Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis (Nahid et al, CID 2016)

APPENDIX B: GRADE Evidence Profiles

Evidence profile 1
Date: 05/16/2014
PICO Question 1 (part 1): Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis?

Comparison: Incentives and enablers in addition to curative therapy versus curative therapy alone.

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	incentives and enablers	none	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 8 months)												
1 [a]	randomized trials	serious [1]	not serious	not serious	serious [2]		151/2107 (7.2%)	137/1984 (6.9%)	**RR 1.04** (0.83 to 1.30)	3 more per 1000 (from 12 fewer to 21 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success (follow up: 8 months)												
2 [a, b]	randomized trials	serious [1]	not serious	not serious	serious [3]	dose response gradient [4]	1709/2243 (76.2%)	1502/2113 (71.1%)	**RR 1.05** (0.96 to 1.14)	36 more per 1000 (from 28 fewer to 100 more)	⨁⨁◯◯ LOW	CRITICAL
Adherence - Intensive phase (follow up: 8 months)												
1 [b]	randomized trials	not serious	not serious	not serious	not serious	none	136	129	-	MD **4.7 lower** (8.58 lower to 0.82 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Adherence - Continuation phase (follow up: 8 months)												
1 [b]	randomized trials	not serious	not serious	not serious	not serious	none	136	129	-	MD **0.1 lower** (1.71 lower to 1.51 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Acquisition of resistance (follow up: 8 months)												
1 [a]	randomized trials	serious [1]	not serious	not serious	very serious [2]		1/2107 (0.0%)	3/1984 (0.2%)	**RR 0.31** (0.03 to 3.01)	1 fewer per 1000 (from 1 fewer to 3 more)	⨁◯◯◯ VERY LOW	CRITICAL

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	incentives and enablers	none	Relative (95% CI)	Absolute (95% CI)		
Treatment completion (follow up: 8 months)												
1 [a]	randomized trials	serious [1]	not serious	not serious	not serious		911/2107 (43.2%)	694/1984 (35.0%)	**RR 1.24** (1.14 to 1.34)	84 more per 1000 (from 49 more to 119 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events (follow up: 8 months; assessed with: presence of itch w/w/o rash)												
1 [b]	randomized trials	not serious	not serious	not serious	serious [5]	none	28/136 (20.6%)	12/129 (9.3%)	**RR 2.21** (1.18 to 4.16)	113 more per 1000 (from 17 more to 294 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

Notes:

1. Nurses were more likely to give food vouchers to patients who were unemployed and to women; children were less likely to get vouchers. In addition, 36.2% of those eligible did not receive vouchers and 32.3% received a voucher for only 1-3 months.
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. The effects at the ends of the confidence interval would lead to different clinical decisions.
4. There was a strong dose-response relationship between frequency of receipt of the food voucher and treatment success (p <0.001).
5. The sample sizes are smaller than the optimal information size.

Evidence Profile References:

a. Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials 2013; 14:154.
b. Martins N, Morris P, Kelly PM. Food incentives to improve completion of tuberculosis treatment: randomised controlled trial in Dili, Timor-Leste. BMJ 2009; 339:b4248.

Evidence profile 2
Date: 05/16/2014
PICO Question 1 (part 2): Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with TB?

Comparison: Reminders and tracers versus curative therapy alone.

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	reminder and tracers	none	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [a]	randomized trials	not serious	not serious	serious [1]	serious [2]	none	3/240 (1.3%)	8/240 (3.3%)	**RR 0.38** (0.10 to 1.40)	21 fewer per 1000 (from 13 more to 30 fewer)	⨁⨁◯◯ LOW	CRITICAL
Treatment success												
4 [a,b,c,d]	randomized trials	serious [3]	serious [4]	serious [1]	serious [5]	none	361/389 (92.8%)	303/389 (77.9%)	**RR 1.12** (1.01 to 1.26)	93 more per 1000 (from 8 more to 203 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment completion												
1 [c]	randomized trials	serious [6]	not serious	not serious	very serious [2]	none	0/30 (0.0%)	6/31 (19.4%)	**RR 0.08** (0.00 to 1.35)	178 fewer per 1000 (from 68 more to 194 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence (assessed with: % making 6/12 collection and % non-attendance.)												
2 [c,f]	randomized trials	serious [7]	not serious	not serious	not serious	none	361/547 (66.0%)	94/200 (47.0%)	**RR 1.41** (1.14 to 1.76)	193 more per 1000 (from 66 more to 357 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Default												
1 [a]	randomized trials	not serious	not serious	serious [8]	not serious	none	2/240 (0.8%)	24/240 (10.0%)	**RR 0.08** (0.02 to 0.35)	92 fewer per 1000 (from 65 fewer to 98 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Sputum/culture conversion at 2 months												

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	reminder and tracers	none	Relative (95% CI)	Absolute (95% CI)		
2 [a,b]	randomized trials	serious [9]	not serious	serious [10]	not serious	none	209/247 (84.6%)	166/248 (66.9%)	**RR 1.26** (1.14 to 1.40)	174 more per 1000 (from 94 more to 268 more)	⨁⨁◯◯ LOW	IMPORTANT

MD – mean difference, RR – relative risk

Notes:

1. The intervention also included patient education.
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. In one study, 47% of patients in the control group did not return medication self-administration calendars vs 11% in the intervention group. One study provides no information on random sequence generation, allocation concealment, of blinding of outcome assessment. One study does not perform blinding of outcome assessment.
4. Test of heterogeneity: p=0.02.
5. The effects at the ends of the confidence interval might lead to different clinical decisions.
6. The study provides no information on random sequence generation, allocation concealment, of blinding of outcome assessment.
7. One study provides no information on blinding or random sequence generation. The other study is quasi-randomized (rotating type of reminder delivered by day of the week) and no information on blinding or allocation concealment.
8. Study measures proportion of patients converted at the end of 1 month rather than time to smear conversion.
9. In one study, 47% of patients in the control group did not return medication self-administration calendars vs 11% in the intervention group.
10. Study measures default or treatment interruption for 2 or more consecutive months rather than adherence.

Evidence Profile References:

a. Mohan A, Nassir H, Niazi A. Does routine home visiting improve the return rate and outcome of DOTS patients who delay treatment? East. Mediterr. Health J. 2003; 9:702–8.
b. Iribarren S, Beck S, Pearce PF, et al. TextTB: A Mixed Method Pilot Study Evaluating Acceptance, Feasibility, and Exploring Initial Efficacy of a Text Messaging Intervention to Support TB Treatment Adherence. Tuberc. Res. Treat. 2013; 2013:349394.
c. Kunawararak P, Pongpanich S, Chantawong S, et al. Tuberculosis treatment with mobile-phone medication reminders in northern Thailand. Southeast Asian J. Trop. Med. Public Health 2011; 42:1444–51.
d. Paramasivan R, Parthasarathy RT, Rajasekaran S. Short course chemotherapy : a controlled study of indirect defaulter retrieval method. Indian Journal of Tuberculosis. 1993 Oct; 40(4): 185-90.
e. Krishnaswami K V, Somasundaram PR, Tripathy SP, Vaidyanathan B, Radhakrishna S, Fox W. A randomised study of two policies for managing default in out-patients collecting supplies of drugs for pulmonary tuberculosis in a large city in South India. Tubercle 1981; 62:103–12.
f. Tanke ED, Leirer VO. Automated telephone reminders in tuberculosis care. Med. Care 1994; 32:380–9.

Evidence profile 3
Date: 05/16/2014
PICO Question 1 (part 3): Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with TB?
Comparison: Patient education and counseling versus curative therapy alone.

Quality assessment							Events/№ of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	patient education and counseling	none	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [a]	randomized trials	not serious	not serious	not serious	serious [1]	none	16/504 (3.2%)	16/515 (3.1%)	**RR 1.02** (0.52 to 2.02)	1 more per 1000 (from 15 fewer to 32 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment success												
2 [a,b]	randomized trials	serious [2]	serious [3]	not serious	serious [4]	none	321/604 (53.1%)	262/615 (42.6%)	**RR 1.40** (0.90 to 2.17)	170 more per 1000 (from 43 fewer to 498 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence												
1 [c]	randomized trials	serious [2]	not serious	not serious	not serious	none	30/56 (53.6%)	17/58 (29.3%)	**RR 1.83** (1.14 to 2.92)	243 more per 1000 (from 41 more to 563 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion												
1 [b]	randomized trials	serious [5]	not serious	not serious	not serious	none	72/100 (72.0%)	42/100 (42.0%)	**RR 1.71** (1.32 to 2.22)	298 more per 1000 (from 134 more to 512 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

Notes:

1. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
2. One study used an inferior randomization technique with no concealment or blinding.
3. Test of heterogeneity significant: $p < 0.05$
4. The effects at the ends of the confidence interval would lead to different clinical decisions.
5. Study did not provide information on method of randomization, allocation concealment, or blinding.

Evidence Profile References:

a. Liefooghe R, Suetens C, Meulemans H, Moran MB, De Muynck A. A randomised trial of the impact of counselling on treatment adherence of tuberculosis patients in Sialkot, Pakistan. Int. J. Tuberc. Lung Dis. **1999**; 3:1073–80.
b. Janmeja a K, Das SK, Bhargava R, Chavan BS. Psychotherapy improves compliance with tuberculosis treatment. Respiration. **2005**; 72:375–80.
c. Clark PM, Karagoz T, Apikoglu-Rabus S, Izzettin FV. Effect of pharmacist-led patient education on adherence to tuberculosis treatment. Am. J. Health. Syst. Pharm. **2007**; 64:497–505.

Evidence profile 4
Date: 2014.05.16
PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?
Comparison: SAT versus DOT.

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAT	DOT	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 6-9 months)												
4 [a,b,c,d]	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	25/689 (3.6%)	42/914 (4.6%)	**RR 0.73** (0.45 to 1.19)	12 fewer per 1000 (from 9 more to 25 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success (follow up: range 6-9 months)												
5 [a,b,c,d,e]	randomized trials	serious [3]	not serious	not serious	not serious	none	566/775 (73.0%)	747/1001 (74.6%)	**RR 0.94** (0.89 to 0.98)	45 fewer per 1000 (from 15 fewer to 82 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion (follow up: range 6-9 months)												
4 [a,b,c,d]	randomized trials	serious [1]	not serious	not serious	not serious [2]	none	56/689 (8.1%)	76/914 (8.3%)	**RR 0.97** (0.69 to 1.36)	2 fewer per 1000 (from 26 fewer to 30 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Relapse (follow up: 24 months; assessed with: two or > cultures + in a 2-month period)												
1 [f]	randomized trials	serious [4]	not serious	not serious	very serious [2]	none	15/290 (5.2%)	23/259 (8.9%)	**RR 0.58** (0.31 to 1.09)	37 fewer per 1000 (from 8 more to 61 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Adherence (follow up: range 6 or more months)												
1 [e]	randomized trials	serious [5]	not serious	not serious	serious [2]	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94** (0.87 to 1.02)	58 fewer per 1000 (from 19 more to 126 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Time to smear conversion (follow up: mean 6 months) [7]												
1 [a]	randomized	serious [6]	not serious	serious [7]	not serious	none	345/422	366/414 (88.4%)	**RR 0.92** (0.87 to	71 fewer per 1000 (from	⨁⨁◯◯	IMPORTANT

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAT	DOT	Relative (95% CI)	Absolute (95% CI)		
	trials						(81.8%)		0.98)	18 fewer to 115 fewer)	LOW	

MD – mean difference, RR – relative risk

Notes:

1. All 4 studies identified are unblinded. One study has poor random sequence generation. 3 studies had loss to follow up >20%
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. All 5 studies identified are unblinded. One study has poor random sequence generation. 3 studies had loss to follow up >20%.
4. No information on random sequence generation, allocation concealment, or blinding.
5. Not a robust randomization method, unblinded
6. Study was unblinded and does not provide information on allocation concealment.
7. The authors measured proportion of patients who turned smear negative at the end of 3 months of treatment rather than measure the time it took each patient to convert individually.

Evidence Profile References:

a. Kamolratanakul P, Sawert H, Lertmaharit S, et al. Randomized controlled trial of directly observed treatment (DOT) for patients with pulmonary tuberculosis in Thailand. Trans. R. Soc. Trop. Med. Hyg. 93:552–7.
b. Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. Lancet **2001**; 357:664–9.
c. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. Lancet **1998**; 352:1340–3.
d. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. A randomised controlled trial of lay health workers as direct observers for treatment of tuberculosis. Int. J. Tuberc. Lung Dis. **2000**; 4:550–4.
e. MacIntyre CR, Goebel K, Brown G V, Skull S, Starr M, Fullinfaw RO. A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting. Int. J. Tuberc. Lung Dis. **2003**; 7:848–54.
f. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. Tuberculosis Research Centre. Int. J. Tuberc. Lung Dis. **1997**; 1:509–17.

Evidence profile 5
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: Daily versus 3-times weekly regimens.

From a systematic review that included only one randomized trial; therefore, the estimates are from within trial comparisons (i.e., direct head-to-head comparisons).

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
No of studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily throughout	Thrice weekly throughout	Relative (95% CI)	Absolute (95% CI)		
Failure												
1 [a]	randomized trials	serious[1]	not serious	not serious	very serious[2]	none	0/168 (0%)	0/174 (0%)	0	0	⨁◯◯◯ VERY LOW	CRITICAL
Relapse												
1 [a]	randomized trials	serious[1]	not serious	not serious	very serious[2,3]	none	1/161 (0.4%)	4/164 (2.4%)	**RR 4.0** (0.7 to 24)	20 more per 1000 (from 50 fewer to 200 more)	⨁◯◯◯ VERY LOW	CRITICAL
Acquired Drug Resistance among patients who failed or relapsed												
1 [a]	randomized trials	serious[1]	not serious	not serious	very serious[2]	none	0/168 (0%)	0/174 (0%)	0	0	⨁◯◯◯ VERY LOW	CRITICAL

Notes:

1. Method of allocation concealment and randomization was not given. Trial participants were not blinded to the therapy allocated, and blinding of assessors was not described.
2. Only one study with inadequate sample size.
3. The effects at the ends of the confidence interval would lead to different clinical decisions.

Evidence Profile References:

a. Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for treating tuberculosis in adults. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD000970. DOI: 10.1002/14651858.CD000970. Mwandumba, 2001

Evidence profile 6
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: Daily throughout versus 3-times weekly throughout.

From a systematic review of 57 randomized trials published between 1965 and 2009; the systematic review performed across trial comparisons by treating the arms of the trials as independent cohorts (i.e., NOT limited to direct head-to-head comparisons).

Quality assessment							Events/№ of patients Pooled estimate (95% CI)		Effect		Certainty in the Evidence	Importance
No of treatment arms	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily throughout	Thrice weekly throughout	Relative (95% CI)	Absolute (95% CI)		
Failure												
279 [a]	randomized trials	not serious [1]	serious[2]	not serious	not serious	none	179 / 11,510 0.4% (0.2 to 0.7)	38 / 2,865 0.5% (0 to 1.0)	**RR 0.7** (0.3 to 1.4)	1 more per 1000 (from 6 fewer to 9 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Relapse												
268 [a]	randomized trials	not serious [1]	serious[2]	not serious	not serious	none	566 / 9,829 4.8% (3.6 to 6.0)	150 / 2,455 5.7% (3.1 to 9.3)	**RR 1.2** (0.8 to 1.9)	23 more per 1000 (from 15 fewer to 40 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Acquired Drug Resistance among patients who failed or relapsed												
224 [a]	randomized trials	not serious [1]	serious[2]	not serious	not serious	none	67 / 8,541 0.3% (0.1 to 0.6)	35 / 2,283 0.9% (0 to 2.0)	**RR 2.4** (1.1 to 5.5)	4 more per 1000 (from 5 fewer to 19 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Notes:

1. The comparisons were done across trials rather than within trials; however, the panel decided that this was not serious enough to warrant downgrading the certainty in the evidence.
2. There was considerable heterogeneity of results between studies

Evidence Profile References:

a. Menzies D, Benedetti A, Paydar A, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009; 6(9): e1000146.

Evidence profile 7
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: Daily throughout versus 2-times weekly throughout.

From a systematic review of 57 randomized trials published between 1965 and 2009; the systematic review performed across trial comparisons (i.e., not limited to direct head-to-head comparisons).

Quality assessment							Events/№ of patients Pooled estimate (95% CI)		Effect		Certainty in the Evidence	Importance
No of treatment arms	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily throughout	Twice weekly throughout	Relative (95% CI)	Absolute (95% CI)		
Failure												
279 [a]	randomized trials	not serious [1]	serious [2]	not serious	serious [3]	none	179 / 11,510 0.4% (0.2 to 0.7)	1 / 223 0.3% (0 to 0.9)	**RR 0.6** (0.2 to 4.0)	1 fewer per 1000 (from 5 fewer to 4 more)	⨁⨁◯◯ LOW	CRITICAL
Relapse												
268 [a]	randomized trials	not serious [1]	serious [2]	not serious	serious [3]	none	566 / 9,829 4.8% (3.6 to, 6.0)	4 / 211 1.9% (0 to 6.4)	**RR 0.7** (0.4 to 3.5)	31 f ewer per 1000 (from 110 fewer to 56 more)	⨁⨁◯◯ LOW	CRITICAL
Acquired Drug Resistance among patients who failed or relapsed												
224 [a]	randomized trials	not serious [1]	serious [2]	not serious	serious [3]	none	67 / 8,541 0.3% (0.1 to 0.6)	1 / 223 0.4% (0 to 1.3)	**RR 0.9** (0.2 to, 5.5)	1 more per 1000 (from 19 fewer to 22 more)	⨁⨁◯◯ LOW	CRITICAL

Notes:

1. The comparisons were done across trials (treating different arms as independent cohorts) rather than within trials; however, the panel decided that this was not serious enough to warrant downgrading the certainty in the evidence.
2. There was considerable heterogeneity of results between studies
3. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes in the twice-weekly arms are smaller than the optimal information size.

Evidence Profile References:

a. Menzies D, Benedetti A, Paydar A, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009; 6(9): e1000146.

Evidence profile 8
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: Daily throughout versus 3-times weekly throughout.

From three systematic reviews of randomized trials plus controlled observational studies (i.e., retrospective or prospective cohort studies).

Quality assessment							Events/№ of patients Pooled estimate (95% CI)		Effect		Certainty in the Evidence	Importance
No of studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily throughout	Thrice weekly throughout	Relative (95% CI)	Absolute (95% CI)		
Failure (Updated review in HIV infected)												
33 [c]	randomized trials & observational studies	serious [1,2]	serious [2]	not serious[3]	serious [4]	none	99 / 2813 2.7% (1.6 to 3.7)	32 / 464 5.2% (1.5 to 8.8)	**RR 2.0** (0.8 to 5.0)	26 more per 1000 (from 10 fewer to 65 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse (2 reviews)												
32 HIV Uninfected [a]	randomized trials & observational studies	serious [1,2]	serious [2]	not serious	not serious	none	30 / 1554 1.9% (1.4 to 2.7)	60 / 1853 3.2% (2.5 to 4.1)	**RR 2.8** (1.4 to 5.7)	13 more per 1000 (from 4 more to 35 more)	⨁⨁◯◯ LOW	CRITICAL
33 HIV Infected [b,c]	randomized trials & observational studies	serious [1,2]	serious [2]	not serious[3]	serious [4]	none	142 / 1267 6.2% (0.6 to 11.7)	44 / 210 24.6% (0 to 57)	**RR 2.2** (0.7 to 7.3)	184 more per 1000 (from 45 fewer to 390 more)	⨁◯◯◯ VERY LOW	CRITICAL
Acquired drug resistance in Failures and Relapses (1 review)												
33 HIV Infected [c]	randomized trials & observational studies	serious [1,2]	serious [2]	not serious[3]	serious [5]	none	2 / 60 4.2% (0 to 12.9)	18 / 188 11.4% (0 to 66)	**RR 3.7** (0.7 to 19)	72 more per 1000 (from 24 fewer to 340 more)	⨁◯◯◯ VERY LOW	CRITICAL

Notes:

1. The status of ARV therapy in many studies differed from the status of ARV therapy in the population for whom the recommendation is intended; evidence that this difference is important is that thrice weekly was significantly worse.

2. In several of the systematic reviews, comparisons were done across trials (treating different arms as independent cohorts) rather than within trials; however, the panel decided that this was not serious enough to warrant downgrading the certainty in the evidence.
3. There was considerable heterogeneity of results between studies (I squared values ranged from 54% for acquired resistance, to 72% for failure, and 88% for relapse.)
4. The effects at the ends of the confidence interval would lead to different clinical decisions.
5. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes in the twice-weekly arms are smaller than the optimal information size.

Evidence Profile References:

a. Chang KC, Leung CC, Yew WW, Chan SL, Tam CM. Dosing schedules of 6-month regimens and relapse for pulmonary tuberculosis. Am J Respir Crit Care Med 2006; 174(10): 1153-8.
b. Ahmed Khan F, Minion J, Pai M, Benedetti A, Harries AD, Menzies D. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. Clin Infect Dis 2010; 50(9): 1288-99.
c. Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clin Infect Dis 2012; 55(8): 1154-63.

Evidence profile 9
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: Daily throughout versus intermittent throughout.

From two systematic reviews of randomized trials in children.

Quality assessment							Summary of findings					
							Events/ No of patients (Pooled estimate)		Effect		Certainty in the Evidence	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Daily throughout	Intermittent throughout	Relative (96% CI)	Absolute (95% CI)		
"Cure" - based on clinical and radiologic improvement												
4 [a]	randomized trials	very serious [1]	not serious	very serious [2]	not serious	none	15/234 (6.4%)	41/215 (19.1%)	**OR: 0.3** (0.1 to 0.5)	127 more per 1000 (from 60 more to 180 more)	⨁◯◯◯ VERY LOW	CRITICAL
4 [b]	randomized trials	very serious [1]	not serious	very serious [2]	serious [3]	none	41/243 (16.9%)	36/222 (16.2%)	**OR: 1.0** (0.9 to 1.1)	7 fewer per 1000 (from 50 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL

Notes:

1. None of the trials were free of risk of bias. All were open label. One trial (Te Water Naude, 2000) at high risk of selection bias.
2. Serious indirectness: No study used currently recommended regimens. Regimens differed in ways other than schedule alone; some components of cure were surrogates for patient-important outcomes; and, few (<5%) participants had microbiologically confirmed disease. Two trials (Kansoy, 1996, and Ramachandran, 1998) used longer duration treatment in daily arms than the intermittent arms, and two trials used non-standard regimens in intermittent arms (Kansoy, 1996, Ramachandran, 1998).
3. Serious imprecision: 4 small trials. The 95% CI of the effect estimate indicated only non-appreciable benefit with both interventions, but the sample size was smaller than the optimal information size for equivalence.

Evidence Profile References:

a. Menon PR, Lodha R, Sivanandan S, Kabra SK. Intermittent or daily short course chemotherapy for tuberculosis in children: meta-analysis of randomized controlled trials. Indian Pediatr 2010; 47(1): 67-73.
b. Bose A, Kalita S, Rose W, Tharyan P. Intermittent versus daily therapy for treating tuberculosis in children. Cochrane Database Syst Rev 2014; 1: CD007953.

Evidence profile 10
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: Daily throughout versus intermittent throughout.

From a systematic review of randomized trials plus controlled observational studies (i.e., retrospective or prospective cohort studies) in HIV infected patients (33 studies with a total of 47 different treatment arms).

Quality assessment							Summary of findings					
							Events/No. patients Pooled estimate (95% CI)		Effect:		Certainty in the Evidence	Importance
No. of treatment arms	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent throughout	Daily Initially	Relative (95% CI)	Absolute (95% CI)		
Failure												
47 [a]	randomized trials & observational studies	very serious[1,2]	serious [3]	not serious	not serious	Possible reporting bias.	32/464 5.2% (1.5 to 8.8)	99/2813 2.7% (1.6 to 3.7)	**RR 2.0** (0.8 to 5.0)	25 more per 1000 (from 22 fewer to 72 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse												
27 [a]	randomized trials & observational studies	very serious[1,2]	serious [3]	not serious	not serious	Possible reporting bias.	44/210 24.6% (0 to 56.7)	142/1267 6.2% (0.6 to 11.7)	**RR 2.2** (0.7 to 7.3)	184 more per 1000 (from 55 fewer to 560 more)	⨁◯◯◯ VERY LOW	CRITICAL

Death												
47 [a]	randomized trials & observational studies	very serious[1,2]	serious [3]	not serious	not serious	Possible reporting bias.	52/516 10.1% (4.3 to 15.8)	480/3293 11.5% (8.2 to 14.8)	**RR 0.7** (0.3 to 1.4)	14 fewer per 1000 (from 105 fewer to 76 more)	⊕◯◯◯ VERY LOW	CRITICAL

Notes:

1. Comparisons were done across trials (treating different arms as independent cohorts) rather than within trials; however, the panel decided that this was not serious enough to warrant downgrading the certainty in the evidence. Some studies were cohorts, with inherent limitations in selection of patients and confounding by indication.
2. Serious limitations included: some studies had incomplete bacteriologic confirmation of active cases and some failed to bacteriologically confirm relapse or failure.
3. There was considerable heterogeneity of results between studies. (I squared values ranged from 54% for acquired resistance, to 72% for failure, and 88% for relapse.)

Evidence Profile References:

a. Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clin Infect Dis 2012; 55(8): 1154-63.

Evidence profile 11
Date: 2014.05.16
PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Comparison: INH plus Rifapentine given once weekly versus INH plus rifampin given 2-3 times weekly in the final four months of a six month regimen.

Derived from four reports of three trials: Vernon 2009 with 61 HIV infected participants and TB Trials Consortium 2002 with 928 participants; Tam 2002 with 534 HIV uninfected participants; and Jindani 2014 with 349 participants (26% HIV infected).

Quality assessment							Summary of findings					
							Events/ No of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	INH & Rifapentine	INH & Rifampin	Risk Difference Or Odds ratio (95% CI)	Absolute (95% CI)		
Failure and Relapse (Rifapentine 1200 mg once weekly [with INH 900mg] in a heterogeneous population of HIV infected and uninfected patients)												
1 [a]	randomized trial	not serious	not serious	serious [1]	serious [2]	none	29 / 212 2.7%	27 / 188 3.7%	RD -1.0% (-6.6 to 5.7)	4 fewer per 1000 (from 66 fewer to 57 more)	⨁⨁◯◯ LOW	CRITICAL
Failure and Relapse (Rifapentine 600 mg once weekly [with INH 900mg] in HIV infected patients)												
1 [b]	randomized trial	not serious	not serious	not serious	serious [2]	none	5/30 17.8%	3/31 10%	RD 7.8% (-5% to 20%)	78 more per 1000 (from 50 fewer to 200 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Failure and Relapse (Rifapentine 600 mg once weekly (with INH 900mg) in HIV uninfected patients)												
1 [c]	randomized trial	not serious	not serious	not serious	serious [2]	none	46/502 9.2%	28/502 5.6%	RD 3.6% (0.4 to 6.8)	36 more per 1000 (from 4 more to 68 more)	⨁⨁⨁◯ MODERATE	CRITICAL

1 [d]	randomized trial	not serious	not serious	serious [3]	serious [4]	none	40/362 11.0%	7/172 4.2%	OR 2.7 (1.1 to 6.3)	68 more per 1000 (from 5 more to 194 more)	⨁⨁◯◯ LOW	CRITICAL

Notes:

1. The comparison of interest was INH and RPT versus standard therapy (INH and RIF in continuation); however, the actual comparison performed was moxifloxacin and RPT versus standard therapy (INH and RIF in continuation).
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. In this trial, half the patients received their weekly 1200mg RPT only two weeks out of three by design.
4. The sample size in the INH and RIF arm was smaller than the optimal information size.

Evidence Profile References:

a. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med 2014; 371(17): 1599-608.
b. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. Lancet 1999; 353(9167): 1843-7.
c. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-uninfected patients: a randomised clinical trial. Lancet 2002; 360(9332): 528-34.
d. Tam CM, Chan SL, Lam CW, et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. Am J Respir Crit Care Med 1998; 157(6 Pt 1): 1726-33.

Evidence profile 12
Date: 2014.05.16
PICO Question 5: Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients co-infected with HIV?
Comparison: 6 months of rifampin versus 8 months or longer of rifampin.

From a systematic review of randomized trials plus controlled observational studies (i.e., retrospective or prospective cohort studies).

Quality assessment							Summary of Findings					
							Events/No patients Pooled estimate 95% CI		Estimate		Certainty in the Evidence	Importance
No of Treatment arms	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	6 months	≥8 months	Relative (95% CI)	Absolute (95% CI)		
Failure												
47 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting bias.	55/1620 2.6% (1.2 to 4.0)	29/658 2.7% (0.5 to 5.0)	**RR 0.8** (0.4 to 1.5)	1 fewer per 1000 (from 38 fewer to 25 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse												
27 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting bias. Dose response [4]	119/830 9.1% (0.4 to 17.8)	29/425 4.7% (0 to 11.2)	**RR 2.4** (1.2 to 5.0)	44 more per 1000 (from 15 more to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL

Relapse – in patients NOT taking ART (anti-retroviral therapy)												
8 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting and selection bias.	158 / 872 18%	15 / 328 5%	**aOR 3.1** (1.4 to 6.7)	130 more per 1000 (from 50 more to 260 more)	⨁◯◯◯ VERY LOW	CRITICAL
Death												
47 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting bias.	209/1829 9.6% (5.9 to 12.5)	107/765 13.9% (7.3 to 20.4)	**RR 0.9** (0.5 to 1.6)	43 fewer per 1000 (from 145 fewer to 52 more)	⨁◯◯◯ VERY LOW	CRITICAL

Notes:

1. Some studies had incomplete confirmation of active cases and some failed to confirm relapse or failure.
2. In the systematic review, several comparisons were done across trials (treating different arms as independent cohorts) rather than within trials; however, the panel decided that this was not serious enough to warrant further downgrading the certainty in the evidence
3. There was considerable heterogeneity of results between studies.
4. Dose response gradient - with longer Rifampin duration there was a steady decline in rate of failure and relapse.

Evidence Profile References:

a. Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clin Infect Dis 2012; 55(8): 1154-63.

Evidence profile 13
Date: 05/16/2014
PICO Question 6: Does initiation of anti-retroviral therapy during TB treatment compared to at the end of TB treatment improve outcomes among TB patients co-infected with HIV?
Comparison: Early versus late initiation of ART.

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late ART	Relative (95% CI)	Absolute (95% CI)		
IRIS												
8 [a,b,c,d,e,f,g,h]	randomized trials	not serious	serious [1]	not serious	not serious	strong association	371/2416 (15.4%)	195/2173 (9.0%)	**RR 1.88** (1.31 to 2.69)	79 more per 1000 (from 28 more to 152 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality												
8 [a,b,c,d,e,f,g,h]	randomized trials	not serious	not serious	not serious	not serious	none	175/2349 (7.4%)	207/2041 (10.1%)	**RR 0.76** (0.57 to 1.01)	24 fewer per 1000 (from 1 more to 44 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
AIDS-defining illness or death												
4 [a,c,d,h]	randomized trials	not serious	not serious	not serious	not serious	strong association	121/1136 (10.7%)	141/891 (15.8%)	**RR 0.66** (0.47 to 0.91)	54 fewer per 1000 (from 14 fewer to 84 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Treatment success												
4 [a,b,d,h]	randomized trials	not serious	not serious	not serious	not serious	none	857/1039 (82.5%)	653/811 (80.5%)	**RR 1.02** (0.98 to 1.07)	16 more per 1000 (from 16 fewer to 56 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Grade 3-4 adverse event												
5 [a,c,d,e,f]	randomized trials	not serious	not serious	not serious	not serious	none	597/1961 (30.4%)	561/1747 (32.1%)	**RR 0.95** (0.87 to 1.04)	16 fewer per 1000 (from 13 more to 42 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Relapse												
4 [b,e,h,i]	randomized trials	not serious	not serious	not serious	very serious [2]	none	31/1268	30/1237	**RR 0.97** (0.52 to 1.83)	1 fewer per 1000 (from 12 fewer to 20 more)	⨁⨁◯◯ LOW	IMPORTANT

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late ART	Relative (95% CI)	Absolute (95% CI)		
							(2.4%)	(2.4%)				
Treatment completion												
3 [a,b,d]	randomized trials	not serious	not serious	not serious	serious [2]	none	232/963 (24.1%)	184/753 (24.4%)	**RR 1.06** (0.90 to 1.25)	15 more per 1000 (from 24 fewer to 61 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

Notes:

1. Test for heterogeneity: p=0.001, IRIS I^2= 72%.
2. The effects at the ends of the confidence interval would lead to different clinical decisions.

Evidence Profile References:

a. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010; 362(8): 697-706.
b. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011; 365(16): 1471-81.
c. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 2011; 365(16): 1482-91.
d. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011; 365(16): 1492-501.
e. Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-infected adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. Lancet Infect Dis 2014; 14(7): 563-71.
f. Manosuthi W, Mankatitham W, Lueangniyomkul A, et al. Time to initiate antiretroviral therapy between 4 weeks and 12 weeks of tuberculosis treatment in HIV-infected patients: results from the TIME study. J Acquir Immune Defic Syndr 2012; 60(4): 377-83.
g. Shao HJ, Crump JA, Ramadhani HO, et al. Early versus delayed fixed dose combination abacavir/lamivudine/zidovudine in patients with HIV and tuberculosis in Tanzania. AIDS Res Hum Retroviruses 2009; 25(12): 1277-85.
h. Sinha S, Shekhar RC, Singh G, et al. Early versus delayed initiation of antiretroviral therapy for Indian HIV-Infected individuals with tuberculosis on antituberculosis treatment. BMC Infect Dis 2012; 12: 168
i. Chamie G, Charlebois ED, Srikantiah P, et al. *M. tuberculosis* microbiologic and clinical treatment outcomes in a randomized trial of immediate versus CD4(+)-initiated antiretroviral therapy in HIV-infected adults with a high CD4(+) cell count. Clin Infect Dis. 2010 Aug 1;51(3):359-62.

Evidence profile 14
Date: 05/16/2014

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Comparison: systemic corticosteroid therapy versus placebo.

Quality assessment							№ of patients		Effect		Certainty in the Evidence	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroids**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
5 [a,b,c,d,e]	randomized trials	not serious	very serious [1]	not serious	serious [2]	none	142/897 (15.8%)	142/882 (16.1%)	**RR 0.54** (0.23 to 1.26)	**74 fewer per 1000** (from 42 more to 124 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Adherence												
2 [d,e]	randomized trials	serious [3]	very serious [1]	serious [3]	not serious	none	744/888 (83.8%)	785/907 (86.5%)	**RR 0.91** (0.75 to 1.12)	**78 fewer per 1000** (from 104 more to 216 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Constrictive pericarditis												
3 [c,d,e]	randomized trials	not serious	not serious	not serious	very serious [2]	none	36/768 (4.7%)	56/747 (7.5%)	**RR 0.72** (0.32 to 1.58)	**21 fewer per 1000** (from 43 more to 51 fewer)	⊕⊕◯◯ LOW	IMPORTANT

MD – mean difference, RR – relative risk

Events:

1. Inconsistent findings between studies. Death I^2= 70% Adherence I^2=89%.
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. Different definitions of adherence were used by different studies

Evidence Profile References:

a. Strang JI, Kakaza HH, Gibson DG, Girling DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet **1987**; 2(8573): 1418-22.
b. Strang JI, Kakaza HH, Gibson DG, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. Lancet **1988**; 2(8614): 759-64.
c. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart **2000**; 84(2): 183-8.
d. Mayosi BM, Ntsekhe M, Smieja M. Immunotherapy for tuberculous pericarditis. N Engl J Med **2014**; 371(26): 2534.
e. Reuter H, Burgess LJ, Louw VJ, Doubell AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovasc J S Afr. 2006 Sep-Oct;17(5):233-8.

Evidence profile 15
Date: 05/16/2014
PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?
Comparison: systemic corticosteroid therapy versus placebo.

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroid	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5 [a,b,c,d,e]	randomized trials	not serious	not serious	not serious	serious [1]	none	118/454 (26.0%)	147/423 (34.8%)	**RR 0.72** (0.52 to 1.00)	97 fewer per 1000 (from 0 fewer to 167 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Death or severe disability												
4 [b,c,d,e]	randomized trials	serious [2]	not serious	not serious	not serious	none	172/425 (40.5%)	192/393 (48.9%)	**RR 0.80** (0.67 to 0.97)	98 fewer per 1000 (from 15 fewer to 161 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Relapse												
2 [a,e]	randomized trials	serious [2]	not serious	not serious	serious [1]	none	41/303 (13.5%)	48/301 (15.9%)	**RR 0.84** (0.58 to 1.24)	26 fewer per 1000 (from 38 more to 67 fewer)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
2 [c,e]	randomized trials	serious [2]	not serious	not serious	not serious	none	211/335 (63.0%)	231/301 (76.7%)	**RR 0.85** (0.77 to 0.94)	115 fewer per 1000 (from 46 fewer to 177 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

Notes:

1. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
2. Not all studies blinded

Evidence Profile References:

a. Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. J Med Assoc Thai **1996**; 79(2): 83-90.
b. Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tuberculous meningitis. Tuber Lung Dis **1994**; 75(3): 203-7.
c. Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann Trop Med Parasitol **2009**; 103(7): 625-34.
d. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics **1997**; 99(2): 226-31.
e. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med **2004**; 351(17): 1741-51.

Evidence profile 16
Date: 05/16/2014
PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients (adults and children) with pauci-bacillary TB (i.e., smear negative, culture negative)?
Comparison: Treatment for less than six months versus treatment for six months.

Quality assessment							Events/№ of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment for less than 6 months	Treatment for 6 month	Relative (95% CI)	Absolute (95% CI)		
Relapse rate 2 vs. 12 mos.												
1 [a]	randomized trials	serious [1]	not serious	very serious [2]	not serious	none	45/245 (18.4%)	8/253 (3.2%)	**RR 6.01** (2.91 to 12.40)	158 more per 1000 (from 60 more to 360 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse rate 3 vs. 12 mos.												
1 [a]	randomized trials	serious [1]	not serious	very serious [2]	serious [3]	none	21/241 (8.7%)	8/253 (3.2%)	**RR 2.77** (1.24 to 6.19)	56 more per 1000 (from 8 more to 164 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse rate 4 vs. 6 mos., culture positive												
1 [b]	randomized trials	serious [1]	not serious	very serious [2]	serious [4]	none	12/352 (3.4%)	20/380 (5.3%)	**RR 0.62** (0.30 to 1.28)	20 fewer per 1000 (from 15 more to 37 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse rate 3 vs. 4 mos., culture negative												
1 [b]	randomized trials	serious [1]	not serious	very serious [2]	serious [3]	none	48/709 (6.8%)	24/650 (3.7%)	**RR 1.83** (1.13 to 2.96)	31 more per 1000 (from 5 more to 72 more)	⨁◯◯◯ VERY LOW	CRITICAL

MD – mean difference, RR – relative risk
Notes:

1. No information was provided on randomization methods
2. Regimens involved are no longer in use.
3. The sample sizes are smaller than the optimal information size.
4. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.

Evidence Profile References:

a. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60 months. Tuberculosis Research Centre, Madras, And National Tuberculosis Institute, Bangalore. Am. Rev. Respir. Dis. 1984; 130:23–8.
b. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am. Rev. Respir. Dis. 1989; 139:871–6.