THE ROLE OF PSYCHO-EMOTIONAL AND SOCIO-ECONOMIC SUPPORT FOR TREATMENT OF TUBERCULOSIS PATIENTS

Alimova Gulruh Salimovna

Bukhara state medical institute, department of phthisiology and pulmononlogy

In 2013, 9 million people developed TB and 1.5 million died from this disease [1,2]. TB is the most commoncause of death in people with HIV [1]. The treatment duration for TB is long, at least 6 months for drug-susceptible TB and 18–24 months for multidrug-resistant tuberculosis (MDR-TB) that does not respond to the two most effective anti-TB drugs isoniazid and rifampicin. The long treatment, adverse drug reactions during treatment, stigma and financial burden of TB contribute to non-adherence to treatment and unsuccessful treatment outcomes [38]. In addition, ensuring patient adherence to treatment through facility-based directly observed therapy (DOT) competes with work related priorities of patients, adding to the financial burden coming from out-of-pocket and indirect costs related to treatment [7,9], even though anti-TB drugs are provided free of charge in most countries [1,10]. The quick improvement of TB symptoms early in treatment also contributes to patients' stopping treatment prematurely (i.e. loss to follow-up) as competing interests take priority [9,11]. Poor treatment adherence and loss to follow-up increase morbidity, mortality, and the risk of drug resistance development, and can lead to prolonged transmission of TB [12–17]. Adherence to tuberculosis treatment improves the chance of cure and reduces acquisition of drug resistance and ongoing transmission of TB. The use of DOT through a patient-centered approach, which often requires enablers, is recommended to encourage adherence to TB treatment [18,19]. In some settings and circumstances, incentives alone or in addition to enablers are used to motivate patients to adhere to and complete their full course of treatment [9,16,2022].

Social support through various educational, emotional, and/or material (in-kind or services) interventions are being provided by numerous TB programmes to remove or alleviate barriers to treatment adherence [9,20,23–25], including the financial burden associated with TBillness and its treatment. Despite the fact that different types of social support interventions (SSI) are implemented, countries still struggle to develop systems that are able to provide SSI in an efficient, effective and sustainable way [26]. WHO guidelines for the programmatic management of drug resistant TB and the new End TB Strategy recommend the use of SSI in TBpatients, though WHO has not yet systematically assessed the evidence to support such a recommendation [2,19,27]. Hence, a systematic review of relevant literature on the effects of SSI on TBtreatment adherence, treatment outcomes, and financial burden will be informative for national and global policy making. The primary aim of this systematic review was to identify SSI provided to TB and MDR-TB patients and assess the evidence of their effects on treatment adherence, treatment outcomes and financial burden related to TB illness. The secondary aim was to describe the funding sources for and ownership of local organizations in the identified interventions. Methods This review followed standard methods as defined by the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) guidelines [28,29]. The PRISMA checklist is enclosed in the supporting information (S1 PRISMA Checklist). Literature search In this review we searched for two main categories of SSI, namely PE support and SE support. PEsupport includes both emotional support through psychological interventions (e.g. counseling by health care workers) and companionship support through provision of help for patients to participate in a social network (e.g. peer counseling for patients and their support network) [19]. We did not consider interventions aimed only at providing improved information or education to TB patients, given the recent systematic review showing a lack of evidence related to TBtreatment [17]. In addition, reminder systems were not considered social support interventions [30]. SE support entails delivering services, material goods

and/or financial assistance [19,31,32]. Financial assistance was categorized according to Richter et al. [7]as"direct transfers of money, such as cash paid as part of a social security system or a program incentive, transport reimbursements, treatment allowances, and the like that are paid directly to affected individuals". Indirect assistance was defined as: "indirect transfers through, for example, food packages or vouchers, travel vouchers, and payment of health insurance for individuals, households or families". Some forms of indirect assistance may also be converted into cash. We included tax exemption under indirect assistance. Enterprise assistance was defined as"training programs or microcredit that aim to assist individuals or families to generate income" [7]. We searched for studies assessing the effects of socio-economic and/or psycho-emotional interventions on treatment adherence and/or treatment outcomes and/or financial burden. The study population consisted of patients initiated on anti-TB treatment, including treatment for MDR-TB. Outcomemeasures Treatment adherence, treatment outcomes and financial burden were considered as the primary outcome measures. Adherence was calculated as the percentage of prescribed doses actually taken. Treatment outcomes were defined according to WHO definitions, where cure and completed treatment are defined as successful treatment outcomes [1]. Unsuccessful treatment outcomes for active TB treatment included death, treatment failure and loss to follow-up (previously named default). Patients with transfer-out or missing treatment outcomes were excluded from the analysis. As timing of loss to follow-up per individual was not available for studies reporting on treatment outcomes but not treatment adherence, for these studies loss to follow-up was not included in calculation of treatment adherence.

Incentives and enablers. All the RCTs defined their support as incentives. Incentives are rewards for adherence while enablers assist patients to overcome barriers to treatment adherence. Most studies provided support to all TB patients. In studies where only poor patients were supported [64]; it may be that the support in fact was in the form of enablers. Risk of bias and quality of evidence Risk of bias was assessed for all included RCTs, including six Cluster Randomized Trials

[47,50–52,60,67]. Only five out of eleven RCTs described an adequate randomization approach [50–52,58,60]. For the majority of the studies it was not described whether investigators were blinded to the outcome, and assessment of reporting bias was not possible due to a lack of information. None of the Cluster Randomized Trials assessed baseline imbalances between clusters or took random effects into account in the analysis. Ten NRS were assessed on risk of bias, including eight cohort studies and two case-control studies. Four studies [20,56,63,66] were not included in the meta-analysis and risk of bias assessment; reasons for exclusion. Only three NRS adjusted for one or more confounders in the analysis [44,48,53]. Five additional studies were not included because of inadequacy of follow-up and/or assessment of outcome measures [44,48,53,62,68]. More information on the risk of bias assesment of the RCTs and NRS can be found in the supportive information S1–S3 Tables. Quality of evidence was assessed for the included RCTs per outcome measure. The quality of evidence for the RCTs was downgraded with one level for risk of bias, two levels on indirectness of studies and one level for limitations in consistency of the results. Hence,theoverallqualityofevidenceofthissystematic review is considered to be very low [40,69–74]. The quality of evidence per outcome measure is similar to the overall quality of evidence and retrievable in the summary of findings table (Table 4). No rating up for the overall quality of evidence was possible. Based on the funnel plot for the results of the ten RCTsincluded in the meta-analysis, it was not possible to determine whether publication bias was present (Fig 2)[28]

Eleven RCTs, eight cohort studies, and two case-control studies were included in the metaanalysis, including 17 743 patients (9655 patients participating in RCTs and 8088 patients in NRS). Most data originated from Brazil, China, Russia, Senegal and South Africa. No evidence was found concerning the effect of SSI on financial burden. Only one NRS measured the costeffectiveness ratio of the provided economic support [64]. Studies assessing the effect of SSI on treatment adherence were too heterogeneous to pool. Meta-analysis of different outcome measures are presented separately (Figs 3 and 4).

Treatment outcomes. In total, nine RCTs had treatment success as an outcome measure (Fig 3). The overall effect of these studies showed a significant positive effect (RR 1.17; CI 1.091.25), however significant heterogeneity was observed (I2 of 72.8%, P = <0.001). Stratified analyses were performed for the different types of interventions. Three studies provided PE support [50,52,55] including counseling, psychotherapy and the organization of self-help groups. A significant pooled effect was found for this intervention (RR 1.37; CI 1.08–1.73). The association between SE support and treatment success was examined by four studies [47,49,58,60] providing food supplementation and economic support. A significant pooled effect was found for this intervention (RR 1.08; CI 1.03–1.13). Combined support was provided by three studies [51,52,67]. Also, a significant pooled effect was found for these interventions on successful treatment outcomes (RR 1.17; CI 1.12–1.22). No significant heterogeneity was observed in two of three stratified analyses (SE: I2 of 14%, P = 0.32; combined: I2 of 0%, P = 0.42). Studies that provided PE support were substantially heterogenic and the p-value for the Chi2 test was significant (I2 of 78%, P = 0.01) (Fig 3). A sensitivity analysis was performed on the effect of PE support on treatment success, comparing high vs. low risk of bias studies. Omitting one high risk of bias study removed heterogeneity (I2 of 0%, P = 0.53) (data not shown), and did not change effect size (RR 1.20; CI 1.07–1.35) [55]. Sensitivity analysis on MDR-TB patients vs. nonMDR-TBpatients did not change the effect size and statistical significance (data not shown).

Nine studies had unsuccessful treatment outcomes as an outcome measure including seven also having treatment success as an outcome measure (Fig 4). An overall significant protective effect was found (RR 0.53; CI 0.41–0.70), however, substantial heterogeneity was observed (I2 of 80.2% and P =<0.001). Stratified analyses were performed on the different interventions provided. Four studies investigated the effect of PE support on unsuccessful treatment outcomes, including counseling, psychotherapy and the organization of self-help groups [46,50,52,55]. Two studies examined the effect of SE support, including food

supplementation and economic support [47,58] and four studies assessed the effect of combined support [51,52,61,67]. A significant reduction in unsuccessful treatment outcomes was found for all three stratified analyses: PE support (RR 0.46; CI 0.22–0.96), SE support (RR 0.78; CI 0.690.88) and a combination of PE and SE support (RR 0.42; CI 0.23–0.75). Heterogeneity was considered to be very low for the studies that provided SE support interventions (I2 of 0% and P=0.37). The studies that provided PE support and combined support were substantially heterogenic (PE: I2 of 85%, P = <0.001 and combined: I2 of 64% (P = 0.03) (Fig 4). A sensitivity analysis was performed in the PE stratum on the basis of higher risk of bias compared to the other studies [46,55]. Removal of one high-risk of bias study [46] decreased the I2 to 0% (P =0.54) and the effect size changed but remained statistically significant (RR 0.33; CI 0.22-0.50). Omitting both biased studies did not change heterogeneity or the effect size. Sensitivity analysis on risk of bias was not possible in the studies providing a combination of PE and SE support, due to the fact that 3 out of 4 studies were classified as biased studies. Sensitivity analyses on MDR-TBpatients vs. non-MDR TB patients did not change the effect size or heterogeneity significantly (data not shown).

Treatment adherence. Three RCTs assessed the effect of PE and/or SE on treatment adherence. A PE-intervention study conducted in Mexico showed a significant improvement in treatment adherence (RR 1.20; CI 1.03–1.39). A study from the USA did not show significantly higher levels of adherence in the intervention group compared to the group that received usual care (RR 1.11; CI 0.92–1.33). A third study from Timor-Leste showed no effect for patients that received SE support compared to patients that did not receive this support (RR 1.01; CI .0.85–1.21). Above-described interventions were not pooled as they were too heterogeneous. Financial burden. None of the RCTs examined the effect of PE or SE support on financial burden for TB patients. Non-randomized studies. Due to the fact that the studies' characteristics were heterogeneous on several levels and at higher risk of bias than the RCTs, we chose not to pool the effects for these studies (S1 and S3 Figs) [28,75]. Seven NRSs reported an effect of social

support on successful treatment outcomes. Effects of interventions on successful treatment outcomes (RR) ranged from 1.03 to 2.51 (CI 0.96–2.99). Five of seven NRSs reported significant effect sizes Arecent systematic review concluded that the economic burden for patients is considered to be high, loss of income is an important indirect cost factor for TB patients, and transport and nutritional supplementation were important direct cost components [8]. A study in Peru evaluated the expenses for MDR-TB patients that received free treatment and found that having MDR-TBwasassociated with high costs, which was associated with adverse outcomes (population attributable fraction 18–20%) [76]. In line with our review, these two studies suggest that economic support is of great importance for improving treatment outcomes. Some of the findings of this review however differ from those from other SSI-related reviews. A recent review [77] on RCTs assessing the effect of material incentives on TB treatment adherence and completion of TB treatment identified two trials, both included in our review as well [47,60], and neither demonstrated a clear benefit. However, in one trial the incentive was not well received by the patients and in the other trial fidelity to the intervention was low. A review of Sinclair et al. did not find any evidence that food supplementation had a beneficial impact on treatment outcomes [78]. This may be explained by their focus on micronutrient supplementation alone as reflected in their search strategy. In a systematic review about strategies to reduce loss to follow-up in drug-resistant patients, a comprehensive package of interventions (e.g. financial support and food supplementation) was associated with reduced loss to follow-up [79]. Our review included studies focusing on all TB patients, not only those with MDR-TB [79]. As mentioned in the methods section, we did not consider interventions aimed only at providing improved information or education to TB patients, given the recent systematic review showing a lack of its evidence related to TB treatment [17]. Some of the intervention packages included in our review included an information or education component, but it was not possible to delineate the effects of this specific component in our review. We also did not include interventions focusing

only on reminder systems, as these are not considered PE or SE support. However, reminder systems can be integrated into SSI programs to enhance its effects since pre-appointment reminder phone calls and letters or home visits did have a small but potentially relevant effect on treatment completion [30]. There were some limitations to our review. Only a limited number of studies were available on the effect of PE/SE support interventions on TB treatment outcomes and very limited evidence on treatment adherence and financial burden. Within the identified studies, wewerenotabletostratifyresultsbythetypeof organization and quality of health service delivery due to insufficient information, although it is known that organization and quality of health service delivery influence treatment adherence [9]. Some NRSs only provided support to subgroups of patients including poor patients [64], patients that already received support before referral to the intervention studied [66] and non-adherent patients [20]. This precludes conclusions on the effects of these interventions when provided to all patients. Such patient selection may have led to overestimations in the observed effect of the PE/SE interventions. On the other hand, selecting patients most in need seems prudent and is in practice applied in resource-limited settings. Although the number of studies included in the meta-analysis was small, the optimal size criterion was sufficient both for the overall meta-analysis and stratified analyses as examined by calculation of the sample size for the overall effect and subgroup analyses [72]. We could not examine for a dose response rate across all included studies, as most studies did not include a comprehensive description of interventions. However, one study did show a positive dose-response within their study regarding provision of indirect economic support: among patients in the intervention group whoreceived the voucher at least once, treatment success rates significantly improved [47]. Furthermore, the more frequent the vouchers were received by patients, the higher their probability of treatment success [47]. Plausible heterogeneity was observed and seven out of eleven RCTs had a high risk of bias on one or two domains. However, we did not exclude studies on the basis of heterogeneity only, as this may introduce bias [42]. Conclusions This

review provides evidence to endorse implementation of SSI in order to improve treatment outcomes. Firstly, PE and combined PE/SE support have a beneficial impact on treatment success. Secondly, SE support and a combination of PE/SE support are associated with reductions in unsuccessful treatment outcomes. No conclusions can be drawn considering the overall effect of PE and/or SE support on treatment adherence and financial burden due to a lack of evidence. Our findings need to be interpreted with caution, as the quality of the evidence included in the meta-analysis is "very low" based on the GRADE approach. In addition, most support included multifaceted types of interventions, so no conclusions can be drawn on the effect of individual interventions. Simultaneously, this might signify that multifaceted types of interventions are needed to improve treatment outcomes. High quality evidence, from welldesigned randomized studies in larger sized populations, would provide more certainty on the effects of different PE and SE interventions. Cluster-randomized studies would provide an opportunity to compare differential packages and delineate the importance of specific components. In addition, more systematic data collection on PE and SE as already used by TB programs to monitor implementation and evaluate its effects and qualitative data collection in both studies and program settings to assess which interventions are most appreciated and most feasible to implement on a wide scale, would be useful. Reports should include information on costs and sustainability to provide information on efficiency and scalability.

References:

1. WHO(2014) Global tuberculosis report 2014. Geneva: WorldHealth Organization.

2. WHO(reviewedMarch2015)FactsheetN°104.

3. Baral S, Karki D, Newell J (2007) Causesof stigma anddiscrimination associated with tuberculosis in Nepal: a qualitative study. BMC Public Health 7: 211. PMID: 17705841

4. Vijay S, Kumar P, ChauhanLS, VolleporeBH, KizhakkethilUP, Rao SG(2010)Riskfactors associated with default among

newsmearpositive TBpatients treated under DOTSin India. PLoSOne 5: e10043. doi: 10.1371/journal.pone.0010043 PMID: 20386611

5. EastwoodS, Hill P(2004) A gender-focusedqualitative study of barriers to accessing tuberculosis treatment in the Gambia, West Africa. Int J Tuberc Lung Dis 8: 70–75. PMID: 14974748

6. Torun T, GungorG, OzmenI, Bolukbasi Y, MadenE, BicakciB, etal.(2005)Sideeffectsassociated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 9: 1373–1377. PMID: 16468160

7. Richter LM, Lonnroth K, DesmondC,JacksonR, JaramilloE, Weil D(2014) Economic Support to Patients in HIV and TB Grantsin Rounds 7 and 10 from the Global Fund to Fight AIDS, Tuberculosis andMalaria. PLoS One 9:e86225.doi:10.1371/journal.pone.0086225 PMID: 24489702

8. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lonnroth K (2014) Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. Eur Respir J.

9. MunroSA, LewinSA, SmithHJ, Engel ME, FretheimA, VolminkJ(2007) Patient adherenceto tuberculosis treatment: a systematic review of qualitative research. PLoS Med 4: e238. PMID: 17676945

Ngamvitha yapong -YanaiJ, Luangjina S, Nedsuwan S, KantipongP, WongyaiJ, IshikawaN(2013) Engaging womenvolunteers of high socioeconomic status in supportingsocioeconomically disadvantaged tuberculosis patients in Chiang Rai, Thailand. Western Pac Surveill Response J 4: 34–38. doi: 10.5365/WPSAR.2012.3.4.013 PMID: 23908953

11. KaonaFA, Tuba M, Siziya S, Sikaona L (2004) An assessment of factors contributing to treatment adherence and knowledge of TB transmission amongpatientson TBtreatment.BMCPublicHealth 4: 68. PMID:15625004

12. WHO(2009)Guidelinesforsurveillance of drugresistance in tuberculosis– 4th ed. WHO/HTM/TB/ 2009.422. Geneva: WorldHealth Organisation.

13. ZignolM, HosseiniMS, WrightA, WeezenbeekCLv, NunnP, WattCJ, etal.(2006)GlobalIncidenceof Multidrug-Resistant Tuberculosis. Journal of Infectious Diseases 194: 479–485. PMID: 16845631

14. MMWR(2003)TreatmentofTuberculosis, AmericanThoracicSociety, CDC, andInfectiousDiseases Society of America. American Journal of Respiratory and Critical Care Medicine 167: 603–662. PMID: 12588714

15. Pablos-MendezA, KnirschCA, BarrRG, LernerBH, FriedenTR(1997)Nonadherenceintuberculosis treatment: predictors and consequences in New York City. Am J Med 102:164–170.PMID:9217566

16. FriedenTR, MunsiffSS(2005)TheDOTSstrategyforcontrollingtheglobal tuberculosis epidemic. Clin Chest Med 26:197–205, v.PMID:15837105

17. M'ImunyaJM, KredoT, VolminkJ(2012)Patienteducation andcounselling for promotingadherence to treatment for tuberculosis. Cochrane Database Syst Rev 5: Cd006591.doi: 10.1002/14651858. CD006591.pub2PMID:22592714

18. WHO(2015)Pursuehigh-qualityDOTSexpansionandenhancement. WorldHealthOrganization.

19. WHO(2014) Companion handbook tothe WHO guidelinesfortheprogrammaticmanagementofdrugresistant tuberculosis. In: Rich M, Jaramillo E, editors. Geneva, Switzerland: WHO Document Production Services.

20. BockNN, SalesRM, RogersT, DeVoeB(2001) Aspoonfulofsugar...:improvingadherencetotuberculosis treatment using financial incentives. Int J Tuberc Lung Dis 5: 96–98. PMID: 11263524

21. FriedenTR(2000)Directlyobservedtreatment, short-course (DOTS): ensuring cure of tuberculosis. Indian J Pediatr 67: S21–27. PMID: 11129903

22. VolminkJ, MatchabaP, GarnerP(2000) Directlyobservedtherapyandtreatmentadherence.Lancet 355: 1345–1350.PMID:10776760

23. JakubowiakWM, BogorodskayaEM, BorisovSE, DanilovaID, LomakinaOB, KourbatovaEV(2007) Social support and incentives

programme for patients with tuberculosis: experience from the Russian Federation. Int J Tuberc Lung Dis 11: 1210–1215. PMID: 17958983

24. BeloMT, SeligL, LuizRR, HansonC, LunaAL, TeixeiraEG , etal.(2006)Choosingincentivesto stimulate tuberculosis treatment compliance in a poor county in Rio de Janeiro state, Brazil. Med Sci Monit 12: Ph1–5. PMID:16641886

25. GarnerP, SmithH, MunroS, VolminkJ(2007) Promotingadherencetotuberculosis treatment.Bull World Health Organ 85:404–406.PMID:17639229

26. WiseJ(1998)WHOidentifies16countriesstrugglingto control tuberculosis. BMJ 316: 955.

27. WHO (Emergencyupdate, 2008) Guidelines for theprogrammatic managementofdrug-resistant tuberculosis Geneva: WorldHealth Organization.

28. HigginsJPT, GreenS (UpdatedMarch2011) CochraneHandbookforSystematicReviewsofInterventions, Version 5.1.0: The Cochrane Collaboration.

29. MoherD, LiberatiA, Tetzlaff J, Altman DG (2009)Preferred reporting items for systematic reviews and meta-analyses: the PRISMAstatement. Ann Intern Med 151:264–269, w264.PMID:19622511

30. LiuQ, AbbaK, AlejandriaMM, SinclairD, BalanagVM, LansangMA(2014)Remindersystemsto improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. Cochrane DatabaseSyst Rev 11:Cd006594.doi:10.1002/14651858.CD006594.pub3PMID:25403701