995–2000	PC	Turkey	142	Individualised	DOT (always)	Health worker Family member	Daily (DOT)	NS	Hospital Home	Yes	NS	Sick leave	NS	Failure to complete treatment for any reason
Keshavjee et al.[55]	2000–2004	RC	Russia	608 (29 XDR)	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (in-patient 2–4 months) Hospital (out-patient) Clinic Home	Yes	Yes: thoughout	Nutritional support; transport reimbursement; disability allowance; home visits; accommodation	No	WHO definition*
Khurram et al.[56]	2007–2010	RC	Pakistan	30	Individualised	DOT (partial)	Nurse	NS	Yes	Hospital (in-patient)	Variable	Yes: throughout	Nutritional support	No	WHO definition*
Kim et al.[57]	2000–2002	RC	South Korea	1407 (75 XDR-TB)	Individualised	Never	NA	NS	NA	NA	No	Yes: Timing unclear	NS	NS	WHO definition*
Kim et al.[58]	1996–2005	RC	South Korea	211 (43 XDR-TB)	Individualised	Never	NA	NS	NA	NA	No	No	NS	NS	WHO definition*
Kim et al.[59]	1988–1996	RC	South Korea	1011	Individualised	Never	NA	NS	NA	NA	No: patient had to pay for >30%	NS	Yes: Reminder postcards/ telephone calls	NS	Patient who had interrupted treatment for 2 consecutive months or more and never returned to treatment
Kliiman and Altraja[60]	2003–2005	RC	Estonia	235 (54 XDR)	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital Clinic	Yes	NS	Nutritional support; transport reimbursement; defaulter tracing	Yes	WHO definition*
Kunawararak et al.[61]	2008–2009	PC	Thailand	38	Standardised	DOT (always)	Family member	Monthly	No	Home	NS	Yes: throughout (medication education)	Mobile phone reminders	NS	NS

APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/ XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/ enablers provided	Legal action used	Default definition
Kvasnovsky et al.[62]	2006–2008	RC	South Africa	206 XDR	Standardised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (in-patient) Clinic	Yes	Yes: throughout	Nutritional support; accommodation; access to voluntary HIV test and treatment	NS	WHO definition*
Kwon et al.[63]	1995–2004	RC	South Korea	155 (27 XDR-TB)	Individualised	DOT (partial)	Nurse	NS	Yes	Hospital (in-patient)	NS	NS	NS	NS	WHO definition*
Laniado-Laborín et al.[64]	2006–2010	RC	Mexico	42 (2 XDR-TB)	Individualised	DOT (always)	CHW	Daily (DOT)	Yes	Clinic Home	Yes	Yes: throughout	Nutritional support; home visits; adherence measured with strict DOT, bi-weekly health promoter report	NS	WHO definition*
Leimane et al.[65]	2000–2004	RC	Latvia	1027 (48 XDR-TB)	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (in-patient) Hospital (out-patient)	Yes	Yes: throughout	Nutritional support; transport reimbursement; disability allowance; sick leave (mentions lack of proper side effect management and comprehensive care)	Yes: involuntary isolation	WHO definition*
Liu et al.[66]	1996–2009	RC	China	576 (48 XDR-TB)	Individualised	DOT (post 2001)	NS	NS	NS	Hospital Ambulatory	No	NS	Telephone follow up	NS	WHO definition*
Lockman et al.[67]	1994–1998	RC	Estonia	46	Individualised	DOT (rarely)	Nurse	NS	Yes	Hospital (in-patient)	Yes	No	NS	NS	Failure of a patient to return for a prescription to receive anti-tuberculosis drugs for >2 months or as a known break in treatment of >2 months
Loveday et al.[68]	2008–2009	PC	South Africa	419	Standardised	DOT (partial)	Nurse Family member (rarely done)	NS	NS	Hospital Home	Yes	Yes: throughout; patients rarely reminded of availability	Decentralised care	NS	WHO definition*
Loveday et al.[68]	2008–2009	PC	South Africa	441	Standardised	DOT (partial)	Nurse Family member (rarely done)	NS	NS	Hospital (in-patient: longer for centralised arm) Home	Yes	Yes: throughout; patients rarely reminded of availability	NS	NS	WHO definition*
Malla et al.[69]	2005–2006	RC	Nepal	175	Standardised	DOT (always)	Health worker	Daily (DOT)	NS	Clinic	Yes	NS	Treatment supporter (nominated by patient); defaulter tracing	NS	NS

APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/enablers provided	Legal action used	Default definition
Masjedi et al.[70]	2002–2006	PC	Iran	43	Standardised	DOT (partial)	CHW	NS	Yes	Hospital in-patient (until sputum conversion)	Yes	Yes: timing unclear (psychological)	Nutritional assessment and dietary advice; accommodation; disability allowance; sick leave	NS	WHO definition*
Migliori et al.[71]	1999–2006	RC	Estonia Germany Italy Russia	425 (64 XDR-TB)	Individualised	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mitnick et al.[72]	1996–1999	RC	Peru	75	Individualised	DOT (always)	CHWs	2–3×/d (DOT)	Some paid, some compensated with food baskets	Clinic Home	Yes	Yes: throughout (group therapy, education)	Nutritional support; income generation activities; transport reimbursement; home visits; housing improvements; socioeconomic support	NS	Withdrawal from treatment was defined by ⩾1 months of missed treatment during Year 1, and ⩾2 months missed during Year 2
Mitnick et al.[73]	1999–2002	RC	Peru	651 (48 XDR-TB)	Individualised	DOT (always)	CHWs	2–3×/day (DOT)	Some paid, some compensated with food baskets	Clinic Home	Yes	Yes: throughout (group therapy, education, psychiatric)	Nutritional support; income generation activities; transport reimbursement; home visits; housing improvements; socioeconomic support	NS	Physician-defined end point assigned on failure of attempts to return to treatment those patients who had not been adhering to their treatment regimen
Mohammadi et al.[74]	2000–2005	RC	Oman	13	Individualised	DOT (always)	NS	<1/month	NS	Hospital Clinic	Yes	NS	NS	'Enforced DOTS'	NS
Munsiff et al.[75]	1992–1997	RC	USA	610	Individualised	DOT (always)	Nurse CHW	Daily (DOT)	Yes	Hospital (out-patient) Clinic Home Hospital in-patients not eligible for DOT	Yes	Yes: (timing unclear) (psychological)	Nutritional support; transport reimbursement; home visits	Yes (17%)	Default includes patients who move to another jurisdiction, are lost or refuse treatment
Ollé-Goig et al.[76]	1983–1993	RC	Bolivia	143	Individualised	Never	NA	NS	NA	NA	NS	NS	Nutritional support	NS	A patient who interrupted the consultations before finishing the treatment regimen and did not return to centre

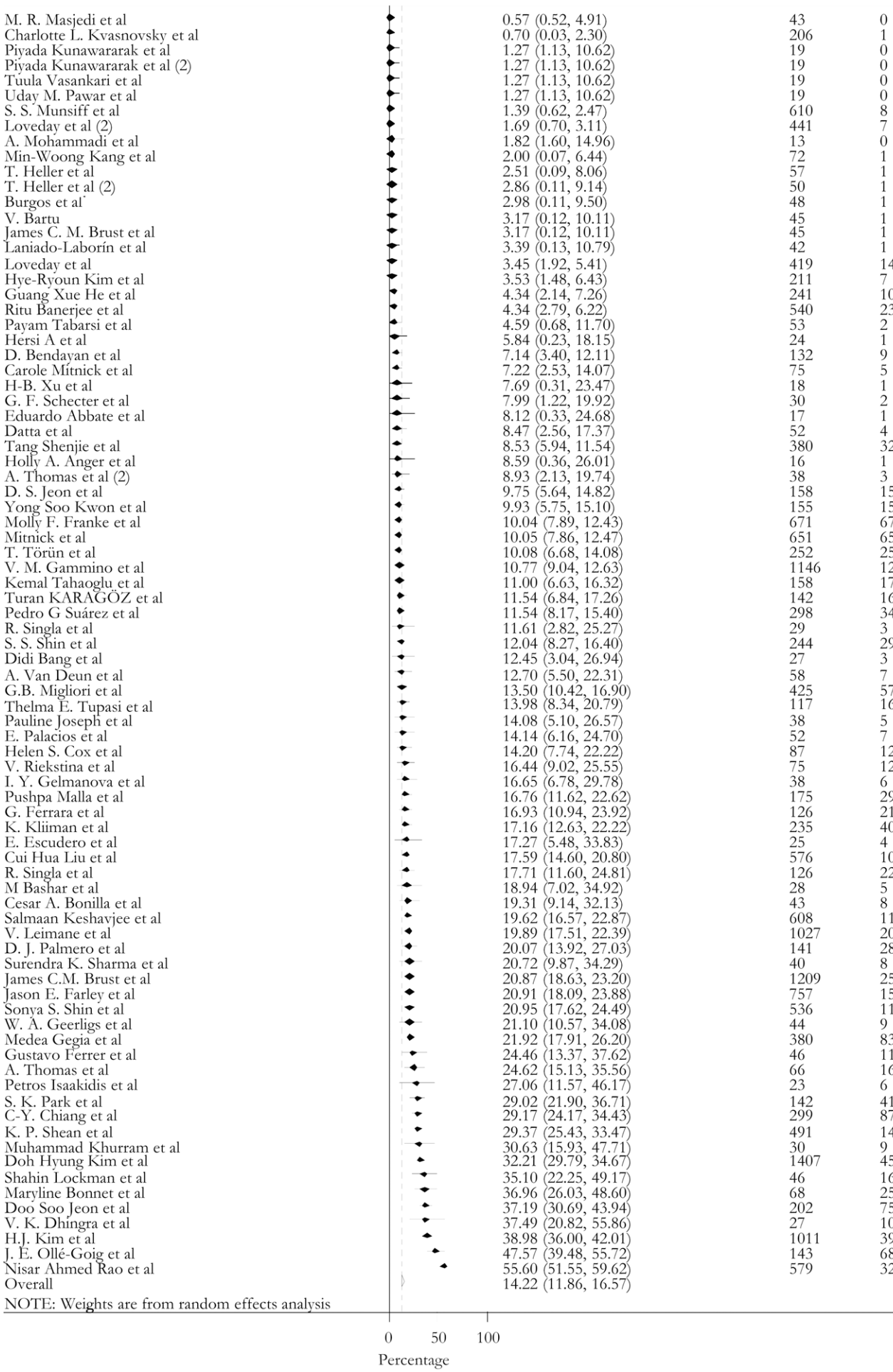
APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/enablers provided	Legal action used	Default definition
Palacios et al.[77]	1996–2005	RC	Peru	52	Individualised (n = 44) Standardised (n = 8)	DOT (always)	CHWs	Daily (DOT)	NS	Clinic Home Hospital (in-patient) if unstable	Yes	Psychosocial support (not free)	Nutritional support; income generation activities; home visits	NS	WHO definition*
Palmero et al.[78]	1996–1999	RC	Argentina	141	Individualised	DOT (partial)	Nurse	1/week	Yes	Hospital	NS	NS	Accommodation; defaulter tracing	NS	More than 1 month's absence from weekly medical appointments
Park et al.[79]	1998–2000	RC	South Korea	142	Standardised	Never	NA	NS	NA	NA	Yes	NS	NS	No	NS
Pawar et al.[80]	2004–2007	PC	India	25	Individualised	DOT (timing unclear)	NS	NS	NS	NS	No	NS	NS	NS	NS
Rao et al.[81]	1996–2007	RC	Pakistan	579	Individualised	DOT (partial)	NS	Monthly	NS	Hospital (in-patient for 3–6 months)	NS	NS	Defaulter tracing (minimal)	NS	WHO definition*
Riekstina et al.[82]	2002	PC	Latvia	75	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (in-patient) Clinic	Yes	Yes (timing unclear)	Nutritional support; transport reimbursement; sick leave; reminder devices; nurse recorded medication intake every day	NS	WHO definition*
Schecter et al.[83]	2003–2007	RC	USA	30	Individualised	DOT (always)	CHW	Daily (DOT)	Yes	Clinic Home	Variable	Yes (variable)	Nutritional support; transport reimbursement; accommodation; home visits	NS	WHO definition*
Sharma et al.[84]	2005–2008	PC	India	40	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	'Standard definitions'
Shean et al.[85]	1992–2002	RC	South Africa	491	Individualised	DOT (partial)	NS	Weekly (nurses)	NS	Hospital (in-patient) Clinic	Yes	Yes: limited informal	TB grants	NS	NS
Shin et al.[86]	2000–2004	RC	Russia	536 (34 XDR-TB)	Individualised	DOT (always)	Nurse	Daily (DOT)	Yes	Hospital (in-patient) Hospital (out-patient) Clinic Outposts	Yes	Yes: psychiatric (frequency/timing not stated	Nutritional support; transport reimbursement; accommodation; disability allowance	Yes	Laserson et al. definition‡

APPENDIX B (*Continued*)

Study	Years	Type of study	Country	Population size (MDR/XDR-TB patients)	Regimen	DOT	DOT provider	Contact with HCW after discharge	DOT provider paid	DOT location	User fees charged	Access to counselling	Incentive/enablers provided	Legal action used	Default definition
Singla et al.[87]	2006–2011	PCS	India	29 (16 XDR-TB)	Individualised	Never	NA	Every 2 weeks	NA	NA	No	No	Adherence monitored by checking empty blister packets	NS	Laserson et al. definition‡
Singla et al.[88]	2002–2006	RC	India	126	Standardised	DOT (always)	CHW Family member (evening dose)	Daily (DOTS)	CHW paid	Hospital (1 month) Clinic	Yes	NS	Adherence measured by checking empty blister packets at each out-patients appointment	NS	NS
Suárez et al.[89]	1997–1999	PC	Peru	298	Standardised	DOT (always)	Nurse	Daily (DOT)	Yes	Clinic	Yes	NS	Nutritional support (food parcels); appointment cards	NS	Patients who did not attend to take their drugs for ⩾1 month
Tabarsi et al.[90]	2004–2007	RC	Iran	53	Standardised	DOT (always)	NS	Daily (DOT) 1×/6 months	NS	Hospital (in-patient) Clinic	Yes	Yes: timing unclear (psychological)	Nutritional assessments and advice	NS	WHO definition*
Tang et al.[91]	2007–2009	RC	China	380 (94 XDR-TB)	Individualised	DOT (always)	Family member	NS	NS	Out-patient	NS	NS	NS	NS	WHO definition*
Thomas et al.[92]	1999–2003	RC	India	66 (4 XDR-TB)	Individualised	None	HCW	3×/week	NS	NS	NS	NS	NS	NS	NS
Thomas et al.[92]	2006–2007	RC	India	38 (6 XDR-TB)	Individualised	DOT (timing unclear)	HCW	Daily (DOT)	NS	NS	NS	NS	NS	NS	NS
Törün et al.[93]	1992–2004	RC	Turkey	252	Individualised	DOT (partial)	NS	NS	NS	Hospital	Yes	NS	Extended sick leave	NS	WHO definition*
Tupasi et al.[94]	1999–2002	RC	The Philippines	117	Individualised	DOT (always)	Health worker	Daily (DOT)	Yes	Hospital Clinic Home	Yes	Yes: throughout (education, psychosocial)	Defaulter tracing	NS	Laserson et al. definition‡
Van Deun et al.[95]	1997–1999	PC	Bangladesh	58	Standardised	DOT (partial)	Health worker	At least 1/month	NS	Hospital (3 months) Out-patient (last 6 months SAT)	Yes	Yes: timing unclear	Nutritional support	NS	NS
Vasankari et al.[96]	1994–2005	RC	Finland	19	Individualised	NS	NS	NS	NS	NS	NS	Not stated	NS	NS	WHO definition*
Xu et al.[97]	2007–2010	RC	China	18 (15 XDR-TB)	Individualised	DOT (always)	Nurse CHW	Daily (DOT)	NS	Hospital (in-patient) Out-patient	No	NS	NS	NS	Laserson et al. definition‡

* World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 4th ed. WHO/HTM/TB/2009. 420. Geneva, Switzerland: WHO, 2009.
† One arm of the Heller study excluded, as default rates for patients treated in the community only calculated at 6 months.
‡ Laserson K F, Thorpe L E, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9: 640–645.
MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug resistant tuberculosis; DOT = directly observed treatment; HCW = health care worker; RC = retrospective cohort; NA = not applicable; NS = not stated; WHO = World Health Organization; CHW = community health worker; PC = prospective cohort; SAT = self-administered treatment; PCS = prospective case series; HIV = human immunodeficiency virus.


Study
Default (95% CI)
n
e
M. R. Masjedi et al 0.57 (0.52, 4.91) 43 0
Charlotte L. Kvasnovsky et al 0.70 (0.03, 2.30) 206 1
Piyada Kunawararak et al 1.27 (1.13, 10.62) 19 0
Piyada Kunawararak et al (2) 1.27 (1.13, 10.62) 19 0
Tuula Vasankari et al 1.27 (1.13, 10.62) 19 0
Uday M. Pawar et al 1.27 (1.13, 10.62) 19 0
S. S. Munsiff et al 1.39 (0.62, 2.47) 610 8
Loveday et al (2) 1.69 (0.70, 3.11) 441 7
A. Mohammadi et al 1.82 (1.60, 14.96) 13 0
Min-Woong Kang et al 2.00 (0.07, 6.44) 72 1
T. Heller et al 2.51 (0.09, 8.06) 57 1
T. Heller et al (2) 2.86 (0.11, 9.14) 50 1
Burgos et al 2.98 (0.11, 9.50) 48 1
V. Bartu 3.17 (0.12, 10.11) 45 1
James C. M. Brust et al 3.17 (0.12, 10.11) 45 1
Laniado-Laborín et al 3.39 (0.13, 10.79) 42 1
Loveday et al 3.45 (1.92, 5.41) 419 14
Hye-Ryoun Kim et al 3.53 (1.48, 6.43) 211 7
Guang Xue He et al 4.34 (2.14, 7.26) 241 10
Ritu Banerjee et al 4.34 (2.79, 6.22) 540 23
Payam Tabarsi et al 4.59 (0.68, 11.70) 53 2
Hersi A et al 5.84 (0.23, 18.15) 24 1
D. Bendayan et al 7.14 (3.40, 12.11) 132 9
Carole Mitnick et al 7.22 (2.53, 14.07) 75 5
H-B. Xu et al 7.69 (0.31, 23.47) 18 1
G. F. Schecter et al 7.99 (1.22, 19.92) 30 2
Eduardo Abbate et al 8.12 (0.33, 24.68) 17 1
Datta et al 8.47 (2.56, 17.37) 52 4
Tang Shenjie et al 8.53 (5.94, 11.54) 380 32
Holly A. Anger et al 8.59 (0.36, 26.01) 16 1
A. Thomas et al (2) 8.93 (2.13, 19.74) 38 3
D. S. Jeon et al 9.75 (5.64, 14.82) 158 15
Yong Soo Kwon et al 9.93 (5.75, 15.10) 155 15
Molly F. Franke et al 10.04 (7.89, 12.43) 671 67
Mitnick et al 10.05 (7.86, 12.47) 651 65
T. Törün et al 10.08 (6.68, 14.08) 252 25
V. M. Gammino et al 10.77 (9.04, 12.63) 1146 123
Kemal Tahaoglu et al 11.00 (6.63, 16.32) 158 17
Turan KARAGÖZ et al 11.54 (6.84, 17.26) 142 16
Pedro G Suárez et al 11.54 (8.17, 15.40) 298 34
R. Singla et al 11.61 (2.82, 25.27) 29 3
S. S. Shin et al 12.04 (8.27, 16.40) 244 29
Didi Bang et al 12.45 (3.04, 26.94) 27 3
A. Van Deun et al 12.70 (5.50, 22.31) 58 7
G.B. Migliori et al 13.50 (10.42, 16.90) 425 57
Thelma E. Tupasi et al 13.98 (8.34, 20.79) 117 16
Pauline Joseph et al 14.08 (5.10, 26.57) 38 5
E. Palacios et al 14.14 (6.16, 24.70) 52 7
Helen S. Cox et al 14.20 (7.74, 22.22) 87 12
V. Riekstina et al 16.44 (9.02, 25.55) 75 12
I. Y. Gelmanova et al 16.65 (6.78, 29.78) 38 6
Pushpa Malla et al 16.76 (11.62, 22.62) 175 29
G. Ferrara et al 16.93 (10.94, 23.92) 126 21
K. Kliiman et al 17.16 (12.63, 22.22) 235 40
E. Escudero et al 17.27 (5.48, 33.83) 25 4
Cui Hua Liu et al 17.59 (14.60, 20.80) 576 101
R. Singla et al 17.71 (11.60, 24.81) 126 22
M Bashar et al 18.94 (7.02, 34.92) 28 5
Cesar A. Bonilla et al 19.31 (9.14, 32.13) 43 8
Salmaan Keshavjee et al 19.62 (16.57, 22.87) 608 119
V. Leimane et al 19.89 (17.51, 22.39) 1027 204
D. J. Palmero et al 20.07 (13.92, 27.03) 141 28
Surendra K. Sharma et al 20.72 (9.87, 34.29) 40 8
James C.M. Brust et al 20.87 (18.63, 23.20) 1209 252
Jason E. Farley et al 20.91 (18.09, 23.88) 757 158
Sonya S. Shin et al 20.95 (17.62, 24.49) 536 112
W. A. Geerligs et al 21.10 (10.57, 34.08) 44 9
Medea Gegia et al 21.92 (17.91, 26.20) 380 83
Gustavo Ferrer et al 24.46 (13.37, 37.62) 46 11
A. Thomas et al 24.62 (15.13, 35.56) 66 16
Petros Isaakidis et al 27.06 (11.57, 46.17) 23 6
S. K. Park et al 29.02 (21.90, 36.71) 142 41
C-Y. Chiang et al 29.17 (24.17, 34.43) 299 87
K. P. Shean et al 29.37 (25.43, 33.47) 491 144
Muhammad Khurram et al 30.63 (15.93, 47.71) 30 9
Doh Hyung Kim et al 32.21 (29.79, 34.67) 1407 453
Shahin Lockman et al 35.10 (22.25, 49.17) 46 16
Maryline Bonnet et al 36.96 (26.03, 48.60) 68 25
Doo Soo Jeon et al 37.19 (30.69, 43.94) 202 75
V. K. Dhingra et al 37.49 (20.82, 55.86) 27 10
H.J. Kim et al 38.98 (36.00, 42.01) 1011 394
J. E. Ollé-Goig et al 47.57 (39.48, 55.72) 143 68
Nisar Ahmed Rao et al 55.60 (51.55, 59.62) 579 322
Overall 14.22 (11.86, 16.57)
NOTE: Weights are from random effects analysis
0
50
100
Percentage

APPENDIX D

Table D.1 Country characteristics

	Studies *n*	Patients *n*	Default % (95%CI)	*P* value
Economic development*				
Low-income	2	233	15.5 (10.9–20.1)	Reference
Lower middle-income	18	1892	22.1 (13.1–31.1)	0.20
Upper middle-income	32	9270	11.7 (8.6–14.8)	0.17
High-income	23	5282	14.4 (8.8–20.0)	0.76
Region†				
Africa	8	3625	11.7 (5.3–18.2)	Reference
Eastern Mediterranean	5	718	18.5 (0–43.9)	0.4
Europe	20	4337	15.8 (12.5–19.0)	0.27
South East Asia	14	729	12.8 (7.9–17.7)	0.4
The Americas	17	2804	11.8 (8.0–15.6)	0.97
Western Pacific	13	4935	18.7 (11.1–26.4)	0.17
DR-TB burden, %‡				
0–4.9	33	5948	12.7 (8.4–17.0)	Reference
5–9.9	29	6462	17.2 (13.0–21.4)	0.14
>10	15	5459	14.9 (12.4–17.4)	0.39

*According to World Bank classification.
†According to World Health Organization classification.
‡According to World Health Organization, Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO progress report. WHO/HTM/TB/2011.3. Geneva, Switzerland: WHO, 2011.
CI = confidence interval; DR-TB = drug-resistant tuberculosis.

Table D.2 Provision of treatment

	Studies *n*	Patients *n*	Default % (95%CI)	*P* value
Regimen				
Standardised	17	4289	9.3 (5.6–13.0)	Reference
Individualised	58	13826	16.6 (13.3–19.9)	0.004
Mixed	2	139	14.2 (8.5–19.9)	0.16
Cohort size				
<100	40	1582	11.3 (8.7–13.9)	Reference
100–499	25	6055	15.3 (11.8–18.8)	0.07
500–999	8	4857	18.7 (9.5–27.9)	0.13
>1000	5	5800	24.5 (14.8–34.2)	0.01
DOT				
None	10	3352	26.2 (15.5–37.0)	Reference
Partial	24	6635	16.9 (12.0–21.9)	0.12
Always	36	7635	12.1 (9.4–14.8)	0.01
DOT provider				
Health care worker	22	6069	18.1 (13.5–22.7)	Reference
Family/community health worker	9	954	6.1 (2.1–10.0)	<0.01
Mix	17	2345	9.6 (6.7–12.4)	<0.01
DOT location				
Facility	36	9845	17.3 (13.4–21.3)	Reference
Home/mixed	23	4010	14.9 (12.3–17.4)	0.32
Home visits				
No/not stated	63	15888	15.4 (12.5–18.4)	Reference
Yes	15	2406	12.2 (7.6–16.9)	0.3

CI = confidence interval; DOT = directly observed treatment.

Table D.3 Counselling

	Studies *n*	Patients *n*	Default % (95%CI)	*P* value
Any counselling (combines next four subgroups)				
No	62	15 492	15.1 (12.1–18.1)	Reference
Yes	16	2 802	14.0 (9.1–18.9)	0.70
Psychiatric				
No/not stated	75	17 020	15.1 (7.1–23.0)	Reference
Yes	3	1 274	14.9 (12.4–17.4)	0.96
Group therapy				
No/not stated	75	17 545	15.0 (12.4–17.6)	Reference
Yes	3	749	10.4 (5.1–15.8)	0.97
Psychosocial				
No/not stated	65	16 305	14.9 (12.0–17.7)	Reference
Yes	13	1 989	15.1 (9.0–21.3)	0.95
Substance abuse support				
No/not stated	77	18 256	14.9 (12.3–17.4)	Reference
Yes	1	38	16.6 (5.1–28.1)	0.78
Education				
No/not stated	68	16 799	15.6 (12.8–18.4)	Reference
Yes	10	1 495	9.3 (5.2–13.3)	0.01

CI = confidence interval.

Table D.4 Other

	Studies *n*	Patients *n*	Default % (95%CI)	*P* value
Incentives/enablers				
No/not stated	31	8734	12.9 (9.4–16.5)	Reference
Yes	47	9560	16.2 (12.6–19.8)	0.20
Nutrition support				
No/not stated	50	12652	14.7 (11.2–18.1)	Reference
Yes	28	5642	15.2 (11.6–18.9)	0.85
Free care				
Yes	47	10700	14.2 (11.5–16.8)	Reference
No	9	3350	17.4 (6.6–28.2)	0.57
Transport				
No/not stated	60	14632	15.2 (12.1–18.2)	Reference
Yes	18	3662	13.9 (9.3–18.5)	0.64
Accommodation				
No/not stated	64	16379	15.1 (12.2–17.9)	Reference
Yes	14	1915	14.1 (8.4–19.7)	0.76
Sick leave				
No/not stated	72	16728	15.2 (12.5–17.8)	Reference
Yes	6	1566	11.7 (3.4–20.0)	0.43
Any financial support (combines next 3 subgroups)				
No	69	15263	15.0 (12.3–17.7)	Reference
Yes	9	3031	14.3 (7.5–21.0)	0.85
Disability allowance				
No/not stated	72	15996	14.9 (12.3–17.5)	Reference
Yes	6	2298	14.8 (5.9–23.6)	0.98
Financial support				
No/not stated	75	17077	14.9 (12.3–17.4)	Reference
Yes	3	1217	15.6 (2.2–29.0)	0.92
Income generation activities				
No/not stated	75	17516	15.1 (12.5–17.7)	Reference
Yes	3	778	9.9 (7.8–12.0)	<0.01
Reminder devices				
No/not stated	72	16733	14.7 (12.2–17.2)	Reference
Yes	6	1561	16.2 (2.1–30.3)	0.84
Defaulter tracing				
No/not stated	69	16883	13.7 (11.3–16.1)	Reference
Yes	9	1411	23.5 (10.4–36.6)	0.15
Location				
Urban	54	11360	16.4 (13.0–19.8)	Reference
Mixed	22	6470	12.6 (9.3–15.9)	0.12
Rural	2	464	3.4 (1.8–5.1)	<0.01
Study design				
Retrospective	54	15094	15.5 (12.3–18.7)	Reference
Prospective	23	3200	15.5 (12.9–17.4)	0.68
Legal action				
Yes	5	2421	12.3 (1.5–23.1)	Reference
No	73	15873	15.1 (12.4–17.8)	0.62

CI = confidence interval.

Table D.5 Combination interventions

	Studies *n*	Patients *n*	Default % (95%CI)	*P* value
Nutrition and transport costs				
No	62	14715	15.0 (12.0–18.0)	Reference
Yes	16	3579	14.7 (9.6–19.7)	0.92
Financial support and nutrition and transport costs				
No	76	17568	15.1 (12.5–17.7)	Reference
Yes	2	726	9.7 (7.5–11.8)	0.002

CI = confidence interval.

RÉSUMÉ

CONTEXTE : L'extension du traitement de la tuberculose à germes multirésistants (TB-MDR) constitue une priorité mondiale de santé. Toutefois, les régimes actuels de traitement sont longs et comportent d'importants effets collatéraux et par voie de conséquence, les taux signalés d'abandon du traitement sont élevés. Cette revue systématique a visé à identifier les stratégies de réduction des abandons du traitement.

MÉTHODES : Nous avons mené une recherche systématique jusqu'à mai 2012 pour identifier les études décrivant les interventions de soutien aux patients bénéficiant d'un traitement de la TB-MDR. L'influence potentielle des interventions étudiées a été explorée par analyse de sous-groupes.

RÉSULTATS : Dans 31 pays, 75 études ont fourni des résultats finaux pour 18 294 patients. Les taux d'abandon vont de 0,5% à 56%, la proportion combinée étant de 14% (IC95% 12,4–17,4). Les stratégies identifiées comme en association avec une diminution des taux d'abandon ont comporté l'engagement des travailleurs de santé de la collectivité comme pourvoyeurs du traitement directement observé (DOT), la fourniture du DOT d'un bout à l'autre du traitement, des tailles plus petites de cohortes et l'éducation des patients.

INTERPRETATION : Les interventions actuelles en vue de soutenir l'adhésion et la rétention sont médiocrement décrites et reposent sur de faibles évidences. Cette revue a permis d'identifier un certain nombre d'interventions prometteuses et non-coûteuses réalisables pour la mise en œuvre et l'extension des programmes de TB-MDR. Les taux élevés d'abandon signalés dans de nombreux programmes soulignent le besoin de raffiner davantage et d'évaluer des ensembles simples d'interventions de soutien aux patients.

RESUMEN

MARCO DE REFERENCIA: La ampliación de escala del tratamiento contra la tuberculosis multidrogorresistente (TB-MDR) constituye una prioridad sanitaria mundial. Sin embargo, los regímenes actuales son prolongados, se asocian con un número considerable de reacciones adversas y en consecuencia se notifican altas tasas de abandono terapéutico. En el presente examen sistemático se intentó determinar las estrategias que favorecen la disminución de los abandonos del tratamiento.

MÉTODOS: Se llevó a cabo una búsqueda sistemática hasta mayo del 2012 de los estudios que describían intervenciones de apoyo a los pacientes que reciben tratamiento contra la TB-MDR. Mediante análisis por subgrupos se examinó la posible influencia de las intervenciones de los estudios.

RESULTADOS: Setenta y cinco estudios aportaron desenlaces correspondientes a 18 294 pacientes en 31 países. Las tasas de abandono terapéutico oscilaron entre 0,5% y 56%, con una proporción acumulada de 14,8% (IC95% 12,4–17,4). Se observó que las estrategias asociadas con tasas inferiores de abandono fueron la participación de profesionales de salud comunitarios como proveedores del tratamiento directamente observado (DOT), el suministro de DOT durante todo el tratamiento, el menor tamaño de las cohortes y la provisión de educación a los pacientes.

CONCLUSIÓN: La descripción de las intervenciones actuales que refuerzan el cumplimiento terapéutico y la permanencia de los pacientes en el tratamiento es insuficiente y se fundamenta en pruebas poco convincentes. Con el presente examen sistemático se definió una serie de intervenciones promisorias y poco costosas que son factibles en la ejecución y la ampliación de escala de los programas de atención de la TB-MDR. Las altas tasas de abandono terapéutico notificadas en muchos programas ponen de manifiesto la urgente necesidad de definir y evaluar mejor las intervenciones con grupos sencillos de medidas de apoyo a los pacientes.