II. MDR-TB regimen composition – systematic reviews of individual medicines in adults (PICO 1)

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: A later generation fluoroquinolone compared to no later generation fluoroquinolone for adults with rifampicin-resistant TB or MDR-TB[a]

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):1212.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	A LATER GENERATION FLUOROQUINOLONE	NO LATER GENERATION FLUOROQUINOLONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on later generation fluoroquinolone versus no fluoroquinolone, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	691/833 (83.0%)	301/678 (44.4%)	**OR 2.5** (1.0 to 5.9)[c]	**390 more per 1,000** (from 30 fewer to 640 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on later generation fluoroquinolone versus ofloxacin, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	691/833 (83.0%)	3386/4624 (73.2%)	**OR 1.9** (1.0 to 3.6)[c]	**100 more per 1,000** (from 15 fewer to 240 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse in patients on later generation fluoroquinolone versus no fluoroquinolone or ciprofloxacin or ofloxacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)[d]												
48	observational studies	serious[e]	not serious	not serious	not serious	none	4270/4978 (85.8%)[f]	3397/4046 (84.0%)[g]		**10 fewer per 1,000** (from 78 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	A LATER GENERATION FLUOROQUINOLONE	NO LATER GENERATION FLUOROQUINOLONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on later generation fluoroquinolone versus no fluoroquinolone or ciprofloxacin or ofloxacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
47	observational studies	serious[e]	not serious	not serious	not serious	none	4270/5474 (78.0%)[h]	3397/4958 (68.5%)[i]		**23 more per 1,000** (from 60 fewer to 108 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on later-generation fluoroquinolone												
13	observational studies	serious	not serious	not serious	not serious	none[j]	10/827 (1.2%)[k]		not estimable[j]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on ofloxacin or ciprofloxacin (assessed with: aggregated data meta-analysis 2015)												
9	observational studies	serious	not serious	not serious	not serious	none[j]	401/1408 (28.5%)[l]		not estimable[j]		⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; FE: fixed effects; OR: odds ratio

[a] Use of later generation fluoroquinolones (moxifloxacin, gatifloxacin or levofloxacin) is compared with use of ofloxacin or no fluoroquinolone alongside other drugs in the MDR-TB regimen; one outcome related to severe adverse events of ofloxacin also included in this table.

[b] In the individual patient data analysis (Ahuja SD, et al.), most patients received individualized treatment, with substantial risk of confounding by indication (as well as selection bias).

[c] Odds ratio adjusted for age, HIV status, sputum smear positivity, cavitation on chest radiograph, and prior treatment with first-line and second-line TB drugs.

[d] Adjustment for individual patient characteristics not possible; the adjusted values of the pooled proportions (with their 95% CL) shown in footnotes below.

[e] In 20 studies the patients were given standardized regimens, but in the remaining studies therapy was individualized, leading to risk of confounding by indication.

[f] Adjusted proportion: 91% (95% CL: 85%–95%).

[g] Adjusted proportion: 92% (95% CL: 87%–96%).

[h] Adjusted proportion: 80% (95% CL: 74%–85%).

[i] Adjusted proportion: 78% (95% CL: 74%–85%).

[j] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[k] Pooled proportion: FE 95% CL: 0.6%–2.4%.

[l] Pooled proportion: FE 95% CL: 1.9%–4.1%.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: Gatifloxacin compared to no gatifloxacin for the treatment of adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684–92. (2) Butov DA, Efremenko YV, Prihoda ND, Yurchenko LI, Sokolenko NI, Arjanova OV, et al. Adjunct immune therapy of first-diagnosed TB, relapsed TB, treatment-failed TB, multidrug-resistant TB and TB/HIV. Immunotherapy 2012;4(7):687–695. (3) Xu HB, Jiang RH, Xiao HP. Clofazimine in the treatment of multidrug-resistant tuberculosis. Clin Microbiol Infect. 2012;18(11):1104–1110. (4) Xu HB, Jiang RH, Li L, Xiao HP. Linezolid in the treatment of MDR-TB: a retrospective clinical study. Int J Tuberc Lung Dis. 2012;16(3):358–363. (5) Carroll MW, Lee M, Cai Y, Hallahan CW, Shaw PA, Min JH, et al. Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. Int J Tuberc Lung Dis. 2012;16(7):961–966. (6) Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS One 2013;8(7):e67030. (7) Jo KW, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2014:18(1):39–43. (8) Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2008;12(2):128–138.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	GATIFLOXACIN	NO GATIFLOXACIN	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death (assessed with: Van Deun 2010; Butov 2011; Xu 2012a, 2012b)[a]												
4	observational studies	very serious[b]	serious	not serious	serious	strong association	189/225 (84.0%)	174/268 (64.9%)		**191 more per 1,000** (116 more to 265 more)	⨁◯◯◯ VERY LOW	CRITICAL
Death versus all other outcomes (assessed with: Van Deun 2010, Butov 2011, Xu 2012a, 2012b)[a]												
4	observational studies	very serious[b]	serious	not serious	serious	none	6/225 (2.7%)	23/268 (8.6%)		**59 fewer per 1,000** (20 fewer to 99 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	GATIFLOXACIN	NO GATIFLOXACIN	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on gatifloxacin versus no gatifloxacin (assessed with: comparative observational studies: Caroll 2012; Jawahar 2013; Jo 2014; Rustomjee 2008; Van Deun 2010)[a]												
5	observational studies	very serious	serious	not serious	serious	none[c]	15/422 (3.6%)[d]	137/1711 (8.0%)[e]	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects

[a] In the no gatifloxacin group the other fluoroquinolone used was either ofloxacin, levofloxacin or moxifloxacin.

[b] Small observational studies using individualized regimens with substantial potential for bias; in the Van Deun, et al. study gatifloxacin was used as part of shorter MDR-TB regimens reserved for patients selected upon specific criteria.

[c] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[d] Pooled proportion: FE 95% CL: 2.0%–5.8%.

[e] Pooled proportion: FE 95% CL: 6.8%–9.4%.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: A second-line injectable compared to no second line injectable for adults with rifampicin-resistant TB or MDR-TB[a]

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	A SECOND-LINE INJECTABLE	NO SECOND LINE INJECTABLE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on kanamycin or amikacin, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2572/3467 (74.2%)	557/981 (56.8%)	**aOR 1.6** (1.2 to 2.0)[c]	**170 more per 1,000** (from 55 more to 280 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on capreomycin, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	733/1018 (72.0%)	557/981 (56.8%)	**aOR 1.3** (0.5 to 3.7)[c]	**150 more per 1,000** (from 75 fewer to 310 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse in patients on kanamycin or amikacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)[d]												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3336/3935 (84.8%)[g,h]	3378/3942 (85.7%)[g,i]	not estimable	**36 more per 1,000** (from 38 fewer to 110 more)	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	A SECOND-LINE INJECTABLE	NO SECOND LINE INJECTABLE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on kanamycin or amikacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3336/4741 (70.4%)[g,j]	3378/4282 (78.9%)[g,k]	not estimable	**21 more per 1,000** (from 90 fewer to 131 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse in patients on capreomycin versus no other second-line injectable drug, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3960/4658 (85.0%)[l]	2754/3219 (85.6%)[m]	not estimable	**5 fewer per 1,000** (from 73 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on capreomycin versus no other second-line injectable drug, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3960/5141 (77.0%)[n]	2754/3882 (70.9%)[o]	not estimable	**69 more per 1,000** (from 31 fewer to 168 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on amikacin, capremycin or kanamycin (assessed with: aggregated data meta-analysis 2015)												
19	observational studies	serious[f]	not serious	not serious	not serious	none[p]	184/2538 (7.2%)[q]	-	not estimable[p]	-	⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; FE: fixed effects

[a] In this analysis, the use of a specific injectable agent (amikacin, kanamycin or capreomycin) is compared with no use of that particular agent, although another second-line injectable agent may have been used as part of the MDR-TB regimen.

[b] Individual patient data taken from 32 observational studies in which most patients received individualized treatment. Risk of selection bias, and confounding by indication.

[c] aOR: Odds ratio adjusted for age, HIV, positivity on sputum-smear microscopy, chest radiograph cavitation, and prior treatment with first-line and second-line TB drugs.

[d] In the aggregated data meta-analysis patients with XDR-TB were excluded where possible.

[e] In total, 61 cohorts provided end-of-treatment outcome information: in 23 cohorts the patients were given standardized regimens and in 38 cohorts therapy was individualized, leading to risk of confounding by indication. Of the 61 cohorts, 18 cohorts did not specify which second-line injectable agent was used, and therefore only the remaining 43 cohorts were retained for this analysis.

[f] Potential confounding from preferential inclusion of capreomycin in the individualized regimens of patients with more advanced resistance patterns or disease.

[g] Given that amikacin or kanamycin were used in almost all studies, the comparison is made between studies in which 72%–100% of patients received the injectable agent (intervention group) versus a comparator group of studies in which 0%–71% of patients received one of these agents.

[h] Adjusted proportion: 94% (95% CL: 90%–97%).

[i] Adjusted proportion: 89% (95% CL: 83%–96%).

[j] Adjusted proportion: 82% (95% CL: 75%–88%).
[k] Adjusted proportion: 78% (95% CL: 70%–86%).
[l] Adjusted proportion: 92% (95% CL: 87%–97%).
[m] Adjusted proportion: 93% (95% CL: 86%–97%).
[n] Adjusted proportion: 77% (95% CL: 69%–84%).
[o] Adjusted proportion: 83% (95% CL: 76%–89%).
[p] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.
[q] Pooled proportion: FE 95% CL: 6.2%–8.4%.

Author(s): Menzies R, Bastos M, Lan Z (11 November 2015)

Question: Ethionamide/prothionamide compared to no ethionamide/prothionamide for adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	ETHIONAMIDE/ PROTHIONA-MIDE	NO ETHIONAMIDE/ PROTHIONA-MIDE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on ethionamide/prothionamide as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012))[a]												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	4101/5667 (72.4%)	878/1487 (59.0%)	**aOR 1.9** (1.5 to 2.3)[c]	**130 fewer per 1000** (from 65 more to 185 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on ethionamide/prothionamide as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
17	observational studies	serious	not serious	not serious	not serious	none[d]	173/2106 (8.2%)[e]	-	not estimable[d]		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limit; FE: fixed effects

[a] In this analysis, use of ethionamide is combined with prothionamide, and compared to results in patients who did not get either of these drugs, but received multiple other drugs.

[b] This is individual patient data taken from 32 observational studies in which most patients received individualized treatment. There is risk of selection bias and confounding by indication.

[c] aOR: Odds ratio adjusted for age, HIV, acid fast bacillus smear, chest radiograph cavitation, and prior treatment with first-line, and second-line TB drugs.

[d] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[e] Pooled proportion: FE 95% CL:7.0%–9.6%.

Author(s): Menzies R, Bastos M, Lan Z (11 November 2015)

Question: Cycloserine/terizidone compared to no cycloserine/terizidone for adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300. (2) Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis. 2013;17(10):1257–66. (3) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CYCLOSERINE/ TERIZIDONE	NO CYCLOSERINE/ TERIZIDONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Success versus failure/relapse/death for cycloserine and terizidone from Individual patient data meta-analysis (Ahuja SD, et al. PLOS Med 2012)[a]												
32	observational studies	serious	serious	not serious	not serious	none	3115/4240 (73.5%)	1864/2914 (64.0%)	**OR 1.5** (0.9 to 2.2)[a]	**95 more per 1,000** (from 73 more to 117 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success versus failure/relapse for cycloserine and terizidone (assessed with: aggregated data meta-analysis 2015)												
53	observational studies	serious	serious	not serious	serious	none	4474/5285 (84.7%)[2]	1969/2479 (79.4%)[3]	not estimable	**49 more per 1,000** (from 56 fewer to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success versus failure/relapse/death for cycloserine and terizidone (assessed with: aggregated data meta-analysis 2015)												
53	observational studies	serious	serious	not serious	serious	none	4474/5916 (75.6%)[4]	1969/2823 (69.7%)[5]	not estimable	**5 fewer per 1,000** (from 139 fewer to 129 more)	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CYCLOSERINE/ TERIZIDONE	NO CYCLOSERINE/ TERIZIDONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Drug discontinued due to major psychiatric toxicity from cycloserine used to treat MDR-TB (assessed with: Hwang, et al. Int J Tuberc Lung Dis. 2012 (systematic review))[b]												
26	observational studies	serious	serious	not serious	serious	none[c]	144/1923 (7.5%)	-	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL
Drug discontinued due to toxicity (all types) from cycloserine used to treat MDR-TB (assessed with: Hwang TJ, et al. Int J Tuberc Lung Dis. 2012 (systematic review))[b]												
27	observational studies	serious	serious	not serious	serious	none[c]	201/2164 (9.3%)	-	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on cycloserine as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
16	observational studies	serious	not serious	not serious	not serious	none[c]	96/2140 (4.5%)[d]	-	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL
Drug discontinued due to toxicity (all types) from terizidone used to treat MDR-TB (assessed with: Hwang TJ, et al. Int J Tuberc Lung Dis. 2012 (systematic review))[b]												
10	observational studies	serious	serious	not serious	serious	none[c]	111/707 (15.7%)	-	not estimable[c,e]		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects; OR: odds ratio

[a] Adjusted for age, extent of disease, HIV, and prior treatment with first-line or second-line TB drugs. Patients on cycloserine and terizidone were combined together for this analysis.

[b] No regional differences observed.

[c] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[d] Pooled proportion: FE 95% CL: 3.6%–5.5%.

[e] Terizidone and cycloserine were compared in three of the studies. Authors reported no differences and concluded that the effect of terizidone varied from not being different to being moderately better than cycloserine.

Author(s): Menzies R, Bastos M, Lan Z (11 November 2015)

Question: Linezolid compared to no linezolid for adult patients on treatment for MDR-TB/XDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Altet MN, Vidal R, Milá C, Rodrigo T, Casals M, Mir I, et al. Monitoring changes in anti-tuberculosis treatment: associated factors determined at the time of diagnosis. Int J Tuberc Lung Dis. 2013;17(11):1435–41. (2) Carroll MW, Lee M, Cai Y, Hallahan CW, Shaw PA, Min JH, et al. Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. Int J Tuberc Lung Dis. 2012;16(7):961–966. (3) De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S, et al. Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. Eur Respir J. 2013;41(6):1386–92. (4) Jiang R-H, Xu H-B, Li L. Comparative roles of moxifloxacin and levofloxacin in the treatment of pulmonary multidrug-resistant tuberculosis: a retrospective study. Int J Antimicrob Agents. 2013;42(1):36–41. (5) Koh W-J, Kwon OJ, Gwak H, Chung JW, Cho S-N, Kim WS, et al. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. J Antimicrob Chemother. 2009;64(2):388–91. (6) Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis. N Engl J Med. 2012;367(16):1508–18. (7) Mignone F, Codecasa LR, Scolfaro C, Raffaldi I, Lancella L, Ferrarese M, et al. The spread of drug-resistant tuberculosis in children: an Italian case series. Epidemiol Infect. 2014;142(10):2049–56. (8) Padayatchi N, Mac Kenzie WR, Hirsch-Moverman Y, Feng P-J, Villarino E, Saukkonen J, et al. Lessons from a randomised clinical trial for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2012;16(12):1582–7. (9) Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK, et al. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. Eur Respir J. 2012;39(4):956–962. (10) Schecter GF, Scott C, True L, Raftery A, Flood J, Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis. 2010;50(1):49–55. (11) Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015;45(1):161–70. (12) Udwadia ZF, Sen T, Moharil G. Assessment of linezolid efficacy and safety in MDR- and XDR-TB: an Indian perspective. Eur Respir J. 2010;35(4):936–938–940.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	LINEZOLID	NO LINEZOLID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in XDR-TB patients given linezolid (assessed with: RCT in China, 2009–2011 (Tang, et al, 2015))[a]												
1	randomized trials	serious	not serious	not serious	serious	strong association	23/29 (79.3%)[b]	11/29 (37.9%)[c]	not estimable	**414 more per 1,000** (from 184 more to 644 more)	⨁⨁⨁◯ MODERATE	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	LINEZOLID	NO LINEZOLID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus. failure/relapse/death/default in MDR-TB or XDR-TB patients given linezolid (assessed with: 1RCT + 6 observational studies combined)												
7	observational studies[d]	very serious	serious	not serious	serious	none	153/198 (77.3%)[e]	387/606 (63.9%)[f]	not estimable	**134 more per 1,000** (from 64 more to 204 more)	⨁◯◯◯ VERY LOW	CRITICAL
Death (versus all other outcomes) in MDR-TB and XDR-TB patients given linezolid (assessed with: 1RCT + 6 observational studies combined)												
7	observational studies[d]	very serious	serious	not serious	serious	none	21/212 (9.9%)	65/468 (13.9%)	not estimable	**40 fewer per 1,000** (91 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL
Grade 3–4 Serious adverse events and/or drugs stopped due to linezolid (assessed with: internal comparator groups)[g,h]												
4	observational studies[h,i]	very serious	serious	not serious	serious	none	11/49 (22.4%)	112/1305 (8.6%)	not estimable	**139 more per 1,000** (21 more to 257 more)	⨁◯◯◯ VERY LOW	CRITICAL
Grade 3–4 Serious adverse events and/or drugs stopped due to linezolid 600 mg/day (assessed with: largely uncontrolled observational studies)[j]												
8	observational studies[i,j]	very serious	serious	not serious	serious	none	28/190 (14.7%)[k]		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limit; RCT: randomized controlled trial

[a] Method of randomization not described, hence risk of allocation bias unknown. Study was not blinded, hence risk of ascertainment bias, and small number of subjects.

[b] 95% CL: 65%–94%.

[c] 95% CL: 20%–56%.

[d] All were small studies. The 1 RCT was very small and unblinded with unclear randomization. The 6 observational had individualized regimens.

[e] 95% CL: 73%–84%.

[f] 95% CL: 46%–90%.

[g] Not showing the effects in two studies for patients receiving 1200 mg per day (9/51; 18%).

[h] Altet 2013; Carroll 2012; Mignone 2014; Padayatchi 2012 (only Padayatchi reported the dose).

[i] The intervention group was given linezolid at a start dose of 1200 mg per day for 4–6 weeks and followed by a dose of 300–600 mg per day.

[j] Koh 2009; Schecter 2010; Udwadia 2010; Singla 2012; Lee 2012; De Lorenzo 2013; Jiang 2013; Padayatchi 2012 (only Padayatchi reported SAE in group not receiving linezolid; Singla (600 mg vs 1200 mg) and De Lorenzo (600 mg vs >600 mg) compared SAE at different doses).

[k] 95% CL: 10%–21%.

Author(s): Ronald L, Cerigo H, Fox G, Menzies R (11 November 2015)

Question: Clofazimine compared to no clofazimine for the treatment of adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care (as well as non-tuberculous mycobacteria (NTM) in some outcomes for SAE)

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CLOFAZIMINE	NO CLOFAZIMINE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in MDR-TB patients on clofazimine (assessed with: individual patient data meta-analysis (2010))[a]												
31	observational studies	very serious	serious	not serious	not serious	none	459/806 (56.9%)[b]	3292/4970 (66.2%)[c]	**adjusted OR 1.4** (0.4 to 4.0)	**10 more per 1,000** (from 220 fewer to 340 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/death in non-XDR MDR-TB patients with clofazimine in their regimen (assessed with: 1 RCT 2010–2011 (Tang S, et al. 2015))												
1	randomized trials	serious[d]	not serious[e]	not serious	serious[e]	strong association	39/49 (79.6%)[f]	28/47 (59.6%)[g]	not estimable	**200 more per 1,000** (from 60 fewer to 450 more[m]	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment success versus failure/relapse/death (assessed with: 1 RCT + 5 cohorts of MDR/XDR patients)[h]												
6	observational studies[i]	very serious	serious	not serious	serious	none	75/102 (73.5%)[j]	68/92 (73.9%)[k]	not estimable	**10 fewer per 1,000** (from 210 fewer to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events resulting in drug discontinuation in MDR-/XDR-TB patients on clofazimine (assessed with: comparative studies)[l]												
5	observational studies	very serious	serious	not serious	serious	none	2/81 (2.5%)	281/658 (42.7%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CLOFAZIMINE	NO CLOFAZIMINE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Serious adverse events resulting in drug discontinuation in NTM patients on clofazimine (assessed with: uncontrolled studies)[l]												
6	observational studies	very serious	serious	serious	serious	none	25/195 (12.8%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events resulting in drug discontinuation in NTM patients on clofazimine (assessed with: comparative studies only)[l]												
4	observational studies	very serious	serious	serious	serious	none	6/181 (3.3%)	15/167 (9.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; RE: random effects

[a] Outcomes were compared in persons who received clofazimine versus those who received no Group 5 drugs. Adjusted estimate from propensity score matching was done, patients with clofazimine matched to patients from centres where clofazimine was not used.

[b] RE value on pooled meta-analysis: 63% (95% CL: 49%–78%).

[c] RE value on pooled meta-analysis: 62% (95% CL: 45%–79%).

[d] Method of randomization not described, and no blinding, increasing risk of allocation bias and ascertainment bias.

[e] One study in five centres in one country (China) only.

[f] 95% CL: 68%–91%.

[g] 95% CL: 46%–74%.

[h] Benefit was seen in one RCT, but in 5 small observational studies patients receiving clofazimine had worse outcomes. These regimens were individualized so there is risk of bias (confounding by indication).

[i] one randomized control trial + 5 cohorts.

[j] Adjusted proportion 73%; 95% CL: 64%–82%.

[k] Adjusted proportion 89%; 95% CL: 73%–100%.

[l] Adverse events reported in patients taking clofazimine were attributed to the drug by authors who were unblinded and used non-standardized methods to define, ascertain and report adverse events. No valid comparisons are possible with patients not taking clofazimine, because adverse events in patients not receiving clofazimine could be due to other drugs received concomitantly.

[m] P=0.04; treatment failure also significantly lower than in control (11% versus 29%; P=0.03).

Author(s): Winters N, Butler-Laporte G, Menzies D (11 November 2015)

Question: Macrolides (clarithromycin, azithromycin) compared to no macrolides for treatment of adults with rifampicin-resistant TB or MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care (as well as non-tuberculous mycobacteria (NTM) in some outcomes for SAE)

Bibliography: Winters N, Butler-Laporte G, Menzies D. Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment. Eur Respir J. 2015;46(5):1461–70.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	MACROLIDES (CLARITHRO-MYCIN, AZITHROMYCIN)	NO MACROLIDES	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success in MDR-TB patients on clarithromycin (HIV uninfected)												
2	observational studies[a]	serious	not serious	not serious	serious	none	20/61 (32.8%)	59/191 (30.9%)	not estimable	**19 more per 1,000** (from 10 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on clarithromycin (HIV uninfected) (assessed with: randomized controlled trials)												
3	randomized trials	not serious	serious	serious[b]	serious	none[c]	31/174 (17.8%)	26/175 (14.9%)	not estimable	**10 more per 1,000** (from 60 fewer to 70 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on clarithromycin (HIV uninfected) (assessed with: uncontrolled cohorts)												
15	observational studies[d]	serious[e]	serious	serious[b]	not serious	none	41/615 (6.7%)	-	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on clarithromycin (HIV infected) (assessed with: randomized controlled trials)												
8	randomized trials	not serious	not serious	serious[b]	serious	none[c,f]	108/1088 (9.9%)	118/1111 (10.6%)	not estimable	**7 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁◯◯ LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT			
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	MACROLIDES (CLARITHRO-MYCIN, AZITHROMYCIN)	NO MACROLIDES	RELATIVE (95% CL)	ABSOLUTE (95% CL)	CERTAINTY OF EVIDENCE	IMPORTANCE
Serious adverse events in NTM patients on clarithromycin (HIV infected) (assessed with: uncontrolled cohorts)												
6	observational studies[d]	serious[e]	not serious	serious[b]	not serious	none	122/584 (20.9%)[g]	-	not estimable[e]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on azithromycin (HIV uninfected) (assessed with: uncontrolled cohorts)												
5	observational studies[d]	serious[e]	serious	serious[b]	not serious	none	7/197 (3.6%)[h]		not estimable[e]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on azithromycin (HIV infected) (assessed with: randomized controlled trials)												
7	randomized trials	not serious	serious	serious[b]	serious	none[c,f]	113/1215 (9.3%)	57/1196 (4.8%)	not estimable	**40 more per 1,000** (from 30 fewer to 100 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death in MDR-TB patients on macrolides (assessed with: individual patient data meta-analysis (Ahuja SD, et al. 2012; Fox G, et al. 2015))												
31	observational studies	very serious	serious	not serious	not serious	none[i]	254/396 (64.1%)[j]	3292/4970 (66.2%)[k]	**adjusted OR 0.7** (0.3 to 1.9)[l]	**20 more per 1,000** (from 120 fewer to 150 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] Controlled cohorts.

[b] Based on studies of patients on preventive or curative treatment for non-tuberculous mycobacterial disease.

[c] Patients with advanced HIV, and studies from pre-antiretrovirals era.

[d] Un-controlled cohorts.

[e] Unblinded studies; adverse events attributed to study drugs by authors with non-standardized methods.

[f] Serious adverse events expected to be more frequent in these patients (advanced HIV disease and no antiretroviral treatment).

[g] 95% CL: 12%–27%.

[h] 95% CL: 0%–8%.

[i] Adjusted estimates using propensity score matching.

[j] Adjusted estimate: 75% (95% CL: 69%–81%).

[k] Adjusted estimates 73% (95% CL: 66%–81%).

[l] Adjusted odds ratio estimated using propensity score matching. Reference population for this estimate is patients in centres where this drug was not used at all.

Author(s): Fox G, Menzies R, et al. (11 November 2015)

Question: Thioacetazone compared to no thioacetazone for treatment of adults with rifampicin-resistant TB and MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care.

Bibliography: (1) Fox G, et al. Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis (under review). (2) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	THIOACETAZONE	NO THIOACETAZONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on thioacetazone as part of MDR-TB treatment (assessed with: individual patient data meta-analysis)												
31[a]	observational studies	very serious	serious[b]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	491/612 (80.2%)[c]	3670/5647 (65.0%)[d]	**adjusted OR 2.1** (0.8 to 5.5)[e]	**22 more per 1,000** (from 31 less to 74 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; RE: random effects

[a] In 7 of these studies at least one person received thioacetazone (range: 1–671 per study).

[b] I-squared = 0% (95% CL: 0%–71%).

[c] RE adjusted % = 80% (95% CL: 77%–83%).

[d] RE adjusted % = 72% (95% CL: 63%–80%), among controls who did not receive thioacetazone in studies where thioacetazone was not given

[e] Adjusted using RE multivariable analysis with propensity score matching to adjust for potential confounding between patients taking thioacetazone and matched controls in studies where thioacetazone was not used

[f] RE analysis, only including 7 studies where thioacetazone was used.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: *p*-aminosalicylic acid compared to no *p*-aminosalicylic acid for treatment of adults with rifampicin-resistant TB or MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	*P*-AMINOSALICYLIC ACID	NO *P*-AMINOSALICYLIC ACID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on *p*-aminosalicylic acid (PAS), as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (2012))												
32	observational studies	serious[a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2162/2871 (75.3%)	2817/4283 (65.8%)	**aOR 1.0** (0.8 to 1.4)[b]	**105 more per 1,000** (from 110 fewer to 120 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse in patients on PAS as part of a MDR-TB regimen (assessed with: aggregate data meta-analysis (2015)												
55	observational studies	serious[c]	not serious	not serious	not serious	none[d]	4981/5744 (86.7%)[e]	2968/3595 (82.6%)[f]		**49 more per 1,000** (from 7 fewer to 107 more)[l] [l]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on PAS as part of a MDR-TB regimen (assessed with: aggregate data meta-analysis (2015)[g]												
55	observational studies	serious[c]	not serious	not serious	not serious	none[d]	4981/6276 (79.4%)[h]	2968/4521 (65.6%)[i]		**54 more per 1,000** (from 34 fewer to 144 more)[l]	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on PAS, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
16	observational studies	serious	not serious	not serious	not serious	none[j]	208/1706 (12.2%)[k]		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects

[a] Individual patient data taken from 32 observational studies in which most patients received individualized treatment. Risk of selection bias, and confounding by indication.

[b] aOR: Odds ratio adjusted for age, HIV, acid-fast bacillus smear, chest radiograph cavitation, and prior treatment with first line, and second line TB drugs.

[c] Very serious limitations – all studies were observational – leading to risk of selection and information bias. In 20 studies the patients were given standardized regimens, but in the remaining 40 studies therapy was individualized, leading to risk of confounding by indication.

[d] Unadjusted analysis.

[e] Pooled proportion: 93% (95% CL: 83%–96%).

[f] Pooled proportion: 90% (95% CL: 85%–95%).

[g] From aggregate data meta-analysis: Patients with XDR-TB excluded from analyses, where possible.

[h] Pooled proportion: 81% (95% CL: 75%–87%).

[i] Pooled proportion: 78% (95% CL: 71%–85%).

[j] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[k] Pooled proportion: FE 95% CL: 10.6%–13.9%.

[l] Risk difference from adjusted analysis.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: Pyrazinamide compared to no pyrazinamide for adults with rifampicin-resistant TB or MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care.

Bibliography: (1) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	PYRAZINAMIDE	NO PYRAZINAMIDE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on pyrazinamide as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
20	observational studies	serious	not serious	not serious	not serious	none	2454/3775 (65.0%)	55/89 (61.8%)	**aOR 1.3** (1.1 to 1.6)[a]	**32 more per 1000** (from 10 more to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3–4 events, or drugs stopped due to adverse events) in patients on pyrazinamide as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
19	observational studies	serious	not serious	not serious	not serious	none[b]	56/2023 (2.8%)[c]		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects

[a] aOR: odds ratio adjusted for age, HIV, acid-fast bacillus smear, chest radiograph cavitation, and prior treatment with first-line and second-line TB drugs.

[b] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[c] Pooled proportion: FE 95% CL: 2.1%–3.7%.