

Supplementary Materials for
"An Updated Systematic Review and Meta-Analysis for Treatment of Multidrug-Resistant Tuberculosis"

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PICO¹ Questions

In patients with rifampicin resistance (RR-TB) or MDR-TB, which individual drugs in the regimens are more or less likely to lead to the outcomes listed below?

Population	Intervention	Comparator	Outcomes
RR-TB only MDR-TB <u>without</u> resistance <u>or</u> severe intolerance to the second line drugs MDR-TB <u>with</u> resistance <u>or</u> severe intolerance to a. Fluoroquinolones b. 2 nd line injectables, both classes c. Pyrazinamide d. 2 or 3 Group 4 drugs ² e. Fluoroquinolones + 2 nd line injectables (i.e. XDR-TB +/- other resistance) Children (0-4, 5-14y), persons with HIV, pregnant women, persons with diabetes	A 2 nd line regimen which includes:		<ul style="list-style-type: none"> • Cured/completed by the end of treatment • Culture conversion by 6 months • Failure • Relapse • Survival (or death) • Adverse reactions from TB drugs (severity, type, organ class)
	- pyrazinamide	- no pyrazinamide	
	- injectable agents (Km/Am/Cm)	- no injectable agents (Km/Am/Cm)	
	- prothionamide/ethionamide	- no prothionamide/ethionamide	
	- cycloserine	- no cycloserine	
	- PAS	- no PAS	
	- later-generation fluoroquinolone	- no later-generation fluoroquinolone	
	- bedaquiline	- no bedaquiline	
	- delamanid	- no delamanid	

¹ PICO = Population, Intervention, Comparator, Outcome

² Group 4 drugs are: ethionamide, prothionamide, cycloserine, terizidone, PAS

Search Strategy

Medline search

MDR or XDR

1. exp multidrug resistant tuberculosis/ or exp extensively drug resistant tuberculosis/
2. (multidrug resistant tuberculosis or extensive* drug resistant tuberculosis or MDR-TB or XDR-TB).ti,ab,kw.
3. (tuberc* and (MDR or XDR or drug resistanc* or multidrug resistanc* or multi drug resistanc* or poly drug resistanc* or extensive* drug resistanc*)).ti,ab,kw.

Drugs

4. exp Fluoroquinolones/ or exp Quinolones/ or exp Levofloxacin/ or (fluoroquinolone* or quinolone* or levofloxacin or Levaquin or moxifloxacin or Avelox).ti,ab,kw.
5. exp Kanamycin/ or exp Amikacin/ or exp Capreomycin/ or exp Aminoglycosides/ or (Kanamycin or Amikacin or Capreomycin or (tuberc* and injectable*)).ti,ab,kw.
6. exp Pyrazinamide/ or exp Ethambutol/ or exp Cycloserine/ or exp Ethionamide/ or exp Prothionamide/ or (Pyrazinamide or Ethambutol or para-aminosalicylic acid or Cycloserine or Ethionamide or Prothionamide).ti,ab,kw.
7. high dose.ti,ab,kw. and ((INH or isoniazid).ti,ab,kw. or exp isoniazid/)

Efficacy

8. exp Treatment Outcome/ or exp Prognosis/ or exp Death/ or exp Mortality/ or exp Treatment Failure/ or exp Survival/ or exp Recurrence/ or exp Patient Dropouts/ or exp Patient Compliance/
9. (Treatment Outcome* or Prognosis or Death or Mortality or Treatment Failure or drug treatment failure or failure or Survival or Recurrence or relapse or Patient Dropout* or dropout or non-compliance or compliance or efficacy or effective* or cure or success* or default or adheren* or conversion* or microbiologic conversion or smear conversion or culture conversion or sputum conversion).ti,ab,kw.

Toxicity

10. exp Treatment Outcome/ or exp Prognosis/ or exp Death/ or exp Mortality/ or exp Treatment Failure/ or exp Survival/ or exp Recurrence/ or exp Toxicity Tests/ or exp Drug Tolerance/ or exp "Drug-Related Side Effects and Adverse Reactions"/
11. (Treatment outcome* or Prognosis or Death or Mortality or Treatment Failure or drug treatment failure or failure or Survival or Recurrence or relapse or Toxicity Test* or toxicity or Drug Tolerance or toler* or intolerance or Side Effect* or Adverse Drug Reaction* or adverse drug event* or adverse event* or adverse reaction* or safe* or drug safety).ti,ab,kw.

New drugs

12. (Bedaquiline or TMC-207 or delamanid or OPC-67683).ti,ab,kw.

Final steps

13. 1 or 2 or 3
14. 4 or 5 or 6 or 7
15. 8 or 9
16. 10 or 11
17. 13 and 14 and 15
18. 13 and 14 and 16
19. 12 and 13 and 15
20. 12 and 13 and 16

21. limit 17 to (humans and yr="2009 -Current")
22. limit 18 to (humans and yr="2009 -Current")
23. limit 19 to (humans and yr="2012 -Current")
24. limit 20 to (humans and yr="2012 -Current")
25. 21 or 22
26. 23 or 24
27. 25 or 26

(EmBase and the Cochrane Library were searched using the same strategy)

Abstraction Form

Study ID:

Reviewer:

Date of Review:

Inclusion criteria

Author, Year	
Lab-confirmed MDR-TB	Yes / No / Not reported
Number of participants with MDR-TB \geq 25	Yes / No
Definition of Outcomes	Meet WHO/Laserson's criteria or not
TB site stratified by site of diseases	i.e. pulmonary, extrapulmonary
Eligible	Yes / No
If not eligible, what is the reason?	

Demographic and clinical information

Author, Year	
Study years	
Study location	
Study design	
Male : Female	
Age	
HIV (n of tested)	
ARV treatment (n receiving/HIV+)	
Diabetes	
AFB Smear	
Cavitation	
Bilateral disease	
Any previous TB treatment	
Previous FLD treatment only	
Previous SLD treatment	

Drug resistance profile

Methods of MDR confirmation	
DST methods for drugs tested	

XDR in total MDR patients	
Pre-XDR SLI	
Pre-XDR FQN	
Median No. of drugs resistant to	
Z resistance	
E resistance	
S resistance	
KM resistance	
AM resistance	
CM resistance	
OFX resistance	
CFX resistance	
MFX resistance	
LFX resistance	
PAS resistance	
CS resistance	
ETO resistance	
PTO resistance	
Other	

Treatment regimens

Standardized or Individualized	
DOT?	
No. of drugs used	
Total treatment duration	
Intensive phase duration	
Z used	
E used	
S used	
KM/AM used	
CM used	
OFX/CFX used	
MFX used	

LFX used	
GFX used	
PAS used	
CS/TRD used	
ETO/PTO used	
High-dose INH used	
Any Group 5 drugs used	
Bedaquiline used	
Delamanid used	

Treatment outcomes

6-month culture conversion	
Cure	
Complete	
Failure	
Death	
Loss to follow-up	
Relapse	
Follow-up months	
Reported adverse events?	
Grade 3-5 AEs	
Drug stopped due to AEs	
Drug responsible for AEs	
Any additional information	