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Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review

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Take home message:
To effectively improve retention rates in the treatment of drug-resistant tuberculosis, psychosocial support - provided through one-on-one counselling and home visits – should be provided throughout treatment, rather than only during the intensive phase.

ABSTRACT

Background: The global loss to follow-up (LTFU) rate among drug-resistant TB (DR-TB) patients remains high at 15%. We conducted a systematic review to explore interventions to reduce LTFU during DR-TB treatment.

Methods: We searched for studies published between Jan. 2000 and Dec. 2017 that provided any form of psychosocial or material support for patients with DR-TB. We estimated point estimates and 95% confidence intervals (CI) of the proportion LTFU. We performed subgroup analyses and pooled estimates using an exact binomial likelihood approach.

Findings: We included 35 DR-TB cohorts from 25 studies. Cohorts that received any form of psychosocial or material support had lower LTFU rates than those that received standard care. Psychosocial support throughout treatment – via counselling sessions or home visits – was associated with lower LTFU rates compared to when support was provided through a limited number of visits or not at all, with pooled proportions LTFU of 8.4% (4.0-16.7%) and 20.5% (15.2 – 27.0%), respectively.

Conclusion: Our review suggests psychosocial support should be provided throughout DR-TB treatment in order to reduce treatment LTFU. Future studies should explore the potential of providing self-administered therapy complemented with psychosocial support during the continuation phase.

INTRODUCTION

Approximately 15% of 1.67 million annual global deaths due to tuberculosis (TB) are from rifampicin-resistant (RR) or multidrug-resistant tuberculosis (MDR-TB), a strain resistant to at least rifampicin and isoniazid, the two most effective first-line anti-TB drugs [1]. Treating RR/MDR-TB with second-line drugs is significantly costlier, longer, more toxic, and less effective than treating drug-susceptible TB. Rates of treatment non-completion and interruption rates in RR/MDR-TB are thus significantly higher. Approximately 15% of all RR/MDR-TB patients are lost to follow-up from treatment, defined as interrupting treatment for more than two months, and only half are successfully treated [1].

Treatment non-adherence and interruption diminish the quality-of-life of people living with RR/MDR-TB [2] and increase disease transmission. Developing effective interventions to improve adherence and retention in RR/MDR-TB care is crucial. An earlier systematic review [3] found MDR-TB treatment strategies that used a more comprehensive approach – including financial and nutritional support – tended to have fewer losses to follow-up. However, the review, which included 75 studies, did not identify any non-observational, experimental trials for inclusion, and thus was subject to a high risk for confounding bias.

In light of increased global efforts to improve treatment and management for RR/MDR-TB, we have synthesized new evidence, including observational and quasi-experimental studies published since the earlier systematic review, on the effectiveness of interventions in RR/MDR-TB treatment that include various combinations of psychosocial, educational or material support. We describe and assess these interventions, their effectiveness in reducing losses to follow-up and improving adherence, and issues affecting their implementation.

METHODS

This review is reported according to the PRISMA statement [4], registered on the PROSPERO database (#CRD42016052854), and analyzed according to MOOSE guidelines [5].

Search strategy

We searched MEDLINE (PubMed), EMBASE and EMBASE Classic, and ISI-Web of Science, Scopus, PsychInfo, Global Health, Social Work abstracts, and Cochrane CENTRAL, for studies published between 2000 (the year the WHO first launched DOTS-Plus pilot projects for treatment and management of MDR-TB [6]) and Dec. 14, 2017. Our search strategy combined the following concepts: 1) tuberculosis; 2) adherence/compliance/default/drop-out; 3) concordance or contract; 4) linkage/referral/tracing; 4) reminder/monitor; 5) training/education/counselling; 6) motivational/behavioural/social support; 6) patient-centred care/retention; 7) health system/services intervention/program/strategy; 8) cash/reimbursement/refund/reward/incentives; 10) dietary/nutritional supplement or food; 11) directly observed therapy (DOT); and 15) evaluation (see **Supplement Table 1** for search details). No geographic or language restrictions were applied. We identified additional articles from reference lists of identified original articles, and four recent systematic reviews on: strategies for reducing MDR-TB patient losses to follow-up [3]; decentralized models of MDR-TB care [7]; community-based MDR-TB treatment [8]; and DOT in MDR-TB treatment [9].

Study screening and eligibility criteria

We included primary studies that: 1) reported final treatment outcomes including losses to follow-up; and 2) examined a health services intervention targeting patients with RR/MDR-TB that included *at least* some form of psychosocial, educational or material support. We defined each as: any support provided to address psychological or social issue; any education or counselling provided pertaining to TB treatment; and any nutritional (e.g. food package or hot meals) or financial (e.g. reimbursement for treatment-related expenses and lost wages) support, respectively. Studies only examining surgical or drugs-related interventions were not included, other exclusion criteria included: 1) fewer than 10 cases of RR/MDR-TB; 2) only children (<18 years old) included, due to their likely dependence on adult caregivers for adherence; 3) only interim outcomes reported (defined as outcomes, such as 6-month sputum conversion, that occurred before the planned end of treatment); 4) no details on drug susceptibility testing for at least rifampicin; or 5) no treatment with second-line drugs. One reviewer (SL) screened all titles and abstracts, and two independent reviewers (SL and AD) screened full reports of potentially relevant studies, discrepancies were resolved by discussion. We contacted authors of published abstracts and studies to obtain further information when necessary.

Types of outcome measures

Our primary outcome of interest was loss to follow-up, defined as treatment interruption for ≥2 months [1]. Secondary outcomes included any measures of treatment adherence.

Data extraction and analysis

One reviewer (SL) extracted outcomes data, participant characteristics, details on study interventions, and information necessary to assess study quality. We used the ROBINS-I tool [10] to assess the quality of cohort studies, and the Cochrane Risk of Bias Tool [11] for quasi-experimental trials. All extracted data were entered into Microsoft® Excel™.

We estimated unadjusted risk ratios and 95% confidence intervals to compare the proportions lost to follow-up in each arm/cohort in comparative studies. We conducted pooled analyses of all study cohorts to analyze the association between different types of support and losses to follow-up. We used the exact binomial likelihood approach, including a random effect to account for between-study heterogeneity, to estimate pooled proportions lost to follow-up and 95% confidence intervals. This approach produces less biased estimates of the pooled effect and the between-study variability than normal approximation approaches [12]. We investigated heterogeneity using the I^2 statistic via subgroup analyses, and explored differences in geographic regions, XDR status, HIV prevalence, previous treatment, treatment delivery methods and types of adherence support. Cochran's Q test was done to test for subgroup differences. In our main analyses, we excluded patients who died or failed treatment (to exclude from the denominator patients who could not have experienced the outcome of lost to follow-up), and patients who were transferred out or not evaluated for final treatment outcomes. We conducted sensitivity analyses in which we considered patients who were transferred out or not evaluated, or those who died, as patients lost to follow-up. All statistical analyses were done in R (*R Foundation for Statistical Computing, Vienna, Austria*).

RESULTS

Description of included studies

Our search strategy identified 5911 studies, of these we included 23 cohort studies and 2 quasi-experimental

trials [13-37] in our analyses (Fig. 1). These 25 studies included 35 different cohorts of RR/MDR-TB patients, distinguished by the different types and levels of adherence support. The types of treatment support provided to the included cohorts are summarized in **Table 1**. All but three studies [20, 22, 37] were conducted in high burden TB/MDR-TB countries [1].

Quality of Studies

We did not exclude any study based on our assessment of quality (see **Supplement Tables 4-5** for summaries and **Supplement Tables 9-10** for details). All included studies used routinely collected data within local TB systems to ascertain treatment outcomes. Reporting of intervention details varied across studies, and it was difficult to evaluate the fidelity of intervention implementation and delivery in three studies [19, 20, 25]. Some studies did not provide important patient characteristics, such as: any previous TB treatment (n=2); previous treatment with second-line drugs (n=13); XDR-status (n=6); and HIV-status (n=6; these studies were conducted in settings where less than 10% of TB patients are infected with HIV) (see **Supplement Table 2**).

Five cohort studies included two or more separate cohort groups [14-17, 37], which allowed for comparison of outcomes. However, we excluded the control cohort in the study by Yu et al. [37] because we were not able to obtain adequate details on the care provided, nor the number of patients lost to follow-up. Of the remaining four studies, two compared patient cohorts before and after implementation of an intervention [14, 17], and two analyzed concurrent cohort groups receiving different types of care [15-16]. None of the studies provided adjusted estimates for the effect of intervention on loss to follow-up rates to account for potential confounding. All four studies were considered to have serious risks of biases due to confounding, and two to have moderate risks of biases due to missing data (patients who were transferred out or not evaluated for final treatment outcomes) (**Supplement Table 4**).

There were two trials included in our analysis [13, 18]. Both were cluster randomized trials where health care facilities were randomized to provide routine care or the study interventions. The overall risk of performance bias was high for both studies because sites selected to implement the intervention were unblinded (**Supplement Table 5**). This could have a spillover effect and positively affect standard elements of care, thereby possibly overestimating the benefit of the intervention. However, sites providing routine care could have also improved their care to compensate for the absence of an intervention, thereby underestimating the benefit. Furthermore, due to the small number of clusters randomized in each study, patient and site characteristics were not balanced between the intervention and control arms, which could lead to residual confounding. Baral et al. [13] adjusted for age and sex, but neither study accounted for clustering by site or other important baseline confounders.

Results of Head-to-Head Comparisons

The results from comparative cohort studies and trials are shown in **Fig. 2**. The standard-of-care (study control) varied across the studies (see **Table 1** and **Supplement Table 8** for details). Given the variation in the control groups as well as the types of support provided in the intervention groups, pooling of intervention effects was not possible. Patients who received some form of psychosocial, educational or material support, in addition to the standard care, were less likely to be lost to follow-up, with the exception of the study by Cox et al. [14]. In

their pilot intervention study, Cox et al. [14] found no difference (risk ratio=1.04; 95%CI 0.83-1.32) between the control group, which received hospital-initiated MDR-TB treatment, and the intervention group, which received community-based, clinic-initiated treatment with routine counselling sessions and access to peer support group. The greatest reduction in losses to follow-up was seen in two cohorts that received support through daily home visits by community health workers, as well as home-based DOT, when compared to the standard-of-care [15-16]. In the cluster randomized trial by Baral et al. [13], the addition of individually tailored counselling sessions provided by nurses reduced the risk of lost to follow-up by 70%, but this estimate was very imprecise (risk ratio = 0.31; 95%CI 0.07-1.26), and adding a monthly income supplement did not improve the effect (risk ratio = 0.73; 95%CI 0.31-1.72).

Pooled Results Across Studies

Results from all study cohorts, in both comparative and non-comparative studies, that received any form of psychosocial, educational or material support were pooled in the following analysis (see **Supplement Table 2** for characteristics of included study cohorts). We excluded the standard-of-care or control groups in 2 studies that did not provide any psychosocial, educational or material support [13, 16], as well as one comparative cohort study [14] because its intervention group was a subsample of a larger single-cohort study [31].

Final treatment outcomes were reported for a total of 6655 RR/MDR-TB patients in 31 included study cohorts (**Supplement Table 3**). After excluding patients who died, failed treatment, or were transferred out or not evaluated for final treatment outcomes, there remained a total of 5114 patients (median of 84 patients per study cohort). The pooled proportion lost to follow-up was 17% (95%CI 12-23%), as seen in the forest plot (**Fig. 3**). Study heterogeneity was high across all included study cohorts (I^2=96%), and remained high in subgroup analyses by WHO region (except in the Americas region, likely because all three cohorts were largely based in Lima, Peru, within approximately the same period), HIV infection rate, proportions with XDR-TB, previous TB treatment (with or without second-line drugs), and start year of the study (**Fig. 4**).

In subgroup analyses, study cohorts with more frequent contact with health workers throughout treatment – in the form of DOT visits, home visits or individual counselling sessions – tended to have fewer losses to follow-up (**Fig. 5**). Additionally, provision of financial support to reimburse rent or travel expenses, as well as to compensate lost wages during treatment, was also associated with fewer losses to follow-up. There was weak evidence of any association between providing food packages, group counselling, or counselling to family members, and losses to follow-up. In order to distinguish the effect of frequent DOT from that of adherence support, subgroup analyses according to types of support provided were restricted to study cohorts that received either twice-daily or daily DOT throughout treatment (**Fig. 6**). Within these cohorts, those that received individual counselling throughout treatment [15-16, 21, 23-26, 28-30, 32-33, 36-37] had fewer losses to follow-up than those that received a fixed [13, 17, 19, 20, 31], or unspecified [15, 27, 34] number of individual counselling sessions at the start of treatment. Similarly, those that received any home visits by health workers also had fewer losses to follow-up [15-16, 20, 23, 29-30, 32, 37]. Sensitivity analyses where patients who were transferred out **(Supplement Figs. 20-22),** or who died (**Supplement Figs. 23-25**), were also considered as lost to follow-up yielded similar results. Furthermore, the findings remained consistent across

strata of study cohorts stratified by prevalence of HIV co-infection (**Supplement Figs. 26-29**), and previous TB treatment (**Supplement Figs. 30-33**).

Other adherence outcomes

Three studies additionally reported the proportion of doses taken (or missed) by patients (**Supplement Table 6**), two of which did not include a comparison control group. In comparing treatment adherence before and after patients were enrolled into the study intervention, Gelmanova et al. [23] found an increase in proportion of doses taken from 52.2% (95%CI 47.5-56.9) to 81.4% (95%CI 76.8-86.0). These patients received increased staff time from nurses, as well as expanded access to psychosocial support, after study enrolment.

Feasibility of Implementation of Interventions

A summary of feasibility and implementation issues associated with study interventions is provided in **Supplement Table 7**. Reported issues included: reluctance from health providers to follow new intervention-directed procedures [16-17]; difficulties identifying and training support workers [29, 35]; and lack of clarity in intervention implementation [16]. Among studies that reported on cost-effectiveness, all found that the study intervention reduced losses to follow-up, and was more cost-effective than the standard treatment practices in their respective setting [23, 29, 34].

DISCUSSION

Strategies to improve retention-in-care and treatment adherence among DR-TB patients are greatly needed to increase treatment success rates globally. This review found a broad range of adherence support interventions, all of which included some degree of educational and psychosocial counselling, as well as a variety of material support. However, very few studies reported on adherence outcomes in addition to patient losses to follow-up.

Our review found individual counselling support and home visits by health workers, provided throughout treatment, were associated with fewer losses to follow-up than when they were provided only at the start of treatment, or not at all. This association remained even after restricting the analyses to studies that provided daily DOT throughout treatment. Thus, although our study found lower lost to follow-up rates among studies that provided more frequent DOT, this could be conflated with the associated frequency of contact with providers as well as psychosocial or educational support. This is supported by findings from Mohr et al. [17], which showed that self-administered therapy – supplemented with routine home visits by community health workers – during the continuation phase yielded a similar lost to follow-up rate compared to daily clinic-based DOT without home visits. Furthermore, Gelmanova et al. [23] showed significant improvements in treatment adherence rates among MDR-TB patients when staff time allocated to each patient was increased. These findings are consistent with those reported in a recent Cochrane systematic review (Karumbi 2015), which found daily DOT did not improve TB cure rates, compared to self-administered therapy, when the frequency of contact with providers increased from monthly to every two weeks or more.

This review also provided evidence to support the effectiveness of financial compensation for rent or travel expenses, as well as lost wages, but not of group counselling, involvement of family in counselling sessions, or nutritional support, on improving retention-in-care. The lack of effectiveness of those strategies could be due

to residual confounding. For example, Cox et al. [14] found no effect of a community-based pilot intervention (which provided routine counselling and access to a peer support group), and suggested this may be due to the higher numbers of patients who initiated treatment under intervention, who otherwise would not have received treatment. Furthermore, very few studies reported on implementation issues and fidelity of intervention delivery [16-17, 23, 28-29, 34-35]. Thus, the reported intervention effectiveness may reflect issues with delivery such as: low engagement of patients and families in support groups [38]; lack of buy-in from health workers [16-17, 32, 39]; or providers selectively providing adherence incentives, such as food packages, to patients deemed most worthy [40]. Future research should explore these issues through process evaluations [41].

One major limitation of this review was the sparse descriptions of interventions provided by many studies. We made extensive efforts to contact authors for details, although we were not always successful. Among studies for which we were able to acquire sufficient details, we observed a wide variation in the educational and psychosocial support provided. Although nearly all studies provided individual counselling to patients, the specifics of the counselling were not often described sufficiently to gauge whether it encompassed social and emotional support and/or treatment education. Thus, we considered individual counselling to broadly include any one-on-one time spent between patients and health workers to address psychological, social, or treatment-related issues, which could include both psychosocial and educational support, and was identified by the authors as beyond the current standard of care at the study sites. The observed benefit from these forms of support could therefore have resulted from added interactions between patients and their providers, beyond DOT and routine medical check-ups. However, it is difficult to assess the degree or depth of these interactions. The benefit could also be underestimated due to the lack of training provided in some studies compared to others.

Despite these limitations, the review provides a timely update on strategies to improve MDR-TB treatment retention-in-care, including results of two recent cluster randomized trials [13, 18]. Unlike the earlier review [3] which included all studies reporting treatment outcomes for RR/MDR-TB patients, we restricted our analysis to only those studies that explicitly provided patients with some form of psychosocial, educational or material support, allowing a more nuanced analysis comparing the effectiveness of different types of support. Notably, no interventions utilized e-health tools to promote adherence to RR/MDR-TB treatment.

Our review provides the motivation for further examination of adherence interventions in RR/MDR-TB, preferably through RCTs, that compare the effectiveness of DOT to self-administered therapy, coupled with increased psychosocial and economic support throughout the treatment course. As evidenced by some recent cohort studies, and supported by expert commentaries [42-43], a shift to self-administered therapy has the potential to relieve health worker burden so that their time and resources may be utilized to build health literacy, empower patients, and deliver higher quality, patient-centered care.

ACKNOWLEDGEMENT

Table 1. Description of treatment support provided in included study cohorts*

Study	N	Country, Study period	DOT Frequency (intensive/ continuation phase)	DOT location	Individual counselling	Home visits available	Financial support offered	Food packages provided	Group counselling	Counselling/ education offered to family
Studies with two or more patient cohorts										
Baral 2014 [13] (Control)**	33	Nepal, 2008	Daily/Daily	Clinic	No	No	No	No	No	N.S.
Baral 2014 [13] (Arm 1)	33	Nepal, 2008	Daily/Daily	Clinic	2 to 5 tailored sessions by trained nurse	No	No	No	Every 2-3 weeks	N.S.
Baral 2014 [13] (Arm 2)	42	Nepal, 2008	Daily/Daily	Clinic	2 to 5 tailored sessions by trained nurse	No	2000 Nepali Rupees per month	No	Every 2-3 weeks	N.S.
Cox 2014 [14] (Control)**	216	South Africa, 2005-2010	Daily/Daily	In-patient, hospital/Clinic	N.S.	No	No	No	No	No
Cox 2014 [14] (Intervention)**	571	South Africa, 2005-2010	Daily/Daily	Clinic	Routine counselling at start of treatment	No, but home assessment done by CHW at start of treatment	No	No	Weekly peer support groups	N.S.
Huerga 2017 [15] (Homa Bay)	28	Kenya, 2006-2012	Twice-Daily/Twice-Daily	Clinic/home	Weekly to monthly counselling sessions, and as needed	Daily home visits by CHW	Rent and travel	No	No	N.S.
Huerga 2017 [15] (Mathare)	70	Kenya, 2006-2012	Daily/Daily	Clinic	Weekly to monthly counselling sessions, and as needed	No	Rent and travel expenses	Daily hot meal & monthly food basket	No	N.S.
Huerga 2017 [15] (Nairobi)	71	Kenya, 2006-2012	Daily/Daily	Clinic	Counselling by nurses on request by doctors	No	Rent and travel expenses	No	No	N.S.
Loveday 2015 [16] (Hospital)**	813	South Africa, 2008-2010	Daily/None	In-patient, hospital	N.S.	No	No	No	No	N.S.
Loveday 2015 [16] (Site 1)	125	South Africa, 2008-2010	Daily/Daily	Clinic/home	Weekly educational sessions	Daily home visits by CHW	Travel expenses	No	No	Yes
Loveday 2015 [16] (Site 2 & 3)	350	South Africa,	Daily/None	Clinic/home	Unspecified frequency and	No	Travel expenses	No	No	Yes

Study	N	Country, Year								
		2008-2010			duration					
Loveday 2015 [16] (Site 4)	261	South Africa, 2008-2010	Daily/None	Clinic	Unspecified frequency and duration	No	Travel expenses	No	No	Yes
Mohr 2017 [17] (SAT)	244	South Africa, 2010-2014	Daily/None	Clinic	4 standardized sessions during intensive phase, and 1 at start of continuation phase	Weekly visits by CHW at the start of continuation phase, monthly after	No	No	No	N.S.
Mohr 2017 [17] (SOC)	160	South Africa, 2010-2014	Daily/Daily	Clinic	4 standardized sessions during intensive phase	No	No	No	No	N.S.
Taneja 2017 [18] (Control)	50	India, 2014	Thrice-Weekly/None	Health facility (public/ private/NGO)	Thrice weekly during intensive phase, weekly thereafter	No	No	No	No	N.S.
Taneja 2017 [18] (Intervention)	50	India, 2014	Thrice-Weekly/None	Health facility (public/private /NGO)	Fortnightly at home & thrice weekly at clinic during intensive phase, weekly at clinic & every 45 days at home thereafter	Fortnightly visits from homecare team during intensive phase, and every 45 days thereafter	No	Daily provision of eggs and multigrain biscuits	No	Yes
Studies with a single patient cohort										
Alene 2017 [19]	481	China, 2011-2014	Daily/Daily	Clinic/home	Throughout initial hospitalization (1-2 months)	None specified	No	No	No	Yes
Bastard 2015 [20]	403	Armenia/ Georgia, 2002-2010	Daily/Daily	Clinic/home	Routine sessions	Daily by health personnel or CHW	Travel expenses	Yes, unspecified	Yes, unspecified	N.S.
Cox 2007 [21]	87	Uzbekist an, 2003-2005	Daily/Daily	Clinic	Daily counselling, or as needed	No	Travel expenses	Four meals daily during hospitalization; monthly food parcels after	No	N.S.
Escudero 2006 [22]	25	Spain, 1998-2000	Daily/None	In-patient, hospital	Repeatedly during hospitalization, monthly thereafter, by clinician/psycholog	No	No	No	No	N.S.

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Gelmanova 2011 [23]	38	Russia, 2006-2008	Twice-Daily/Twice-Daily	Hospital/Home	Daily counselling, or as needed, by nurses and psychologist	Twice daily by a team of two nurses	Travel passes	Daily food parcels	No	Yes
Isaakidis 2011 [24]	35	India, 2007-2011	Twice-Daily/Twice-Daily	Health facility (public/ private/ NGO)	Monthly psychosocial follow-up	No	No	No	No	N.S.
Joseph 2011 [25]	38	India, 2006-2007	Daily/Daily	Health facility (public/ private/NGO)	Initial education by medical officer and social worker, followed by daily adherence advice from trained DOT provider	No	No	No	No	Yes
Keshavjee 2008 [26]	608	Russia, 2000-2004	Daily/Daily	In-patient, hospital; Clinic/rural health outpost	Daily counselling, or as needed	No	No	Monthly food packages and meals for adherent patients	No	N.S.
Kliiman 2009 [27]	235	Estonia, 2003-2005	Daily/Daily	In-patient, hospital; Clinic	N.S.	No	Travel expenses	Yes, unspecified	No	N.S.
Meressa 2015 [28]	612	Ethiopia, 2009-2014	Daily/Daily	Clinic/home	Monthly counselling	Monthly visits by outpatient team	Rent and travel expenses	Monthly food baskets	No	Yes
Mitnick 2003 [29]	75	Peru, 1996-1999	Daily/Daily	Clinic/home	Daily counselling, or as needed	Daily by CHW	Travel expenses	Yes, unspecified	Weekly, bi-monthly social support groups	Yes
Mitnick 2008 [30]	650	Peru, 1999-2002	Daily/Daily	Clinic/home	Daily counselling, or as needed	Daily by CHW	Travel expenses	Yes, unspecified	Weekly, bi-monthly social support groups	Yes
Mohr 2015 [31]	853	South Africa, 2008-2012	Daily/Daily	Clinic	3 sessions in intensive phase and 1 in continuation phase	No	No	Yes, unspecified	Weekly peer support groups	Yes
Satti 2012 [32]	134	Lesotho, 2008-2009	Twice-Daily/Twice-Daily	Home	Daily counselling, or as needed	Twice daily by trained CHW	Travel expenses	Monthly food packages	No	Yes
Shin 2006 [33]	244	Russia, 1998-2000	Daily/Daily	Clinic/Rural health outpost	Daily counselling, or as needed	No	No	Monthly food packages/ meals for adherent	No	N.S.

patients

Suarez 2002 [34]	298	Peru, 1997-1999	Daily/Daily	Clinic	N.S.	No	No	Weekly food parcels	N.S.	No
Thomas 2007 [35]	66	India, 1999-2003	Thrice-Weekly/Thrice-Weekly	Health facility (public/private/NGO)	Monthly sociological counselling	No	Monthly compensation for lost wages and travel expenses	No	No	N.S.
Vaghela 2015 [36]	101	India, 2009-2010	Daily/Daily	Health facility (public/private/NGO)	Every 15 days during intensive phase, every 45 days thereafter	Visits by CHW every 15 days during intensive phase, every 45 days thereafter	None	Daily provision of eggs and multigrain biscuits	No	Yes
Yu 2015 [37]	126	Taiwan, 2007-2009	Twice-Daily/Twice-Daily	Clinic/home	Daily counselling, or as needed	Daily visits by medical team	Monthly income	No	No	Yes

*Studies with more than one arm/cohort – each arm shown separately. Abbreviations: CHW = community health worker; N.S.= none specified; DOT = directly observed therapy.

**Included in comparative analysis but excluded from pooled analysis (see text for details).

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Identified from search strategy
(after removing duplicates)
n= 5911

5405 title/abstracts excluded

Full text reviewed
n = 111

86 texts excluded after review
30 with no intervention
3 duplicate publications
9 no treatment or adherence outcomes
10 only interim outcomes (<12 months of treatment)
1 only included children
2 only tested change in drug regimen
12 with fewer than 10 RR/MDR patients
12 abstracts only
1 review
1 no MDR-TB specific outcomes
5 contained a subsample of another study

Included 25 studies
(with 35 patient cohorts)
2 cluster randomized controlled trials
4 comparative cohort studies
19 non-comparative cohort studies

Study	Comparison	Control no. LTFU/n	Intervention no. LTFU/n	Risk Ratio	RR	95%-CI
Baral 2014 (RCT)	Clinic DOT vs Clinic DOT+counselling	15/69	2/30		0.31	[0.07; 1.26]
Baral 2014 (RCT)	Clinic DOT vs Clinic DOT+counselling+monthly income	15/69	6/38		0.73	[0.31; 1.72]
Cox 2014 (Cohort)	Hospital vs. Clinic DOT+counselling+support group	152/387	59/144		1.04	[0.83; 1.32]
Huerga 2017 (Cohort)	Clinic DOT vs Clinic DOT+counselling+food baskets	6/49	6/58		0.84	[0.29; 2.45]
Huerga 2017 (Cohort)	Clinic DOT vs Clinic/Home DOT+counselling+home visits	6/49	0/16		0.23	[0.01; 3.88]
Loveday 2015 (Cohort)	Hospital vs. Clinic DOT	230/669	28/163		0.50	[0.35; 0.71]
Loveday 2015 (Cohort)	Hospital vs. Clinic/Home DOT	230/669	70/272		0.75	[0.60; 0.94]
Loveday 2015 (Cohort)	Hospital vs Clinic/Home DOT+counselling+home visits	230/669	9/99		0.26	[0.14; 0.50]
Mohr 2017 (Cohort)	Clinic DOT+counselling vs SAT+counselling+home visits	44/110	47/146		0.80	[0.58; 1.12]
Taneja 2017 (RCT)	Facility DOT vs Facility DOT+home visits+food baskets	21/35	22/42		0.87	[0.59; 1.30]

0.1 0.5 1 2 10

Study cohort	N	No. LTFU		Proportion	95%-CI
Studies with 2 or more arms/cohorts					
Baral 2014 (Arm 1)	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	38	6		0.16	[0.06; 0.31]
Huerga 2017 (Homa Bay)	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	49	6		0.12	[0.05; 0.25]
Loveday 2015 (Site 1)	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	163	28		0.17	[0.12; 0.24]
Mohr 2017 (SAT)	146	47		0.32	[0.25; 0.40]
Mohr 2017 (SOC)	110	44		0.40	[0.31; 0.50]
Taneja 2017 (Control)	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	42	22		0.52	[0.36; 0.68]
Random effects model	1058	261		0.20	[0.12; 0.32]
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.9430$, $p < 0.01$					
Studies with a single cohort					
Alene 2017	405	130		0.32	[0.28; 0.37]
Bastard 2015	298	127		0.43	[0.37; 0.48]
Cox 2007	66	12		0.18	[0.10; 0.30]
Escudero 2006	23	2		0.09	[0.01; 0.28]
Gelmanova 2011	33	6		0.18	[0.07; 0.35]
Isaakidis 2011	20	7		0.35	[0.15; 0.59]
Joseph 2011	30	5		0.17	[0.06; 0.35]
Keshavjee 2008	519	119		0.23	[0.19; 0.27]
Kliiman 2009	206	48		0.23	[0.18; 0.30]
Meressa 2015	517	36		0.07	[0.05; 0.10]
Mitnick 2003	60	5		0.08	[0.03; 0.18]
Mitnick 2008	494	65		0.13	[0.10; 0.16]
Mohr 2015	586	227		0.39	[0.35; 0.43]
Satti 2012	84	1		0.01	[0.00; 0.06]
Shin 2006	216	28		0.13	[0.09; 0.18]
Suarez 2002	273	34		0.12	[0.09; 0.17]
Thomas 2007	41	16		0.39	[0.24; 0.55]
Vaghela 2015	79	7		0.09	[0.04; 0.17]
Yu 2015	106	0		0.00	[0.00; 0.03]
Random effects model	4056	875		0.15	[0.10; 0.22]
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 1.0355$, $p < 0.01$					
Random effects model	**5114**	**1136**		**0.17**	**[0.12; 0.23]**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$					

0   0.1   0.2   0.3   0.4   0.5   0.6   0.7

Subgroup	No. of Study Cohorts	Cochran's Q test (p-value)		Proportion	95%-CI	I2
WHO Region						
African	11	0.04		0.14	[0.08; 0.24]	96%
Americas	3			0.13	[0.11; 0.15]	0%
European	7			0.21	[0.15; 0.29]	89%
Southeast Asia	8			0.25	[0.14; 0.42]	86%
Western Pacific	2			0.01	[0.00; 0.91]	93%
Proportion HIV-infected						
No HIV	7	< 0.01		0.26	[0.15; 0.42]	91%
<10% HIV-infected	12			0.14	[0.08; 0.23]	96%
10-50% HIV-infected	3			0.08	[0.06; 0.10]	0%
>50% HIV-infected	9			0.18	[0.09; 0.33]	97%
Proportion XDR-infected						
No XDR	13	0.22*		0.20	[0.12; 0.30]	93%
<5% with XDR	5			0.30	[0.22; 0.38]	88%
>5% with XDR	6			0.21	[0.13; 0.33]	92%
Not reported	7			0.06	[0.02; 0.14]	90%
Proportion Previously Treated for TB						
<70% previously treated	6	0.61*		0.16	[0.05; 0.38]	98%
70-90% previously treated	8			0.23	[0.13; 0.36]	95%
>90% previously treated	14			0.16	[0.10; 0.25]	95%
Not reported	3			0.10	[0.06; 0.16]	0%
Proportion Previously Treated with SLD						
None previously treated with SLD	4	0.02*		0.41	[0.27; 0.58]	83%
<10% previously treated with SLD	3			0.17	[0.10; 0.27]	80%
>10% previously treated with SLD	8			0.21	[0.11; 0.36]	96%
Not reported	16			0.12	[0.07; 0.18]	93%
Year of study						
1995-1999	6	< 0.01		0.14	[0.09; 0.21]	82%
2000-2004	4			0.27	[0.19; 0.36]	89%
2005-2009	16			0.10	[0.06; 0.17]	94%
2010-2014	5			0.41	[0.32; 0.50]	77%

0   0.2   0.4   0.6   0.8   1

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	4	0.22		0.22	[0.19; 0.25]	0%
Outpatient, twice daily DOT	4			0.06	[0.01; 0.33]	86%
Outpatient, daily DOT	19			0.17	[0.13; 0.23]	94%
Outpatient, thrice-weekly DOT	4			0.19	[0.01; 0.78]	98%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	4	< 0.01		0.04	[0.00; 0.33]	92%
Outpatient, daily DOT	20			0.16	[0.12; 0.21]	94%
Outpatient, thrice-weekly DOT	1			0.39	[0.26; 0.54]	
No DOT	6			0.31	[0.18; 0.46]	92%
Home visits						
Daily	8	0.09		0.06	[0.02; 0.19]	97%
Fortnightly-Monthly	4			0.20	[0.08; 0.42]	96%
None	19			0.22	[0.17; 0.28]	92%
Nutritional support						
Food packages	14	0.51		0.15	[0.10; 0.22]	95%
None	17			0.18	[0.11; 0.29]	96%
Financial support						
Travel expenses	10	< 0.01		0.15	[0.10; 0.24]	94%
Rent/travel expenses	4			0.08	[0.06; 0.10]	0%
Supplemental income	3			0.06	[0.00; 0.61]	96%
None	14			0.24	[0.17; 0.34]	95%
Counselling offered to families						
Counselling/education offered to families	14	0.14		0.13	[0.07; 0.22]	97%
No family involvement specified	17			0.21	[0.15; 0.29]	92%
Type of counselling						
Individual and group counselling	6	0.72		0.19	[0.10; 0.33]	96%
Individual counselling	25			0.16	[0.11; 0.24]	96%
Frequency of individual counselling						
Daily, as needed	9	< 0.01		0.09	[0.05; 0.18]	95%
Weekly or monthly	10			0.17	[0.09; 0.32]	92%
Fixed number of sessions	7			0.31	[0.22; 0.41]	91%
Not specified	5			0.18	[0.14; 0.24]	73%

Subgroup	No. of Study Cohorts	Cochran's Q test (p-value)		Proportion	95%-CI	I2
Frequency of individual counselling						
Daily, as needed	9	< 0.01		0.09	[0.05; 0.18]	95%
Weekly or monthly	6			0.10	[0.06; 0.15]	62%
Fixed number of sessions	6			0.30	[0.20; 0.42]	94%
Not specified	3			0.16	[0.11; 0.23]	67%
Home visits						
Daily	8	< 0.01		0.06	[0.02; 0.19]	97%
Fortnightly-Monthly	2			0.07	[0.05; 0.10]	0%
None	14			0.20	[0.15; 0.26]	91%
Nutritional support						
Food packages	13	1.00		0.13	[0.09; 0.19]	94%
None	11			0.13	[0.06; 0.27]	97%
Financial support						
Travel expenses	8	< 0.01		0.14	[0.07; 0.24]	94%
Rent/travel expenses	4			0.08	[0.06; 0.10]	0%
Supplemental income	2			0.01	[0.00; 0.68]	88%
None	10			0.21	[0.14; 0.30]	94%
Counselling offered to families						
Counselling/education offered to families	11	0.09		0.10	[0.05; 0.19]	97%
No family involvement specified	13			0.18	[0.13; 0.25]	91%
Type of counselling						
Individual and group counselling	6	0.29		0.19	[0.10; 0.33]	96%
Individual counselling	18			0.12	[0.08; 0.19]	95%

0   0.2   0.4   0.6   0.8   1

Table of Contents

Table 1. Search strategy

OVID Database: EMBASE, MEDLINE, Global Health, PsycINFO, Social Work Abstracts
1. exp tuberculosis, multidrug resistant/
2. (mdrtb or xdrtb).mp.
3. (mdr or xdr or ((multidrug or drug) adj resistan*)).mp.
4. (tuberculosis or tb).mp.
5. 3 and 4
6. 1 or 2 or 5
7. exp patient compliance/
8. (dropout* or drop out*).mp.
9. cash.mp.
10. reimburse*.mp.
11. refund*.mp.
12. reward*.mp.
13. incentiv*.mp.
14. voucher*.mp.
15. reminder*.mp.
16. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. (penal* or punish*).mp.
18. (nonadheren* or adheren* or abscond* or attrition* or complian* or noncomplian* or default* or fail* or stop* or refus* or incomplet* or interrupt*).mp.
19. 16 or 17 or 18
20. 6 and 19
21. limit 20 to yr="2000 -Current"

Cochrane CENTRAL
MeSH descriptor: [Tuberculosis, Multidrug-Resistant] explode all trees
(MDR or XDR)
(multidrug or drug) next (resistan*)
(#2 or #3) and (tuberculosis or TB)
#1 or #4
MeSH descriptor: [Patient Compliance] explode all trees
dropout or (drop out)
cash
reimburse*
refund*
reward*
incentiv*
voucher*
reminder*
#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
penal* or punish*
nonadheren* or adheren* or abscond* or attrition* or complian* or noncomplian* or default* or fail* or stop* or refus* or incomplet* or interrupt*
#15 or #16 or #17
#5 and #18
#19 Publication Year from 2000

Web of Science
12. #11
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2000-2017
11. #5 AND #10
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
10. #6 OR #7 OR #8 OR #9
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
9. TS=(nonadheren* OR adheren* OR abscond* OR attrition* OR complian* OR noncomplian* OR default* OR fail* OR stop* OR refus* OR incomplet* OR interrupt*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
8. TS=(reimburs* OR refund* OR reward* OR incentiv* OR voucher* OR reminder* OR monitor* OR penal* OR punish*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
7. TS=(cash)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
6. TS= (dropout* or drop out*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

5. #1 OR #4
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
4. #2 AND #3
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
3. TS=(TB OR Tuberculosis)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
2. TS=(mdr OR xdr OR ((multidrug OR drug) NEAR (resistan*)))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
1. TS= (mdrtb OR xdrtb)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
Scopus
((TITLE-ABS-KEY (droput* OR "drop out*" OR cash OR reimburs* OR refund* OR reward* OR incentiv* OR voucher* OR reminder* OR monitor* OR penal* OR punish* OR nonadheren* OR adheren* OR abscond* OR attrition* OR complian* OR noncomplian* OR default* OR fail* OR stop* OR refus* OR incomplet* OR interrupt*)) AND ((TITLE-ABS-KEY (mdrtb OR xdrtb)) OR ((TITLE-ABS-KEY ((mdr OR xdr OR ((multidrug OR drug) W/3 resistan*))))) AND (TITLE-ABS-KEY (tb OR tuberculosis))))) AND (PUBYEAR > 2000)

Table 2. Characteristics of included study cohorts in pooled analyses

Author, Year (Cohort group/Trial arm)	Study period (years)	Country	N	HIV (%)	XDR (%)	Previously Treated (%)	
						Any	SLD
Studies with two or more cohorts*							
Baral 2014 (Arm 1)	2008	Nepal	33	n/a†	n/a	n/a	n/a
Baral 2014 (Arm 2)	2008	Nepal	42	n/a†	n/a	n/a	n/a
Huerga 2017 (Homa Bay)^^	2006-2012	Kenya	28	17 (60.7)	0	24 (85.7)	n/a
Huerga 2017 (Mathare)^^	2006-2012	Kenya	70	15 (21.4)	0	63 (90.0)	n/a
Huerga 2017 (Nairobi)^^	2006-2012	Kenya	71	11 (15.5)	0	67 (94.4)	n/a
Loveday 2015 (Site 1)	2008-2010	South Africa	125	96/124 (77.4)	0	87 (69.6)	6 (4.8)
Loveday 2015 (Site 2 & 3)	2008-2010	South Africa	350	235/333 (70.6)	0	217 (62.0)	33 (9.4)
Loveday 2015 (Site 4)	2008-2010	South Africa	261	197/235 (83.8)	0	107(41.0)	14 (5.4)
Mohr 2017 (SAT)¥	2010-2014	South Africa	244	180 (73.8)	0	146 (59.8)	33 (13.5)
Mohr 2017 (SOC)¥	2010-2014	South Africa	160	112 (70.0)	0	122 (76.3)	19 (11.9)
Taneja 2017 (Control)	2014	India	50	0	0	50 (100)	0
Taneja 2017 (Intervention)	2014	India	50	0	0	50 (100)	0
Studies with a single cohort							
Alene 2017	2011-2014	China	481	0	10 (2.1)	417 (86.7)	n/a
Bastard 2015	2002-2010	Armenia/ Georgia	393	n/a†	15/247 (6.1)	304 (77.4)	115 (29.3)
Cox 2007	2003-2005	Uzbekistan	87	n/a†	0 (0)	87 (100)	57 (65.5)
Escudero 2006øø	1998-2000	Spain	25	0	1 (4.0)	22 (88.0)	n/a
Gelmanova 2011§	2006-2008	Russia	38	0	2 (5.3)	21 (55.3)	10 (26.3)
Isaakidis 2011	2007-2011	India	58	58 (100)	3/50 (6.0)	51 (87.9)	26 (44.8)
Joseph 2011	2006-2007	India	38	0	0	38 (100)	0
Keshavjee 2008	2000-2004	Russia	608	5/604 (0.8)	29 (4.8)	605 (99.5)	n/a
Kliiman 2009	2003-2005	Estonia	289	11 (3.8)	54 (18.7)	139 (48.1)	n/a
Meressa 2015	2009-2014	Ethiopia	612	133/612 (21.7)	6/612 (1.0)#	603 (98.5)	n/a

Mitnick 2003	1996-1999	Peru	75	1/65 (1.5)	5 (6.7)	75 (100)	n/a
Mitnick 2008§§	1999-2002	Peru	651	9/635 (1.4)	48 (7.4)	649 (99.7)	420/648 (64.5)
Mohr 2015~	2008-2012	South Africa	853	605 (70.9)	39 (4.6)	576 (67.5)	0
Satti 2012ø	2008-2009	Lesotho	134	94 (70.2)	n/a	129 (96.3)	18 (13.4)
Shin 2006	1998-2000	Russia	244	0	n/a	239 (98.0)	n/a
Suarez 2002	1997-1999	Peru	298	n/a†	n/a	298 (100)	n/a
Thomas 2007	1999-2003	India	66	n/a†	1/33 (3.0)	66 (100)	n/a
Vaghela 2015	2009-2010	India	101	2 (2.0)	n/a	n/a	n/a
Yu 2015 ~	2007-2009	Taiwan	124	n/a†	n/a	60 (48.4)	n/a

*Studies with more than one arm/cohort – each arm shown separately.

#Presumed XDR-TB

~Includes 190 patients with mono-RR-TB.

^^In the full sample (from all three study sites), resistance to second-line drugs were as follows: CPM 1/63 (1.6%), KM 1/63 (1.6%), and OFX 3/47 (6.4%).

¥ Includes unknown number of patients with mono-RR-TB. Of 244 in the SAT cohort, 67 patients had recorded outcomes before end of 6 months (16 LTFU; 33 died; 1 failure; 17 were transferred out). Of the 160 in the DOT cohort, 42 had recorded outcomes before end of 6 months (19 LTFU; 13 died; 2 failures; 8 were transferred out). These patients were excluded from analysis in the published study, however, they were included in this analysis (except those transferred out/not evaluated).

†The estimated prevalence of HIV among TB patients: 6.3% in Armenia; 3.5% in Uzbekistan; 6% in Peru; 2.2% in Georgia; 4.7% in Nepal; 3% in India (WHO 2017); and 2.4% in Taiwan.

Table 3. Treatment outcomes at end of study of cohorts included in pooled analyses*

Author, Year (Cohort group)	Sample size (n)	Lost to follow-up (%)	Success (%)	Failure (%)	Death (%)	Transferred out/not evaluated (%)	Still on treatment** (%)
Studies with two or more cohorts							
Baral 2014 (Arm 1)	33	2 (6.1)	28 (84.8)	2 (6.1)	1 (3.0)	0 (0)	0 (0)
Baral 2014 (Arm 2)	42	6 (14.3)	32 (76.2)	2 (4.8)	2 (4.8)	0 (0)	0 (0)
Huerga 2017 (Homa Bay)	28	0 (0.0)	16 (57.1)	0 (0)	5 (17.9)	7 (25.0)	0 (0)
Huerga 2017 (Mathare)	70	6 (8.6)	52 (74.3)	0 (0)	4 (5.7)	8 (11.4)	0 (0)
Huerga 2017 (Nairobi)	71	6 (8.5)	43 (60.6)	1 (1.4)	12 (16.9)	9 (12.7)	0 (0)
Loveday 2015 (Site 1)	125	9 (7.2)	90 (72.0)	7 (5.6)	17 (13.6)	2 (1.6)	0 (0)
Loveday 2015 (Site 2 & 3)	350	70 (20.0)	202 (57.7)	23 (6.6)	47 (13.4)	8 (2.3)	0 (0)
Loveday 2015 (Site 4)	261	28 (10.7)	135 (51.7)	19 (7.3)	69 (26.4)	10 (3.8)	0 (0)
Mohr 2017 (SAT)	244	47 (19.3)	99 (40.6)	8 (3.3)	48 (19.7)	42 (17.2)	0 (0)
Mohr 2017 (SOC)	160	44 (27.5)	66 (41.3)	7 (4.4)	19 (11.9)	24 (15.0)	0 (0)
Taneja 2017 (Control)	50	21 (42.0)	14 (28.0)	3 (6.0)	7 (14.0)	5 (10.0)	0 (0)
Taneja 2017 (Intervention)	50	22 (44.0)	20 (40.0)	1 (2.0)	6 (12.0)	1 (2.0)	0 (0)
Studies with a single cohort							
Alene 2017	481	130 (27.0)	275 (57.2)	63 (13.1)	13 (2.7)	0 (0)	0 (0)
Bastard 2015	393	127 (32.3)	171 (43.5)	56 (14.2)	39 (9.9)	0 (0)	0 (0)
Cox 2007	87	12 (13.8)	54 (62.1)	8 (9.2)	13 (14.9)	0 (0)	0 (0)
Escudero 2006	25	2 (8.0)	21 (84.0)	0 (0)	0 (0)	2 (8.0)	0 (0)
Gelmanova 2011	38	6 (15.8)	27 (71.1)	2 (5.3)	2 (5.3)	1 (2.6)	0 (0)
Isaakidis 2011	58	7 (12.1)	13 (22.4)	2 (3.4)	13 (22.4)	0 (0)	23 (39.7)
Joseph 2011	38	5 (13.2)	25 (65.8)	5 (13.2)	3 (7.9)	0 (0)	0 (0)
Keshavjee 2008	608	119 (19.6)	400 (65.8)	58 (9.5)	31 (5.1)	0 (0)	0 (0)
Kliiman 2009	289	48 (16.6)	165 (57.1)	35 (12.1)	48 (16.6)	0 (0)	0 (0)
Meressa 2015	612	36 (5.9)	481 (78.6)	10 (1.6)	85 (13.9)	0 (0)	0 (0)
Mitnick 2003	75	5 (6.7)	55 (73.3)	1 (1.3)	14 (18.7)	0 (0)	0 (0)
Mitnick 2008	651	65 (10.0)	429 (65.90)	18 (2.8)	134 (20.6)	4 (0.6)	1 (0.2)
Mohr 2015	853	227 (26.6)	359 (42.1)	48 (5.6)	123 (14.4)	96 (11.3)	0 (0)
Satti 2012	134	1 (0.7)	83 (61.9)	1 (0.7)	46 (34.3)	3 (2.2)	0 (0)
Suarez 2002	298	34 (11.4)	136 (45.6)	96 (32.2)	32 (10.7)	0 (0)	0 (0)
Shin 2006	244	28 (11.5)	188 (77.0)	16 (6.6)	12 (4.9)	0 (0)	0 (0)
Thomas 2007	66	16 (24.2)	25 (37.9)	17 (25.8)	8 (12.1)	0 (0)	0 (0)
Vaghela 2015	101	7 (6.9)	72 (71.3)	4 (4.0)	17 (16.8)	1 (1.0)	0 (0)
Yu 2015	124	0 (0.0)	106 (85.5)	2 (1.6)	16 (12.9)	0 (0)	0 (0)

*Results for studies with more than one patient cohort are shown separately for each study arm or cohort.
**These are patients who have not yet completed the study's standard treatment duration, and who do not have a final treatment outcome recorded by the end of study.

Table 4. Summary of quality assessment of non-randomized studies (based on Robins-I Tool)

Author, Year	Overall risk of confounding bias	Overall Risk of selection bias	Overall risk due to intervention classification	Overall risk due to deviations from interventions	Overall risk of bias due to missingness	Overall risk of outcome measurement bias	Overall Risk of reporting bias	OVERALL BIAS
Cohort studies without comparison groups								
Alene 2017	n/a	Low	n/a	No information	Low	Low	Low	No information
Bastard 2015	n/a	Low	n/a	No information	Moderate	Low	Low	No information
Cox 2007	n/a	Low	n/a	Low	Low	Low	Low	Low
Escudero 2006	n/a	Low	n/a	Low	Moderate	Low	Low	Moderate
Gelmanova 2011	n/a	Low	n/a	Low	Low	Low	Low	Low
Isaakidis 2011	n/a	Low	n/a	Low	Low	Low	Low	Low
Joseph 2011	n/a	Low	n/a	No information	Low	Low	Low	No information
Keshavjee 2008	n/a	Low	n/a	Low	Low	Low	Low	Low
Kliiman 2009	n/a	Low	n/a	Low	Low	Low	Low	Low
Meressa 2015	n/a	Low	n/a	Low	Low	Low	Low	Low
Mitnick 2003	n/a	Low	n/a	Low	Low	Low	Low	Low
Mitnick 2008	n/a	Low	n/a	Low	Low	Low	Low	Low
Mohr 2015	n/a	Low	n/a	Low	Moderate	Low	Low	Moderate
Satti 2012	n/a	Low	n/a	Low	Low	Low	Low	Low
Shin 2006	n/a	Low	n/a	Low	Low	Low	Low	Low
Suarez 2002	n/a	Low	N/a	Low	Low	Low	Low	Low
Thomas 2007	n/a	Low	n/a	Moderate	Low	Low	Low	Moderate
Vaghela 2015	n/a	Low	n/a	Low	Low	Low	Low	Low
Yu 2015	n/a	Low	n/a	Low	Low	Low	Low	Low
Cohort studies with 2 or more interventions								
Mohr 2017	Serious	Low	Low	Low	Low	Low	Low	Serious
Loveday 2015	Serious	Low	Low	Low	Low	Low	Low	Serious
Cox 2014	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Huerga 2017	Serious	Low	Low	Low	Moderate	Low	Low	Serious

Table 5. Summary of quality assessment of cluster randomized trials

Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting? (reporting bias)	Other bias
Baral 2014	Low	Low	High	Low	Low	Low	Serious risk of confounding bias
Taneja 2017	Low	Low	High	Low	Low	Low	Serious risk of confounding bias

Study cohort	Country	N	No. LTFU		Proportion	95%-CI
African						
Meressa 2015	Ethiopia	517	36		0.07	[0.05; 0.10]
Huerga 2017 (Homa Bay)	Kenya	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	Kenya	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	Kenya	49	6		0.12	[0.05; 0.25]
Satti 2012	Lesotho	84	1		0.01	[0.00; 0.06]
Loveday 2015 (Site 1)	South Africa	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	South Africa	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	South Africa	163	28		0.17	[0.12; 0.24]
Mohr 2015	South Africa	586	227		0.39	[0.35; 0.43]
Mohr 2017 (SAT)	South Africa	146	47		0.32	[0.25; 0.40]
Mohr 2017 (SOC)	South Africa	110	44		0.40	[0.31; 0.50]
Random effects model		2100	474		0.14	[0.08; 0.24]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.1036$, $p < 0.01$						
Americas						
Mitnick 2003	Peru	60	5		0.08	[0.03; 0.18]
Mitnick 2008	Peru	494	65		0.13	[0.10; 0.16]
Suarez 2002	Peru	273	34		0.12	[0.09; 0.17]
Random effects model		827	104		0.13	[0.10; 0.15]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.57$						
European						
Bastard 2015	Armenia/Georgia	298	127		0.43	[0.37; 0.48]
Kliiman 2009	Estonia	206	48		0.23	[0.18; 0.30]
Gelmanova 2011	Russia	33	6		0.18	[0.07; 0.35]
Keshavjee 2008	Russia	519	119		0.23	[0.19; 0.27]
Shin 2006	Russia	216	28		0.13	[0.09; 0.18]
Escudero 2006	Spain	23	2		0.09	[0.01; 0.28]
Cox 2007	Uzbekistan	66	12		0.18	[0.10; 0.30]
Random effects model		1361	342		0.21	[0.15; 0.29]
Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.2683$, $p < 0.01$						
Southeast Asia						
Isaakidis 2011	India	20	7		0.35	[0.15; 0.59]
Joseph 2011	India	30	5		0.17	[0.06; 0.35]
Taneja 2017 (Control)	India	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	India	42	22		0.52	[0.36; 0.68]
Thomas 2007	India	41	16		0.39	[0.24; 0.55]
Vaghela 2015	India	79	7		0.09	[0.04; 0.17]
Baral 2014 (Arm 1)	Nepal	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	Nepal	38	6		0.16	[0.06; 0.31]
Random effects model		315	86		0.25	[0.14; 0.42]
Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.9588$, $p < 0.01$						
Western Pacific						
Alene 2017	China	405	130		0.32	[0.28; 0.37]
Yu 2015	Taiwan	106	0		0.00	[0.00; 0.03]
Random effects model		511	130		0.01	[0.00; 0.91]
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 14.2069$, $p = 1.00$						
Random effects model		**5114**	**1136**		**0.17**	**[0.12; 0.23]**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$						
Test for subgroup differences: $\chi^2_4 = 10.29$, df = 4 ($p = 0.04$)						

0   0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 1. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by WHO region. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	% HIV-infected	N	No. LTFU	Proportion	95%-CI
No HIV					
Alene 2017	0	405	130	0.32	[0.28; 0.37]
Escudero 2006	0	23	2	0.09	[0.01; 0.28]
Gelmanova 2011	0	33	6	0.18	[0.07; 0.35]
Joseph 2011	0	30	5	0.17	[0.06; 0.35]
Shin 2006	0	216	28	0.13	[0.09; 0.18]
Taneja 2017 (Control)	0	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	0	42	22	0.52	[0.36; 0.68]
Random effects model		784	214	0.26	[0.15; 0.42]
Heterogeneity: I^2 = 91%, τ^2 = 0.7742, $p < 0.01$					
<10% HIV-infected					
Keshavjee 2008	0.8	519	119	0.23	[0.19; 0.27]
Mitnick 2008	1.4	494	65	0.13	[0.10; 0.16]
Mitnick 2003	1.5	60	5	0.08	[0.03; 0.18]
Vaghela 2015	2	79	7	0.09	[0.04; 0.17]
Kliiman 2009	3.8	206	48	0.23	[0.18; 0.30]
Baral 2014 (Arm 1)	.	30	2	0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	.	38	6	0.16	[0.06; 0.31]
Bastard 2015	.	298	127	0.43	[0.37; 0.48]
Cox 2007	.	66	12	0.18	[0.10; 0.30]
Suarez 2002	.	273	34	0.12	[0.09; 0.17]
Thomas 2007	.	41	16	0.39	[0.24; 0.55]
Yu 2015	.	106	0	0.00	[0.00; 0.03]
Random effects model		2210	441	0.14	[0.08; 0.23]
Heterogeneity: I^2 = 96%, τ^2 = 0.9583, $p < 0.01$					
10-50% HIV-infected					
Huerga 2017 (Nairobi)	15.5	49	6	0.12	[0.05; 0.25]
Huerga 2017 (Mathare)	21.4	58	6	0.10	[0.04; 0.21]
Meressa 2015	21.7	517	36	0.07	[0.05; 0.10]
Random effects model		624	48	0.08	[0.06; 0.10]
Heterogeneity: I^2 = 0%, τ^2 = 0, $p = 0.31$					
>50% HIV-infected					
Huerga 2017 (Homa Bay)	60.7	16	0	0.00	[0.00; 0.21]
Mohr 2017 (SOC)	70	110	44	0.40	[0.31; 0.50]
Satti 2012	70.1	84	1	0.01	[0.00; 0.06]
Loveday 2015 (Site 2 & 3)	70.6	272	70	0.26	[0.21; 0.31]
Mohr 2015	70.9	586	227	0.39	[0.35; 0.43]
Mohr 2017 (SAT)	73.8	146	47	0.32	[0.25; 0.40]
Loveday 2015 (Site 1)	77.4	99	9	0.09	[0.04; 0.17]
Loveday 2015 (Site 4)	83.8	163	28	0.17	[0.12; 0.24]
Isaakidis 2011	100	20	7	0.35	[0.15; 0.59]
Random effects model		1496	433	0.18	[0.09; 0.33]
Heterogeneity: I^2 = 97%, τ^2 = 1.3181, $p < 0.01$					
Random effects model		5114	1136	0.17	[0.12; 0.23]
Heterogeneity: I^2 = 96%, τ^2 = 1.0401, $p < 0.01$					
Test for subgroup differences: χ^2_3 = 17.56, df = 3 ($p < 0.01$)					

Figure 2. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by HIV prevalence. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. For studies that did not report HIV prevalence, all were assumed to have <10% HIV prevalence according to country-level estimates of HIV prevalence among TB patients (see Supplement Table 3). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	% with XDR	N	No. LTFU		Proportion	95%-CI
No XDR						
Cox 2007	0	66	12		0.18	[0.10; 0.30]
Huerga 2017 (Homa Bay)	0	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	0	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	0	49	6		0.12	[0.05; 0.25]
Joseph 2011	0	30	5		0.17	[0.06; 0.35]
Loveday 2015 (Site 1)	0	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	0	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	0	163	28		0.17	[0.12; 0.24]
Meressa 2015	0	517	36		0.07	[0.05; 0.10]
Mohr 2017 (SAT)	0	146	47		0.32	[0.25; 0.40]
Mohr 2017 (SOC)	0	110	44		0.40	[0.31; 0.50]
Taneja 2017 (Control)	0	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	0	42	22		0.52	[0.36; 0.68]
Random effects model		1603	306		0.20	[0.12; 0.30]
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.8868$, $p < 0.01$						
<5% with XDR						
Alene 2017	2.1	405	130		0.32	[0.28; 0.37]
Thomas 2007	3	41	16		0.39	[0.24; 0.55]
Escudero 2006	4	23	2		0.09	[0.01; 0.28]
Mohr 2015	4.6	586	227		0.39	[0.35; 0.43]
Keshavjee 2008	4.8	519	119		0.23	[0.19; 0.27]
Random effects model		1574	494		0.30	[0.22; 0.38]
Heterogeneity: $I^2 = 88\%$, $\tau^2 = 0.1322$, $p < 0.01$						
>5% with XDR						
Gelmanova 2011	5.3	33	6		0.18	[0.07; 0.35]
Isaakidis 2011	6	20	7		0.35	[0.15; 0.59]
Bastard 2015	6.1	298	127		0.43	[0.37; 0.48]
Mitnick 2003	6.7	60	5		0.08	[0.03; 0.18]
Mitnick 2008	7.4	494	65		0.13	[0.10; 0.16]
Kliiman 2009	18.7	206	48		0.23	[0.18; 0.30]
Random effects model		1111	258		0.21	[0.13; 0.33]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.4326$, $p < 0.01$						
Not reported						
Baral 2014 (Arm 1)	.	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	.	38	6		0.16	[0.06; 0.31]
Satti 2012	.	84	1		0.01	[0.00; 0.06]
Shin 2006	.	216	28		0.13	[0.09; 0.18]
Suarez 2002	.	273	34		0.12	[0.09; 0.17]
Vaghela 2015	.	79	7		0.09	[0.04; 0.17]
Yu 2015	.	106	0		0.00	[0.00; 0.03]
Random effects model		826	78		0.06	[0.02; 0.14]
Heterogeneity: $I^2 = 90\%$, $\tau^2 = 1.1221$, $p = 0.23$						
Random effects model		5114	1136		0.17	[0.12; 0.23]

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$
Test for subgroup differences: $\chi_3^2 = 14.44$, df = 3 ($p < 0.01$)

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 3. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by XDR status. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; XDR = extensively drug-resistant TB.

Study Cohort	% with XDR	N	No. LTFU		Proportion	95%-CI
No XDR						
Cox 2007	0	66	12		0.18	[0.10; 0.30]
Huerga 2017 (Homa Bay)	0	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	0	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	0	49	6		0.12	[0.05; 0.25]
Joseph 2011	0	30	5		0.17	[0.06; 0.35]
Loveday 2015 (Site 1)	0	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	0	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	0	163	28		0.17	[0.12; 0.24]
Meressa 2015	0	517	36		0.07	[0.05; 0.10]
Mohr 2017 (SAT)	0	146	47		0.32	[0.25; 0.40]
Mohr 2017 (SOC)	0	110	44		0.40	[0.31; 0.50]
Taneja 2017 (Control)	0	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	0	42	22		0.52	[0.36; 0.68]
Random effects model		1603	306		0.20	[0.12; 0.30]
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.8868$, $p < 0.01$						
<5% with XDR						
Alene 2017	2.1	405	130		0.32	[0.28; 0.37]
Thomas 2007	3	41	16		0.39	[0.24; 0.55]
Escudero 2006	4	23	2		0.09	[0.01; 0.28]
Mohr 2015	4.6	586	227		0.39	[0.35; 0.43]
Keshavjee 2008	4.8	519	119		0.23	[0.19; 0.27]
Random effects model		1574	494		0.30	[0.22; 0.38]
Heterogeneity: $I^2 = 88\%$, $\tau^2 = 0.1322$, $p < 0.01$						
>5% with XDR						
Gelmanova 2011	5.3	33	6		0.18	[0.07; 0.35]
Isaakidis 2011	6	20	7		0.35	[0.15; 0.59]
Bastard 2015	6.1	298	127		0.43	[0.37; 0.48]
Mitnick 2003	6.7	60	5		0.08	[0.03; 0.18]
Mitnick 2008	7.4	494	65		0.13	[0.10; 0.16]
Kliiman 2009	18.7	206	48		0.23	[0.18; 0.30]
Random effects model		1111	258		0.21	[0.13; 0.33]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.4326$, $p < 0.01$						
Random effects model		**4288**	**1058**		**0.22**	**[0.16; 0.28]**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.6453$, $p < 0.01$						
Test for subgroup differences: $\chi^2_2 = 3.04$, df = 2 ($p = 0.22$)				0 0.1 0.2 0.3 0.4 0.5 0.6 0.7		

Figure 4. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by XDR status, excluding studies that did not report XDR status. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report XDR status among patients were excluded (n=7). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; XDR = extensively drug-resistant TB.

Study Cohort	% previously treated	N	No. LTFU	Proportion	95%-CI
<70% previously treated					
Loveday 2015 (Site 4)	46.4	163	28	0.17	[0.12; 0.24]
Kliiman 2009	48.1	206	48	0.23	[0.18; 0.30]
Yu 2015	48.4	106	0	0.00	[0.00; 0.03]
Gelmanova 2011	55.3	33	6	0.18	[0.07; 0.35]
Mohr 2017 (SAT)	59.8	146	47	0.32	[0.25; 0.40]
Mohr 2015	67.5	586	227	0.39	[0.35; 0.43]
Random effects model		1240	356	0.16	[0.05; 0.38]
Heterogeneity: I^2 = 98%, τ^2 = 1.8966, p < 0.01					
70-90% previously treated					
Loveday 2015 (Site 2 & 3)	71.4	272	70	0.26	[0.21; 0.31]
Loveday 2015 (Site 1)	74.4	99	9	0.09	[0.04; 0.17]
Mohr 2017 (SOC)	76.2	110	44	0.40	[0.31; 0.50]
Bastard 2015	77.4	298	127	0.43	[0.37; 0.48]
Huerga 2017 (Homa Bay)	85.7	16	0	0.00	[0.00; 0.21]
Alene 2017	86.7	405	130	0.32	[0.28; 0.37]
Isaakidis 2011	87.9	20	7	0.35	[0.15; 0.59]
Escudero 2006	88	23	2	0.09	[0.01; 0.28]
Random effects model		1243	389	0.23	[0.13; 0.36]
Heterogeneity: I^2 = 95%, τ^2 = 0.6886, p < 0.01					
>90% previously treated					
Huerga 2017 (Mathare)	90	58	6	0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	94.4	49	6	0.12	[0.05; 0.25]
Satti 2012	96.3	84	1	0.01	[0.00; 0.06]
Shin 2006	98	216	28	0.13	[0.09; 0.18]
Meressa 2015	98.5	517	36	0.07	[0.05; 0.10]
Keshavjee 2008	99.5	519	119	0.23	[0.19; 0.27]
Mitnick 2008	99.7	494	65	0.13	[0.10; 0.16]
Cox 2007	100	66	12	0.18	[0.10; 0.30]
Joseph 2011	100	30	5	0.17	[0.06; 0.35]
Mitnick 2003	100	60	5	0.08	[0.03; 0.18]
Suarez 2002	100	273	34	0.12	[0.09; 0.17]
Taneja 2017 (Control)	100	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	100	42	22	0.52	[0.36; 0.68]
Thomas 2007	100	41	16	0.39	[0.24; 0.55]
Random effects model		2484	376	0.16	[0.10; 0.25]
Heterogeneity: I^2 = 95%, τ^2 = 1.0007, p < 0.01					
Not reported					
Baral 2014 (Arm 1)	.	30	2	0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	.	38	6	0.16	[0.06; 0.31]
Vaghela 2015	.	79	7	0.09	[0.04; 0.17]
Random effects model		147	15	0.10	[0.06; 0.16]
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.41					
Random effects model		5114	1136	0.17	[0.12; 0.23]
Heterogeneity: I^2 = 96%, τ^2 = 1.0401, p < 0.01					
Test for subgroup differences: χ^2_3 = 4.91, df = 3 (p = 0.18)					

0   0.1   0.2   0.3   0.4   0.5   0.6   0.7

Figure 5. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated for any type of TB. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	% previously treated	N	No. LTFU	Proportion	95%-CI
<70% previously treated					
Loveday 2015 (Site 4)	46.4	163	28	0.17	[0.12; 0.24]
Kliiman 2009	48.1	206	48	0.23	[0.18; 0.30]
Yu 2015	48.4	106	0	0.00	[0.00; 0.03]
Gelmanova 2011	55.3	33	6	0.18	[0.07; 0.35]
Mohr 2017 (SAT)	59.8	146	47	0.32	[0.25; 0.40]
Mohr 2015	67.5	586	227	0.39	[0.35; 0.43]
Random effects model		1240	356	0.16	[0.05; 0.38]
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.8966$, $p < 0.01$					
70-90% previously treated					
Loveday 2015 (Site 2 & 3)	71.4	272	70	0.26	[0.21; 0.31]
Loveday 2015 (Site 1)	74.4	99	9	0.09	[0.04; 0.17]
Mohr 2017 (SOC)	76.2	110	44	0.40	[0.31; 0.50]
Bastard 2015	77.4	298	127	0.43	[0.37; 0.48]
Huerga 2017 (Homa Bay)	85.7	16	0	0.00	[0.00; 0.21]
Alene 2017	86.7	405	130	0.32	[0.28; 0.37]
Isaakidis 2011	87.9	20	7	0.35	[0.15; 0.59]
Escudero 2006	88	23	2	0.09	[0.01; 0.28]
Random effects model		1243	389	0.23	[0.13; 0.36]
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.6886$, $p < 0.01$					
>90% previously treated					
Huerga 2017 (Mathare)	90	58	6	0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	94.4	49	6	0.12	[0.05; 0.25]
Satti 2012	96.3	84	1	0.01	[0.00; 0.06]
Shin 2006	98	216	28	0.13	[0.09; 0.18]
Meressa 2015	98.5	517	36	0.07	[0.05; 0.10]
Keshavjee 2008	99.5	519	119	0.23	[0.19; 0.27]
Mitnick 2008	99.7	494	65	0.13	[0.10; 0.16]
Cox 2007	100	66	12	0.18	[0.10; 0.30]
Joseph 2011	100	30	5	0.17	[0.06; 0.35]
Mitnick 2003	100	60	5	0.08	[0.03; 0.18]
Suarez 2002	100	273	34	0.12	[0.09; 0.17]
Taneja 2017 (Control)	100	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	100	42	22	0.52	[0.36; 0.68]
Thomas 2007	100	41	16	0.39	[0.24; 0.55]
Random effects model		2484	376	0.16	[0.10; 0.25]
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 1.0007$, $p < 0.01$					
Random effects model		4967	1121	0.18	[0.12; 0.24]
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 1.1008$, $p < 0.01$					
Test for subgroup differences: $\chi_2^2 = 1.00$, df = 2 ($p = 0.61$)					

0   0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 6. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated for any type of TB, excluding studies that did not report proportions previously treated. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report proportions with any previous TB treatment were excluded (n=3). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	% previously treated with SLD	N	No. LTFU		Proportion	95%-CI
None previously treated with SLD						
Joseph 2011	0	30	5		0.17	[0.06; 0.35]
Mohr 2015	0	586	227		0.39	[0.35; 0.43]
Taneja 2017 (Control)	0	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	0	42	22		0.52	[0.36; 0.68]
Random effects model		693	275		0.41	[0.27; 0.58]
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.3557$, $p < 0.01$						
<10% previously treated with SLD						
Loveday 2015 (Site 1)	4.8	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 4)	5.4	163	28		0.17	[0.12; 0.24]
Loveday 2015 (Site 2 & 3)	9.4	272	70		0.26	[0.21; 0.31]
Random effects model		534	107		0.17	[0.10; 0.26]
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.1864$, $p < 0.01$						
>10% previously treated with SLD						
Mohr 2017 (SOC)	11.9	110	44		0.40	[0.31; 0.50]
Satti 2012	13.4	84	1		0.01	[0.00; 0.06]
Mohr 2017 (SAT)	13.5	146	47		0.32	[0.25; 0.40]
Gelmanova 2011	26.3	33	6		0.18	[0.07; 0.35]
Bastard 2015	29.3	298	127		0.43	[0.37; 0.48]
Isaakidis 2011	44.8	20	7		0.35	[0.15; 0.59]
Mitnick 2008	64.5	494	65		0.13	[0.10; 0.16]
Cox 2007	65.5	66	12		0.18	[0.10; 0.30]
Random effects model		1251	309		0.21	[0.11; 0.36]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 0.9799$, $p < 0.01$						
Not reported						
Alene 2017	.	405	130		0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	.	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	.	38	6		0.16	[0.06; 0.31]
Escudero 2006	.	23	2		0.09	[0.01; 0.28]
Huerga 2017 (Homa Bay)	.	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	.	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	.	49	6		0.12	[0.05; 0.25]
Keshavjee 2008	.	519	119		0.23	[0.19; 0.27]
Kliiman 2009	.	206	48		0.23	[0.18; 0.30]
Meressa 2015	.	517	36		0.07	[0.05; 0.10]
Mitnick 2003	.	60	5		0.08	[0.03; 0.18]
Shin 2006	.	216	28		0.13	[0.09; 0.18]
Suarez 2002	.	273	34		0.12	[0.09; 0.17]
Thomas 2007	.	41	16		0.39	[0.24; 0.55]
Vaghela 2015	.	79	7		0.09	[0.04; 0.17]
Yu 2015	.	106	0		0.00	[0.00; 0.03]
Random effects model		2636	445		0.12	[0.07; 0.18]
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.7489$, $p < 0.01$						
Random effects model		5114	1136		0.17	[0.12; 0.23]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$						
Test for subgroup differences: $\chi^2_3 = 16.57$, df = 3 ($p < 0.01$)						

0   0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 7. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated with second-line TB drugs. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; SLD = second-line drugs.
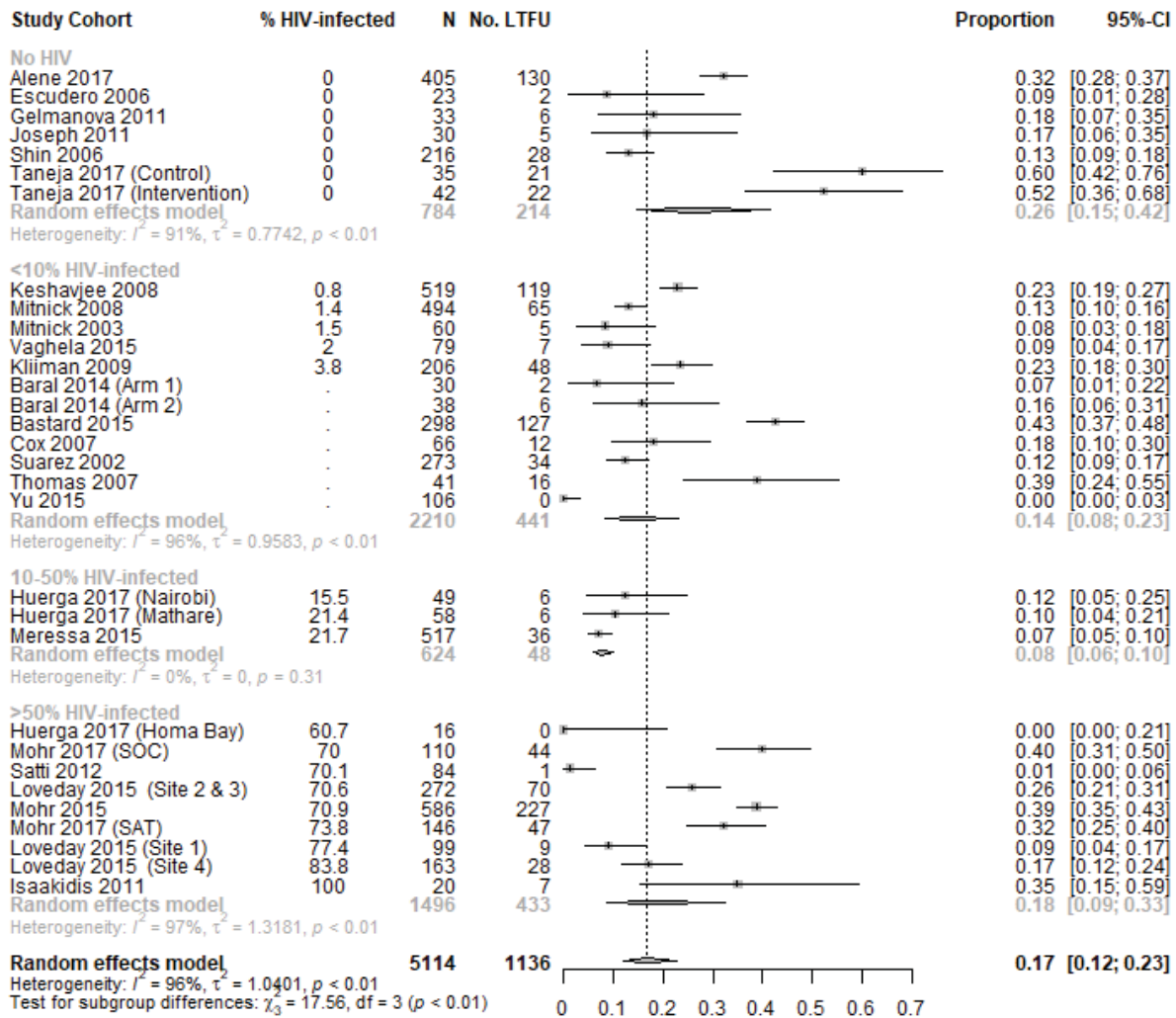
Study Cohort	% previously treated with SLD	N	No. LTFU		Proportion	95%-CI
None previously treated with SLD						
Joseph 2011	0	30	5		0.17	[0.06; 0.35]
Mohr 2015	0	586	227		0.39	[0.35; 0.43]
Taneja 2017 (Control)	0	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	0	42	22		0.52	[0.36; 0.68]
Random effects model		693	275		0.41	[0.27; 0.58]
Heterogeneity: I^2 = 83%, τ^2 = 0.3557, p < 0.01						
<10% previously treated with SLD						
Loveday 2015 (Site 1)	4.8	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 4)	5.4	163	28		0.17	[0.12; 0.24]
Loveday 2015 (Site 2 & 3)	9.4	272	70		0.26	[0.21; 0.31]
Random effects model		534	107		0.17	[0.10; 0.26]
Heterogeneity: I^2 = 80%, τ^2 = 0.1864, p < 0.01						
>10% previously treated with SLD						
Mohr 2017 (SOC)	11.9	110	44		0.40	[0.31; 0.50]
Satti 2012	13.4	84	1		0.01	[0.00; 0.06]
Mohr 2017 (SAT)	13.5	146	47		0.32	[0.25; 0.40]
Gelmanova 2011	26.3	33	6		0.18	[0.07; 0.35]
Bastard 2015	29.3	298	127		0.43	[0.37; 0.48]
Isaakidis 2011	44.8	20	7		0.35	[0.15; 0.59]
Mitnick 2008	64.5	494	65		0.13	[0.10; 0.16]
Cox 2007	65.5	66	12		0.18	[0.10; 0.30]
Random effects model		1251	309		0.21	[0.11; 0.36]
Heterogeneity: I^2 = 96%, τ^2 = 0.9799, p < 0.01						
Random effects model		2478	691		0.24	[0.16; 0.35]
Heterogeneity: I^2 = 96%, τ^2 = 0.8755, p < 0.01						
Test for subgroup differences: χ^2_2 = 8.17, df = 2 (p = 0.02)						

0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 8. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated with second-line TB drugs, excluding studies that did not report proportions previously treated with SLD. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report proportions with any previous treatment with second-line drugs were excluded (n=16). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; SLD = second-line drugs.
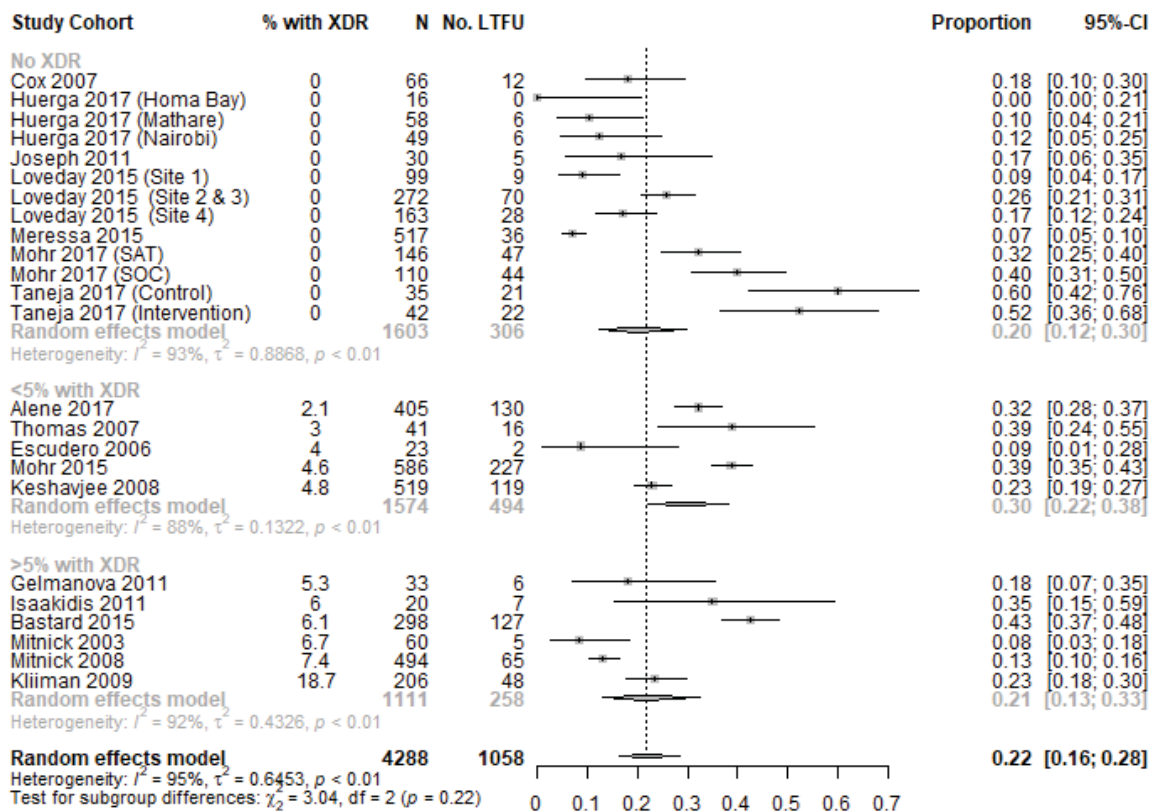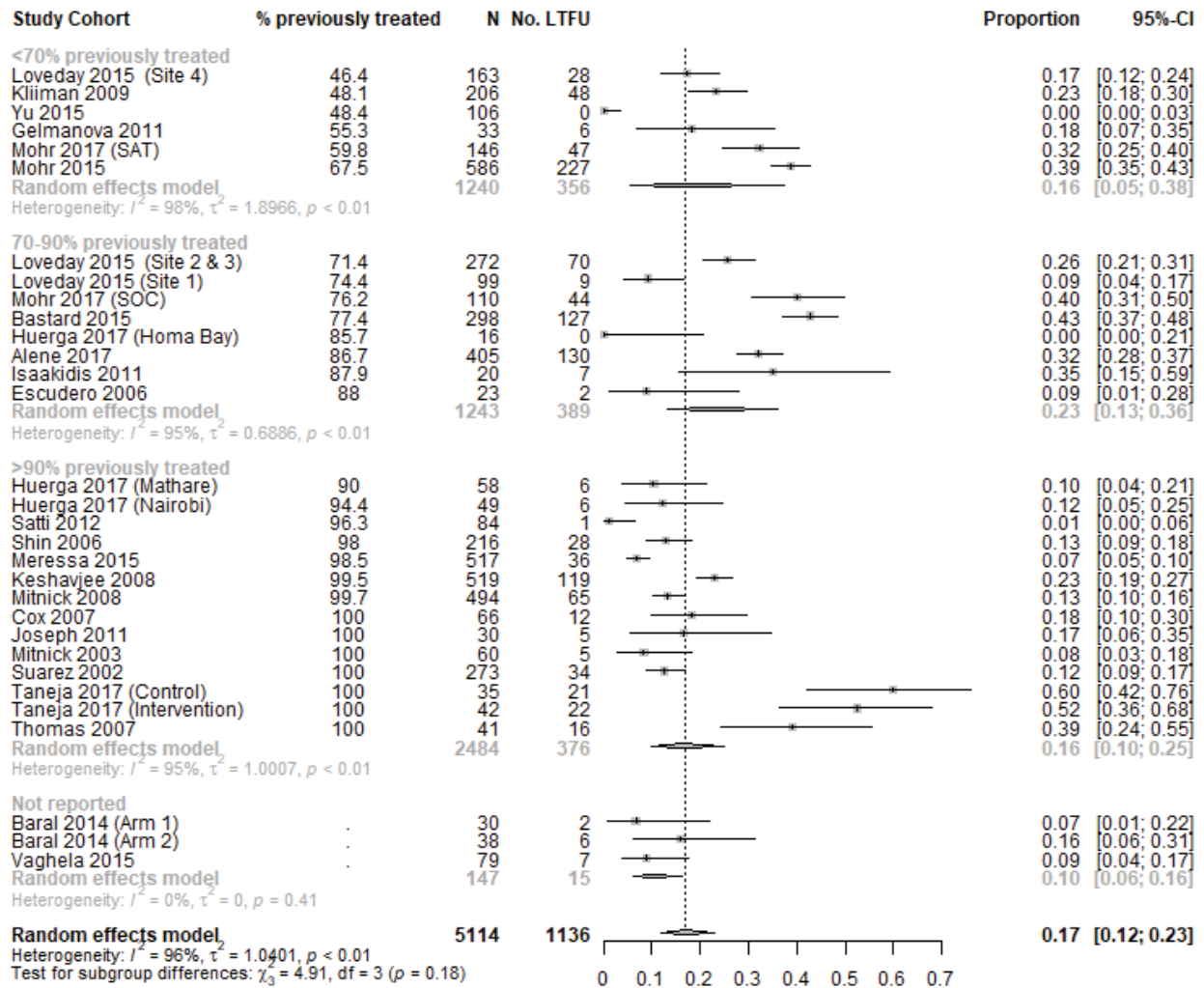
Study Cohort	Study Year	N	No. LTFU	Proportion	95%-CI
1995-1999					
Escudero 2006	1998-2000	23	2	0.09	[0.01; 0.28]
Mitnick 2003	1996-1999	60	5	0.08	[0.03; 0.18]
Mitnick 2008	1999-2002	494	65	0.13	[0.10; 0.16]
Shin 2006	1998-2000	216	28	0.13	[0.09; 0.18]
Suarez 2002	1997-1999	273	34	0.12	[0.09; 0.17]
Thomas 2007	1999-2003	41	16	0.39	[0.24; 0.55]
Random effects model		1107	150	0.14	[0.09; 0.21]
Heterogeneity: $I^2 = 82\%$, $\tau^2 = 0.2516$, $p < 0.01$					
2000-2004					
Bastard 2015	2002-2010	298	127	0.43	[0.37; 0.48]
Cox 2007	2003-2005	66	12	0.18	[0.10; 0.30]
Keshavjee 2008	2000-2004	519	119	0.23	[0.19; 0.27]
Kliiman 2009	2003-2005	206	48	0.23	[0.18; 0.30]
Random effects model		1089	306	0.27	[0.19; 0.36]
Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.1804$, $p < 0.01$					
2005-2009					
Baral 2014 (Arm 1)	2008	30	2	0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	2008	38	6	0.16	[0.06; 0.31]
Gelmanova 2011	2006-2008	33	6	0.18	[0.07; 0.35]
Huerga 2017 (Homa Bay)	2006-2012	16	0	0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	2006-2012	58	6	0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	2006-2012	49	6	0.12	[0.05; 0.25]
Isaakidis 2011	2007-2011	20	7	0.35	[0.15; 0.59]
Joseph 2011	2006-2007	30	5	0.17	[0.06; 0.35]
Loveday 2015 (Site 1)	2008-2010	99	9	0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	2008-2010	272	70	0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	2008-2010	163	28	0.17	[0.12; 0.24]
Meressa 2015	2009-2014	517	36	0.07	[0.05; 0.10]
Mohr 2015	2008-2012	586	227	0.39	[0.35; 0.43]
Satti 2012	2008-2009	84	1	0.01	[0.00; 0.06]
Vaghela 2015	2009-2010	79	7	0.09	[0.04; 0.17]
Yu 2015	2007-2009	106	0	0.00	[0.00; 0.03]
Random effects model		2180	416	0.10	[0.06; 0.17]
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 1.0720$, $p < 0.01$					
2010-2014					
Alene 2017	2011-2014	405	130	0.32	[0.28; 0.37]
Mohr 2017 (SAT)	2010-2014	146	47	0.32	[0.25; 0.40]
Mohr 2017 (SOC)	2010-2014	110	44	0.40	[0.31; 0.50]
Taneja 2017 (Control)	2014	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	2014	42	22	0.52	[0.36; 0.68]
Random effects model		738	264	0.41	[0.32; 0.50]
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.1242$, $p < 0.01$					
Random effects model		5114	1136	0.17	[0.12; 0.23]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$					
Test for subgroup differences: $\chi^2_3 = 34.63$, df = 3 ($p < 0.01$)					

Figure 9. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by the year study recruitment started. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report proportions with any previous treatment with second-line drugs were excluded (n=16). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; SLD = second-line drugs.
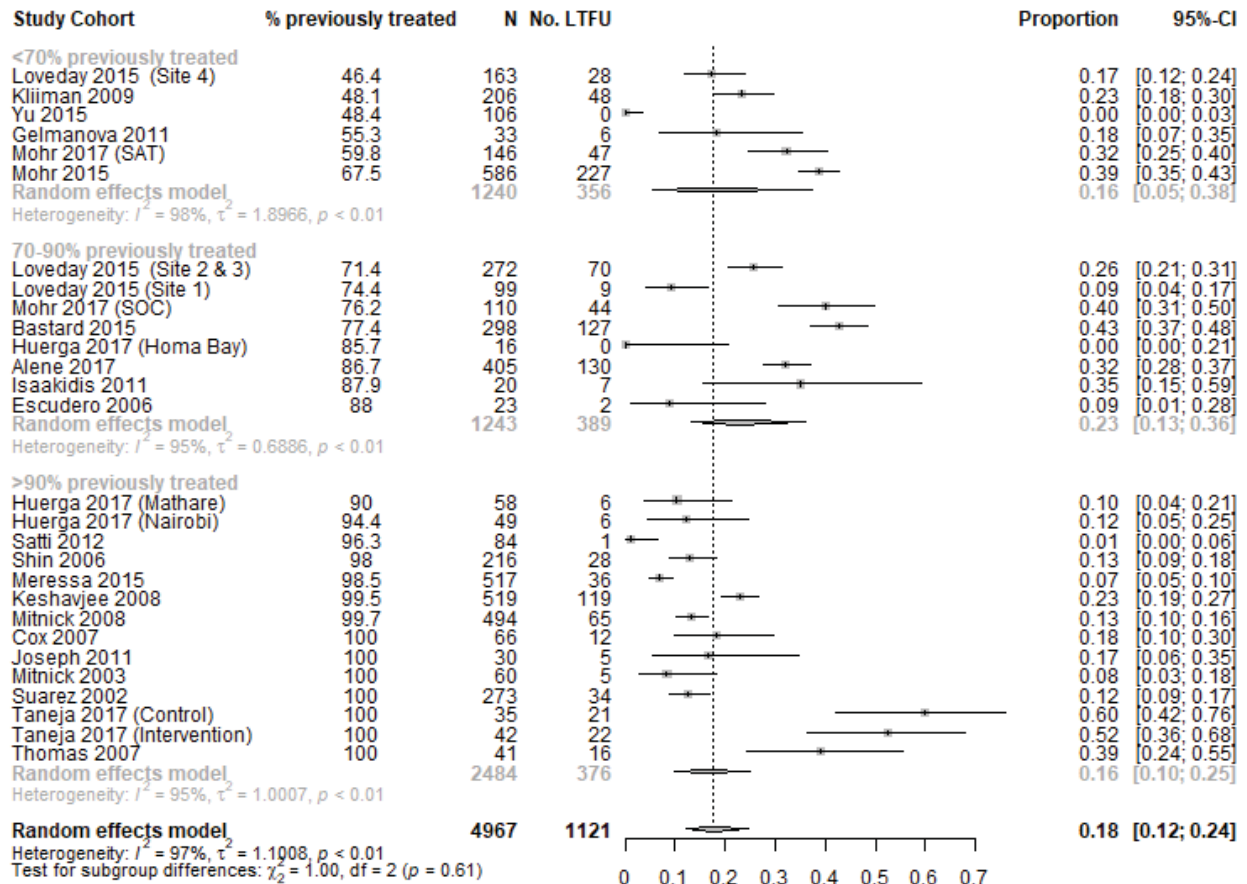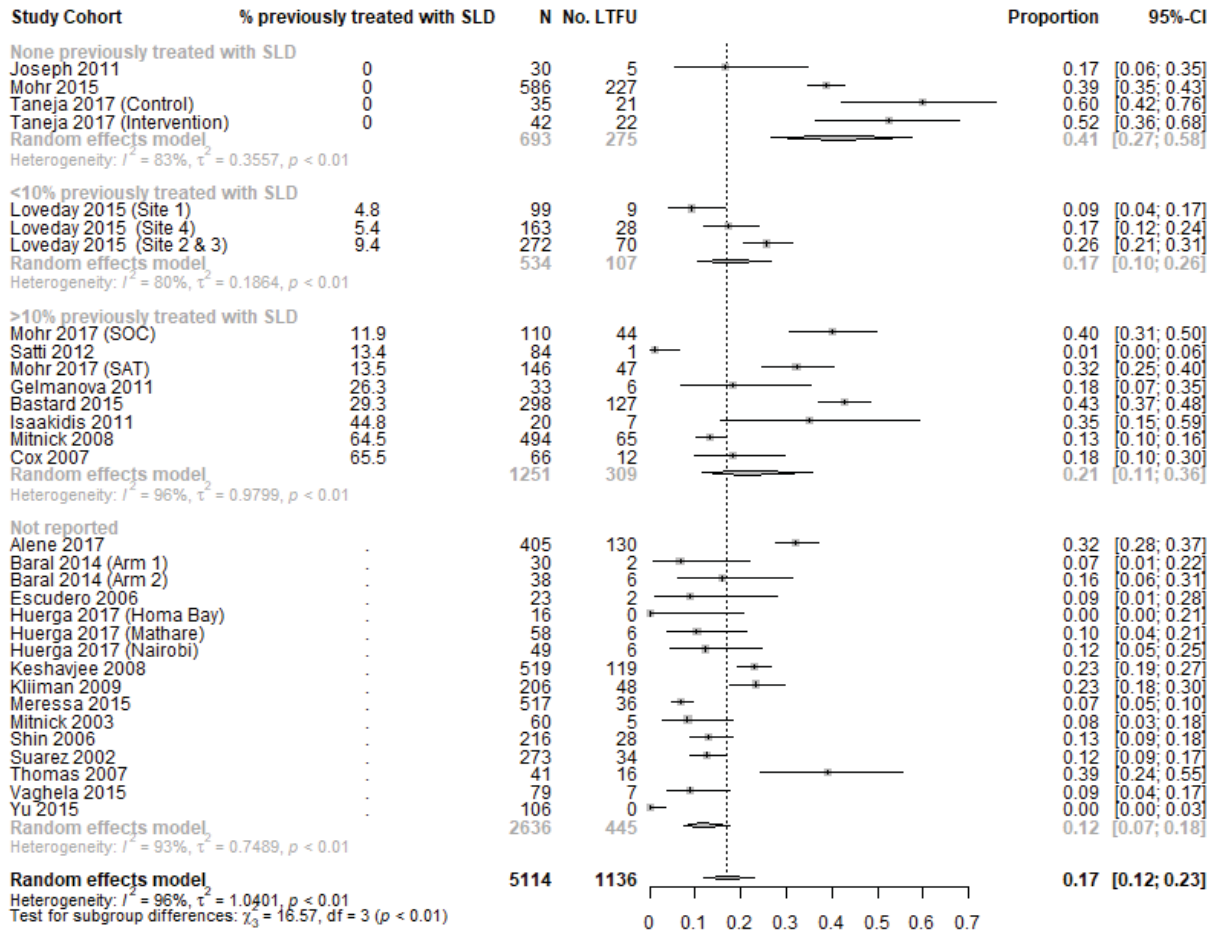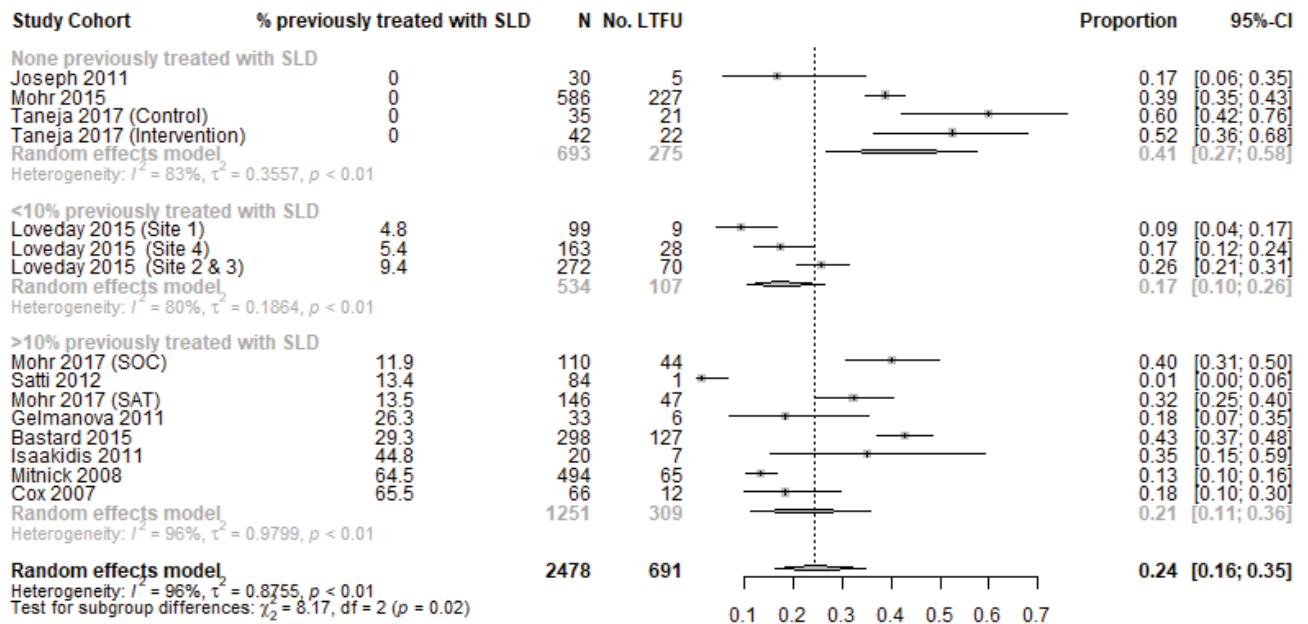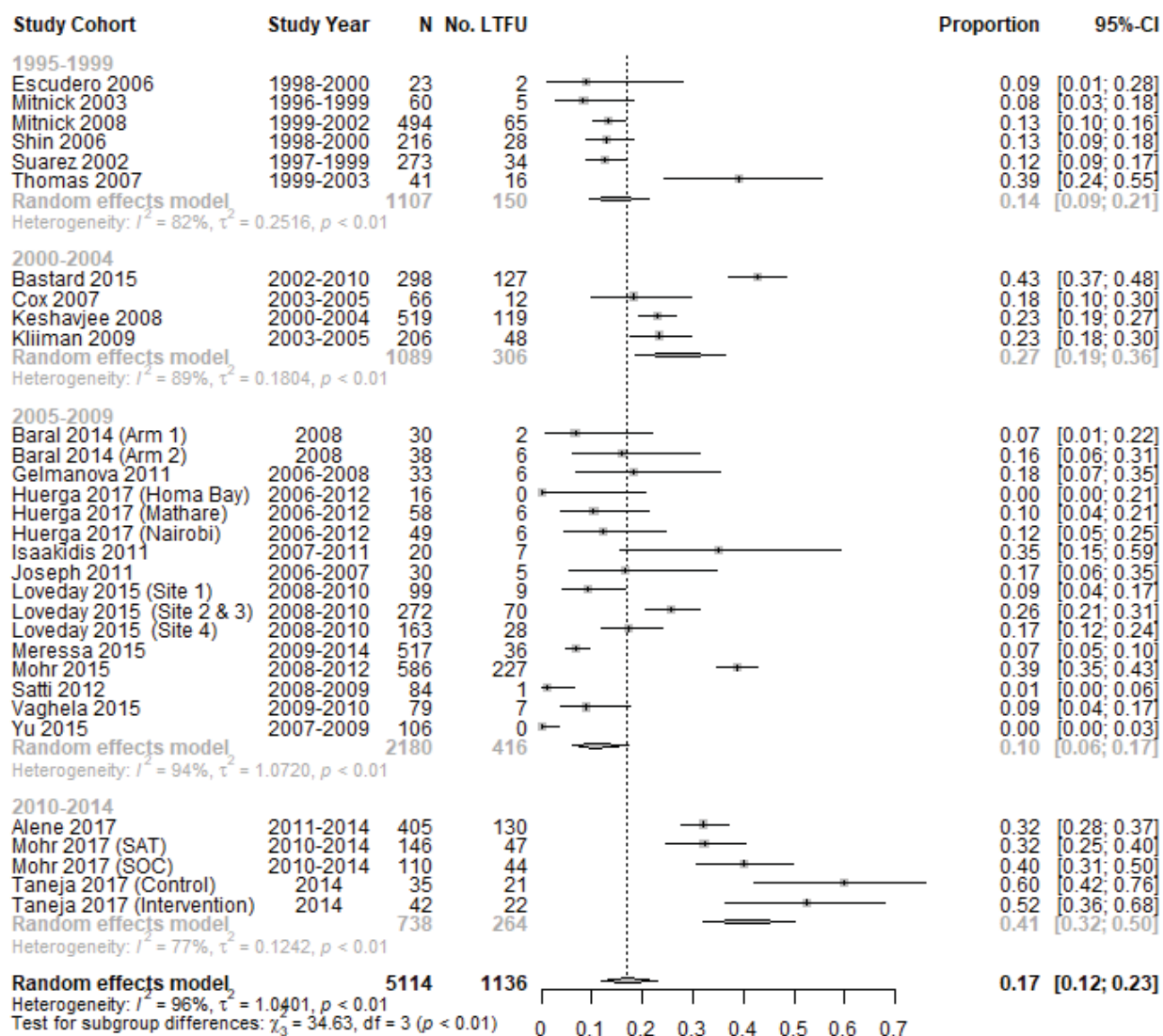
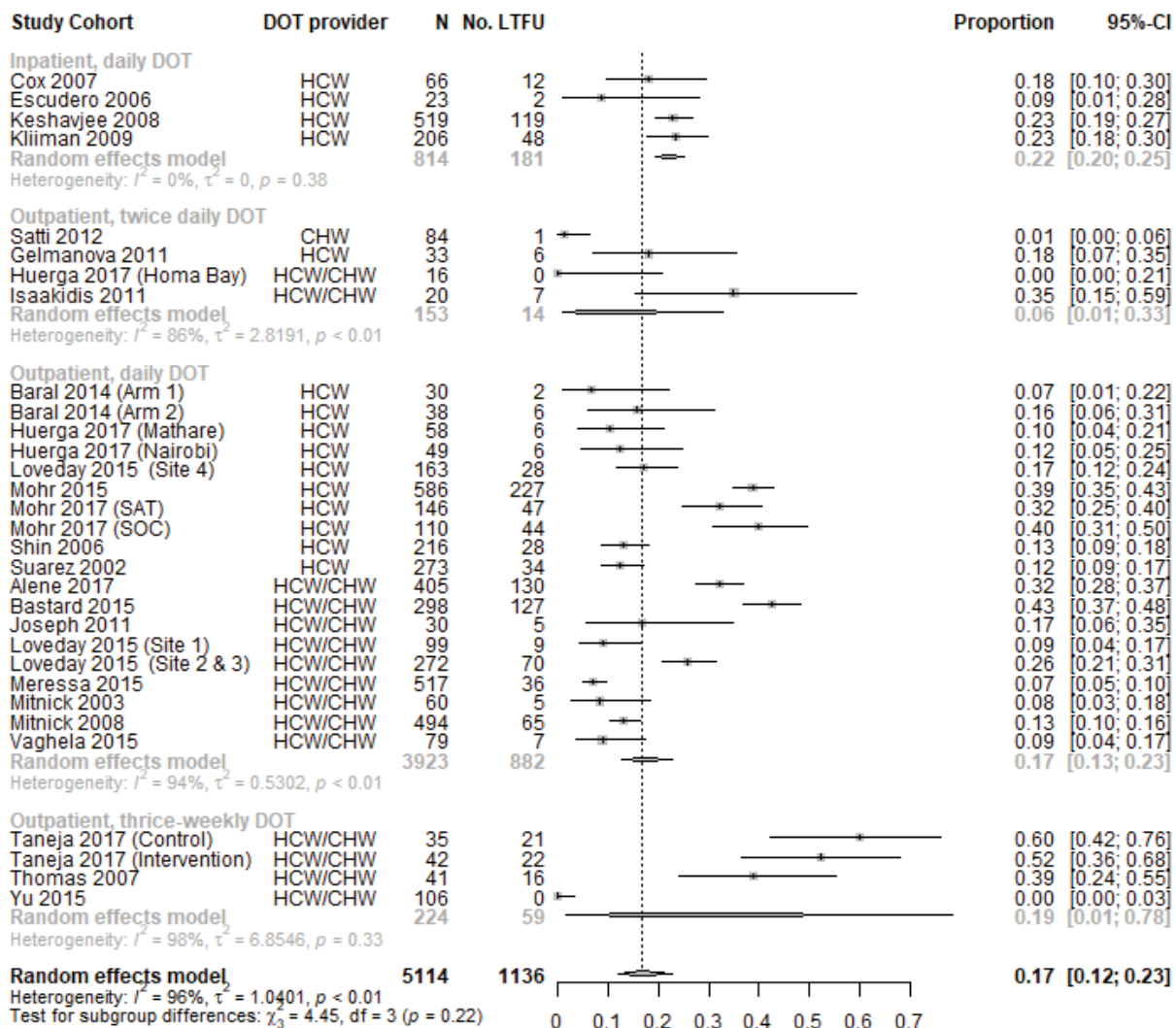| Study Cohort	DOT provider	N	No. LTFU	Proportion	95%-CI
Inpatient, daily DOT					
Cox 2007	HCW	66	12	0.18	[0.10; 0.30]
Escudero 2006	HCW	23	2	0.09	[0.01; 0.28]
Keshavjee 2008	HCW	519	119	0.23	[0.19; 0.27]
Kliiman 2009	HCW	206	48	0.23	[0.18; 0.30]
Random effects model		814	181	0.22	[0.20; 0.25]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.38$					
Outpatient, twice daily DOT					
Satti 2012	CHW	84	1	0.01	[0.00; 0.06]
Gelmanova 2011	HCW	33	6	0.18	[0.07; 0.35]
Huerga 2017 (Homa Bay)	HCW/CHW	16	0	0.00	[0.00; 0.21]
Isaakidis 2011	HCW/CHW	20	7	0.35	[0.15; 0.59]
Random effects model		153	14	0.06	[0.01; 0.33]
Heterogeneity: $I^2 = 86\%$, $\tau^2 = 2.8191$, $p < 0.01$					
Outpatient, daily DOT					
Baral 2014 (Arm 1)	HCW	30	2	0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	HCW	38	6	0.16	[0.06; 0.31]
Huerga 2017 (Mathare)	HCW	58	6	0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	HCW	49	6	0.12	[0.05; 0.25]
Loveday 2015 (Site 4)	HCW	163	28	0.17	[0.12; 0.24]
Mohr 2015	HCW	586	227	0.39	[0.35; 0.43]
Mohr 2017 (SAT)	HCW	146	47	0.32	[0.25; 0.40]
Mohr 2017 (SOC)	HCW	110	44	0.40	[0.31; 0.50]
Shin 2006	HCW	216	28	0.13	[0.09; 0.18]
Suarez 2002	HCW	273	34	0.12	[0.09; 0.17]
Alene 2017	HCW/CHW	405	130	0.32	[0.28; 0.37]
Bastard 2015	HCW/CHW	298	127	0.43	[0.37; 0.48]
Joseph 2011	HCW/CHW	30	5	0.17	[0.06; 0.35]
Loveday 2015 (Site 1)	HCW/CHW	99	9	0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	HCW/CHW	272	70	0.26	[0.21; 0.31]
Meressa 2015	HCW/CHW	517	36	0.07	[0.05; 0.10]
Mitnick 2003	HCW/CHW	60	5	0.08	[0.03; 0.18]
Mitnick 2008	HCW/CHW	494	65	0.13	[0.10; 0.16]
Vaghela 2015	HCW/CHW	79	7	0.09	[0.04; 0.17]
Random effects model		3923	882	0.17	[0.13; 0.23]
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.5302$, $p < 0.01$					
Outpatient, thrice-weekly DOT					
Taneja 2017 (Control)	HCW/CHW	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	HCW/CHW	42	22	0.52	[0.36; 0.68]
Thomas 2007	HCW/CHW	41	16	0.39	[0.24; 0.55]
Yu 2015	HCW/CHW	106	0	0.00	[0.00; 0.03]
Random effects model		224	59	0.19	[0.01; 0.78]
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 6.8546$, $p = 0.33$					
Random effects model		5114	1136	0.17	[0.12; 0.23]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$					
Test for subgroup differences: $\chi^2_3 = 4.45$, df = 3 ($p = 0.22$)					

Figure 10. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by DOT frequency method during the intensive phase. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker; DOT = daily observed therapy.
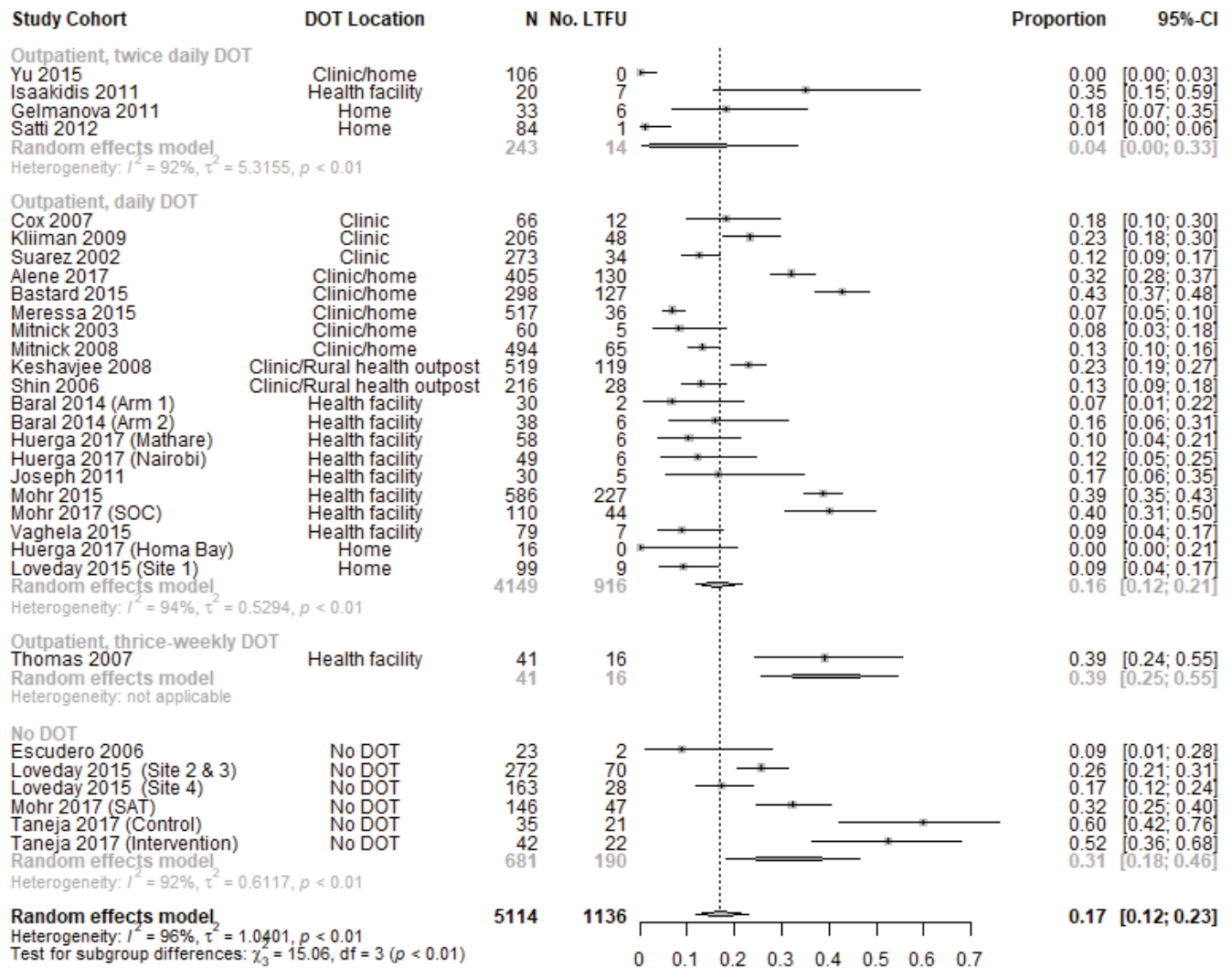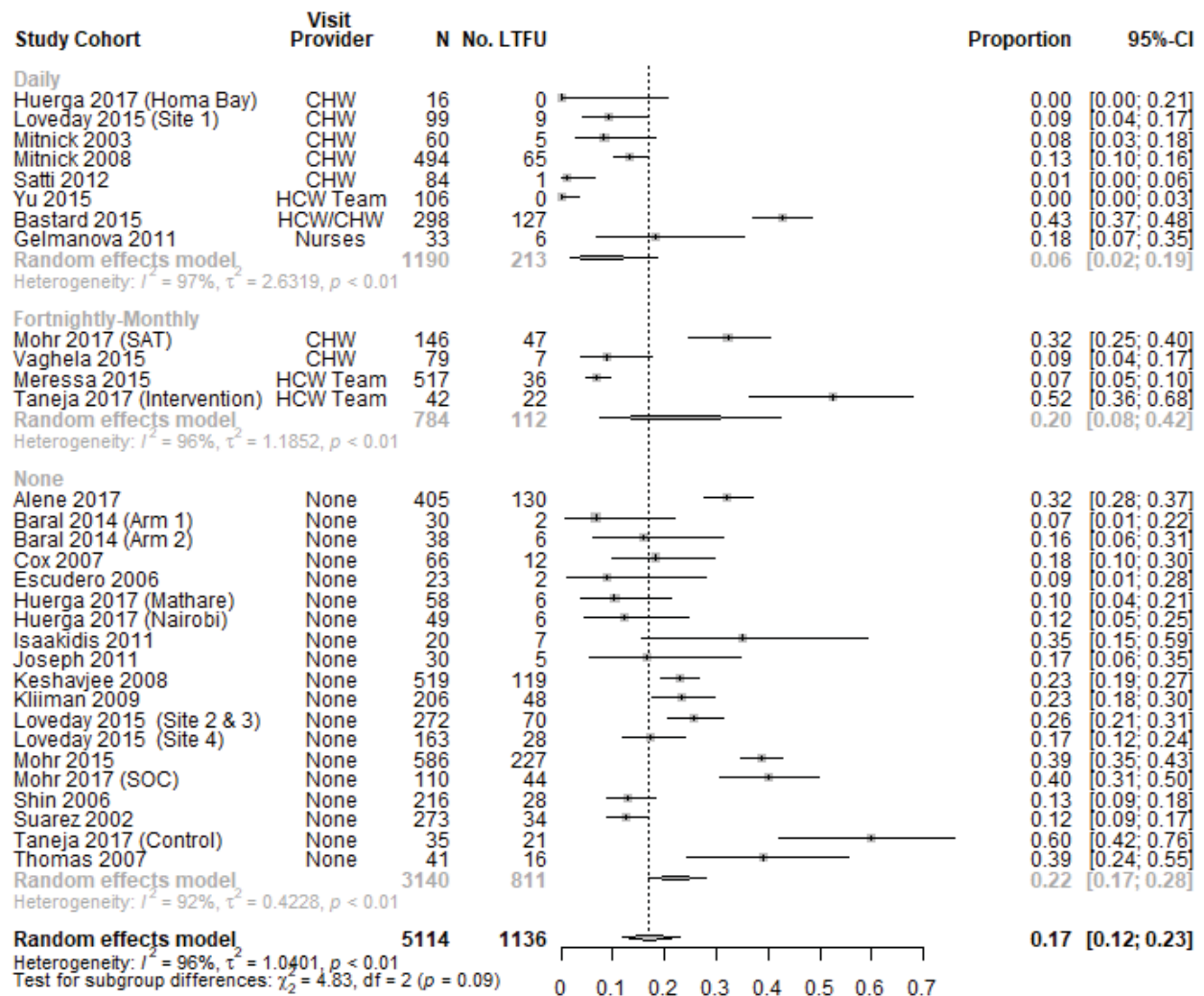
Study Cohort	DOT Location	N	No. LTFU		Proportion	95%-CI
Outpatient, twice daily DOT						
Yu 2015	Clinic/home	106	0		0.00	[0.00; 0.03]
Isaakidis 2011	Health facility	20	7		0.35	[0.15; 0.59]
Gelmanova 2011	Home	33	6		0.18	[0.07; 0.35]
Satti 2012	Home	84	1		0.01	[0.00; 0.06]
Random effects model		243	14		0.04	[0.00; 0.33]
Heterogeneity: I^2 = 92%, τ^2 = 5.3155, p < 0.01						
Outpatient, daily DOT						
Cox 2007	Clinic	66	12		0.18	[0.10; 0.30]
Kliiman 2009	Clinic	206	48		0.23	[0.18; 0.30]
Suarez 2002	Clinic	273	34		0.12	[0.09; 0.17]
Alene 2017	Clinic/home	405	130		0.32	[0.28; 0.37]
Bastard 2015	Clinic/home	298	127		0.43	[0.37; 0.48]
Meressa 2015	Clinic/home	517	36		0.07	[0.05; 0.10]
Mitnick 2003	Clinic/home	60	5		0.08	[0.03; 0.18]
Mitnick 2008	Clinic/home	494	65		0.13	[0.10; 0.16]
Keshavjee 2008	Clinic/Rural health outpost	519	119		0.23	[0.19; 0.27]
Shin 2006	Clinic/Rural health outpost	216	28		0.13	[0.09; 0.18]
Baral 2014 (Arm 1)	Health facility	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	Health facility	38	6		0.16	[0.06; 0.31]
Huerga 2017 (Mathare)	Health facility	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	Health facility	49	6		0.12	[0.05; 0.25]
Joseph 2011	Health facility	30	5		0.17	[0.06; 0.35]
Mohr 2015	Health facility	586	227		0.39	[0.35; 0.43]
Mohr 2017 (SOC)	Health facility	110	44		0.40	[0.31; 0.50]
Vaghela 2015	Health facility	79	7		0.09	[0.04; 0.17]
Huerga 2017 (Homa Bay)	Home	16	0		0.00	[0.00; 0.21]
Loveday 2015 (Site 1)	Home	99	9		0.09	[0.04; 0.17]
Random effects model		4149	916		0.16	[0.12; 0.21]
Heterogeneity: I^2 = 94%, τ^2 = 0.5294, p < 0.01						
Outpatient, thrice-weekly DOT						
Thomas 2007	Health facility	41	16		0.39	[0.24; 0.55]
Random effects model		41	16		0.39	[0.25; 0.55]
Heterogeneity: not applicable						
No DOT						
Escudero 2006	No DOT	23	2		0.09	[0.01; 0.28]
Loveday 2015 (Site 2 & 3)	No DOT	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	No DOT	163	28		0.17	[0.12; 0.24]
Mohr 2017 (SAT)	No DOT	146	47		0.32	[0.25; 0.40]
Taneja 2017 (Control)	No DOT	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	No DOT	42	22		0.52	[0.36; 0.68]
Random effects model		681	190		0.31	[0.18; 0.46]
Heterogeneity: I^2 = 92%, τ^2 = 0.6117, p < 0.01						
Random effects model		5114	1136		0.17	[0.12; 0.23]
Heterogeneity: I^2 = 96%, τ^2 = 1.0401, p < 0.01						
Test for subgroup differences: χ^2_3 = 15.06, df = 3 (p < 0.01)						

0   0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 11. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by DOT frequency during the continuation phase. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker; DOT = daily observed therapy.
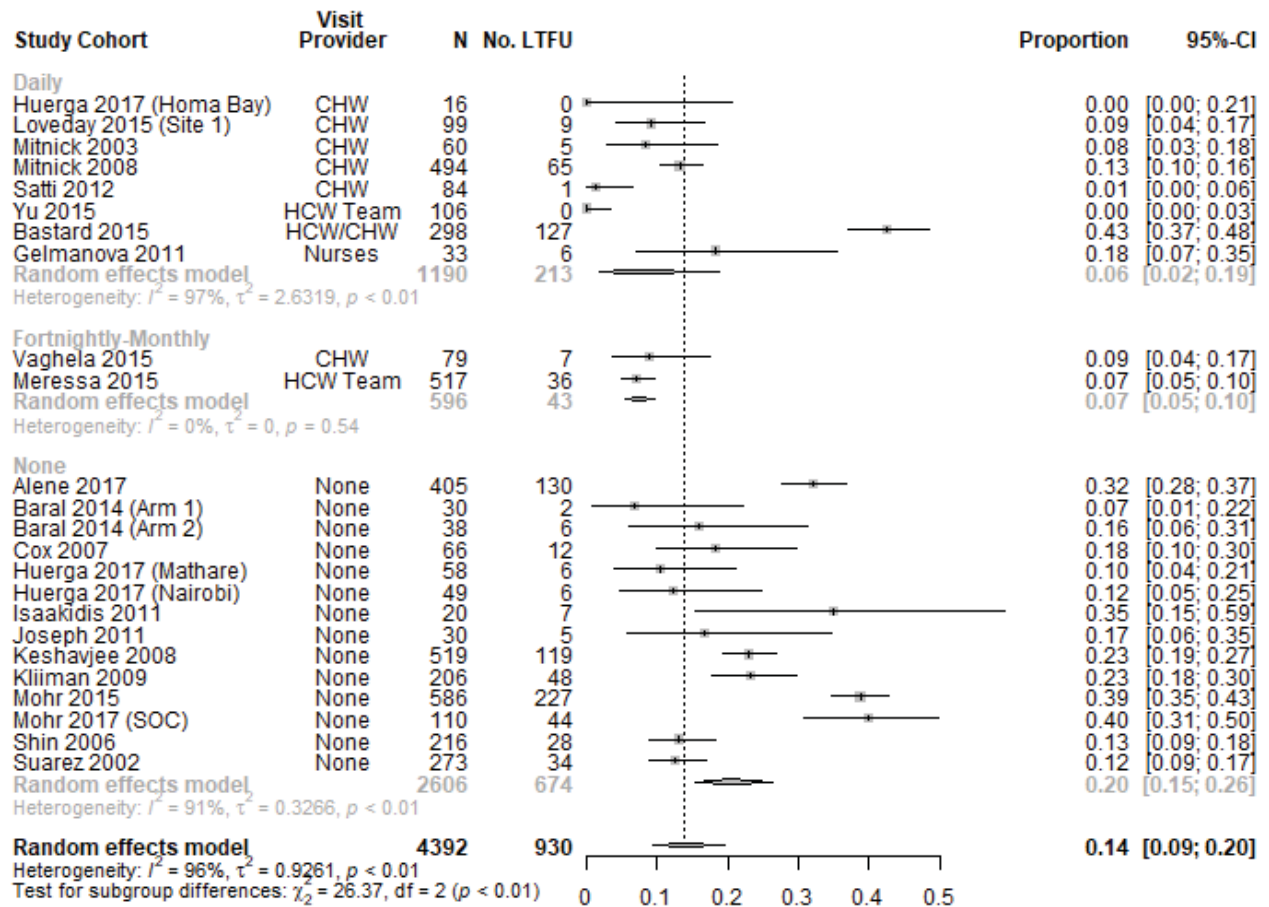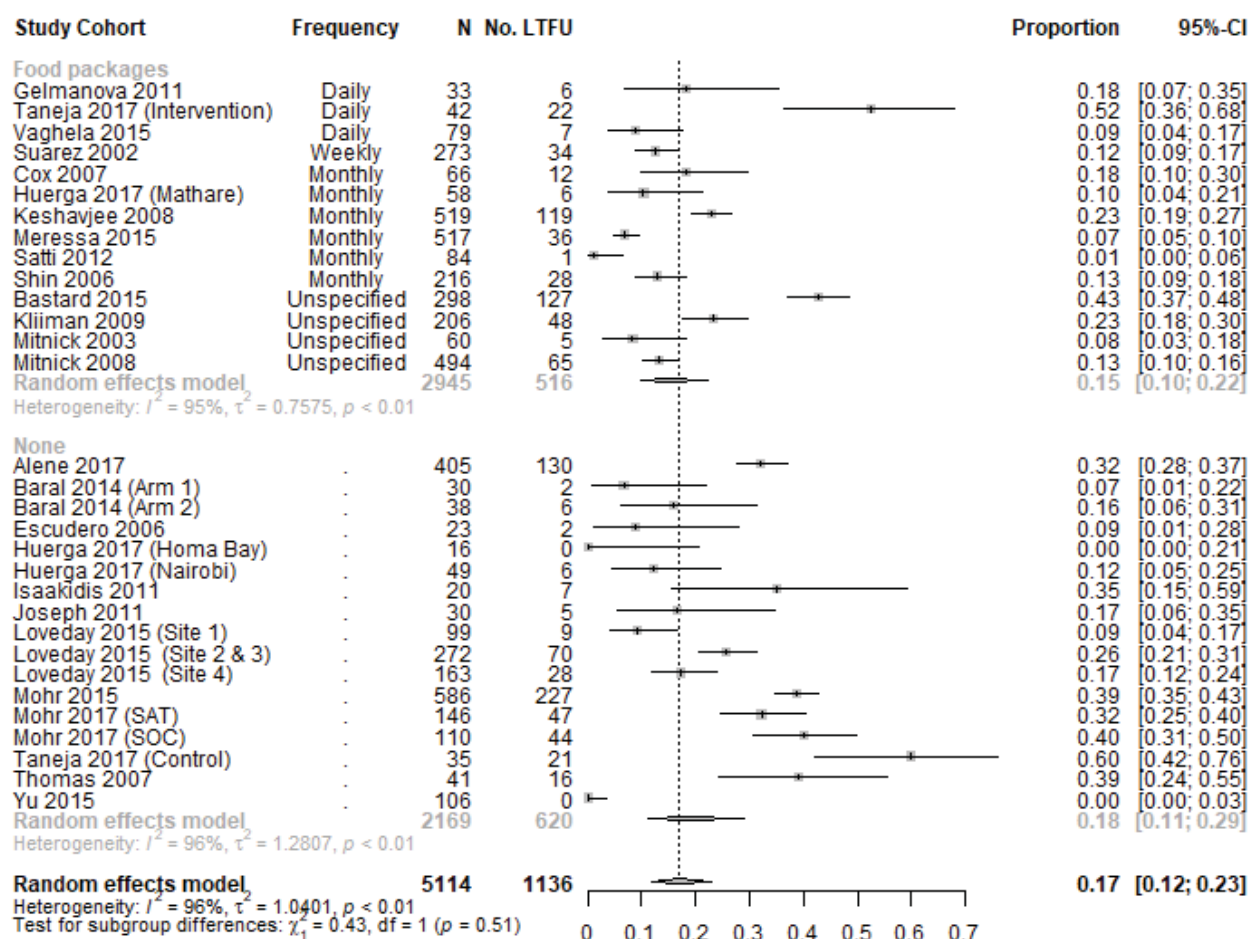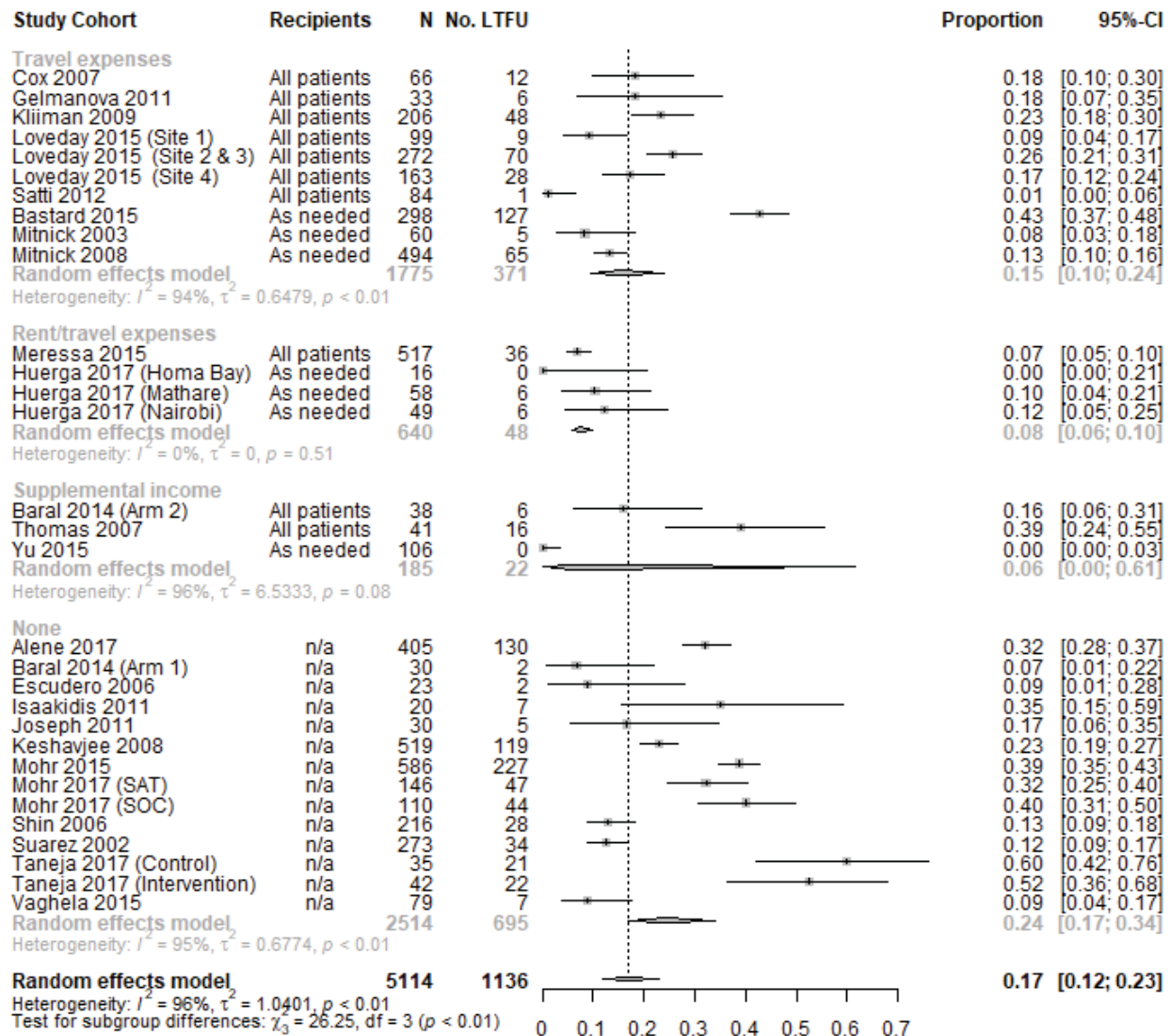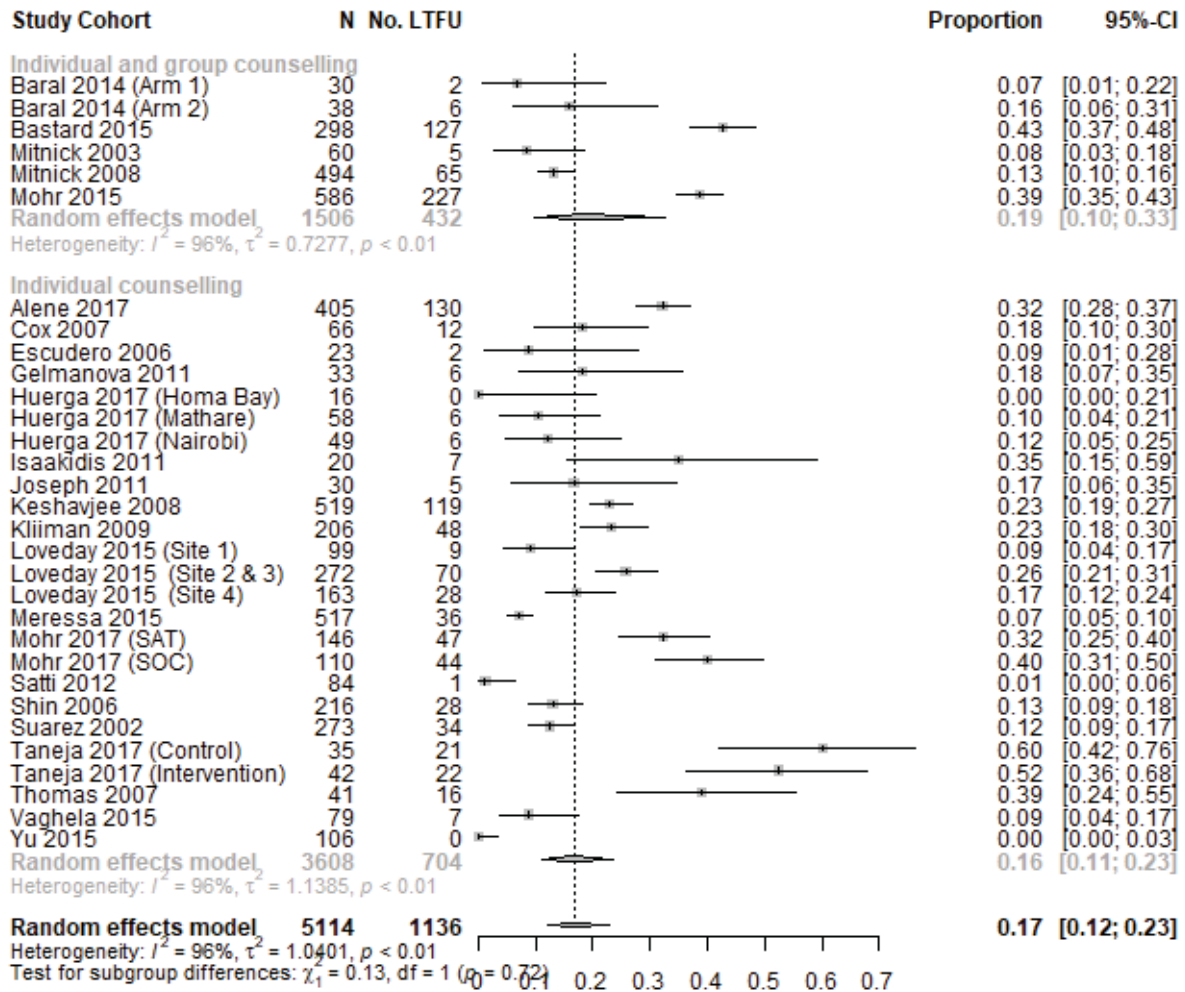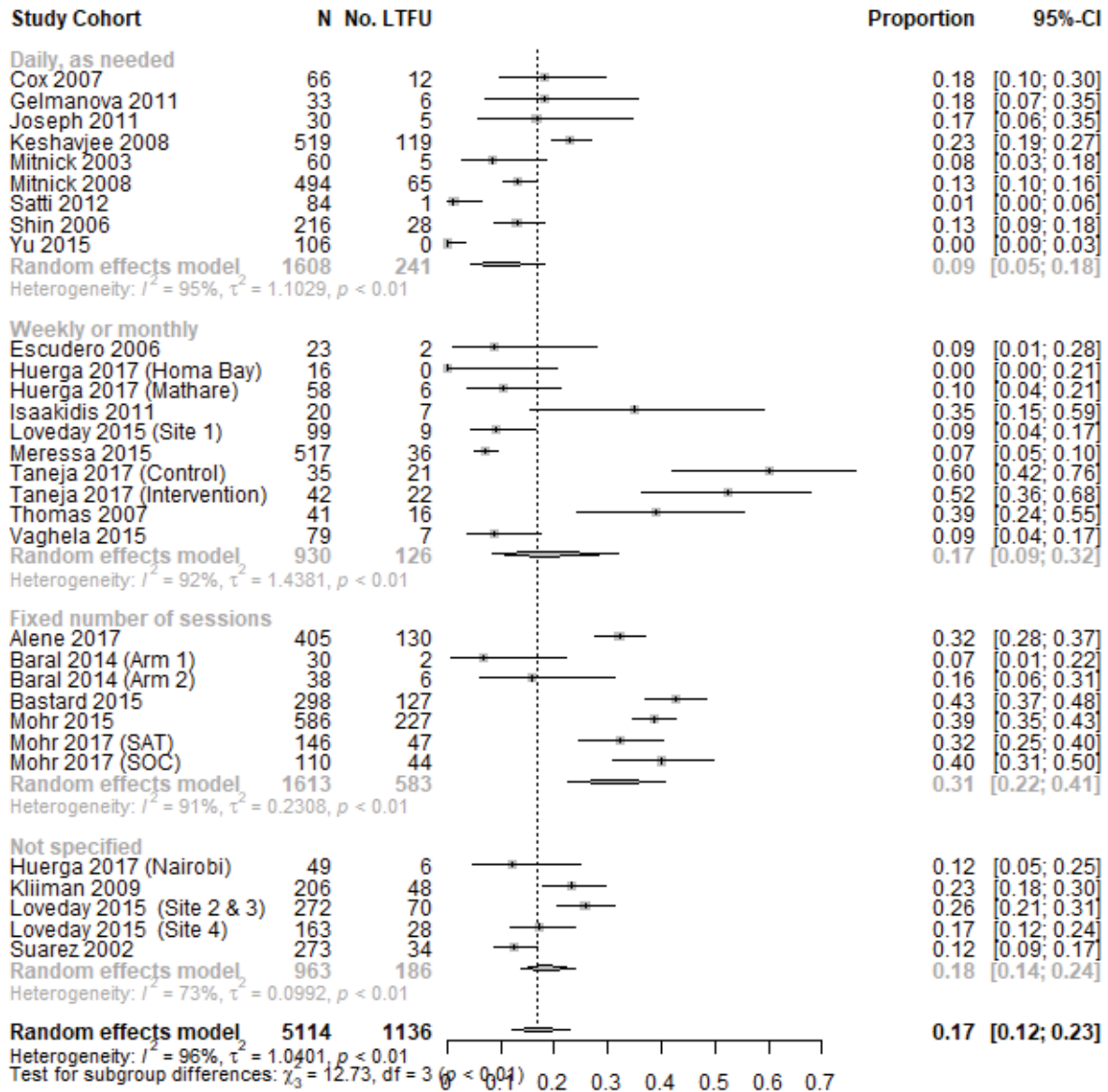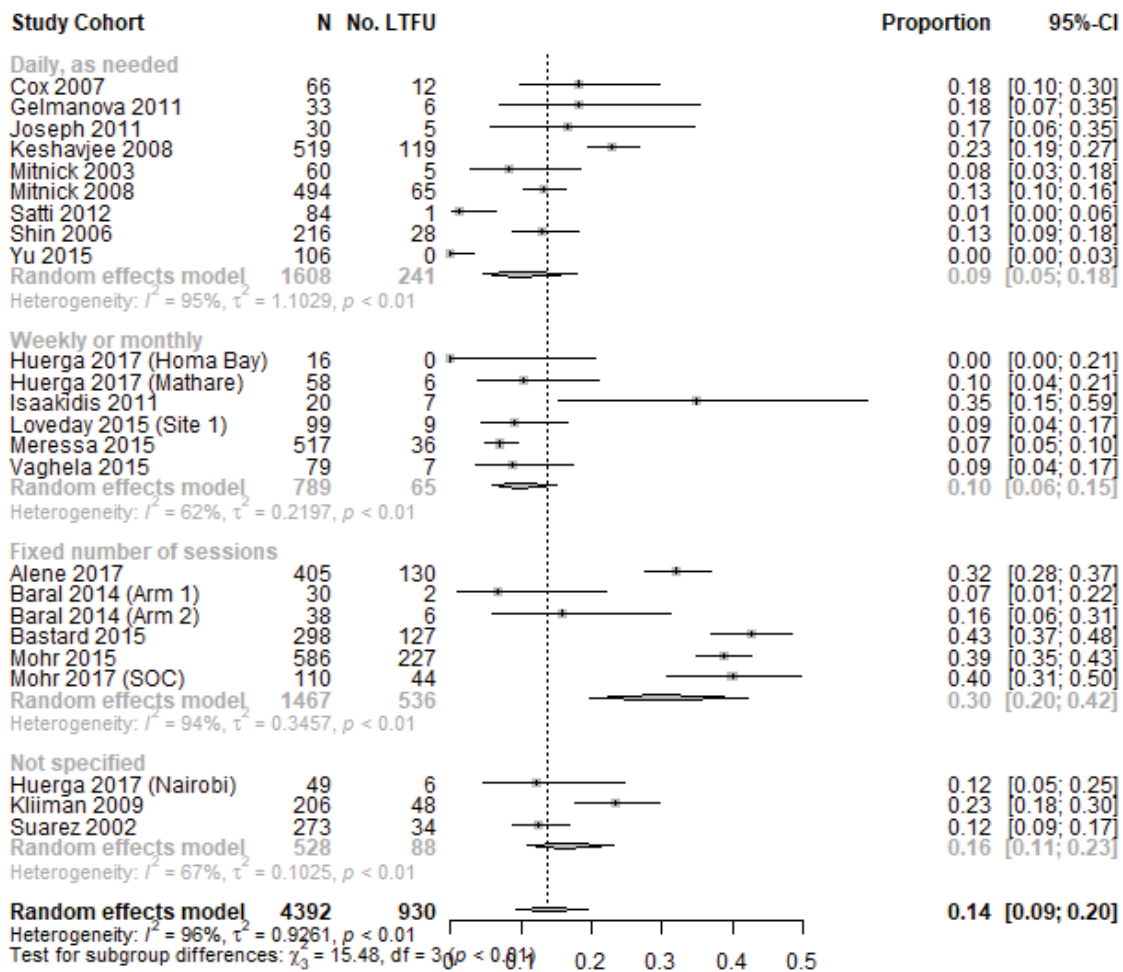
Study Cohort	Visit Provider	N	No. LTFU	Proportion	95%-CI
Daily					
Huerga 2017 (Homa Bay)	CHW	16	0	0.00	[0.00; 0.21]
Loveday 2015 (Site 1)	CHW	99	9	0.09	[0.04; 0.17]
Mitnick 2003	CHW	60	5	0.08	[0.03; 0.18]
Mitnick 2008	CHW	494	65	0.13	[0.10; 0.16]
Satti 2012	CHW	84	1	0.01	[0.00; 0.06]
Yu 2015	HCW Team	106	0	0.00	[0.00; 0.03]
Bastard 2015	HCW/CHW	298	127	0.43	[0.37; 0.48]
Gelmanova 2011	Nurses	33	6	0.18	[0.07; 0.35]
Random effects model		1190	213	0.06	[0.02; 0.19]
Heterogeneity: I^2 = 97%, τ^2 = 2.6319, $p < 0.01$					
Fortnightly-Monthly					
Mohr 2017 (SAT)	CHW	146	47	0.32	[0.25; 0.40]
Vaghela 2015	CHW	79	7	0.09	[0.04; 0.17]
Meressa 2015	HCW Team	517	36	0.07	[0.05; 0.10]
Taneja 2017 (Intervention)	HCW Team	42	22	0.52	[0.36; 0.68]
Random effects model		784	112	0.20	[0.08; 0.42]
Heterogeneity: I^2 = 96%, τ^2 = 1.1852, $p < 0.01$					
None					
Alene 2017	None	405	130	0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	None	30	2	0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	None	38	6	0.16	[0.06; 0.31]
Cox 2007	None	66	12	0.18	[0.10; 0.30]
Escudero 2006	None	23	2	0.09	[0.01; 0.28]
Huerga 2017 (Mathare)	None	58	6	0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	None	49	6	0.12	[0.05; 0.25]
Isaakidis 2011	None	20	7	0.35	[0.15; 0.59]
Joseph 2011	None	30	5	0.17	[0.06; 0.35]
Keshavjee 2008	None	519	119	0.23	[0.19; 0.27]
Kliiman 2009	None	206	48	0.23	[0.18; 0.30]
Loveday 2015 (Site 2 & 3)	None	272	70	0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	None	163	28	0.17	[0.12; 0.24]
Mohr 2015	None	586	227	0.39	[0.35; 0.43]
Mohr 2017 (SOC)	None	110	44	0.40	[0.31; 0.50]
Shin 2006	None	216	28	0.13	[0.09; 0.18]
Suarez 2002	None	273	34	0.12	[0.09; 0.17]
Taneja 2017 (Control)	None	35	21	0.60	[0.42; 0.76]
Thomas 2007	None	41	16	0.39	[0.24; 0.55]
Random effects model		3140	811	0.22	[0.17; 0.28]
Heterogeneity: I^2 = 92%, τ^2 = 0.4228, $p < 0.01$					
Random effects model		5114	1136	0.17	[0.12; 0.23]
Heterogeneity: I^2 = 96%, τ^2 = 1.0401, $p < 0.01$					
Test for subgroup differences: χ_2^2 = 4.83, df = 2 (p = 0.09)					

Figure 12. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by frequency of home visits throughout treatment. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. The statistical heterogeneity in subgroup with daily home visits was decreased to I^2=90% when Bastard 2015 was excluded, with a pooled proportion LTFU of 4% (95%CI 1 to 13%), or when both Bastard 2015 and Gelmanova 2011 were excluded, with a pooled proportion LTFU of 3% (95% CI 1 to 12%). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker.

Study Cohort	Visit Provider	N	No. LTFU		Proportion	95%-CI
Daily						
Huerga 2017 (Homa Bay)	CHW	16	0		0.00	[0.00; 0.21]
Loveday 2015 (Site 1)	CHW	99	9		0.09	[0.04; 0.17]
Mitnick 2003	CHW	60	5		0.08	[0.03; 0.18]
Mitnick 2008	CHW	494	65		0.13	[0.10; 0.16]
Satti 2012	CHW	84	1		0.01	[0.00; 0.06]
Yu 2015	HCW Team	106	0		0.00	[0.00; 0.03]
Bastard 2015	HCW/CHW	298	127		0.43	[0.37; 0.48]
Gelmanova 2011	Nurses	33	6		0.18	[0.07; 0.35]
Random effects model		1190	213		0.06	[0.02; 0.19]
Heterogeneity: I^2 = 97%, τ^2 = 2.6319, $p < 0.01$						
Fortnightly-Monthly						
Vaghela 2015	CHW	79	7		0.09	[0.04; 0.17]
Meressa 2015	HCW Team	517	36		0.07	[0.05; 0.10]
Random effects model		596	43		0.07	[0.05; 0.10]
Heterogeneity: I^2 = 0%, τ^2 = 0, $p = 0.54$						
None						
Alene 2017	None	405	130		0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	None	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	None	38	6		0.16	[0.06; 0.31]
Cox 2007	None	66	12		0.18	[0.10; 0.30]
Huerga 2017 (Mathare)	None	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	None	49	6		0.12	[0.05; 0.25]
Isaakidis 2011	None	20	7		0.35	[0.15; 0.59]
Joseph 2011	None	30	5		0.17	[0.06; 0.35]
Keshavjee 2008	None	519	119		0.23	[0.19; 0.27]
Kliiman 2009	None	206	48		0.23	[0.18; 0.30]
Mohr 2015	None	586	227		0.39	[0.35; 0.43]
Mohr 2017 (SOC)	None	110	44		0.40	[0.31; 0.50]
Shin 2006	None	216	28		0.13	[0.09; 0.18]
Suarez 2002	None	273	34		0.12	[0.09; 0.17]
Random effects model		2606	674		0.20	[0.15; 0.26]
Heterogeneity: I^2 = 91%, τ^2 = 0.3266, $p < 0.01$						
Random effects model		4392	930		0.14	[0.09; 0.20]
Heterogeneity: I^2 = 96%, τ^2 = 0.9261, $p < 0.01$						
Test for subgroup differences: χ^2_2 = 26.37, df = 2 ($p < 0.01$)						

Axis: 0 0.1 0.2 0.3 0.4 0.5

Figure 13. Forest plot of proportions lost to follow-up (LTFU) stratified by frequency of home visits throughout treatment, among study cohorts that received twice-daily or daily DOT. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker.
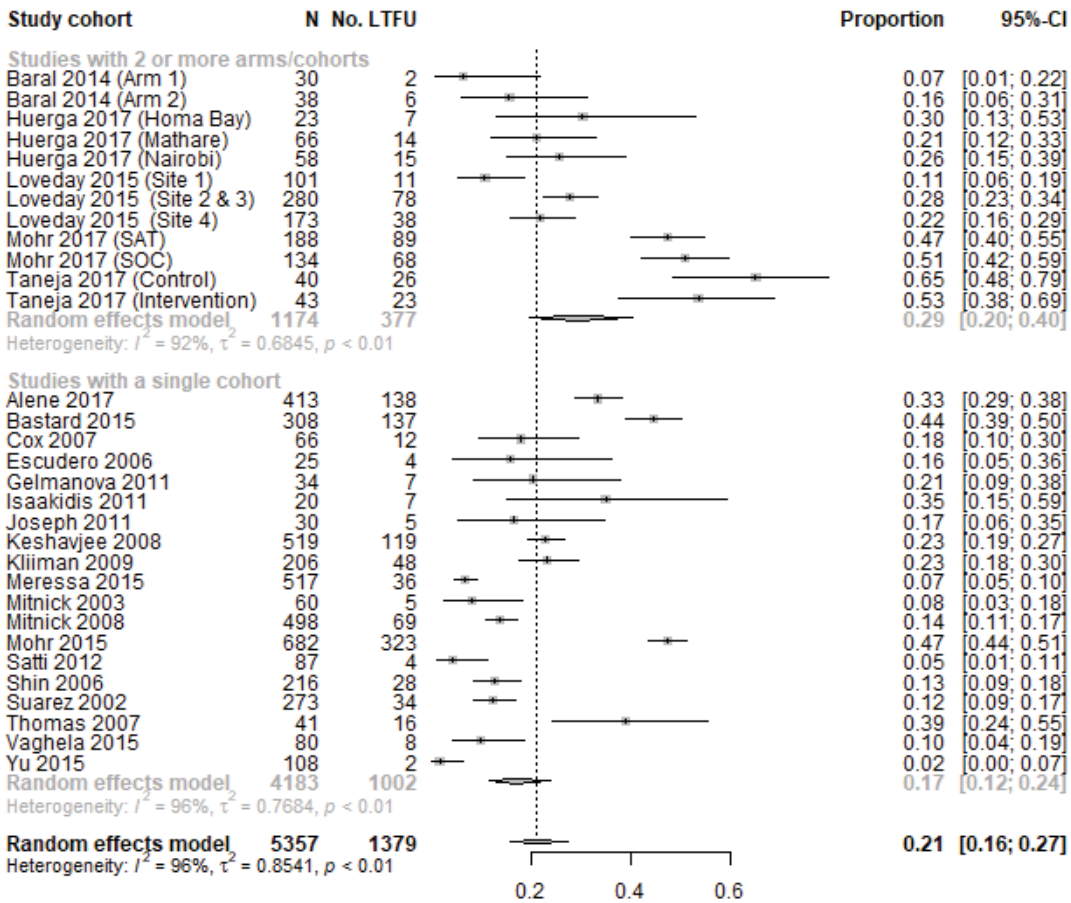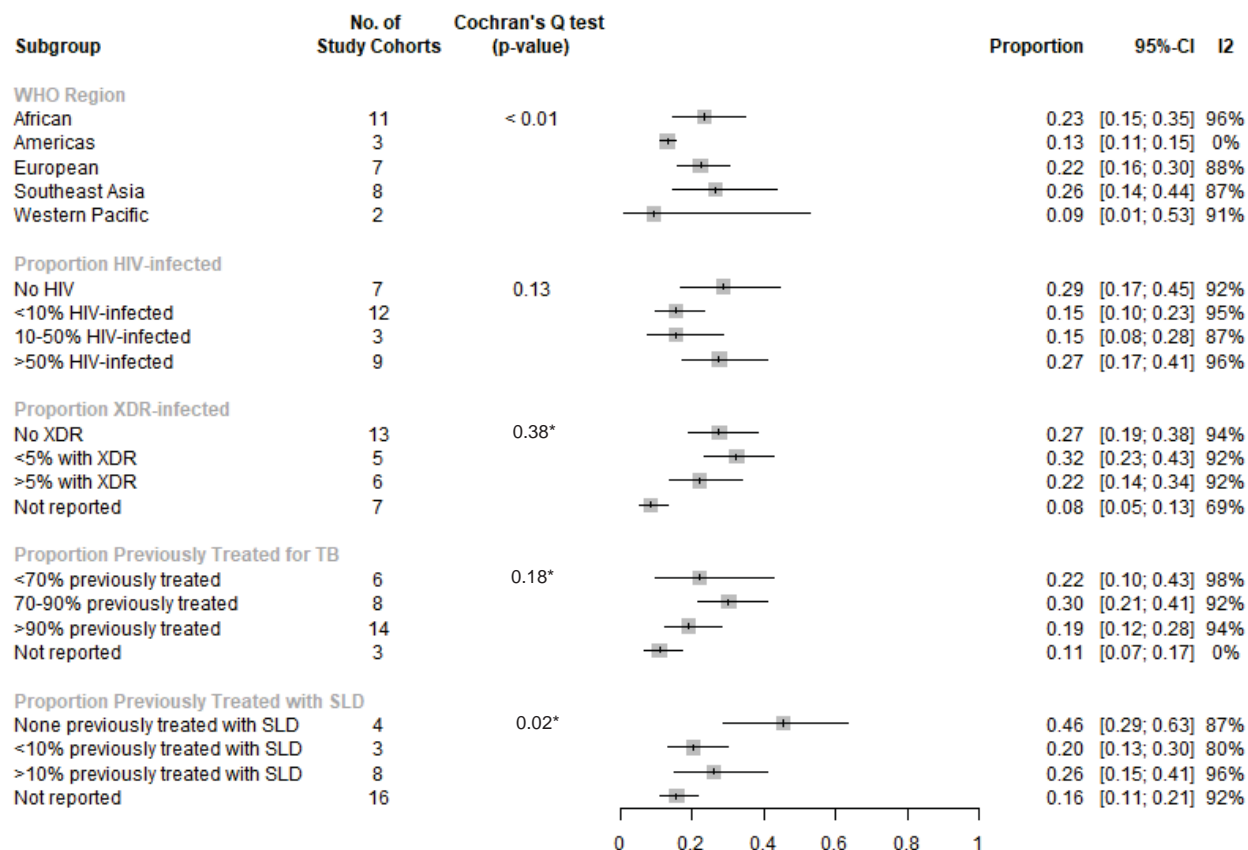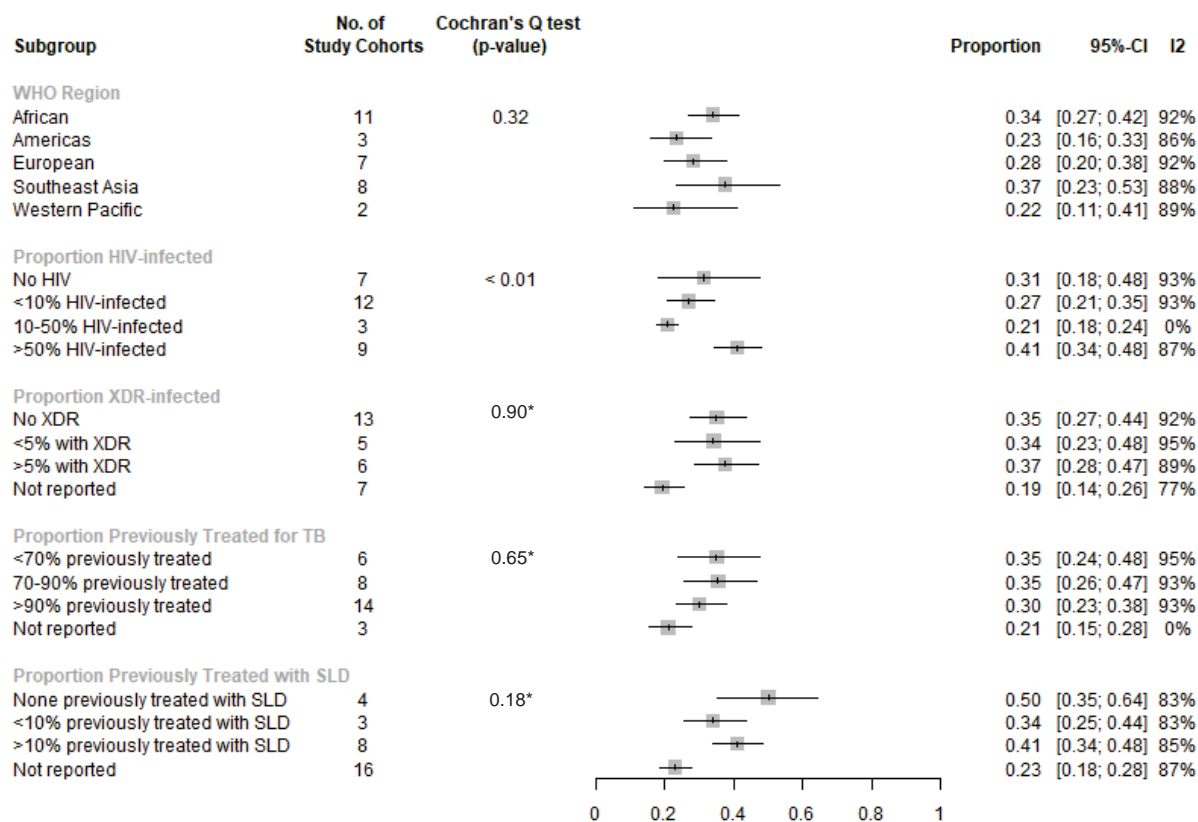
Study Cohort	Frequency	N	No. LTFU		Proportion	95%-CI
Food packages						
Gelmanova 2011	Daily	33	6		0.18	[0.07; 0.35]
Taneja 2017 (Intervention)	Daily	42	22		0.52	[0.36; 0.68]
Vaghela 2015	Daily	79	7		0.09	[0.04; 0.17]
Suárez 2002	Weekly	273	34		0.12	[0.09; 0.17]
Cox 2007	Monthly	66	12		0.18	[0.10; 0.30]
Huerga 2017 (Mathare)	Monthly	58	6		0.10	[0.04; 0.21]
Keshavjee 2008	Monthly	519	119		0.23	[0.19; 0.27]
Meressa 2015	Monthly	517	36		0.07	[0.05; 0.10]
Satti 2012	Monthly	84	1		0.01	[0.00; 0.06]
Shin 2006	Monthly	216	28		0.13	[0.09; 0.18]
Bastard 2015	Unspecified	298	127		0.43	[0.37; 0.48]
Kliiman 2009	Unspecified	206	48		0.23	[0.18; 0.30]
Mitnick 2003	Unspecified	60	5		0.08	[0.03; 0.18]
Mitnick 2008	Unspecified	494	65		0.13	[0.10; 0.16]
Random effects model		2945	516		0.15	[0.10; 0.22]
Heterogeneity: I^2 = 95%, τ^2 = 0.7575, p < 0.01						
None						
Alene 2017	.	405	130		0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	.	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	.	38	6		0.16	[0.06; 0.31]
Escudero 2006	.	23	2		0.09	[0.01; 0.28]
Huerga 2017 (Homa Bay)	.	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Nairobi)	.	49	6		0.12	[0.05; 0.25]
Isaakidis 2011	.	20	7		0.35	[0.15; 0.59]
Joseph 2011	.	30	5		0.17	[0.06; 0.35]
Loveday 2015 (Site 1)	.	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	.	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	.	163	28		0.17	[0.12; 0.24]
Mohr 2015	.	586	227		0.39	[0.35; 0.43]
Mohr 2017 (SAT)	.	146	47		0.32	[0.25; 0.40]
Mohr 2017 (SOC)	.	110	44		0.40	[0.31; 0.50]
Taneja 2017 (Control)	.	35	21		0.60	[0.42; 0.76]
Thomas 2007	.	41	16		0.39	[0.24; 0.55]
Yu 2015	.	106	0		0.00	[0.00; 0.03]
Random effects model		2169	620		0.18	[0.11; 0.29]
Heterogeneity: I^2 = 96%, τ^2 = 1.2807, p < 0.01						
Random effects model		5114	1136		0.17	[0.12; 0.23]

Heterogeneity: I^2 = 96%, τ^2 = 1.0401, p < 0.01
Test for subgroup differences: χ^2_1 = 0.43, df = 1 (p = 0.51)

Figure 14. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by whether of food was provided during treatment. Patients who died, failed treatment, who transferred out 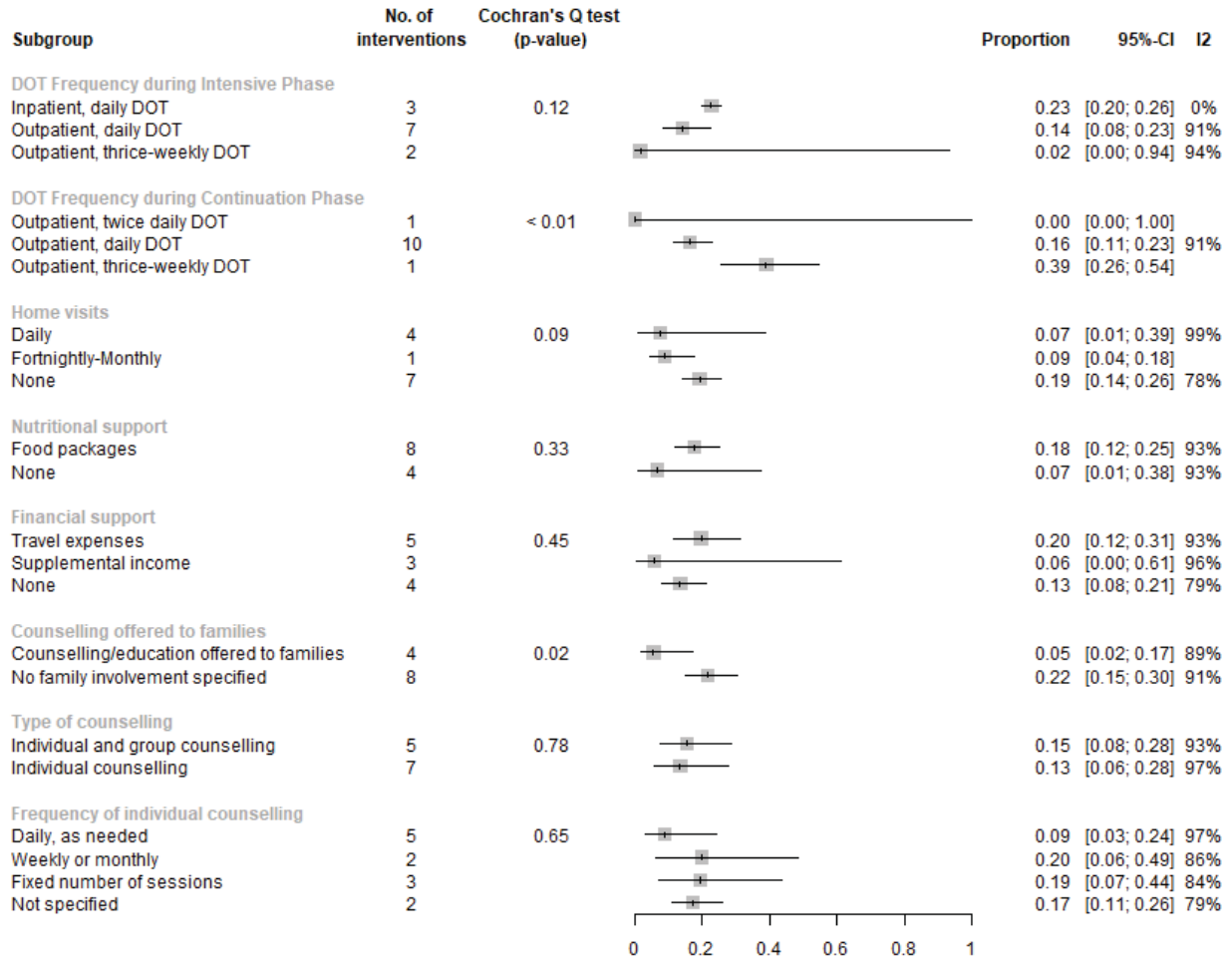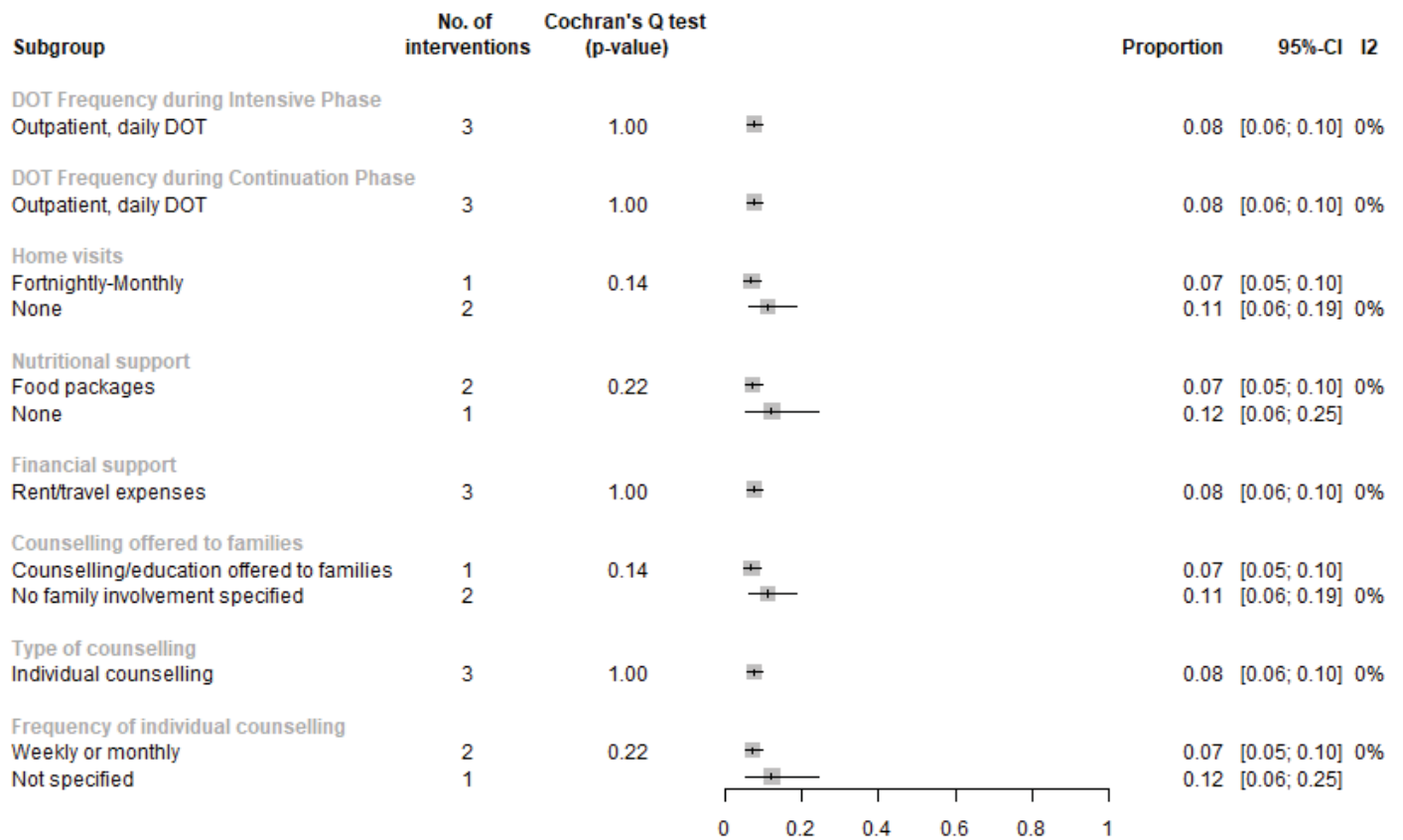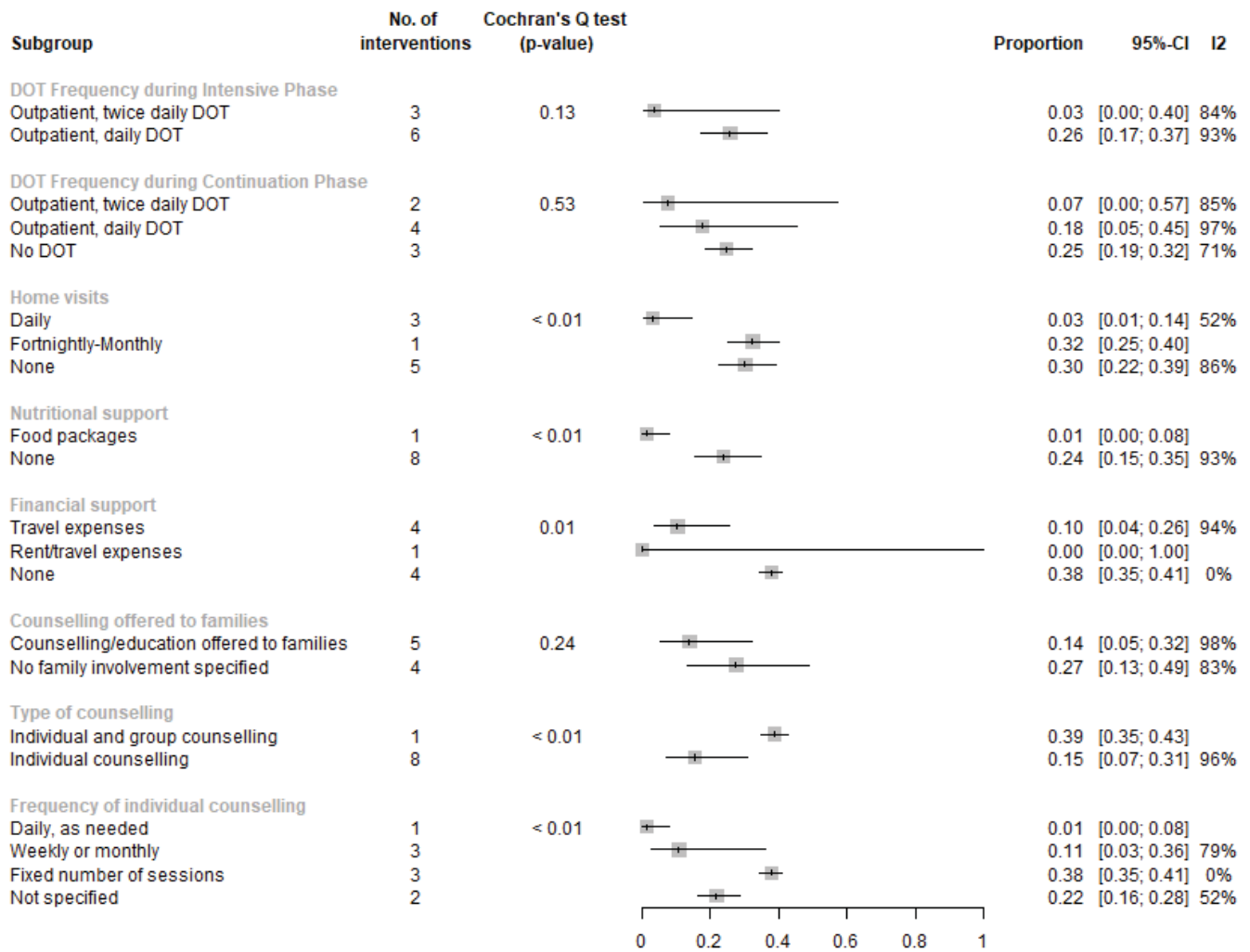or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	Recipients	N	No. LTFU	Proportion	95%-CI
Travel expenses					
Cox 2007	All patients	66	12	0.18	[0.10; 0.30]
Gelmanova 2011	All patients	33	6	0.18	[0.07; 0.35]
Kliiman 2009	All patients	206	48	0.23	[0.18; 0.30]
Loveday 2015 (Site 1)	All patients	99	9	0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	All patients	272	70	0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	All patients	163	28	0.17	[0.12; 0.24]
Satti 2012	All patients	84	1	0.01	[0.00; 0.06]
Bastard 2015	As needed	298	127	0.43	[0.37; 0.48]
Mitnick 2003	As needed	60	5	0.08	[0.03; 0.18]
Mitnick 2008	As needed	494	65	0.13	[0.10; 0.16]
Random effects model		1775	371	0.15	[0.10; 0.24]
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.6479$, $p < 0.01$					
Rent/travel expenses					
Meressa 2015	All patients	517	36	0.07	[0.05; 0.10]
Huerga 2017 (Homa Bay)	As needed	16	0	0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	As needed	58	6	0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	As needed	49	6	0.12	[0.05; 0.25]
Random effects model		640	48	0.08	[0.06; 0.10]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.51$					
Supplemental income					
Baral 2014 (Arm 2)	All patients	38	6	0.16	[0.06; 0.31]
Thomas 2007	All patients	41	16	0.39	[0.24; 0.55]
Yu 2015	As needed	106	0	0.00	[0.00; 0.03]
Random effects model		185	22	0.06	[0.00; 0.61]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 6.5333$, $p = 0.08$					
None					
Alene 2017	n/a	405	130	0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	n/a	30	2	0.07	[0.01; 0.22]
Escudero 2006	n/a	23	2	0.09	[0.01; 0.28]
Isaakidis 2011	n/a	20	7	0.35	[0.15; 0.59]
Joseph 2011	n/a	30	5	0.17	[0.06; 0.35]
Keshavjee 2008	n/a	519	119	0.23	[0.19; 0.27]
Mohr 2015	n/a	586	227	0.39	[0.35; 0.43]
Mohr 2017 (SAT)	n/a	146	47	0.32	[0.25; 0.40]
Mohr 2017 (SOC)	n/a	110	44	0.40	[0.31; 0.50]
Shin 2006	n/a	216	28	0.13	[0.09; 0.18]
Suarez 2002	n/a	273	34	0.12	[0.09; 0.17]
Taneja 2017 (Control)	n/a	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	n/a	42	22	0.52	[0.36; 0.68]
Vaghela 2015	n/a	79	7	0.09	[0.04; 0.17]
Random effects model		2514	695	0.24	[0.17; 0.34]
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.6774$, $p < 0.01$					
Random effects model		**5114**	**1136**	**0.17**	**[0.12; 0.23]**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$					
Test for subgroup differences: $\chi^2_3 = 26.25$, df = 3 ($p < 0.01$)					

Figure 15. Forest plot of proportions lost to follow-up across all study cohorts stratified by type of financial support provided during treatment. Patients who died, failed treatment, who transferred out or whose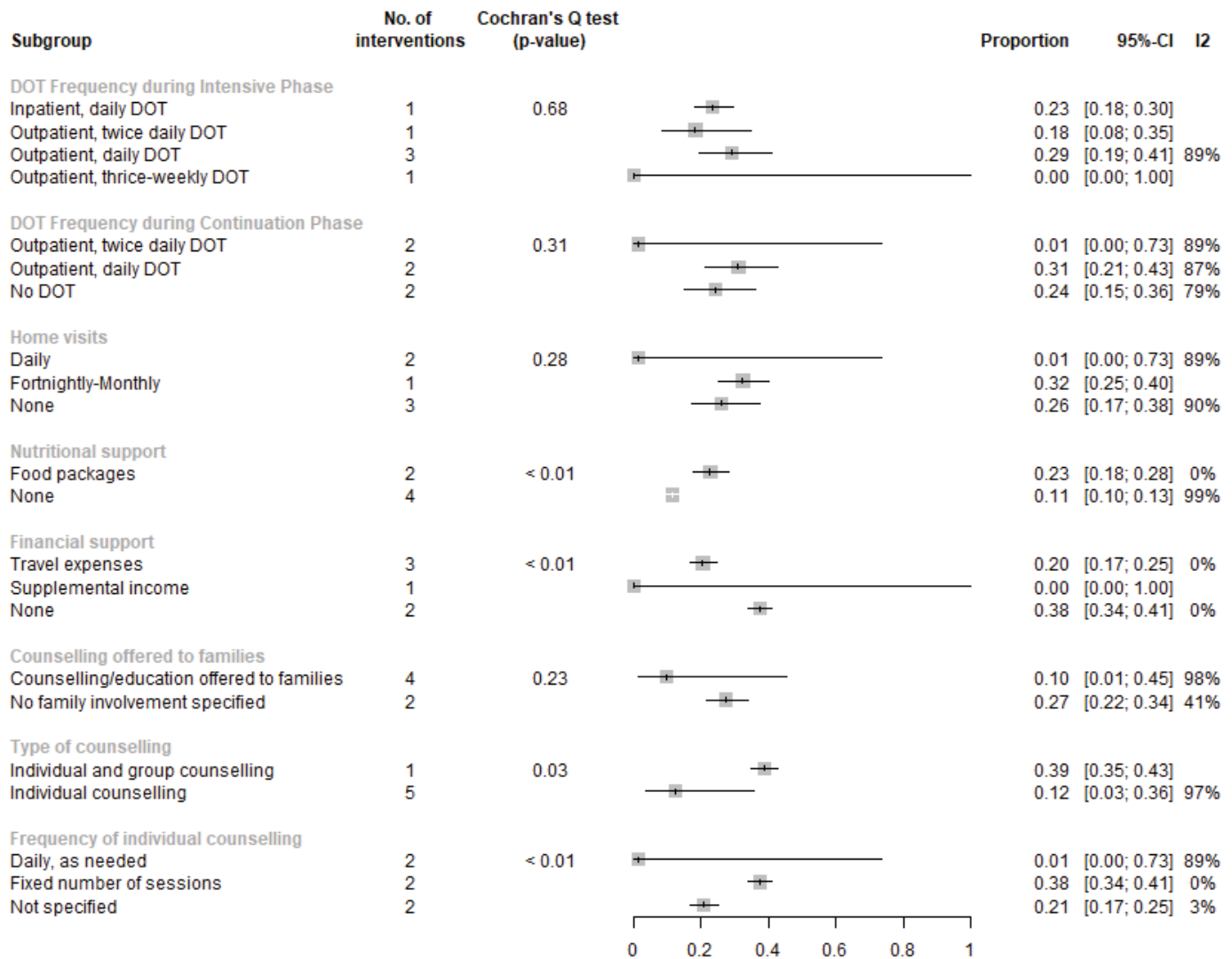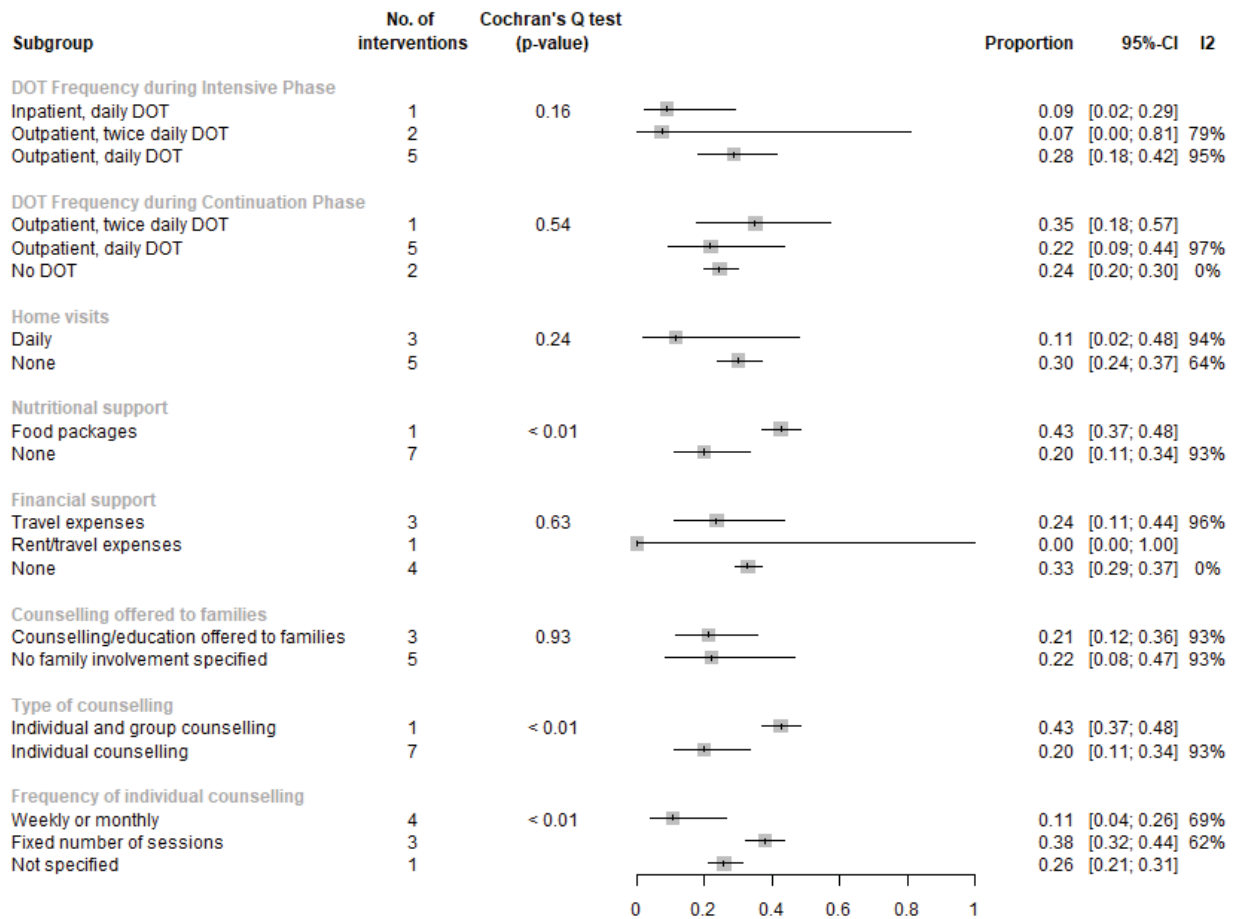 treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.
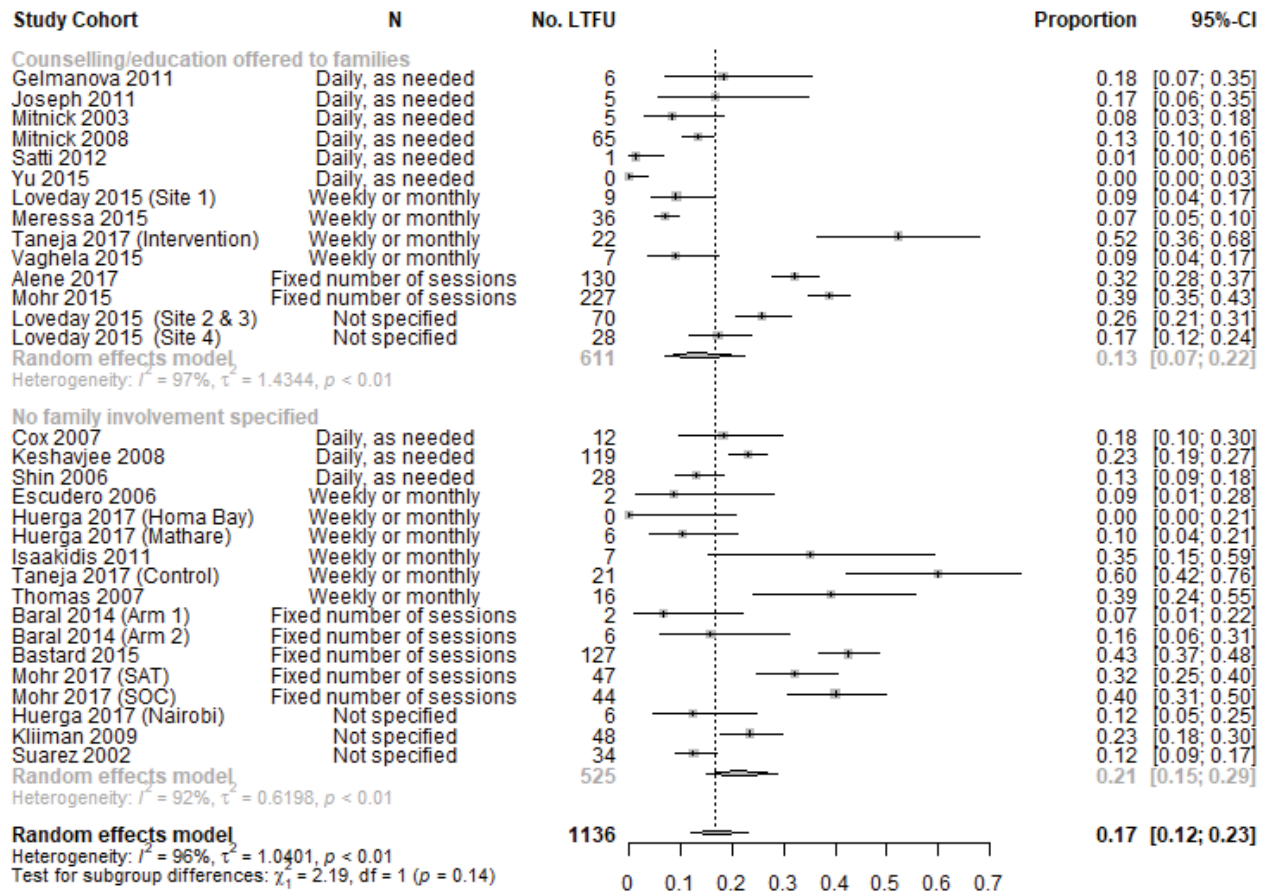
Figure 16. Forest plot of proportions lost to follow-up across all study cohorts stratified by whether families were offered counselling and education. Patients who died, failed treatment, who transferred out 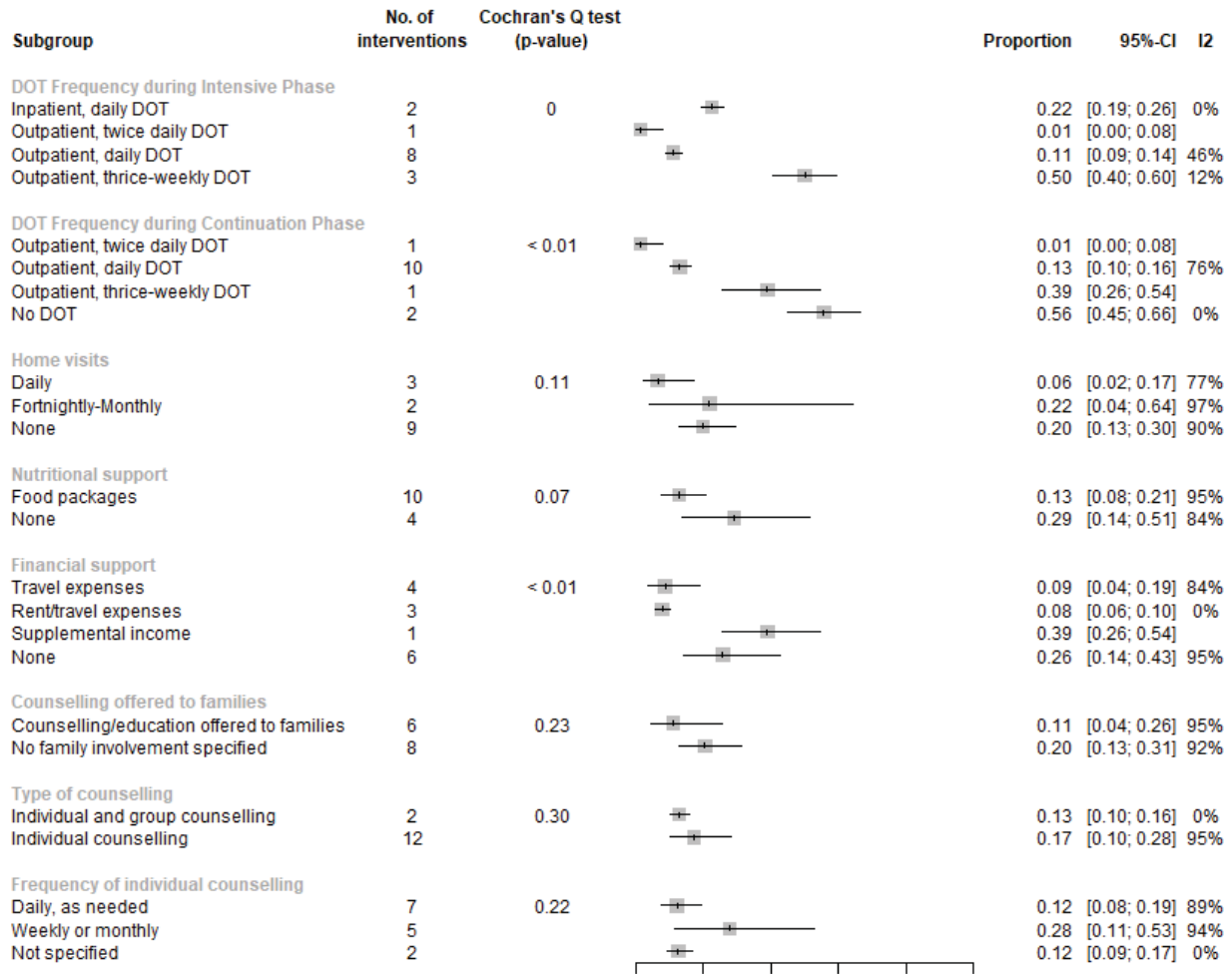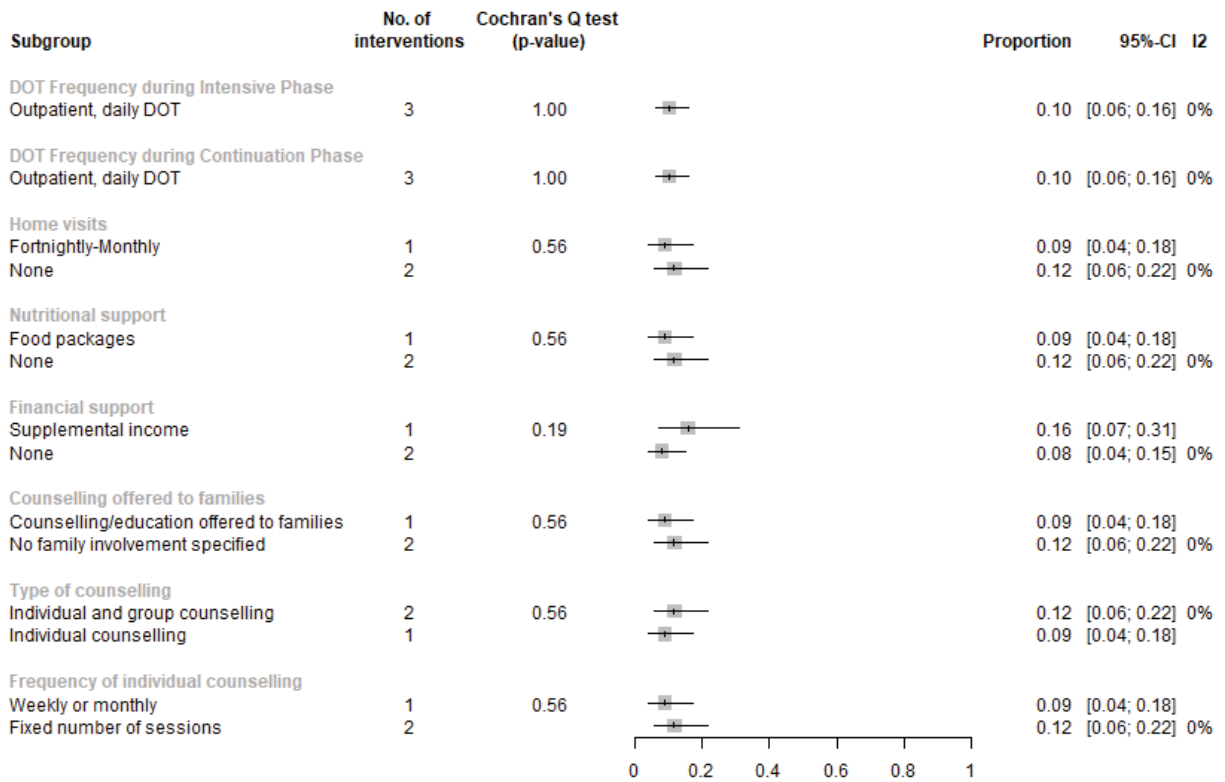or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	N	No. LTFU		Proportion	95%-CI
Individual and group counselling					
Baral 2014 (Arm 1)	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	38	6		0.16	[0.06; 0.31]
Bastard 2015	298	127		0.43	[0.37; 0.48]
Mitnick 2003	60	5		0.08	[0.03; 0.18]
Mitnick 2008	494	65		0.13	[0.10; 0.16]
Mohr 2015	586	227		0.39	[0.35; 0.43]
Random effects model	1506	432		0.19	[0.10; 0.33]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 0.7277$, $p < 0.01$					
Individual counselling					
Alene 2017	405	130		0.32	[0.28; 0.37]
Cox 2007	66	12		0.18	[0.10; 0.30]
Escudero 2006	23	2		0.09	[0.01; 0.28]
Gelmanova 2011	33	6		0.18	[0.07; 0.35]
Huerga 2017 (Homa Bay)	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	58	6		0.10	[0.04; 0.21]
Huerga 2017 (Nairobi)	49	6		0.12	[0.05; 0.25]
Isaakidis 2011	20	7		0.35	[0.15; 0.59]
Joseph 2011	30	5		0.17	[0.06; 0.35]
Keshavjee 2008	519	119		0.23	[0.19; 0.27]
Kliiman 2009	206	48		0.23	[0.18; 0.30]
Loveday 2015 (Site 1)	99	9		0.09	[0.04; 0.17]
Loveday 2015 (Site 2 & 3)	272	70		0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	163	28		0.17	[0.12; 0.24]
Meressa 2015	517	36		0.07	[0.05; 0.10]
Mohr 2017 (SAT)	146	47		0.32	[0.25; 0.40]
Mohr 2017 (SOC)	110	44		0.40	[0.31; 0.50]
Satti 2012	84	1		0.01	[0.00; 0.06]
Shin 2006	216	28		0.13	[0.09; 0.18]
Suarez 2002	273	34		0.12	[0.09; 0.17]
Taneja 2017 (Control)	35	21		0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	42	22		0.52	[0.36; 0.68]
Thomas 2007	41	16		0.39	[0.24; 0.55]
Vaghela 2015	79	7		0.09	[0.04; 0.17]
Yu 2015	106	0		0.00	[0.00; 0.03]
Random effects model	3608	704		0.16	[0.11; 0.23]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.1385$, $p < 0.01$					
Random effects model	**5114**	**1136**		**0.17**	**[0.12; 0.23]**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$					
Test for subgroup differences: $\chi^2_1 = 0.13$, df = 1 ($p = 0.72$)					

0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 17. Forest plot of proportions lost to follow-up across all study cohorts stratified by whether group counselling was offered in addition to individual counselling. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	N	No. LTFU	Proportion	95%-CI
Daily, as needed				
Cox 2007	66	12	0.18	[0.10; 0.30]
Gelmanova 2011	33	6	0.18	[0.07; 0.35]
Joseph 2011	30	5	0.17	[0.06; 0.35]
Keshavjee 2008	519	119	0.23	[0.19; 0.27]
Mitnick 2003	60	5	0.08	[0.03; 0.18]
Mitnick 2008	494	65	0.13	[0.10; 0.16]
Satti 2012	84	1	0.01	[0.00; 0.06]
Shin 2006	216	28	0.13	[0.09; 0.18]
Yu 2015	106	0	0.00	[0.00; 0.03]
Random effects model	1608	241	0.09	[0.05; 0.18]
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 1.1029$, $p < 0.01$				
Weekly or monthly				
Escudero 2006	23	2	0.09	[0.01; 0.28]
Huerga 2017 (Homa Bay)	16	0	0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	58	6	0.10	[0.04; 0.21]
Isaakidis 2011	20	7	0.35	[0.15; 0.59]
Loveday 2015 (Site 1)	99	9	0.09	[0.04; 0.17]
Meressa 2015	517	36	0.07	[0.05; 0.10]
Taneja 2017 (Control)	35	21	0.60	[0.42; 0.76]
Taneja 2017 (Intervention)	42	22	0.52	[0.36; 0.68]
Thomas 2007	41	16	0.39	[0.24; 0.55]
Vaghela 2015	79	7	0.09	[0.04; 0.17]
Random effects model	930	126	0.17	[0.09; 0.32]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 1.4381$, $p < 0.01$				
Fixed number of sessions				
Alene 2017	405	130	0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	30	2	0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	38	6	0.16	[0.06; 0.31]
Bastard 2015	298	127	0.43	[0.37; 0.48]
Mohr 2015	586	227	0.39	[0.35; 0.43]
Mohr 2017 (SAT)	146	47	0.32	[0.25; 0.40]
Mohr 2017 (SOC)	110	44	0.40	[0.31; 0.50]
Random effects model	1613	583	0.31	[0.22; 0.41]
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.2308$, $p < 0.01$				
Not specified				
Huerga 2017 (Nairobi)	49	6	0.12	[0.05; 0.25]
Kliiman 2009	206	48	0.23	[0.18; 0.30]
Loveday 2015 (Site 2 & 3)	272	70	0.26	[0.21; 0.31]
Loveday 2015 (Site 4)	163	28	0.17	[0.12; 0.24]
Suarez 2002	273	34	0.12	[0.09; 0.17]
Random effects model	963	186	0.18	[0.14; 0.24]
Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.0992$, $p < 0.01$				
Random effects model	**5114**	**1136**	**0.17**	**[0.12; 0.23]**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.0401$, $p < 0.01$				
Test for subgroup differences: $\chi_3^2 = 12.73$, df = 3 ($p < 0.01$)				

0   0.1   0.2   0.3   0.4   0.5   0.6   0.7

Figure 18. Forest plot of proportions lost to follow-up across all study cohorts stratified by frequency of individual counselling provided during treatment. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study Cohort	N	No. LTFU		Proportion	95%-CI
Daily, as needed					
Cox 2007	66	12		0.18	[0.10; 0.30]
Gelmanova 2011	33	6		0.18	[0.07; 0.35]
Joseph 2011	30	5		0.17	[0.06; 0.35]
Keshavjee 2008	519	119		0.23	[0.19; 0.27]
Mitnick 2003	60	5		0.08	[0.03; 0.18]
Mitnick 2008	494	65		0.13	[0.10; 0.16]
Satti 2012	84	1		0.01	[0.00; 0.06]
Shin 2006	216	28		0.13	[0.09; 0.18]
Yu 2015	106	0		0.00	[0.00; 0.03]
Random effects model	1608	241		0.09	[0.05; 0.18]
Heterogeneity: I^2 = 95%, τ^2 = 1.1029, p < 0.01					
Weekly or monthly					
Huerga 2017 (Homa Bay)	16	0		0.00	[0.00; 0.21]
Huerga 2017 (Mathare)	58	6		0.10	[0.04; 0.21]
Isaakidis 2011	20	7		0.35	[0.15; 0.59]
Loveday 2015 (Site 1)	99	9		0.09	[0.04; 0.17]
Meressa 2015	517	36		0.07	[0.05; 0.10]
Vaghela 2015	79	7		0.09	[0.04; 0.17]
Random effects model	789	65		0.10	[0.06; 0.15]
Heterogeneity: I^2 = 62%, τ^2 = 0.2197, p < 0.01					
Fixed number of sessions					
Alene 2017	405	130		0.32	[0.28; 0.37]
Baral 2014 (Arm 1)	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	38	6		0.16	[0.06; 0.31]
Bastard 2015	298	127		0.43	[0.37; 0.48]
Mohr 2015	586	227		0.39	[0.35; 0.43]
Mohr 2017 (SOC)	110	44		0.40	[0.31; 0.50]
Random effects model	1467	536		0.30	[0.20; 0.42]
Heterogeneity: I^2 = 94%, τ^2 = 0.3457, p < 0.01					
Not specified					
Huerga 2017 (Nairobi)	49	6		0.12	[0.05; 0.25]
Kliiman 2009	206	48		0.23	[0.18; 0.30]
Suarez 2002	273	34		0.12	[0.09; 0.17]
Random effects model	528	88		0.16	[0.11; 0.23]
Heterogeneity: I^2 = 67%, τ^2 = 0.1025, p < 0.01					
Random effects model	**4392**	**930**		**0.14**	**[0.09; 0.20]**
Heterogeneity: I^2 = 96%, τ^2 = 0.9261, p < 0.01					
Test for subgroup differences: χ_3^2 = 15.48, df = 3 (p < 0.01)					

0.1 0.2 0.3 0.4 0.5

Figure 19. Forest plot of proportions lost to follow-up stratified by frequency of individual counselling provided during treatment, among study cohorts that received twice-daily or daily DOT. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Study cohort	N	No. LTFU		Proportion	95%-CI
Studies with 2 or more arms/cohorts					
Baral 2014 (Arm 1)	30	2		0.07	[0.01; 0.22]
Baral 2014 (Arm 2)	38	6		0.16	[0.06; 0.31]
Huerga 2017 (Homa Bay)	23	7		0.30	[0.13; 0.53]
Huerga 2017 (Mathare)	66	14		0.21	[0.12; 0.33]
Huerga 2017 (Nairobi)	58	15		0.26	[0.15; 0.39]
Loveday 2015 (Site 1)	101	11		0.11	[0.06; 0.19]
Loveday 2015 (Site 2 & 3)	280	78		0.28	[0.23; 0.34]
Loveday 2015 (Site 4)	173	38		0.22	[0.16; 0.29]
Mohr 2017 (SAT)	188	89		0.47	[0.40; 0.55]
Mohr 2017 (SOC)	134	68		0.51	[0.42; 0.59]
Taneja 2017 (Control)	40	26		0.65	[0.48; 0.79]
Taneja 2017 (Intervention)	43	23		0.53	[0.38; 0.69]
Random effects model	1174	377		0.29	[0.20; 0.40]
Heterogeneity: I^2 = 92%, τ^2 = 0.6845, p < 0.01					
Studies with a single cohort					
Alene 2017	413	138		0.33	[0.29; 0.38]
Bastard 2015	308	137		0.44	[0.39; 0.50]
Cox 2007	66	12		0.18	[0.10; 0.30]
Escudero 2006	25	4		0.16	[0.05; 0.36]
Gelmanova 2011	34	7		0.21	[0.09; 0.38]
Isaakidis 2011	20	7		0.35	[0.15; 0.59]
Joseph 2011	30	5		0.17	[0.06; 0.35]
Keshavjee 2008	519	119		0.23	[0.19; 0.27]
Kliiman 2009	206	48		0.23	[0.18; 0.30]
Meressa 2015	517	36		0.07	[0.05; 0.10]
Mitnick 2003	60	5		0.08	[0.03; 0.18]
Mitnick 2008	498	69		0.14	[0.11; 0.17]
Mohr 2015	682	323		0.47	[0.44; 0.51]
Satti 2012	87	4		0.05	[0.01; 0.11]
Shin 2006	216	28		0.13	[0.09; 0.18]
Suarez 2002	273	34		0.12	[0.09; 0.17]
Thomas 2007	41	16		0.39	[0.24; 0.55]
Vaghela 2015	80	8		0.10	[0.04; 0.19]
Yu 2015	108	2		0.02	[0.00; 0.07]
Random effects model	4183	1002		0.17	[0.12; 0.24]
Heterogeneity: I^2 = 96%, τ^2 = 0.7684, p < 0.01					
Random effects model	5357	1379		0.21	[0.16; 0.27]
Heterogeneity: I^2 = 96%, τ^2 = 0.8541, p < 0.01					

0.2 0.4 0.6

Figure 20. Forest plot of proportions lost to follow-up (LTFU), including those who transferred out or without reported final outcomes, across all study cohorts. Patients who died or failed treatment were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Subgroup	No. of Study Cohorts	Cochran's Q test (p-value)		Proportion	95%-CI	I2
WHO Region						
African	11	< 0.01		0.23	[0.15; 0.35]	96%
Americas	3			0.13	[0.11; 0.15]	0%
European	7			0.22	[0.16; 0.30]	88%
Southeast Asia	8			0.26	[0.14; 0.44]	87%
Western Pacific	2			0.09	[0.01; 0.53]	91%
Proportion HIV-infected						
No HIV	7	0.13		0.29	[0.17; 0.45]	92%
<10% HIV-infected	12			0.15	[0.10; 0.23]	95%
10-50% HIV-infected	3			0.15	[0.08; 0.28]	87%
>50% HIV-infected	9			0.27	[0.17; 0.41]	96%
Proportion XDR-infected						
No XDR	13	0.38*		0.27	[0.19; 0.38]	94%
<5% with XDR	5			0.32	[0.23; 0.43]	92%
>5% with XDR	6			0.22	[0.14; 0.34]	92%
Not reported	7			0.08	[0.05; 0.13]	69%
Proportion Previously Treated for TB						
<70% previously treated	6	0.18*		0.22	[0.10; 0.43]	98%
70-90% previously treated	8			0.30	[0.21; 0.41]	92%
>90% previously treated	14			0.19	[0.12; 0.28]	94%
Not reported	3			0.11	[0.07; 0.17]	0%
Proportion Previously Treated with SLD						
None previously treated with SLD	4	0.02*		0.46	[0.29; 0.63]	87%
<10% previously treated with SLD	3			0.20	[0.13; 0.30]	80%
>10% previously treated with SLD	8			0.26	[0.15; 0.41]	96%
Not reported	16			0.16	[0.11; 0.21]	92%

0   0.2   0.4   0.6   0.8   1

Figure 21. Forest plot of pooled proportions lost to follow-up, including those who transferred out or whose treatment outcome was not evaluated, across all study cohorts, stratified by study cohort characteristics. Patients who died or failed treatment were excluded. *Study cohorts that did not report this parameter were excluded from the Cochran's Q test for subgroup differences.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	4	0.86		0.22	[0.20; 0.25]	0%
Outpatient, twice daily DOT	4			0.18	[0.08; 0.36]	76%
Outpatient, daily DOT	19			0.20	[0.15; 0.27]	96%
Outpatient, thrice-weekly DOT	4			0.29	[0.07; 0.70]	96%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	4	< 0.01		0.09	[0.03; 0.28]	85%
Outpatient, daily DOT	20			0.19	[0.15; 0.26]	95%
Outpatient, thrice-weekly DOT	1			0.39	[0.26; 0.54]	
No DOT	6			0.37	[0.24; 0.52]	92%
Home visits						
Daily	8	0.13		0.13	[0.06; 0.24]	94%
Fortnightly-Monthly	4			0.23	[0.08; 0.50]	97%
None	19			0.25	[0.20; 0.32]	93%
Nutritional support						
Food packages	14	0.11		0.17	[0.12; 0.24]	94%
None	17			0.26	[0.18; 0.36]	96%
Financial support						
Travel expenses	10	0.29		0.18	[0.12; 0.26]	93%
Rent/travel expenses	4			0.18	[0.09; 0.31]	84%
Supplemental income	3			0.12	[0.02; 0.42]	90%
None	14			0.28	[0.19; 0.39]	97%
Counselling offered to families						
Counselling/education offered to families	14	0.05		0.16	[0.10; 0.25]	97%
No family involvement specified	17			0.27	[0.20; 0.35]	92%
Type of counselling						
Individual and group counselling	6	0.82		0.20	[0.10; 0.36]	97%
Individual counselling	25			0.21	[0.16; 0.28]	95%
Frequency of individual counselling						
Daily, as needed	9	< 0.01		0.12	[0.07; 0.18]	88%
Weekly or monthly	10			0.24	[0.14; 0.38]	90%
Fixed number of sessions	7			0.35	[0.23; 0.49]	96%
Not specified	5			0.21	[0.17; 0.27]	75%

0   0.2   0.4   0.6   0.8   1

Figure 22. Forest plot of pooled proportions lost to follow-up, including those who transferred out or whose treatment outcome was not evaluated, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died or, failed treatment were excluded.

Study cohort	N	No. LTFU	Proportion	95%-CI
Studies with 2 or more arms/cohorts				
Baral 2014 (Arm 1)	31	3	0.10	[0.02; 0.26]
Baral 2014 (Arm 2)	40	8	0.20	[0.09; 0.36]
Huerga 2017 (Homa Bay)	21	5	0.24	[0.08; 0.47]
Huerga 2017 (Mathare)	62	10	0.16	[0.08; 0.28]
Huerga 2017 (Nairobi)	61	18	0.30	[0.19; 0.43]
Loveday 2015 (Site 1)	116	26	0.22	[0.15; 0.31]
Loveday 2015 (Site 2 & 3)	319	117	0.37	[0.31; 0.42]
Loveday 2015 (Site 4)	232	97	0.42	[0.35; 0.48]
Mohr 2017 (SAT)	194	95	0.49	[0.42; 0.56]
Mohr 2017 (SOC)	129	63	0.49	[0.40; 0.58]
Taneja 2017 (Control)	42	28	0.67	[0.50; 0.80]
Taneja 2017 (Intervention)	48	28	0.58	[0.43; 0.72]
Random effects model	1295	498	0.34	[0.25; 0.45]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.5308$, $p < 0.01$				
Studies with a single cohort				
Alene 2017	418	143	0.34	[0.30; 0.39]
Bastard 2015	337	166	0.49	[0.44; 0.55]
Cox 2007	79	25	0.32	[0.22; 0.43]
Escudero 2006	23	2	0.09	[0.01; 0.28]
Gelmanova 2011	35	8	0.23	[0.10; 0.40]
Isaakidis 2011	33	20	0.61	[0.42; 0.77]
Joseph 2011	33	8	0.24	[0.11; 0.42]
Keshavjee 2008	550	150	0.27	[0.24; 0.31]
Kliiman 2009	254	96	0.38	[0.32; 0.44]
Meressa 2015	602	121	0.20	[0.17; 0.24]
Mitnick 2003	74	19	0.26	[0.16; 0.37]
Mitnick 2008	628	199	0.32	[0.28; 0.35]
Mohr 2015	709	350	0.49	[0.46; 0.53]
Satti 2012	130	47	0.36	[0.28; 0.45]
Shin 2006	228	40	0.18	[0.13; 0.23]
Suarez 2002	281	42	0.15	[0.11; 0.20]
Thomas 2007	49	24	0.49	[0.34; 0.64]
Vaghela 2015	96	24	0.25	[0.17; 0.35]
Yu 2015	122	16	0.13	[0.08; 0.20]
Random effects model	4681	1500	0.29	[0.24; 0.36]
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.3523$, $p < 0.01$				
Random effects model	**5976**	**1998**	**0.31**	**[0.26; 0.37]**
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.4316$, $p < 0.01$				

Axis: 0.2 0.4 0.6 0.8

Figure 23. Forest plot of proportions lost to follow-up (LTFU), including those who died, across all study cohorts. Patients who failed treatment, transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

Subgroup	No. of Study Cohorts	Cochran's Q test (p-value)		Proportion	95%-CI	I2
WHO Region						
African	11	0.32		0.34	[0.27; 0.42]	92%
Americas	3			0.23	[0.16; 0.33]	86%
European	7			0.28	[0.20; 0.38]	92%
Southeast Asia	8			0.37	[0.23; 0.53]	88%
Western Pacific	2			0.22	[0.11; 0.41]	89%
Proportion HIV-infected						
No HIV	7	< 0.01		0.31	[0.18; 0.48]	93%
<10% HIV-infected	12			0.27	[0.21; 0.35]	93%
10-50% HIV-infected	3			0.21	[0.18; 0.24]	0%
>50% HIV-infected	9			0.41	[0.34; 0.48]	87%
Proportion XDR-infected						
No XDR	13	0.90*		0.35	[0.27; 0.44]	92%
<5% with XDR	5			0.34	[0.23; 0.48]	95%
>5% with XDR	6			0.37	[0.28; 0.47]	89%
Not reported	7			0.19	[0.14; 0.26]	77%
Proportion Previously Treated for TB						
<70% previously treated	6	0.65*		0.35	[0.24; 0.48]	95%
70-90% previously treated	8			0.35	[0.26; 0.47]	93%
>90% previously treated	14			0.30	[0.23; 0.38]	93%
Not reported	3			0.21	[0.15; 0.28]	0%
Proportion Previously Treated with SLD						
None previously treated with SLD	4	0.18*		0.50	[0.35; 0.64]	83%
<10% previously treated with SLD	3			0.34	[0.25; 0.44]	83%
>10% previously treated with SLD	8			0.41	[0.34; 0.48]	85%
Not reported	16			0.23	[0.18; 0.28]	87%

Figure 24. Forest plot of pooled proportions lost to follow-up, including those who died, across all study cohorts, stratified by study cohort characteristics. Patients who failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. *Study cohorts that did not report this parameter were excluded from the Cochran's Q test for subgroup differences.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	4	0.55		0.30	[0.23; 0.38]	70%
Outpatient, twice daily DOT	4			0.35	[0.23; 0.51]	72%
Outpatient, daily DOT	19			0.29	[0.24; 0.35]	94%
Outpatient, thrice-weekly DOT	4			0.44	[0.23; 0.68]	92%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	4	< 0.01		0.30	[0.16; 0.50]	89%
Outpatient, daily DOT	20			0.27	[0.23; 0.33]	93%
Outpatient, thrice-weekly DOT	1			0.49	[0.35; 0.63]	
No DOT	6			0.43	[0.30; 0.58]	93%
Home visits						
Daily	8	0.61		0.28	[0.21; 0.36]	89%
Fortnightly-Monthly	4			0.36	[0.22; 0.53]	94%
None	19			0.31	[0.25; 0.39]	95%
Nutritional support						
Food packages	14	0.35		0.28	[0.23; 0.35]	93%
None	17			0.33	[0.25; 0.42]	94%
Financial support						
Travel expenses	10	< 0.01		0.35	[0.30; 0.40]	81%
Rent/travel expenses	4			0.21	[0.18; 0.24]	0%
Supplemental income	3			0.25	[0.12; 0.45]	85%
None	14			0.33	[0.24; 0.44]	96%
Counselling offered to families						
Counselling/education offered to families	14	0.94		0.31	[0.25; 0.37]	93%
No family involvement specified	17			0.31	[0.23; 0.40]	94%
Type of counselling						
Individual and group counselling	6	0.97		0.31	[0.20; 0.44]	96%
Individual counselling	25			0.31	[0.26; 0.37]	93%
Frequency of individual counselling						
Daily, as needed	9	0.19		0.25	[0.21; 0.31]	80%
Weekly or monthly	10			0.33	[0.21; 0.47]	92%
Fixed number of sessions	7			0.38	[0.27; 0.50]	95%
Not specified	5			0.31	[0.22; 0.42]	91%

0   0.2   0.4   0.6   0.8   1

Figure 25. Forest plot of pooled proportions lost to follow-up, including those who died, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who failed treatment, transferred out or whose treatment outcome was not evaluated **were excluded.**

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	1	< 0.01		0.09	[0.02; 0.29]	
Outpatient, twice daily DOT	1			0.18	[0.08; 0.35]	
Outpatient, daily DOT	3			0.20	[0.12; 0.33]	85%
Outpatient, thrice-weekly DOT	2			0.56	[0.45; 0.66]	0%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	1	0.45		0.18	[0.08; 0.35]	
Outpatient, daily DOT	3			0.20	[0.12; 0.33]	85%
No DOT	3			0.38	[0.14; 0.69]	87%
Home visits						
Daily	1	< 0.01		0.18	[0.08; 0.35]	
Fortnightly-Monthly	1			0.52	[0.38; 0.67]	
None	5			0.23	[0.11; 0.42]	92%
Nutritional support						
Food packages	3	0.85		0.24	[0.10; 0.47]	88%
None	4			0.27	[0.12; 0.50]	88%
Financial support						
Travel expenses	1	0.39		0.18	[0.08; 0.35]	
None	6			0.27	[0.14; 0.46]	93%
Counselling offered to families						
Counselling/education offered to families	4	0.63		0.29	[0.18; 0.44]	78%
No family involvement specified	3			0.22	[0.06; 0.54]	91%
Type of counselling						
Individual counselling	7	1.00		0.26	[0.15; 0.42]	91%
Frequency of individual counselling						
Daily, as needed	3	< 0.01		0.14	[0.10; 0.19]	0%
Weekly or monthly	3			0.38	[0.14; 0.69]	87%
Fixed number of sessions	1			0.32	[0.28; 0.37]	

No HIV

Figure 26. Forest plot of pooled proportions lost to follow-up among study cohorts with no reported HIV, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	3	0.12		0.23	[0.20; 0.26]	0%
Outpatient, daily DOT	7			0.14	[0.08; 0.23]	91%
Outpatient, thrice-weekly DOT	2			0.02	[0.00; 0.94]	94%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	1	< 0.01		0.00	[0.00; 1.00]	
Outpatient, daily DOT	10			0.16	[0.11; 0.23]	91%
Outpatient, thrice-weekly DOT	1			0.39	[0.26; 0.54]	
Home visits						
Daily	4	0.09		0.07	[0.01; 0.39]	99%
Fortnightly-Monthly	1			0.09	[0.04; 0.18]	
None	7			0.19	[0.14; 0.26]	78%
Nutritional support						
Food packages	8	0.33		0.18	[0.12; 0.25]	93%
None	4			0.07	[0.01; 0.38]	93%
Financial support						
Travel expenses	5	0.45		0.20	[0.12; 0.31]	93%
Supplemental income	3			0.06	[0.00; 0.61]	96%
None	4			0.13	[0.08; 0.21]	79%
Counselling offered to families						
Counselling/education offered to families	4	0.02		0.05	[0.02; 0.17]	89%
No family involvement specified	8			0.22	[0.15; 0.30]	91%
Type of counselling						
Individual and group counselling	5	0.78		0.15	[0.08; 0.28]	93%
Individual counselling	7			0.13	[0.06; 0.28]	97%
Frequency of individual counselling						
Daily, as needed	5	0.65		0.09	[0.03; 0.24]	97%
Weekly or monthly	2			0.20	[0.06; 0.49]	86%
Fixed number of sessions	3			0.19	[0.07; 0.44]	84%
Not specified	2			0.17	[0.11; 0.26]	79%

Figure 27. Forest plot of pooled proportions lost to follow-up among study cohorts with less than 10% HIV prevalence, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Outpatient, daily DOT	3	1.00		0.08	[0.06; 0.10]	0%
DOT Frequency during Continuation Phase						
Outpatient, daily DOT	3	1.00		0.08	[0.06; 0.10]	0%
Home visits						
Fortnightly-Monthly	1	0.14		0.07	[0.05; 0.10]	
None	2			0.11	[0.06; 0.19]	0%
Nutritional support						
Food packages	2	0.22		0.07	[0.05; 0.10]	0%
None	1			0.12	[0.06; 0.25]	
Financial support						
Rent/travel expenses	3	1.00		0.08	[0.06; 0.10]	0%
Counselling offered to families						
Counselling/education offered to families	1	0.14		0.07	[0.05; 0.10]	
No family involvement specified	2			0.11	[0.06; 0.19]	0%
Type of counselling						
Individual counselling	3	1.00		0.08	[0.06; 0.10]	0%
Frequency of individual counselling						
Weekly or monthly	2	0.22		0.07	[0.05; 0.10]	0%
Not specified	1			0.12	[0.06; 0.25]	

Figure 28. Forest plot of pooled proportions lost to follow-up among study cohorts with 10 to 50% HIV prevalence, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Outpatient, twice daily DOT	3	0.13		0.03	[0.00; 0.40]	84%
Outpatient, daily DOT	6			0.26	[0.17; 0.37]	93%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	2	0.53		0.07	[0.00; 0.57]	85%
Outpatient, daily DOT	4			0.18	[0.05; 0.45]	97%
No DOT	3			0.25	[0.19; 0.32]	71%
Home visits						
Daily	3	< 0.01		0.03	[0.01; 0.14]	52%
Fortnightly-Monthly	1			0.32	[0.25; 0.40]	
None	5			0.30	[0.22; 0.39]	86%
Nutritional support						
Food packages	1	< 0.01		0.01	[0.00; 0.08]	
None	8			0.24	[0.15; 0.35]	93%
Financial support						
Travel expenses	4	0.01		0.10	[0.04; 0.26]	94%
Rent/travel expenses	1			0.00	[0.00; 1.00]	
None	4			0.38	[0.35; 0.41]	0%
Counselling offered to families						
Counselling/education offered to families	5	0.24		0.14	[0.05; 0.32]	98%
No family involvement specified	4			0.27	[0.13; 0.49]	83%
Type of counselling						
Individual and group counselling	1	< 0.01		0.39	[0.35; 0.43]	
Individual counselling	8			0.15	[0.07; 0.31]	96%
Frequency of individual counselling						
Daily, as needed	1	< 0.01		0.01	[0.00; 0.08]	
Weekly or monthly	3			0.11	[0.03; 0.36]	79%
Fixed number of sessions	3			0.38	[0.35; 0.41]	0%
Not specified	2			0.22	[0.16; 0.28]	52%

(x-axis: 0 0.2 0.4 0.6 0.8 1)

Figure 29. Forest plot of pooled proportions lost to follow-up among study cohorts with greater than 50% HIV prevalence, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	1	0.68		0.23	[0.18; 0.30]	
Outpatient, twice daily DOT	1			0.18	[0.08; 0.35]	
Outpatient, daily DOT	3			0.29	[0.19; 0.41]	89%
Outpatient, thrice-weekly DOT	1			0.00	[0.00; 1.00]	
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	2	0.31		0.01	[0.00; 0.73]	89%
Outpatient, daily DOT	2			0.31	[0.21; 0.43]	87%
No DOT	2			0.24	[0.15; 0.36]	79%
Home visits						
Daily	2	0.28		0.01	[0.00; 0.73]	89%
Fortnightly-Monthly	1			0.32	[0.25; 0.40]	
None	3			0.26	[0.17; 0.38]	90%
Nutritional support						
Food packages	2	< 0.01		0.23	[0.18; 0.28]	0%
None	4			0.11	[0.10; 0.13]	99%
Financial support						
Travel expenses	3	< 0.01		0.20	[0.17; 0.25]	0%
Supplemental income	1			0.00	[0.00; 1.00]	
None	2			0.38	[0.34; 0.41]	0%
Counselling offered to families						
Counselling/education offered to families	4	0.23		0.10	[0.01; 0.45]	98%
No family involvement specified	2			0.27	[0.22; 0.34]	41%
Type of counselling						
Individual and group counselling	1	0.03		0.39	[0.35; 0.43]	
Individual counselling	5			0.12	[0.03; 0.36]	97%
Frequency of individual counselling						
Daily, as needed	2	< 0.01		0.01	[0.00; 0.73]	89%
Fixed number of sessions	2			0.38	[0.34; 0.41]	0%
Not specified	2			0.21	[0.17; 0.25]	3%

Figure 30. Forest plot of pooled proportions lost to follow-up among study cohorts with less than 70% previously treated patients, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	1	0.16		0.09	[0.02; 0.29]	
Outpatient, twice daily DOT	2			0.07	[0.00; 0.81]	79%
Outpatient, daily DOT	5			0.28	[0.18; 0.42]	95%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	1	0.54		0.35	[0.18; 0.57]	
Outpatient, daily DOT	5			0.22	[0.09; 0.44]	97%
No DOT	2			0.24	[0.20; 0.30]	0%
Home visits						
Daily	3	0.24		0.11	[0.02; 0.48]	94%
None	5			0.30	[0.24; 0.37]	64%
Nutritional support						
Food packages	1	< 0.01		0.43	[0.37; 0.48]	
None	7			0.20	[0.11; 0.34]	93%
Financial support						
Travel expenses	3	0.63		0.24	[0.11; 0.44]	96%
Rent/travel expenses	1			0.00	[0.00; 1.00]	
None	4			0.33	[0.29; 0.37]	0%
Counselling offered to families						
Counselling/education offered to families	3	0.93		0.21	[0.12; 0.36]	93%
No family involvement specified	5			0.22	[0.08; 0.47]	93%
Type of counselling						
Individual and group counselling	1	< 0.01		0.43	[0.37; 0.48]	
Individual counselling	7			0.20	[0.11; 0.34]	93%
Frequency of individual counselling						
Weekly or monthly	4	< 0.01		0.11	[0.04; 0.26]	69%
Fixed number of sessions	3			0.38	[0.32; 0.44]	62%
Not specified	1			0.26	[0.21; 0.31]	

Figure 31. Forest plot of pooled proportions lost to follow-up among study cohorts with 70% to 90% previously treated patients, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Inpatient, daily DOT	2	0		0.22	[0.19; 0.26]	0%
Outpatient, twice daily DOT	1			0.01	[0.00; 0.08]	
Outpatient, daily DOT	8			0.11	[0.09; 0.14]	46%
Outpatient, thrice-weekly DOT	3			0.50	[0.40; 0.60]	12%
DOT Frequency during Continuation Phase						
Outpatient, twice daily DOT	1	< 0.01		0.01	[0.00; 0.08]	
Outpatient, daily DOT	10			0.13	[0.10; 0.16]	76%
Outpatient, thrice-weekly DOT	1			0.39	[0.26; 0.54]	
No DOT	2			0.56	[0.45; 0.66]	0%
Home visits						
Daily	3	0.11		0.06	[0.02; 0.17]	77%
Fortnightly-Monthly	2			0.22	[0.04; 0.64]	97%
None	9			0.20	[0.13; 0.30]	90%
Nutritional support						
Food packages	10	0.07		0.13	[0.08; 0.21]	95%
None	4			0.29	[0.14; 0.51]	84%
Financial support						
Travel expenses	4	< 0.01		0.09	[0.04; 0.19]	84%
Rent/travel expenses	3			0.08	[0.06; 0.10]	0%
Supplemental income	1			0.39	[0.26; 0.54]	
None	6			0.26	[0.14; 0.43]	95%
Counselling offered to families						
Counselling/education offered to families	6	0.23		0.11	[0.04; 0.26]	95%
No family involvement specified	8			0.20	[0.13; 0.31]	92%
Type of counselling						
Individual and group counselling	2	0.30		0.13	[0.10; 0.16]	0%
Individual counselling	12			0.17	[0.10; 0.28]	95%
Frequency of individual counselling						
Daily, as needed	7	0.22		0.12	[0.08; 0.19]	89%
Weekly or monthly	5			0.28	[0.11; 0.53]	94%
Not specified	2			0.12	[0.09; 0.17]	0%

Figure 32. Forest plot of pooled proportions lost to follow-up among study cohorts with greater than 90% previously treated patients, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Subgroup	No. of interventions	Cochran's Q test (p-value)		Proportion	95%-CI	I2
DOT Frequency during Intensive Phase						
Outpatient, daily DOT	3	1.00		0.10	[0.06; 0.16]	0%
DOT Frequency during Continuation Phase						
Outpatient, daily DOT	3	1.00		0.10	[0.06; 0.16]	0%
Home visits						
Fortnightly-Monthly	1	0.56		0.09	[0.04; 0.18]	
None	2			0.12	[0.06; 0.22]	0%
Nutritional support						
Food packages	1	0.56		0.09	[0.04; 0.18]	
None	2			0.12	[0.06; 0.22]	0%
Financial support						
Supplemental income	1	0.19		0.16	[0.07; 0.31]	
None	2			0.08	[0.04; 0.15]	0%
Counselling offered to families						
Counselling/education offered to families	1	0.56		0.09	[0.04; 0.18]	
No family involvement specified	2			0.12	[0.06; 0.22]	0%
Type of counselling						
Individual and group counselling	2	0.56		0.12	[0.06; 0.22]	0%
Individual counselling	1			0.09	[0.04; 0.18]	
Frequency of individual counselling						
Weekly or monthly	1	0.56		0.09	[0.04; 0.18]	
Fixed number of sessions	2			0.12	[0.06; 0.22]	0%

0   0.2   0.4   0.6   0.8   1

Figure 33. Forest plot of pooled proportions lost to follow-up among study cohorts that did not report the proportion of patients who were previously treated for TB, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Table 6. Additional treatment adherence outcomes reported by study cohorts

Study (sample size, n)	Outcome	Result
Gelmanova 2011 (n= 38)	% Adherence (proportion of prescribed doses taken), mean (SD)	79.0 (16.9)
Bastard 2015 (n=323)	Overall duration of interruptions (days)	Median: 3 (IQR 2-7)
	Max duration of interruptions per patient (days)	Median: 18 (IQR 8-27)
	Time to first interruption, median (IQR), days	95 (42-205)
	Time to first interruption, No. (%)	
	≤ 3 months	155 (48.0)
	3 to <6 months	75 (22.2)
	6 to 12 months	50 (15.5)
	>12 months	43 (13.3)
	Incidence of interruptions due to patient, median (IQR)	1.03 (0.39-2.05)
	Incidence of interruptions due to adverse effects median (IQR)	0 (0-0.17)
	Duration of gaps between interruptions, median (IQR), days	13 (5-37)
	Interruptions of >2 days, No. (%) of patients	272 (84.2)
	Gaps between interruptions >10 days, No. (%)	194 (60.1)
	Adherence ≥ 80%, No. (%)	127 (39.3)
Shin 2006 (n=244)	% missed doses (of all prescribed doses), median (range)	5 (0-45)
	<2% missed doses	52 (21.3)
	≥2% and <5% missed doses	68 (27.9)
	≥5% and <11.0% missed doses	62 (25.4)
	≥11% missed doses	62 (25.4)

Table 7. Summary of feasibility and implementation issues reported by included studies

Study ID	Feasibility of intervention
Gelmanova 2011	The authors estimated an average per patient cost enrolled in the Sputnik program of approximately US$6.50/day, compared to the alternative of in-patient care for the duration of treatment, ranging from US$9.30/day to as high as US$35.00/day.
Loveday 2015	During the implementation and expansion of decentralized care, the four decentralized sites included in the study varied in number of days of hospitalization (from an average of 96 to 180 days), which suggested there were site differences in interpreting and implementing guidelines. The authors concluded that this highlighted "the importance of regular monitoring and support during service expansion, to ensure health systems are functional and new programmes implemented in accordance with guidelines." Many patients were hospitalized longer than the study planned (80 days vs. 2 weeks). Furthermore, the intensity and fidelity of the intervention delivery varied by site: at site 1 where there was more financial resources and ownership/support from the district leadership, there were 16 mobile injection teams – compared to 2 each at sites 2 and 3, and none at site 4 – as well as "additional staff at the out-patient clinic who established systems, implementation of a locally developed patient treatment literacy programme and home assessment by a multidisciplinary team before patient discharge. These programme components were partially implemented at other decentralised sites. Additionally, authors from an earlier study under the same intervention (Brust 2012) concluded, "This illustrates the difficulty in changing a long-standing practice in MDR-TB treatment, where the hospital staff was reluctant to discharge patients who were still culture positive due to concerns that they could transmit the disease to family and/or friends in the community." The authors estimated "the operational costs of the home-based treatment model are approximately 25% those of the centralized in-patient model (B Margot, personal communication), suggesting that the home-based program is both effective and less expensive."
Meressa 2015	The authors provided a gross estimate of program costs, exclusive of second-line drugs, at approximately $2000 per patient over the 2-year treatment period. These costs included: ancillary medications, laboratory monitoring (e.g. cultures, DST and other routine labs), food supplementation, transportation and accommodation for patients, home visits, capacity building, programme management, personnel training, salaries for dedicated staff, salary supplementation of national staff and some infrastructure improvements. These estimates do not include the overhead costs associated with hospital-based care.
Mitnick 2003	The therapy costs per patient ranged from $504 to $32,383 (mean of $15,681 per patient), which were approximately 10 percent of those for hospitalized patients. In a qualitative study (Acha 2007) exploring the social support groups provided under this intervention, the authors found participation varied widely: average of 6 sessions per patient. There were undocumented activities related to participation (spillover effects, such as: "mutual home visits, weekend socialization, and significant friendships among group members", which could contribute to overall treatment adherence. There were logistical challenges to organizing the support groups, including: "finding adequate and low-cost meeting places, ensuring attendance, tardiness and delays (in large part due to Peruvian custom), finding willing facilitators, securing the resources to finance the sessions and excursions, and subsidising transportation costs in necessary cases." Also difficult to find willing facilitators due to TB-related stigma, and lack of prior experience.
Mohr 2017	There was initial reluctance from some care providers to endorse the pilot intervention, as such, some eligible patients in pilot clinics were never offered SAT.
Suarez 2002	The study showed second-line treatment for TB was feasible and cost-effective: "The total programme cost was affordable in the context of the National Tuberculosis Programme's budget, and the mean cost per DALY gained was around US$150-200."
Thomas 2007	Finding DOT providers who could give intramuscular injection to the patients in rural areas was difficult. As such, rural patients received their injections from the village health worker when possible, otherwise either from a private provider by paying a fee or from the primary health center. The authors concluded, "all efforts should be taken before starting treatment to identify a DOT provider nearer to the patient's residence, who could administer injections, possibly by

involving network of private providers available in most villages."

Table 8. Summary of Included Studies.

INCLUDED COHORTS	
Author, Year:	Alene 2017
Study period:	Jan 2011 to Dec 2014
Study setting:	The study was conducted in Hunan Province, in central-south China. Hunan Chest Hospital in Changsha, is the province's only chest hospital. The hospital has 610 beds, and treats and diagnoses patients with chest and lung diseases including TB, MDR-TB, and XDR-TB, referred from throughout the province. The MDR-TB treatment centre was established at the hospital in 2011 and serves as a referral hospital for all HIV-negative persons with presumptive drug resistant TB in the province. The national treatment success rates for people with MDR-TB and XDR-TB in 2013 were 55% and 22%, respectively.
Description of Intervention:	Patients were initially hospitalized for 1 to 2 months during the intensive phase and received DOT by trained medical staff, as well as free nutritional meals, and psychological support and counselling from nurses. After discharge, patients received daily DOT and psychosocial support from trained family members or trained community-based supervisors, and returned to the hospital monthly to collect medication. Education and counselling was routinely provided to patients and families.
Patient eligibility:	All bacteriologically-confirmed MDR-TB patients registered at the treatment centre during the study period were included. Exclusion criteria included: patients who were diagnosed with MDR-TB but did not start treatment (n=8); patients who were transferred out (n=8); and patients co-infected with HIV.
Sample size:	481 (471 MDR-TB; 10 XDR-TB)
Treatment regimen:	Individualized regimen containing four drugs based on DST results and previous TB treatment, usually includes: an injectable agent (kanamycin, amikacin or capreomycin), a fluoroquinolone (i.e. levofloxacin, ofloxacin or moxifloxacin), PAS, prothionamide, pyrazinamide, clarithromycin, ethambutol, or cycloserine).
Treatment duration:	24 months for MDR-TB; 30 months for XDR-TB
Duration of injectable:	6+ months for MDR-TB; 12+ months for XDR-TB
Hospitalization period:	1 to 2 months
Funding source:	Reported no specific funding from public, commercial or not-for-profit organizations
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Bastard 2015
Study period:	Jun 2002 to Jul 2010
Study setting:	Drug-resistant TB programs supported by MSF in Yerevan, Armenia and Abkhazia, Georgia. The programs covered the entire city of Yerevan in Armenia and the autonomous region of Abkhazia in Georgia.
Description of Intervention:	Patients were hospitalized initially and discharged after 2 smear-negative sputum samples. After discharge, DOT 6 days a week at closest health facility, or at home from health personnel or trained community member. Psychological support was

provided, individually and in group sessions, together with socioeconomic support (financial and nutrition support and transport reimbursement).

Patient eligibility:	All DST-confirmed MDR-TB patients who started treatment during the study period and who had a treatment outcome (24+ months follow-up) by 31 July 2010. Patients who were transferred out or still on treatment at the end of study were excluded from analysis.
Sample size:	393
Treatment regimen:	Individualized regimens based on DST results, including at least 4 effective drugs, including 2nd-line drugs (ofloxacin, levofloxacin and moxifloxacin, kanamycin and capreomycin, para-aminosalicylic acid, ethionamide, cycloserine).
Treatment duration:	18 to 24 months
Duration of injectable:	6+ months (4+ months past culture conversion)
Hospitalization period:	Until 2 smear-negative sputum samples
Funding source:	Funding support from MSF.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Cox 2007
Study period:	Oct 2003 to Jan 2005
Study setting:	Nukus City and Chimbay in Karakalpakstan, a semiautonomous region in western Uzbekistan, with high levels of poverty, environmental degradation and slow reform of health services.
Description of Intervention:	The pilot program is a collaborative effort between MSF, the Ministries of Health in Karakalpakstan and Uzbekistan and the National Reference Centre for Mycobacteria in Germany. Patients received counselling, reimbursement for treatment-related transport costs during outpatient care, four meals daily during hospitalization, and monthly food parcels.
Patient eligibility:	Inclusion criteria were: residents of Nukus City and Chimbay; culture positive pulmonary TB; previously been treated in the DOTS program; and no concomitant medical conditions that precluded anti-TB treatment, which included cirrhosis, uncontrolled seizure disorder, significant psychiatric disease and known allergies to second-line anti-TB drugs.
Sample size:	87
Treatment regimen:	A standardized empiric regimen of pyrazinamide, ofloxacin, ethionamide, p-aminosalicylic acid (PAS), cycloserine and either capreomycin or kanamycin, was provided until DST results become available, after which the regimen is adjusted accordingly.
Treatment duration:	Minimum 18 months after culture conversion
Duration of injectable:	6 months
Hospitalization period:	Patients were generally hospitalized for the first six months. The total duration depended on the use of an injectable, availability of family support, and clinical condition.
Funding source:	Funding support from Médecins Sans Frontières, and contributions in kind from the Ministry of Health in Karakalpakstan and the National Reference Center for

	Mycobacteria in German.y
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/ab

Author, Year:	Cox 2014 (*Note: Patients in the pilot program were excluded from main analyses because they formed part of the larger, and more up-to-date, sample in Mohr 2015. However, this study was retained for the analysis of comparative studies.*)
Study period:	Jan 2005 to Dec 2011 (treatment outcomes not available for patients initiating treatment in 2011)
Study setting:	Khayelitsha, a township near Cape Town, South Africa, with high rates of HIV, TB and DR-TB. There are approximately 200 cases of DR-TB diagnosed in Khayelitsha each year, with a HIV infection rate of 72%. Eleven health facilities in Khayelitsha provide integrated HIV and TB services for patients. HIV-infected TB patients are started on antiretroviral therapy shortly after initiating TB treatment. In early 2007, MSF and the City of Cape Town Health Department conducted a review of DR-TB diagnosis and treatment in Khayelitsha, of the 181 patients identified up to the end of 2006, 30% of patients were successfully treated and 70% suffered a poor treatment outcome (including LTFU, failure or death).
Description of Intervention:	A pilot program to provide community-based DR-TB diagnosis and treatment was introduced in late-2007.
	Before pilot program (hospital-based): Hospitalization during intensive phase (6 months) followed by clinic-based DOT without additional support.
	Pilot program (community-based): After diagnosis at a primary care clinic, patients are counselled by a dedicated DR-TB counsellor and treatment is started by the clinic TB medical officer. Patients who are severely ill and requiring hospitalisation, or who have XDR-TB, are referred directly to the tertiary TB hospital for admission. Also includes social assistance and support groups, routine home visit at start of treatment by trained community health worker, and daily DOT at local clinic.
Patient eligibility:	Rifampicin-resistant TB adult patients who resided in Khayelitsha or were diagnosed in one of 10 primary care facilities in the subdistrict. Excluded patients transferred to Khayelitsha after starting treatment elsewhere and those restarted on treatment after previous default or treatment failure.
Sample size:	970 started treatment between 2005 to 2011. Excluding those initiating treatment in 2011: 787 with treatment outcomes available (216 before pilot program; 571 after pilot program).
Treatment regimen:	*Before pilot program*: Standardized treatment regimen. Intensive phase: 5 drugs for 4 months (kanamycin, ethionamide, ofloxacin, ethambutol and pyrazinamide) Continuation phase: 3 drugs (ethionamide, ofloxacin and ethambutol) for 12 to 18 months. Pyrazinamide was continued for extensive cavitary disease. If ethambutol resistance was diagnosed, then ethambutol was replaced with terizidone. *Pilot program*: Standardized regimen adapted based on DST results. Intensive phase: five drugs (kanamycin, ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine) Continuation phase: four drugs (ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine).
Treatment duration:	*Before pilot program*: 16 to 24 months.

	Pilot program: 24+ months
Duration of injectable:	6 months, and at least 4 months after culture conversion.
Hospitalization period:	*Before pilot program*: Minimum 6 months [183/216 (84.7%)] *Pilot program*: Patients were hospitalized only if they were clinically unstable and unable to attend their clinic daily [145/571 (25.4%)]
Funding source:	Program implementation was funded by Medecins Sans Frontieres (MSF Belgium). Programme evaluation was supported by MSF and the University of Cape Town.
Potential conflicts of interest:	The funders were involved in study design, data collection and analysis. However, final preparation of the manuscript and the decision to publish rests with the first author.
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Escudero 2006
Study period:	Jun 1998 to Dec 2000
Study setting:	Hospital La Fuenfría, Madrid.
Description of Intervention:	Psychological support and counselling was provided by repeated clinical interviews during hospitalization and during out-patient follow-up. The clinician and a psychologist focused on the need for optimal treatment adherence and explored the main difficulties patients found in achieving these goals. Patients could be contacted by phone by the medical team after discharge.
Patient eligibility:	Confirmed adult MDR-TB patients without HIV enrolled for treatment at the hospital.
Sample size:	25
Treatment regimen:	Individualized regimen containing one injectable drug plus at least three oral drugs, adjusted based on prior anti-tuberculosis treatment and DST results.
Treatment duration:	18 months or 12 months after first two negative cultures
Duration of injectable:	6 months (5 days/week for months 1-2, 3 days/week for months 3-4, and 2 days/week for months 5-6)
Hospitalization period:	Until first negative sputum culture. Mean 65 days (range 9–483 days).
Funding source:	Not stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Gelmanova 2011
Study period:	Dec 2006 to Nov 2008
Study setting:	Tomsk City metropolitan area (population: 526 000) has a high burden of MDR-TB. The area's DOTS TB program expanded to include MDR-TB treatment in 2000.
Description of Intervention:	The 'Sputnik' program was implemented in Dec 2006 jointly by the Tomsk Oblast Tuberculosis Services (TOTBS) and Partners In Health (PIH). The program goal is to improve treatment adherence among patients with adherence problems in the standard ambulatory care TB program. Most smear-positive patients initiate

treatment in hospitals. After discharge, patients are provided with transportation passes, daily food sets and monthly hygiene sets. The program is staffed by a team of two nurses who visit patients at their convenience and provide twice-daily DOT. A physician joins the team every 10 days for home visits and clinical follow-up. Patients also receive clothing and assistance through state social services. Sputnik has a high nurse-to-patient ratio, and includes provision of cellphones to nursing staff, patient access to specialists and social/psychological support (a psychologist visited patients at home and also worked with family members), and provides additional training to program nurses for addressing patients' biosocial challenges.

Patient eligibility:	MDR-TB patients treated under the Sputnik program. Patients who were referred to the Sputnik program from standard care by a clinical committee included: those who refused to start treatment or stopped taking medications; those missing more than 25% of prescribed doses; those with a history of loss to follow-up in the previous 6 months; and those considered to be at high risk for loss to follow-up for other medical, social or economic reasons. Due to limited program capacity, patients are only referred to the Sputnik program after all standard options are exhausted.
Sample size:	38
Treatment regimen:	Standardized regimen. Intensive phase (6-9 months): 6 drugs- kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol and cycloserine Continuation phase (18 months): 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine. p-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.
Treatment duration:	24+ months
Duration of injectable:	6 to 9 months
Hospitalization period:	Initial hospitalization until smear-negative
Funding source:	Not reported
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	The Sputnik program cost per patient was approximately US$6.50/day. This is compared to average in-patient care of US$9.30/day to US$35.00/day.
Author, Year:	Huerga 2017
Study period:	May 2006 to May 2012
Study setting:	The study took place at three sites in Kenya: Mathare Green House Clinic, which provides free outpatient HIV/TB care to people living in the Mathare slum (population of 340,000); Homa Bay County Hospital, serving a rural area of Western Kenya (population of 360,000); and Kenyatta National Hospital in Nairobi, the largest referral facility in East Africa.
Description of Intervention:	All patients received DOT 6 days a week. Patients at the Mathare and Nairobi sites received clinic-based outpatient care throughout treatment. In Homa Bay, the majority of patients received twice-daily DOT: at the nearest health facility in the morning and by CHWs at patient homes in the evening during the intensive phase, and DOT was provided by CHWs at patient homes during continuous phase.
	TB education and psychosocial counselling were provided at all sites. At the Mathare and Homa Bay sites, counselling sessions were provided by a counsellor following a standardized guide, weekly during the first month of intensive phase, bi-weekly thereafter, followed by monthly during continuation phase. At the Nairobi site, counselling was provided by nurses on request by the doctor available [from email

correspondence with H Huerga].

A multi-disciplinary team provided medical, psychological and social care to the MDR-TB patients. The team is composed of a medical doctor, a clinical officer, a nurse, and a counsellor. In addition, there was a full-time social worker available in Mathare due to the magnitude of the social problems in a slum context. Furthermore, in Homa Bay, for each patient treated at home, two community health workers were identified and trained. Financial support was provided to all patients to cover income losses due to treatment and transport fees to attend the clinic. Patients at the Mathare site also received a daily hot meal at the day-care unit, and a monthly food basket.

Patient eligibility:	All patients who started MDR-TB treatment at the study sites.
Sample size:	169 (70 in Mathare; 28 in Homa Bay; 71 in Nairobi)
Treatment regimen:	Standardized regimen, individualized based on DST results once available. The intensive phase (minimum 6 months) consisted of an injectable agent (kanamycin or capreomycin) and 3 or 4 oral drugs (levofloxacin, prothionamide, cycloserine, or para-aminosalicylic acid). Patients at the Nairobi site were treated with ethambutol or PZA instead of PAS, and until 2009 ofloxacin (OFX) was used instead of LVX. The continuation phase (18 months) included the same drugs as in the intensive phase minus the injectable agent.
Treatment duration:	24+ months
Duration of injectable:	6+ months
Hospitalization period:	None required
Funding source:	Not stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Isaakidis 2011
Study period:	May 2007 to May 2011
Study setting:	An urban, overpopulated slum setting in Mumbai, India. MSF started treating MDR-TB among HIV-infected individuals in May 2007. MDR-TB treatment became available in Mumbai's public sector in late 2010, prior to which it was only available in the private sector.
Description of Intervention:	Patients in stable clinical conditions started treatment on an ambulatory basis, otherwise they were hospitalized under the supervision of the MSF clinical team. Twice-daily DOT by trained DOT provider at a facility no more than 10 minutes walking distance from patients' home, including public health posts, private practitioners and local NGOs. Patients attended the MSF clinic monthly for medical and psychosocial follow-up.
Patient eligibility:	All HIV-infected patients treated for MDR-TB (bacteriologically confirmed or suspected based on clinical findings and treatment history) at the clinic during the study period.
Sample size:	58
Treatment regimen:	Standardized regimen modified based on DST results, included six drugs: pyrazinamide, capreomycin, moxifloxacin, ethionamide, cycloserine and PAS.
Treatment duration:	18+ months

Duration of injectable:	6+ months
Hospitalization period:	Only if patient was clinically unstable for outpatient care.
Funding source:	No external funding sources.
Potential conflicts of interest:	This is an MSF study.
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Joseph 2011
Study period:	Jun 2006 to Sep 2007
Study setting:	Tiruvallur district and the Chennai Corporation area (with a combined population of almost 7.5 million) in southern India, in Chennai, Tamil Nadu. Previous reports from the TB Research Centre (TRC) in Chennai have shown MDR-TB treatment success rates of 37% to 50%.
Description of Intervention:	Hospitalization was recommended for the first two to four weeks of treatment. After discharge, patients attended the nearest health centre of their choice for DOT by trained DOT providers, which included government health care providers, private medical practitioners, and friends and relatives staying close by. DOT providers received one-on-one training from the TRC to administer drugs, counsel patients for drug regularity, identify and refer patients to the medical officer in case of any adverse drug reactions, and send patients to the TRC for monthly follow-ups. Patients were given emergency contact details for the medical officer and TRC field workers.
Patient eligibility:	Patients with DST-confirmed MDR-TB in the study district were traced and enrolled into the study. Exclusion criteria were: under 18 years of age; pregnancy; concurrent major psychiatric illness or serious medical illness; previous treatment (>1 month) with any second line anti-TB drugs; and HIV infection.
Sample size:	38
Treatment regimen:	The standardized regimen consisted of: an intensive phase (6 to 9 months) with 6 drugs (Km, Ofx, Eto, Z, E abd Cs); followed by a continuation phase (18 months) with 4 drugs (Ofx, Eto, E and Cs).
Treatment duration:	24+ months
Duration of injectable:	6 months, or 9 months if culture conversion occurred after the 4th month.
Hospitalization period:	2 to 4 weeks recommended
Funding source:	WHO and the United States Agency for International Development (Model DOTS Project)
Potential conflicts of interest:	Not stated
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Keshavjee 2008
Study period:	Sep 2000 to Nov 2004
Study setting:	Tomsk Oblast in western Siberia, Russia, which has about 1·1 million inhabitants, approximately half of whom live in remote villages.
Description of Intervention:	Patients are routinely hospitalized during intensive phase, and discharged for the continuation phase, unless there is an underlying condition that precludes discharge

	(such as a psychiatric disorder, alcoholism or homelessness). TB physicians routinely assessed all patients initiating treatment for possible alcohol or substance use disorders. Daily DOT was provided by feldshers, who are often nurses at very rural outposts, to supervise the TB and Naltrexone medications, or at TB clinics, TB hospital or day hospital. Supplementary nutritional support is provided to prisoners and in-patients, and monthly food packages and/or free meals are given to fully adherent out-patients.
Patient eligibility:	Patients who started MDR-TB treatment and had documented MDR-TB during the study period.
Sample size:	608
Treatment regimen:	The individualized treatment containing at least 5 drugs, based on DST or drugs thought to be sensitive, including: any first-line oral agent to which isolate is sensitive; an injectable to which an isolate is sensitive; a quinolone; other second-line drug (usually ethionamide or cycloserine or PAS).
Treatment duration:	18 months after culture conversion
Duration of injectable:	6+ months after culture conversion
Hospitalization period:	Routinely hospitalized for the duration of injectable use, between 6 to 9 months.
Funding source:	Financial and travel support from Bill & Melinda Gates Foundation and Eli Lilly Foundation, the Frank Hatch Fellowships in Global Health Equity at the Brigham & Women's Hospital, Infectious Disease Society of America, the Heiser Foundation, and the US National Institutes of Health, and the John D and Catherine T MacArthur Foundation.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Kliiman 2009
Study period:	Jan 2003 to Dec 2005
Study setting:	Estonia, a republic of the former Soviet Union, which has a high burden of MDR-TB and XDR-TB.
Description of Intervention:	Daily DOT at clinics after discharge. Patients received nutritional support and transportation reimbursement for clinic visits.
Patient eligibility:	MDR-TB patients with culture-confirmed pulmonary TB with a recorded treatment outcome.
Sample size:	235 MDR-TB and 54 XDR-TB patients
Treatment regimen:	Individualized regimen based on DST results, containing at least four oral drugs used daily and an injectable daily until culture conversion, and three to five times weekly for another 2 to 3 months after.
Treatment duration:	12 to 18 months after culture conversion
Duration of injectable:	Two to three months after culture conversion
Hospitalization period:	Until culture conversion
Funding source:	None stated
Potential conflicts of interest:	None declared
Issues with implementation (if	n/a

reported):	
Economic information (if reported):	n/a

Author, Year:	Loveday 2015
Study period:	Jul 2008 to Jun 2010
Study setting:	A community-based model of MDR-TB treatment was piloted in 2008 at four community-based sites attached to purposively selected rural hospitals in areas with high reported incidence of MDR-TB, in Kwazulu-Natal, South Africa. Treatment outcomes at the four sites are compared to those at a centralized hospital. Approximately 76% of MDR-TB patients in KwaZulu-Natal are HIV-infected.
Description of Intervention:	Directly observed therapy (DOT) was not consistently implemented and most patients self-administered oral treatment with limited adherence monitoring.
	Hospital site: Patients were initially hospitalized at a centralized, specialist TB hospital, followed by monthly outpatient visits to the same hospital. Patients were often discharged before the completion of the injectable phase and were not provided intensive education (as done at the community-based sites).
	Community-based sites 1-4: Patients were initially hospitalized at rural hospitals attached to community-based sites. Monthly outpatient visits to community-based sites after discharge. Home-based care was available for patients discharged from the community-based sites during the intensive phase of treatment, where injections were administered daily at the local clinic or by mobile injection teams (at sites 1 to 3 only). Education was provided to patients and their families about MDR-TB and HIV. There was some variability in delivery of intervention at the four sites (see Table 4 for details). Additionally at Site 1 (only): Weekly education sessions were held, led by a clinic assistant and a nurse, on MDR-TB and HIV treatment with patients and their treatment supporters (family or friend). After the intensive phase, CHWs replaced nurses in making home visits and providing DOT. Travel expenses incurred by patients and their treatment supporters for clinic visits were reimbursed.
Patient eligibility:	Adult patients (>18 years) with laboratory-confirmed MDR-TB were enrolled. Patients with resistance to any second-line drug, or who received care at both the hospital and a community-based site, or who were participating in an MDR-TB clinical trial, were excluded.
	Hospital site: All eligible MDR-TB patients, excluding those from the catchment areas of the community-based sites.
	Community-based sites: All eligible MDR-TB patients in the catchment areas of the sites.
Sample size:	1549 (813 from hospital; 736 from community-based sites)
Treatment regimen:	Standardized regimen Intensive phase: kanamycin (KM), PZA (Z), EMB (E),ethionamide (ETH), ofloxacin (OFX) and cycloserine (CS) Continuation phase: Z, E, ETH, OFX and CS.
Treatment duration:	22+ months
Duration of injectable:	4 to 6 months
Hospitalization period:	Median 144 days (IQR 83 to 185)
Funding source:	Funding support from the Medical Research Council of South Africa (Cape Town, South Africa), Izumi Foundation (Boston, MA, USA) and a United Way Worldwide grant from the Lilly Foundation/Lilly MDR-TB Partnership (Indianapolis, IN, USA). Additional funding from the Columbia University- Southern African Fogarty AIDS International Training and Research Program (AITRP), Implementation Science Traineeship Program funded by the United States President's Emergency Plan for

AIDS Relief (PEPFAR) through the Fogarty International Center, National Institutes of Health (grant # D43TW00231), Bethesda, MD, the National Institute of Allergy and Infectious Diseases (K23AI083088), Bethesda, MD, USA.

Potential conflicts of interest:	None declared
Issues with implementation (if reported):	Treatment success rates across community-based sites varied widely. This could be due to different interpretation and implementation of guidelines. For instance, the hospitalization period varied from 96 to 180 days.
Economic information (if reported):	n/a

Author, Year:	Meressa 2015
Study period:	Feb 2009 to Dec 2014
Study setting:	St. Peter's Hospital in Addis Ababa, Ethiopia and the University of Gondar Hospital (UoG) in Gondar, northwestern Ethiopia. Ethiopia is a high MDRTB-burdened country. The national MDR-TB treatment program was established in 2009, and is based on a multidisciplinary HIV/TB care model developed in Cambodia. This study reports the treatment outcomes from the first four years of the program.
Description of Intervention:	As outpatients, monthly visits to hospital outpatient clinic and daily DOT at local health centres by health staff or at home by family DOT supporter. Family treatment supporters trained on adherence monitoring. Monthly home visits by outpatient team in Addis Ababa and Gondar. Monthly food basket provided to all patients. Economic assistance, if needed, for transportation and housing. Patients who were initiated on therapy as outpatients were followed by the GHC (Global Health Committee) outpatient team, including roving nurses who provided them with daily injections of the injectable agent (5–6 days per week).
Patient eligibility:	All MDR-TB patients who initiated treatment before December 2012 (with at least 24 months of follow-up by December 2014) at two hospital-based study sites. MDR-TB was presumed for 61 (10.0%) patients, who had documented unsuccessful cure by first-line treatment, but without microbiological confirmation.
Sample size:	612
Treatment regimen:	Standardized second-line drug regimen: (1) at least three oral agents to which the patient was presumed to have susceptibility (eg, levofloxacin, ethionamide, cycloserine or para-aminosalicyclic acid (PAS)), (2) pyrazinamide and (3) an aminoglycoside (amikacin or kanamycin) or polypeptide (capreomycin) injectable agent.
Treatment duration:	18 months after bacteriological conversion
Duration of injectable:	Minimum 8 months. Median 9.6 months (IQR 8.1-11.0 months).
Hospitalization period:	Until smear conversion or clinically stable. A subset of healthier patients was initiated on therapy as outpatients beginning in 2010.
Funding source:	Funding support from the Jolie-Pitt Foundation, the Annenberg Foundation, Lilly MDR Partnership, and Lilly Foundation, the Ethiopian Federal Ministry of Health, The Stanford Center for Innovation in Global Health, the National Institutes of Health (K01 AI104411) and Children's Hospital Boston.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	Gross estimate of programme costs, exclusive of second-line drugs, is approximately $2000 per patient over the 2-year period of treatment. Costs include: ancillary medications, laboratory monitoring, food supplementation, transportation and accommodation for patients, home visits, capacity building, programme

management, personnel training, salaries for dedicated staff and salary supplementation of national staff and some infrastructure improvements. Excludes overhead costs for infrastructure and personnel associated with hospital-based care.

Author, Year:	Mitnick 2003
Study period:	Aug 1996 to Feb 1999
Study setting:	Resource-poor setting, Northern Lima (Carabayllo, Comas, and Independencia districts), Peru.
Description of Intervention:	Patients received limited nutritional, financial, and social support through Socios En Salud. A team of specially trained community health workers, nurses, and physicians provided treatment on an outpatient bases. Daily DOT at homes or local health centres.
Patient eligibility:	Patients who initiated supervised, individualized treatment for MDR-TB before 1 Feb 1999 under a community-based treatment program (joint initiative of an NGO (Socios En Salud) and the Peruvian Ministry of Health). Inclusion criteria were: residence in the government-approved catchment area in northern Lima (Carabayllo, Comas, and Independencia districts); referral to the program by a collaborating health center after the failure of at least one course of directly observed, standardized short-course chemotherapy; laboratory-documented multidrug-resistant tuberculosis; survival until the results of drug-susceptibility testing became available; and provision of written informed consent.
Sample size:	75
Treatment regimen:	Individualized regimens containing a minimum of 5 first and second-line drugs based on DST results. First-line drugs were preferred if susceptible. An injectable was given for at least six months after culture conversion.
Treatment duration:	18+ months (12 consecutive negative cultures)
Duration of injectable:	6+ months after culture conversion
Hospitalization period:	None
Funding source:	Supported by Thomas J. White, the Massachusetts State Laboratory Institute, the National Institute of Allergy and Infectious Diseases, Eli Lilly, and the Bill and Melinda Gates Foundation.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	Cost of therapy ranged from US$504 to $32,383 per patient. Mean of $15,681 was approximately 10% of costs for hospitalized patients.
Author, Year:	Mitnick 2008
Study period:	Feb 1999 to Jul 2002
Study setting:	Metropolitan Lima, Peru. A comprehensive individualized MDR-TB treatment program was introduced in 1996.
Description of Intervention:	Comprehensive supervised outpatient treatment, free of charge to patients. All patients received DOT through local hospitals, health clinics, and daily home visits by community health workers. Patients with emotional and psychosocial difficulties, who had weak social support, or with adherence problems were invited to participate in a social support group that included weekly, and later bi-monthly support groups/group therapy, recreational excursions, symbolic celebrations and family workshops (Acha 2008). Limited nutritional and financial support and opportunities for income generation were provided, as needed. Hospitalization was available, if medically indicated.

Patient eligibility:	All MDR-TB patients who initiated individualized treatment under the program, with baseline DST results for at least four drugs: isoniazid, rifampicin, one fluoroquinolone, and one second-line injectable (kanamycin, capreomycin, or amikacin).
Sample size:	651 (48 XDR-TB patients; 603 MDR-TB patients)
Treatment regimen:	Individualized treatment based on DST results, containing at least five drugs likely to be effective, including a fluoroquinolone and an injectable agent.
Treatment duration:	18+ months
Duration of injectable:	8+ months after culture conversion
Hospitalization period:	Only if medically indicated. Overall, 29 (4.5%; 3/48 XDR-TB patients and 26/603 MDR-TB patients) initiated treatment in hospital. Duration depended on when the patient became clinically stable and ready for discharge.
Funding source:	Supported by grants from the Bill and Melinda Gates Foundation, Thomas J. White, Partners in Health, the Peruvian Ministry of Health, the David Rockefeller Center for Latin American Studies at Harvard University, the Francis Family Foundation, the Pittsfield Anti-tuberculosis Association, the Eli Lilly Foundation, and the Hatch Family Foundation and by career development awards from the National Institute of Allergy and Infectious Diseases (5 K01 A1065836, to Dr. Mitnick) and the National Heart, Lung, and Blood Institute (5 K01 HL080939, to Dr. Becerra).
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Mohr 2015
Study period:	Aug 2008 to Jan 2012
Study setting:	Khayelitsha, a township near Cape Town, South Africa, with high rates of HIV, TB and DR-TB. There are approximately 200 cases of DR-TB diagnosed in Khayelitsha each year, with a HIV infection rate of 72%. Eleven health facilities in Khayelitsha provide integrated HIV and TB services for patients. HIV-infected TB patients are started on antiretroviral therapy shortly after initiating TB treatment.
Description of Intervention:	Individual-specific DR-TB counselling (four sessions throughout treatment – three in the first month of treatment, including a home visit with counselling and education for families by the DR-TB counsellor and a social worker/peer educator/nurse, and one during the continuation phase). Patients are invited to attend weekly peer support groups conducted at the clinics, moderated by a DR-TB counsellor or peer educator. Daily DOT at local clinic. A dedicated social assistant is available in Khayelitsha to assist patients in accessing disability/social grants, and refer patients to other support services. Hospitalization only if patients were clinically unstable and unable to attend their clinic daily.
Patient eligibility:	All DR-TB (resistance to at least Rifampicin) patients registered in Khayelitsha during the study period with known HIV status, and without previous treatment with second line drugs. Patients who transferred from facilities outside the sub-district and those with bacteriologically unconfirmed DR-TB (mostly children aged ≤5 years) were excluded.
Sample size:	853
Treatment regimen:	Standardized regimen adapted to DST results. Intensive phase: 5 drugs (kanamycin, ethionamide, pyrazinamide, ofloxacin, and

either terizidone or cycloserine)
Continuation phase: 4 drugs (ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine).

Treatment duration:	24+ months
Duration of injectable:	6 months
Hospitalization period:	No mandatory hospitalization
Funding source:	Funding support from MSF and Wellcome Trust.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Mohr 2017
Study period:	Jan 2010 to Dec 2014
Study setting:	Khayelitsha is a peri-urban township outside of Cape Town, South Africa, most of the 450,000 residents in informal settlements. There are approximately 200 newly diagnosed RR-TB patients each year, with a case notification rate of 55/100,000 and an HIV co-infection rate of 70%. Progressive implementation of SAT took place from 2012 to 2015 at 5 of 10 primary care clinics in Khayelitsha. These initial pilot clinics were chosen based on available resources, functionality, and willingness of staff to participate. The national LTFU rate among RR-TB patients ranges from 20% to 31%.
Description of Intervention:	*Standard of care (SOC) cohort*: Patients attended the clinic 5 days per week for DOT for the entire treatment. Patients received four standardized counseling sessions provided by trained RR-TB counselors: upon diagnosis; at treatment initiation; during the intensive phase; and upon completion of intensive phase. Patients lost to follow-up were traced telephonically or via home visits from local community health workers or counselors.
	Self-administered therapy (SAT) cohort: The same care is received during the intensive phase. After completion of the intensive phase, patients received tailored counselling from an RR-TB counsellor, which includes discussing the option of SAT. Prior to enrollment into SAT, local community health workers conduced home visits to assess the social situation, identify a treatment supporter, and determine adherence barriers. After enrollment patients received an adherence counseling session by a dedicated MSF counselor, where medications were reviewed, a pillbox was issued and adherence barriers were addressed. Patients received weekly or monthly supply of medications, depending on clinic and patient preference. Community health workers visited weekly initially and monthly as soon as patients were deemed to be doing well in the programme, during which they provided support and addressed adherence barriers.
Patient eligibility:	All RR-TB patients who initiated treatment during the study period, and who had a final treatment outcome before 1 Jan 2017, at the 5 pilot clinics were considered for study enrollment. Patients were excluded if they had a treatment outcome within 6 months of treatment initiation (42 in SOC cohort; 67 in SAT cohort).
	SOC cohort: Eligible RR-TB patients who initiated treatment at least 6 months prior to SAT implementation at their respective clinics. Treatment initiation times for inclusion in the SOC cohort ranged from January 2010 to July 2013.
	SAT cohort: Eligible RR-TB patients who initiated treatment at least 6 months after SAT implementation at their respective clinics were considered for SAT. Treatment

initiation times for patients included in the SAT cohort ranged from Jan 2012 to Dec 2014. Patient eligibility for SAT was assessed based on: treatment adherence history (for RR-TB and concomitant diseases); and clinical status and any adverse events requiring ongoing monitoring. Enrollment decisions were made at weekly clinic meetings attended by community health workers, doctors, RR-TB professional nurses and MSF counsellors. Eligible patients, who gave verbal consent, and who were no longer receiving an injectable agent (including those who were already in the continuation phase) were enrolled.

Sample size:	295 RR-TB patients who completed at least 6 months of treatment (118 in SOC cohort; 177 in SAT cohort); of which 292 had final treatment outcomes by 1 Jan 2017 (118 in SOC cohort; 174 in SAT cohort)
Treatment regimen:	Patients from both cohorts received a standard RR-TB treatment regimen provided to patients contained all or most of the following drugs: kanamycin, moxifloxacin, pyrazinamide, ethambutol, terizidone, ethionamide and high dose isoniazid. The initial phase (6 months, and at least 4 months after culture conversion) consisted of kanamycin, ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine. The continuation phase (at least 18 months) consisted of ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine.
Treatment duration:	24+ months
Duration of injectable:	6+ months, at least 4 months after culture conversion
Hospitalization period:	None
Funding source:	The pilot SAT program was funded by MSF and Cape Town City Health, and the study was funded by MSF.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	Among patients enrolled in the SOC cohort (n=118), 17 (14.4%) were later considered for and received SAT (due to the phased implementation of SAT at the clinics), with a median time to SAT-enrollment of 14.8 months (IQR 12.8-20.3). In addition to these patients, other patients in the SOC cohort might have received an informal version of SAT as facilities occasionally provided a supply of medications for self-administration to relieve pressure on the clinic. These patients however did not receive the specialized counseling and community support integral to the SAT pilot programme. Some eligible patients were never offered SAT due to the slow, phased implementation of the pilot program, reluctance from some providers to provide SAT, and limited resources.
Economic information (if reported):	n/a

Author, Year:	Satti 2012
Study period:	Jan 2008 to Sep 2009
Study setting:	All 10 districts in Lesotho under the national MDR-TB program.
Description of Intervention:	A team of community nurses assessed the home situation, educated families, and arranged for a community health worker to provide twice-daily DOT in the patient's home, who also accompanied the patients for monthly clinic visits. Community health workers received regular training on HIV and MDR-TB, and in psychological support. They were reimbursed for all costs incurred and compensated with performance-based payment. Treatment was provided free-of-charge. All patients received a food package and reimbursement for travel expenses incurred during treatment.
Patient eligibility:	All adult patients (15 years or older) with DST-confirmed MDR-TB, who received second-line TB treatment between Jan. 1, 2008 and Sep. 29, 2009 in the national MDR-TB program.

Sample size:	134
Treatment regimen:	Patients were initiated on a standardized regimen of six drugs –pyrazinamide, kanamycin, levofloxacin, prothionamide (or ethionamide), cycloserine, and para-aminosalicylic acid – until DST results are available, after which it is adjusted accordingly.
Treatment duration:	Median duration of 22.9 months (IQR, 21.6–24.0)
Duration of injectable:	6 months
Hospitalization period:	Not mandatory; patients who were critically ill or who had severe adverse events were hospitalized.
Funding source:	Support received from the Department of Global Health and Social Medicine Research Core at Harvard Medical School
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Shin 2006
Study period:	Jun 1998 to Dec 2000
Study setting:	The Tomsk Oblast in western Siberia, where there is a very high burden of MDR-TB. Half of the population lives Tomsk, the capital city, and the remainder lives in remote rural villages, which are often inaccessible for parts of the year.
Description of Intervention:	Patients are routinely hospitalized during intensive phase, and discharged for the continuation phase, unless there is an underlying condition that precludes discharge (such as a psychiatric disorder, alcoholism or homelessness). TB physicians routinely assessed all patients initiating treatment for possible alcohol or substance use disorders. Daily DOT was provided by feldshers, who are often nurses at very rural outposts, to supervise the TB and Naltrexone medications, or at TB clinics, TB hospital or day hospital. Supplementary nutritional support is provided to prisoners and in-patients, and monthly food packages and/or free meals are given to fully adherent out-patients.
Patient eligibility:	Confirmed or suspected MDR-TB (based on history of previous treatment failures) who were receiving DOTS-Plus treatment from the civilian sector (n=134, 54.9%) and prison sector (n=110, 45.1%)
Sample size:	244
Treatment regimen:	The individualized treatment containing at least 5 drugs, based on DST or drugs thought to be sensitive, including: any first-line oral agent to which isolate is sensitive; an injectable to which an isolate is sensitive; a quinolone; other second-line drug (usually ethionamide or cycloserine or PAS).
Treatment duration:	18+ months
Duration of injectable:	6+ months after culture conversion
Hospitalization period:	Routine hospitalization in the civilian sector during the intensive phase (i.e. duration of injectable). Among civilian patients, 98 (73.1%) started treatment in the hospital (median duration of 7.9 months), the remainder started as outpatients in the day hospital.
Funding source:	Funding for medications and patient care was provided by the Bill & Melinda Gates Foundation and the Open Society Institute. Funding for physician and health care worker training was provided by the Eli Lilly foundation.
Potential conflicts of interest:	None declared

Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Author, Year:	Suarez 2002
Study period:	Oct 1997 to Mar 1999
Study setting:	Peru, a middle-income country where TB treatment is provided free of charge.
Description of Intervention:	Daily DOT by nurses and monthly medical check-up by doctors. Patients were provided appointment cards and weekly food parcels.
Patient eligibility:	Patients with confirmed MDR-TB who were enrolled in the second-line treatment programme in Peru.
Sample size:	298
Treatment regimen:	Standardized regimen consisting of kanamycin (1 g injectable), ciprofloxacin (1 g orally), ethionamide (750 mg orally), pyrazinamide (1500 mg orally), and ethambutol (1200 mg orally). Kanamycin was administered for the first 3 months.
Treatment duration:	18 months
Duration of injectable:	3 months
Hospitalization period:	None
Funding source:	Not declared
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	The average cost per patient for those who completed the full course of treatment was US$2381, with the second-line drugs, at US$824 per patient, being the most expensive item.

Author, Year:	Thomas 2007
Study period:	Jan 1999 to Dec 2003
Study setting:	Predominantly rural sub-district of Tiruvallur district, in south India, and nearby Chennai Sity. The Revised National TB Control Programme (RNTCP) was implemented in Triuvallur district in 1999, the area has 17 governmental health care facilities, including 7 designated microscopy centers.
Description of Intervention:	After discharge, patients attend primary health centres or NGO for thrice-weekly DOT. Monthly clinical assessment and sociological counselling. Reminders were sent one week prior to monthly check up. Financial assistance was provided at the monthly visits for all patients to compensate for loss of wages and travel expenses.
Patient eligibility:	All culture-confirmed MDR-TB patients who were referred to the Tuberculosis Research Centre during the study period from the study area in Tiruvallur district, and from an NGO working in nearby Chennai city.
Sample size:	66
Treatment regimen:	Individualized regimen based on DST results. The regimens used were:
	Group I: $6Sm_3(Km_3)OfxEtoZE$ daily followed by $12OfxEtoZE$ daily
	Group II: Other combinations. E.g.: $6Sm_3(Km_3)OfxEtoZH_{high\ dose}$ daily followed by $12OfxEtoZH$ daily; or $6Sm_3(Km_3)OfxZE$ with Cs/PAS/High dose INH daily followed by 12 months of oral drugs; etc.

Treatment duration:	18+ months
Duration of injectable:	6 months
Hospitalization period:	Recommendation of 1 month. 30 (45%) were not hospitalized, and 10 (15%) hospitalized for <10 days.
Funding source:	Funding support from the World Health Organization and the United States Agency for International Development under the Model DOTS Project.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Vaghela 2015
Study period:	Aug 2009 to Mar 2010
Study setting:	Northeast, East, Central and West districts of Delhi, India – large metropolitan area with a high burden of TB and MDR-TB.
Description of Intervention:	Daily DOT by a DOT Provider at a DOTS-plus centre or hospital. Mobile multi-disciplinary teams, consisting of one male and one female trained community health workers, made home visits every 15 days during intensive phase and every 45 days in continuation phase. The home visits included psychosocial support and counselling for patients and their families, hygiene and nutrition counselling, and nursing care. Patients from very poor socioeconomic backgrounds were provided free multigrain biscuits and an egg per day. Patients were given the mobile numbers for the team members such that in case of an adverse drug reaction or early warning symptoms, they can get immediate attention. Teams assisted patients in registering for financial support under the government TB scheme.
Patient eligibility:	All new MDR-TB patients registered at clinics in the selected districts
Sample size:	101
Treatment regimen:	Standardized regimen.
	Intensive phase: kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol and cycloserine
	Continuation phase: ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine
	P-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.
Treatment duration:	24 to 29 months
Duration of injectable:	6 to 9 months
Hospitalization period:	Not reported
Funding source:	Funded by Eli Lilly and Company (India) Pvt. Ltd.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Yu 2015

Study period:	Jan 2007 to Jun 2008 [updated to 2012 using unpublished data (Yu 2018, accepted manuscript: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy066/4831095?redirectedFrom=fulltext)]
Study setting:	Northern Taiwan, where the government established a new patient-centred MDR-TB treatment program in May 2007 to standardize MDR-TB care, named Taiwan MDR-TB Consortiums (TMTC). Prior to its establishment, MDR-TB patients had to visit either prescribed hospitals or a contracted out-patient clinic for daily injections, and public health nurses were not familiar with the complicated regimens for MDR-TB or the related adverse effects. Between 1992 and 1996, the national lost to follow-up rate among MDR-TB patients was approximately 30%.
Description of Intervention:	Hospitalization was encouraged at treatment initiation. Designated observers and nurses provided DOT and injections to patients, typically at their home. Taiwan CDC also provided NTD 1 million for every patient (a maximum of NTD 2 million for the 2-year treatment period, excluding the cost of medicine) to be used flexibly by the medical team for incentives and enablers to improve adherence. Education and counselling provided by the medical team during home visits to patients and their families. When patients attended out-patient clinics for refills or check-ups, they were accompanied by team members from the TMTC to address hospital affairs and have examinations done in regards of infection control.
Patient eligibility:	All pulmonary, bacteriologically confirmed MDR-TB cases who received treatment with second-line drugs, during the study period. MDR-TB patients with positive culture results after January 2007 were informed and consented to participate in the Consortium program.
Sample size:	126
Treatment regimen:	Individualized regimens based on DST results. Four susceptible drug, including EMB, PZA, a fluoroquinolone, an injectable, and other oral 2nd-line drugs.
Treatment duration:	18 to 24 months (18 months after sputum conversion)
Duration of injectable:	6 months
Hospitalization period:	2 weeks to 2 months
Funding source:	Centers for Disease Control, Taiwan
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
INCLUDED TRIALS	
Author, Year:	Baral 2014 (mixed methods)
Study period:	Jan 2008 to Dec 2008
Study setting:	Nepal, a mid-TB burden country where TB is highly stigmatised. MDR TB treatment is provided from 10 treatment centres and 34 sub-centers throughout the country. There is a well-functioning national TB programme but management is complicated by the country's terrain. A national DOTS-Plus program for MDR-TB was piloted in November 2005. The reported non-completion rates under the program were 22%, 15% and 18% in 2005, 2006 and 2007 respectively. This study was conducted at the 7 DOTS-Plus centres in the Kathmandu Valley.
Randomization:	The seven DOTS-Plus centres were randomized to 3 types of care by randomly selecting from the numbers 1 to 7 (representing each centre): 2 to standard care (controls); 2 to standard care plus counselling; and 3 to standard care plus counselling and financial support. Individual randomization could not be done due to

	the certainty of contamination among patients within a centre.
Trial arms:	Control arm (standard care): Each patient nominated someone (usually a family member) as a treatment supporter. Daily DOT at the clinic.
	Intervention arm 1: Standard care plus individual (2 to 5 sessions) and small-group counselling (every 2-3 weeks) by trained Public Health Nurse. Counselling sessions were between 15 to 30 minutes, and were tailored to issues identified in previous sessions. The general content was information about disease, drugs and treatment, curability, treatment continuation, social barriers such as stigma, support from health workers, community and family members, financial hardship due to MDR TB etc.
	Intervention arm 2: Standard care plus counselling sessions (as in Intervention arm 1), and additionally, patients received financial support (2000 Nepali Rupees (~28USD) per month).
Patient eligibility:	All MDR-TB patients starting treatment at the DOTS-plus centres in 2008 were eligible for study inclusion.
Sample size:	156 (control: 81; intervention 1: 33; intervention 2: 42)
Treatment regimen:	Standardized regimen.
	Intensive phase: five drugs (pyrazinamide, kanamycin, ofloxacin, ethionamide, and cycloserine) for eight months, but is extended to twelve months if the patient is smear- or culture-positive at six months (8Z-Km-Ofx-Eto-Cs/16Z-Ofx-Eto-Cs).
	Continuation phase: same as intensive phase, but without kanamycin.
Treatment duration:	16 months, extended by up to 8 months if culture conversion occurred between 12 and 18 months of treatment
Duration of injectable:	8 to 12 months
Hospitalization period:	Hospitalization only for severe side effects.
Funding source:	Funded by UK Aid from the UK Department for International Development (DFID).
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Taneja 2017
Study period:	Apr 2014 to May 2014
Study setting:	This pilot study was conducted at two sites (Malviya Nagar Government Hospital and Nehru Nagar Chest Clinic, both in New Delhi) randomly selected from a list of 20 hospitals in Delhi, India, at which a cluster trial was being plan.
Randomization:	Cluster randomization by hospital site
Trial arms:	Control arm (Nehru Nagar site): The control arm received regular treatment and investigations as per RNTCP guidelines. During the intensive phase, patients visited the DOTS centre thrice weekly for DOT provided by health workers. During the continuation phase, patients received weekly supplies of drugs from the DOTS centre to be consumed at home. Health education and counselling was given at each visit to the DOTS centre. DOTS health workers were given incentives from program funding for every patient that successfully completed treatment.
	Intervention arm (Malviya Nagar site): In addition to standard care (as in control arm), a team of two trained homecare providers provided comprehensive home-based care to MDR-TB patients and their family members, which included counselling

on the importance of treatment adherence, on their emotional needs, as well as health education on coughing etiquettes, avoiding risk to family members, etc. Additional support included: nursing care and referral to other higher centres in case of illness or mental health issues; physical, mental and vocational rehabilitation; assistance in obtaining Government financial support; support for obtaining or returning to work and school; and nutritional support (eggs and nutritious multigrain provisions) and counselling. The homecare team visited patients fortnightly during the intensive phase and every 45 days during the continuation phase. In addition to providing counselling and education, the team also recorded body weight, side-effects of medicines and complications of the disease. The team also motivated the patients to go for routine sputum microscopy, X-Ray, sputum culture and other relevant investigations.

Patient eligibility:	MDR-TB patients who received treatment for more than 6 months. Exclusion criteria were: any form of disability and comorbidities; and pregnancy.
Sample size:	100 (50 in each arm)
Treatment regimen:	Standardized regimen, adjusted based on DST results, consisting 6 drugs (Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine) during the intensive phase (6 to 9 months), and 4 drug (sLevofloxacin, Ethionamide, Ethambutol and Cycloserine) during continuation phase (18 months).
Treatment duration:	24 to 27 months
Duration of injectable:	6 to 9 months
Hospitalization period:	None
Funding source:	None stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Table 9. Detailed quality assessment of non-randomized studies (based on Robins-I Tool)

Author, Year	Alene 2017
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information – unclear on whether counselling continued after hospital discharge
Overall risk due to deviations from interventions	No information
Bias due to missing data	

Were outcome data available for all, or nearly all, participants?	8/489 (1.6%) patients were not included because their outcomes were not available (i.e. transferred out or not assessed)
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – treatment outcomes were obtained from an internet-based TB Management Information System in the Tuberculosis Control Institute of Hunan Province, and from MDR-TB medical records and the DST registration book at Hunan Chest Hospital.
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	No information
Author, Year	Bastard 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information – unclear how frequent or for how long were individual and group counselling provided for, and whether this was routinely provided to all patients
Overall risk due to deviations from interventions	No information
Bias due to missing data	

Were outcome data available for all, or nearly all, participants?	No – 22/415 (5.3%) were excluded from analysis because they did not have an outcome at the administrative censoring date (12 were still receiving treatment and 10 had transferred out).
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – treatment outcomes obtained from routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	No information

Author, Year	Cox 2007

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No, this was a pilot program with a small sample that appeared to adhere to the protocol.
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – treatment outcomes obtained from routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Escudero 2006
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – provided clear details of intervention implementation and delivery.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Most – 2/25 (8%) patients transferred to other hospitals

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – used routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	Low
Overall Risk of reporting bias	Low
OVERALL BIAS	Moderate
Author, Year	Gelmanova 2011

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No - clear details of intervention implementation and delivery.
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes, except 1/38 (2.6%) patient who was transferred out

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Isaakidis 2011
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – clear details of intervention implementation and delivery.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 23/58 (39.7%) were still on treatment at the end of the observational period, all initiated treatment <24 months before end date. Thus, although they were censored, their exclusion does not affect results.

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Joseph 2011
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information – the intervention required a network of trained DOT providers to deliver treatment, and also weekly delivery of the TB drugs to the DOT providers by research staff, it was not reported whether this was done successfully and that treatment was consistently delivered without interruptions.
Overall risk due to deviations from interventions	No information
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	No information

Author, Year	Joseph 2011

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
Overall risk due to deviations from interventions	Low
Bias due to missing data	Low
Were outcome data available for all, or nearly all, participants?	Yes

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low

OVERALL BIAS	Low

Author, Year	Meressa 2015

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – detailed description of intervention delivery
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low

Author, Year	Mitnick 2003

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data. However, this study used a non-standard definition for lost to follow-up: "Withdrawal from therapy was defined by one or more months of missed therapy during the first year, and two or more months missed during the second year." Of the 5 patients lost to follow-up, it is not clear how many were lost during the first year. If many were lost in the first year, *and* interrupted treatment for less than 2 months, then the lost to follow-up rate would be overestimated in this study compared to other studies. However, this seems unlikely to be true.
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low

Author, Year	Mitnick 2008

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – unlikely given the type of intervention provided was flexible.
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes, except 5/651 (0.8%) who were transferred out (n=4) or still on treatment at end of study (n=1).
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – however, the definition for lost to follow-up was not done according to the same WHO standard as other studies: "Treatment default was a physician-defined end point assigned upon the failure of attempts to return to therapy those patients who had not been adhering to their treatment regimen." Therefore, there is a possibility that among 18/651(2.8%) patients who failed, there could be a proportion who in fact would have been classified as lost to follow-up if they had interrupted therapy for 2 or more consecutive months. However, this would be a small proportion and have little influence on the results.
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low

Author, Year	Mohr 2015

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not beyond what would be expected: "In the earlier years of the programme, DR-TB counselling was less structured and focused primarily on treatment initiation."

Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 96/853 (11.3%) were transferred out of the study clinics, therefore their outcomes were not recorded.
Were participants excluded due to missing data on other variables needed for the analysis?	Yes – 14 patients were included due to unknown HIV status. However, unlikely to affect results.
Overall risk of bias due to missingness	Moderate
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Moderate
Author, Year	Satti 2012
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – very clear description of intervention development and implementation

Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Most – 3/134 (2.2%) of patients were transferred out.
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – used routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low

Author, Year	Shin 2006

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – detailed description of intervention implementation and delivery
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low

OVERALL BIAS	Low

Author, Year	Shin 2006

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – detailed description of intervention implementation and delivery
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low

Author, Year	Thomas 2007

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	Yes – the study reported difficulties identifying DOT providers near patients (as planned in the intervention), therefore patients often travelled further than expected for treatment, or had to pay a fee to receive treatment from a private provider.
Overall risk due to deviations from interventions	Moderate

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Moderate
Author, Year	Vaghela 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – clear implementation and delivery description
Overall risk due to deviations from interventions	Low
Bias due to missing data	

Were outcome data available for all, or nearly all, participants?	Yes – 1/101 (1%) patients transferred out
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Yu 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – the study intervention had a flexible adherence support component.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes – 2/126 (1.6%) patients transferred out
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome	No

	relationship?	
	Bias in selection of the reported result *[different subgroups?]*	No
	Overall Risk of reporting bias	Low
OVERALL BIAS		Low

Cohort studies with 2 or more interventions	

Author, Year	Mohr 2017

Bias due to baseline confounding

Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No – one important potential confounder that was unbalanced at baseline between the SOC and SAT cohorts was history of previous TB treatment. A smaller proportion of patients in the SAT cohort had a TB treatment history (59.8% in SAT cohort vs 76.3% in SOC cohort) – this could confound the relationship between the intervention and the outcome of lost to follow-up, likely biasing the effect of intervention away from the null.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
Overall risk of confounding bias	Serious

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No – patients were selected to receive self-administered therapy (SAT) based on an assessment by the care team made after the intensive phase of treatment, however, the authors did an intention-to-treat analysis where cohort group assignment depended on time of treatment initiation relative to implementation of intervention, and not on whether the patient actually received SAT or not.
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias in classification of interventions

Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	Yes – Due to the staggered recruitment of patients based on the timing of implementation of the intervention (SAT – self-administered therapy), there were some patients in the control (SOC- standard of care) cohort who received the intervention (n=17). However, they tended to only be placed out for SAT late in treatment (median time to SAT-enrollment was 14.8-months (IQR 12.8±20.3)), thus the bias would be minimal and towards the null. Additionally, patients in the SOC-cohort might have received an informal version of SAT as facilities occasionally provided a supply of medications for self-administration to relieve pressure on the clinic, despite clinic DOT being the SOC. This would so slightly bias the estimated effect of SAT towards the null. These patients however, did not receive the specialized counseling and ongoing community support integral to the intervention. Similarly, the
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Yes – the estimated effect was likely biased towards the null due to contamination and slight deviations in the SOC group.
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	No – 42/244 (17.2%) and 24/160 (15.0%) in the SAT and SOC cohorts were transferred out/not evaluated for final treatment outcomes. The proportions were similar across two groups.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No

Were outcome assessors aware of the intervention received by study participants?	Yes
Were the methods of outcome assessment comparable across intervention groups?	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	No
Overall risk of outcome measurement bias	Low

Bias in selection of the reported result

Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Serious

Author, Year	Loveday 2015

Bias due to baseline confounding

Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No - there was no multivariate adjusted analysis for confounders. Some important confounders that were unbalanced at baseline between the two groups included: previous TB treatment (96% among patients at the centralized hospital vs. 60% among patients at the decentralized sites); and sputum smear-positivity (54% among patients at centralized hospital vs. 73% among patients at the decentralized sites). Unclear what direction this would bias the effect estimates.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
Overall risk of confounding bias	Serious

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?　　No

Do start of follow-up and start of intervention coincide for most participants?　　Yes

Overall risk of selection bias　　Low

Bias in classification of interventions

Were intervention groups clearly defined?　　Yes

Was the information used to define intervention groups recorded at the start of the intervention?　　Yes

Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?　　No

Overall risk due to intervention classification　　Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?　　No

If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?　　N/A

Overall risk due to deviations from interventions　　Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?　　Yes – 2.7% among those at the decentralized sites and 0.2% of those at the centralized site were transferred out or were not evaluated for final treatment outcomes.

Were participants excluded due to missing data on intervention status?　　No

Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No
Were outcome assessors aware of the intervention received by study participants?	Yes
Were the methods of outcome assessment comparable across intervention groups?	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	No
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall risk of reporting bias	Low
OVERALL BIAS	Serious
Author, Year	Cox 2014
Bias due to baseline confounding	
Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No - the paper had a multivariate adjusted model for estimating the effect of intervention on 'time to death', but not for lost to follow-up (our primary outcome of interest). The final treatment outcomes were available as stratified by HIV-status in the intervention (community-based model) group, but not for the control (hospital-based model) group. Limited data available on important potential confounders such as additional resistance to second-line drugs, and severity of disease.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A

| *Did the authors control for any post-intervention variables that could have been affected by the intervention?* | N/A |
| Overall risk of confounding bias | Serious |

Bias in selection of participants into the study

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall risk of selection bias	Low

Bias in classification of interventions

Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	Yes
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	N/A
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	No – 10.3% and 4.6% of the community-based and hospital-based cohorts were transferred out or not evaluated for final treatment outcomes.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No
Were outcome assessors aware of the intervention received by study participants?	No
Were the methods of outcome assessment comparable across intervention groups?	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	No
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall risk of reporting bias	Low
OVERALL BIAS	Serious

Author, Year	Huerga 2017
Bias due to baseline confounding	
Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No –there was a multivariate analysis for the "unfavourable outcomes", not for lost to follow-up. Did not report on many potential confounders, however, among those reported, proportions infected with HIV were not balanced at baseline across the three groups (21.4% in Mathare; 60.7% in Homa Bay; and 15.7% in Nairobi), and was associated with unfavourable outcomes in both univariate and multivariate analyses.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
Overall risk of confounding bias	Serious
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No

Do start of follow-up and start of intervention coincide for most participants?	N/A
Overall risk of selection bias	Low

Bias in classification of interventions

Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	No
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	N/A
Overall risk due to deviations from interventions	Low

Bias due to missing data

Were outcome data available for all, or nearly all, participants?	No – 25.0% in Homa Bay, 11.4% in Mathare and 12.7% in Nairobi sites were transferred out or not evaluated for final treatment outcomes. This is likely associated with both the intervention and lost to follow-up.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate

Bias in measurement of outcomes

Could the outcome measure have been influenced by knowledge of the intervention received?	No information
Were outcome assessors aware of the intervention received by study participants?	Yes
Were the methods of outcome assessment comparable across intervention groups?	N/A

Were any systematic errors in measurement of the outcome related to intervention received?	N/A
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall risk of reporting bias	Low
OVERALL BIAS	Serious

Table 10. Detailed quality assessment of cluster randomized trials

Author, year	Baral 2014
Random sequence generation (selection bias)	Low
Support for judgement	"Prior to the start of the formative study, we randomly allocated the DOTS-plus centres to 3 types of care – 2 to counselling, 3 to combined support, and 2 to usual care – by selecting randomly from the numbers 1 to 7"
Allocation concealment (selection bias)	Low
Support for judgement	Cluster randomized trials – all patients at each randomized site received the same treatment. There is low risk of selection bias (of sites) due to lack of allocation concealment.
Blinding of participants and personnel (performance bias)	High
Support for judgement	Site staff likely knew they were randomized to an intervention site or not due to changes in treatment delivery practices. This could have caused better performance in non-intervention duties as well, which could lead to bias.
Blinding of outcome assessment (detection bias)	Low
Support for judgement	Assessment of final treatment outcomes are objective and unlikely to vary based on intervention status.
Incomplete outcome data (attrition bias)	Low
Support for judgement	Final treatment outcomes were reported for all enrolled patients.
Selective outcome reporting? (reporting bias)	Low
Support for judgement	All treatment outcomes were reported.

Other bias	Not enough clusters for randomization to eliminate confounding bias. Likely residual confounding, especially given some baseline imbalances. There was multivariate analysis for loss to follow-up outcome to adjust for age or sex, separately, but not for other important confounders, such as severity of disease.

Author, Year	Taneja 2017
Random sequence generation (selection bias)	Low
Support for judgement	"Cluster trial was being planned in twenty hospitals in Delhi, therefore this pilot study was planned to be conducted with two hospitals. Among the hospitals two hospitals- Malviya Nagar Government Hospital and Nehru Nagar Chest Clinic were selected by simple random sampling using lottery method."
Allocation concealment (selection bias)	Low
Support for judgement	Use of simple random sampling to assign sites to cluster trial, unlikely to induce bias due to lack of concealment
Blinding of participants and personnel (performance bias)	High
Support for judgement	Site staff likely knew they were randomized to an intervention site or not due to changes in treatment delivery practices. This could have caused better performance in non-intervention duties as well, which could lead to bias.
Blinding of outcome assessment (detection bias)	Low
Support for judgement	Assessment of final treatment outcomes are objective and unlikely to vary based on intervention status.
Incomplete outcome data (attrition bias)	Low
Support for judgement	Final treatment outcomes were reported for all enrolled patients.
Selective outcome reporting? (reporting bias)	Low
Support for judgement	All treatment outcomes were reported.
Other bias	There were only two sites included in the study, which is a small sample size and susceptible to confounding. Also cluster design means site-specific characteristics could introduce confounding. There were baseline difference in important covariates such as religion, death of family member due to TB, family members with TB, that could have confounded results. However, there was no multivariate analyses done.