Delamanid & Bedaquiline and Drug-resistant tuberculosis

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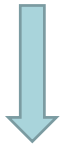
Overview

Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening condition needing long poly-chemotherapy regimens

1.3 million HIV-negative and **0.214 million HIV-positive** **TB deaths**

only **157,903 cases of rifampicin-resistant (RR)-TB** cases detected and reported in 2020



150,359 of them were enrolled on treatment as reported by the World Health Organization (WHO) (World Health Organization, 2021).

overview

MDR : *M. tuberculosis* strains Resistant to at least the two core anti-TB drugs, **isoniazid (INH)** and **rifampicin (RIF)**

PreXDR : *M. tuberculosis* strains that fulfill the definition of MDR/RR-TB and that are also resistant to any FLQ

XDR: MDR plus resistance to FLQs and either linezolid (LZD) or bedaquiline (BDQ), the drugs which proved to be effective and reasonably safe (Group A drug)

New safe and effective drugs

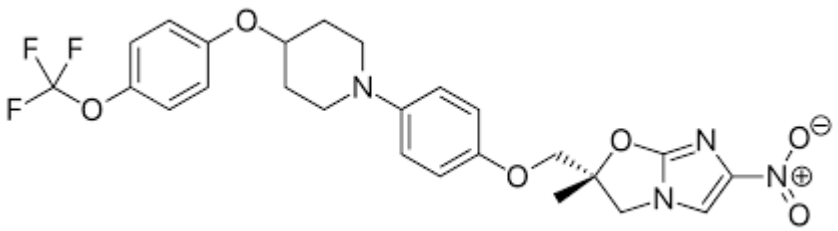
Delamanid & Bedaquiline

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

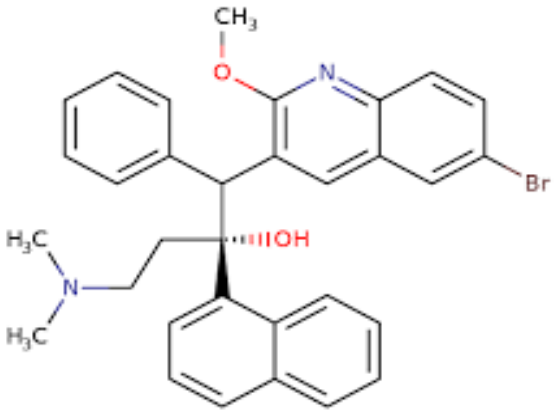
Delamanid

- **DLM** is a promising nitro-dihydro-imidazooxazole derivative



- Inhibits the synthesis of methoxy- and keto-mycolic acid through the F420 coenzyme mycobacteria system, while generating nitrous oxide

- Approved by the European Medicines Agency (EMA) and recommended by WHO in **2014**



Bedaquiline

- ✓ BDQ is a novel oral diarylquinoline drug that inhibits the ATP synthase of *M. tuberculosis*
- ✓ Approved by the US Food and Drug Administration (FDA) and the EMA in **2012** and recommended by WHO in **2013**

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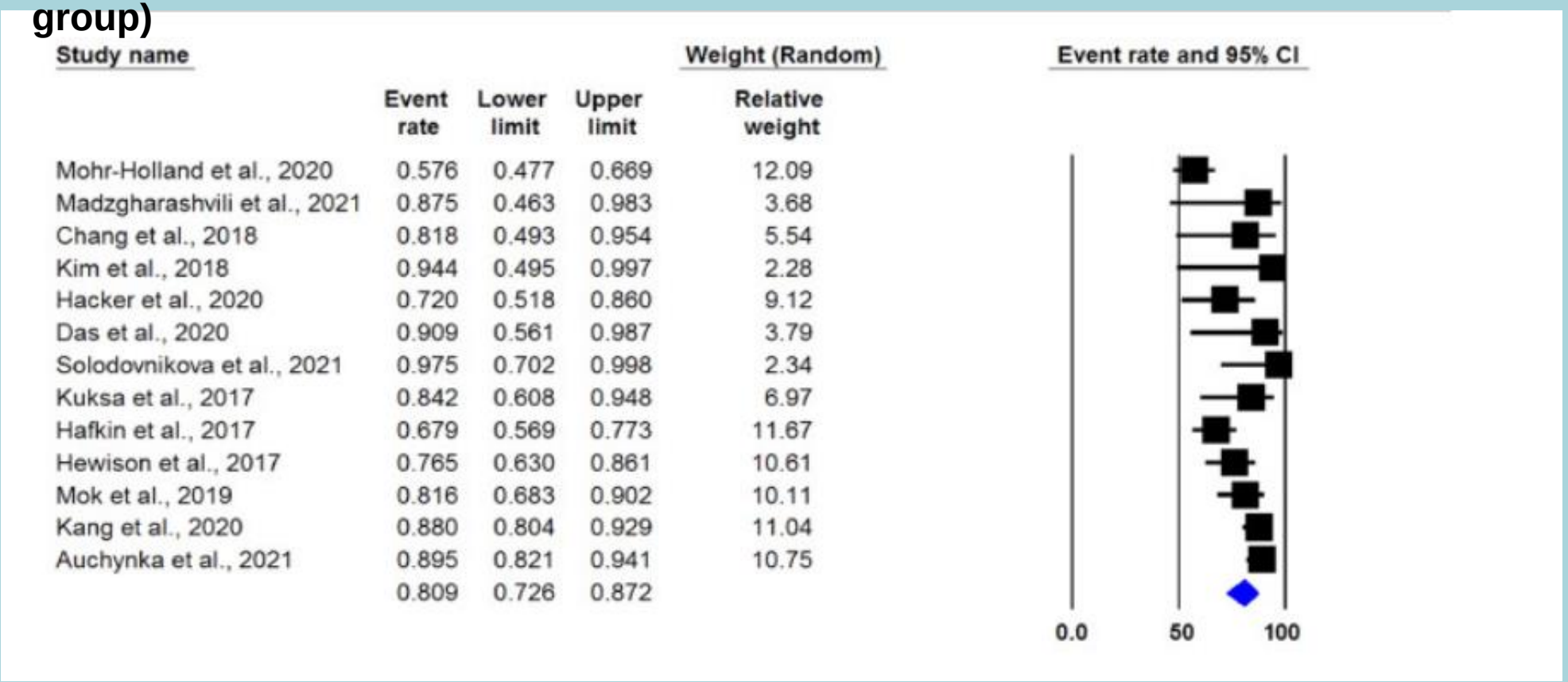
Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis

Mohammad Javad Nasiri [1], Moein Zangiabadian [1], Erfan Arabpour [1], Sirus Amini [1], Farima Khalili [1], Rosella Centis [2], Lia D'Ambrosio [3], Justin T. Denholm [4 5], H. Simon Schaaf [6], Martin van den Boom [7], Xhevat Kurhasani [8], Margareth Pretti Dalcolmo [9], Seif Al-Abri [10], Jeremiah Chakaya [11 12], Jan-Willem Alffenaar [13 14 15], Onno Akkerman [16 17], Denise Rossato Silva [18], Marcela Muñoz-Torrico [19], Barbara Seaworth [20], Emanuele Pontali [21] ... Giovanni Sotgiu [22]

•Outcomes in observational studies

Treatment success rate in observational studies. (DLM-containing regimens group)



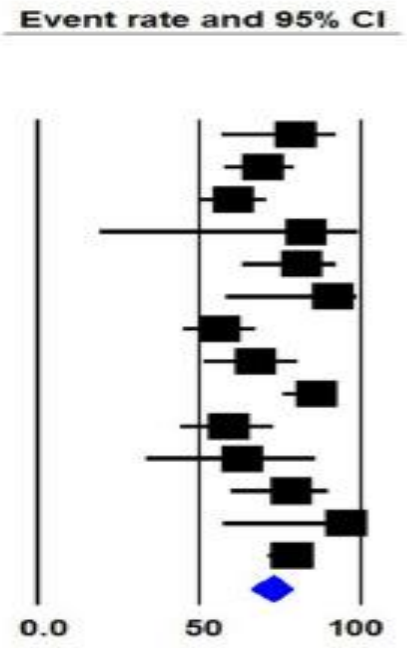
Study name	Event rate	Lower limit	Upper limit	Weight (Random) Relative weight
Mohr-Holland et al., 2020	0.576	0.477	0.669	12.09
Madzgharashvili et al., 2021	0.875	0.463	0.983	3.68
Chang et al., 2018	0.818	0.493	0.954	5.54
Kim et al., 2018	0.944	0.495	0.997	2.28
Hacker et al., 2020	0.720	0.518	0.860	9.12
Das et al., 2020	0.909	0.561	0.987	3.79
Solodovnikova et al., 2021	0.975	0.702	0.998	2.34
Kuksa et al., 2017	0.842	0.608	0.948	6.97
Hafkin et al., 2017	0.679	0.569	0.773	11.67
Hewison et al., 2017	0.765	0.630	0.861	10.61
Mok et al., 2019	0.816	0.683	0.902	10.11
Kang et al., 2020	0.880	0.804	0.929	11.04
Auchynka et al., 2021	0.895	0.821	0.941	10.75
	0.809	0.726	0.872	

The overall pooled treatment success rate in DLM-containing regimens group was found to be 80.9% (95% CI 72.6-87.2, I^2: 73%)

•Outcomes in observational studies

Treatment success rate in observational studies. (DLM and BDQ-containing regimens group)

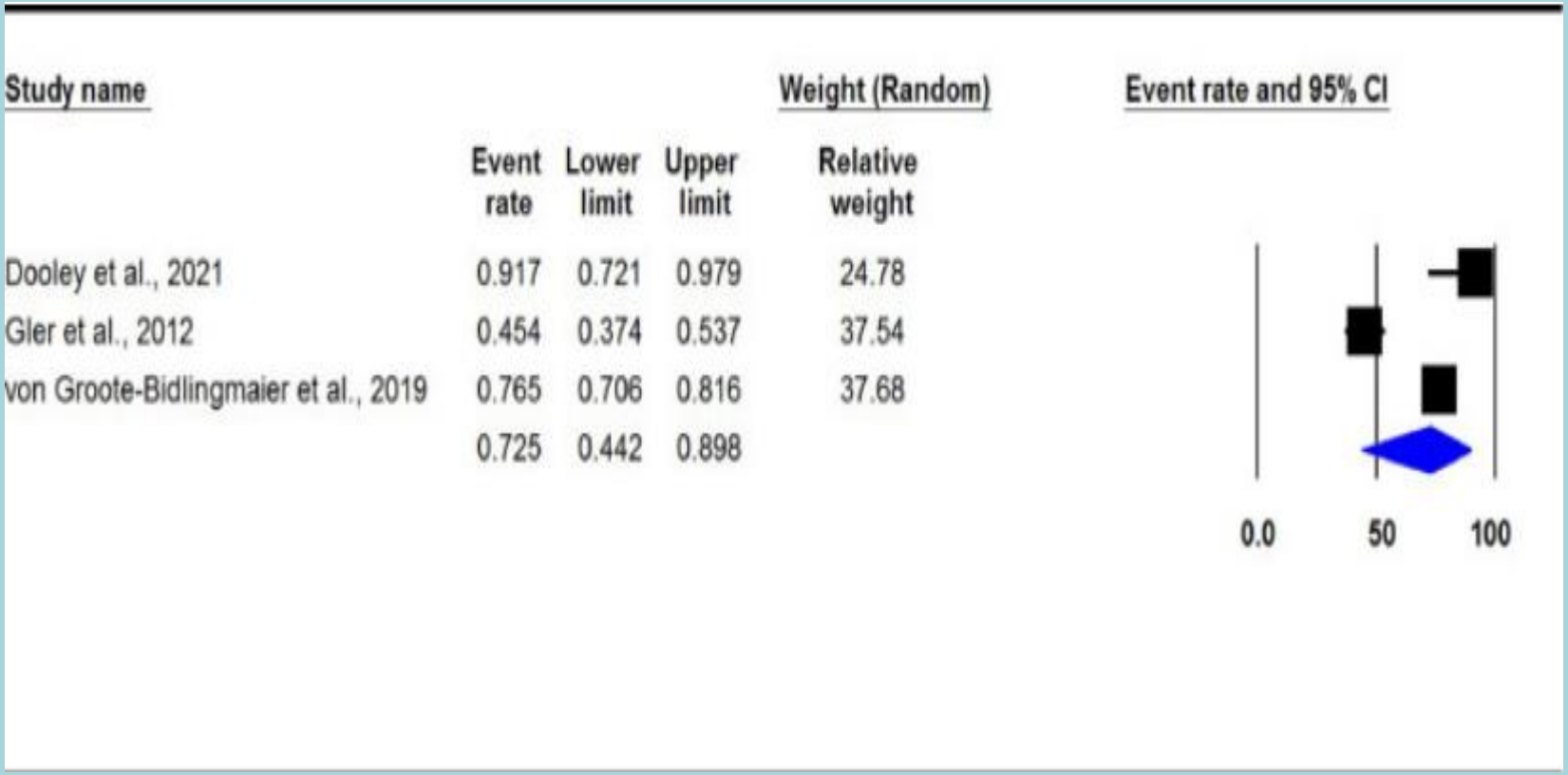
Study name	Event rate	Lower limit	Upper limit	Weight (Random) Relative weight
Auchynka et al., 2021	0.800	0.572	0.923	5.53
Das et al., 2021	0.700	0.583	0.796	10.57
Hafkin et al., 2019	0.607	0.499	0.705	11.34
Madzgharashvili et al., 2021	0.833	0.194	0.990	1.09
Kwon et al., 2021	0.821	0.636	0.924	6.39
Das et al., 2020	0.917	0.587	0.988	2.19
Lee et al., 2020	0.568	0.453	0.675	11.11
Olayanju et al., 2020	0.675	0.517	0.801	9.02
Kang et al., 2020	0.866	0.762	0.929	8.63
Sarin et al., 2019	0.595	0.443	0.731	9.48
Kim et al., 2018	0.636	0.339	0.857	4.78
Ferlazzo et al., 2018	0.786	0.598	0.900	6.87
Pirmahmadzoda et al., 2021	0.958	0.575	0.997	1.24
Ghosh et al., 2021	0.789	0.716	0.848	11.76
	0.728	0.659	0.789	



The overall pooled treatment success rate in DLM- and BDQ-containing regimens group was found to be 72.8% (95% CI 65.9-78.9, I^2: 62%)

•Outcomes in experimental studies

Treatment success rate in experimental studies. (DLM-containing regimens group)



The pooled treatment success rate in in DLM-containing regimens group was 72.5% (95% CI 44.2-89.8, I^2: 95%)

Time to sputum culture conversion

- ✓ The median time to **sputum culture conversion** ranged from **1.1** to **1.7** months in the DLM-containing regimens group

- ✓ The **pooled death rate** and **treatment failure** in DLM-containing regimens group was found to be **7.8%** (95% CI 5.5-11.0, I^2: 13.0%) and **9.2%** (95% CI 7.2-11.6, I^2: 0.0%), respectively.

Adverse events

Adverse effects in included studies (DLM-containing regimens group)

Author	Number of patients	QTcF prolongation	Hepatic disorder/ Elevated liver enzyme	Renal failure/ Increased creatinine	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (Anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (Diarrhea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatologic symptoms
Auchynka et al., 2021	105	-	-	-	-	-	-	-	-	-	-	-	-
Chang et al., 2018	11	0	-	-	-	-	-	-	-	-	-	-	-
Dooley et al., 2021	24	-	-	-	-	-	-	-	-	-	-	-	-
Gler et al., 2012	141	-	-	-	-	-	-	-	-	-	-	-	-
Häcker et al., 2020	25	-	-	-	-	-	-	-	-	-	-	-	-
Hafkin et al., 2017	78	-	-	-	-	-	-	-	-	-	-	-	-
Hewison et al., 2017	51	-	-	-	-	-	-	-	-	-	-	-	-
Kuksa et al., 2017	19	0	0	0	0	0	0	0	0	0	0	0	0
Madzgharashvili et al., 2021	8	0	-	-	-	-	-	-	-	-	-	-	-
Mohr-Holland et al., 2020	99	-	-	-	-	-	-	-	-	-	-	-	-
Mok et al., 2019	49	-	-	-	-	-	-	-	-	-	-	-	-
von Groote-Bidlingmaier et al., 2019	226	-	-	-	-	-	-	-	-	-	-	-	-
Solodovnikova et al., 2021	19	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al., 2018	8	1	-	-	-	-	-	-	-	-	-	-	1
Kang et al., 2020	108	2	-	-	-	-	-	2	-	-	-	-	-
Das et al., 2020	11	1	-	-	-	-	-	-	-	-	-	-	-

QTcF: corrected QT with the Fredericia formula; DLM: delamanid

✓ **In the DLM-containing regimens group :**

- only 4/165 (2.4%) patients had QTcF prolongation
- 2/127 (1.5%) patients with gastrointestinal symptoms
- 1/27 (3.7%) patient with dermatologic symptoms

Adverse events

Adverse effects in included studies (DLM and BDQ-containing regimens group)

Author	Number of patients	QTcF prolongation	Hepatic disorder/ Elevated liver enzyme	Renal failure/ Increased creatinine	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (Anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (Diarrhoea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatologic symptoms
Auchynka et al., 2021	20	-	-	-	-	-	-	-	-	-	-	-	-
Das et al., 2021	70	5	1	-	-	-	-	3	-	-	-	-	-
Hafkin et al., 2019	84	-	-	-	-	-	-	-	-	-	-	-	-
Madzgharashvili et al., 2021	2	0	-	-	-	-	-	-	-	-	-	-	-
Dooley et al., 2021	20	-	-	-	-	-	-	-	-	-	-	-	-
Kwon et al., 2021	28	17	-	-	-	-	-	1	-	-	-	-	-
Das et al., 2020	12	1	-	-	-	-	-	-	-	-	-	-	-
Lee et al., 2020	74	23	-	1	-	-	-	4	-	-	-	-	-
Olayanju et al., 2020	40	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al., 2018	11	2	-	-	-	-	-	-	-	-	-	-	-
Ferlazzo et al., 2018	28	4	-	1	-	-	-	1	1	-	-	2	-
Kang et al., 2020	67	-	-	-	-	-	-	3	-	-	-	-	-
Sarin et al., 2019	42	-	-	-	-	-	-	-	-	-	-	-	-
Pirmahmadzoda et al., 2021	11	-	-	-	-	-	-	-	-	-	-	-	-
Ghosh et al., 2021	147	3	-	-	-	-	-	-	-	-	-	-	-

QTcF: corrected QT with the Fredericia formula; DLM: delamanid; BDQ: bedaquiline

QTcF prolongation (12.8%, 55/427), **psychiatric disorders** (7.1%, 2/28), **gastrointestinal symptoms** (4.5%, 12/267), **peripheral neuropathy** (3.5%, 1/28), **renal failure/ increased creatinine** (2%, 2/102), and **hepatic disorders/elevated liver enzymes** (1.4%, 1/70).

Subgroup analysis

Pooled treatment success rate among subgroups of studies in DLM group

Subgroups	No. of study	No. of patients	Treatment success %(95 % CI)	Heterogeneityl2 (%)	Begg's testP-value
Type of study:					
Observational studiesExperimental studies	13 studies3 studies	591391	80.9 (72.6-87.2)72.5 (44.2-89.8)	7395	0.160.90
Age:					
≤40>40	8 studies5 studies	564195	74.2 (61.3-84)85.6 (79.9-89.9)	85.40.0	0.711.00
Sex:					
MaleFemale	3 studies3 studies	2315	80.7 (59.7-92.1)83.6 (56.5-95.2)	0.00.0	1.001.00
Children/adult:					
Children/adolescentAdult	2 studies14 studies	19963	89.4 (66.0-97.0)78.4 (69.3-85.4)	0.086.0	NA*0.45

* There must be at least three studies to run publication bias.DLM: delamanid; CI: confidence interval

- ✓ The treatment success rate in patients aged ≤40 and >40 in DLM containing regimens was 74.2% and 85.6%, respectively
- ✓ In males and females : 80.7% and 83.6%, respectively
- ✓ In children and adults :89.4% and 78.4%, respectively

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Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Objective:

Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening infectious disease. Treatment requires multiple antimicrobial agents used for extended periods of time. The present study sought to evaluate the treatment success rate of bedaquiline-based regimens in MDR-TB patients.

Methods:

This was a systematic review and meta-analysis of studies published up to March 15, 2021. The pooled treatment success rates and 95% CIs were assessed with the fixed-effect model or the random-effects model. Values of $p < 0.05$ were considered significant for publication bias.

Results:

A total of 2,679 articles were retrieved by database searching. Of those, 29 met the inclusion criteria. Of those, 25 were observational studies (including a total of 3,536 patients) and 4 were experimental studies (including a total of 440 patients). The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0) in the observational studies and 86.1% (95% CI, 76.8-92.1; $p = 0.00$; $I^2 = 75\%$) in the experimental studies. There was no evidence of publication bias ($p > 0.05$).

Conclusions:

In patients with MDR-TB receiving bedaquiline, culture conversion and treatment success rates are high even in cases of extensive resistance.

Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis

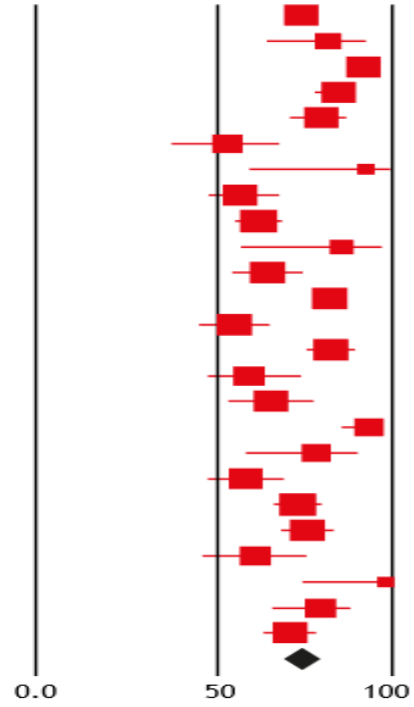
Included studies (n = 29)

Observational studies (n = 25)
Experimental studies (n = 4)

Outcomes in the observational studies

Treatment success rate in the observational studies included in the meta analysis

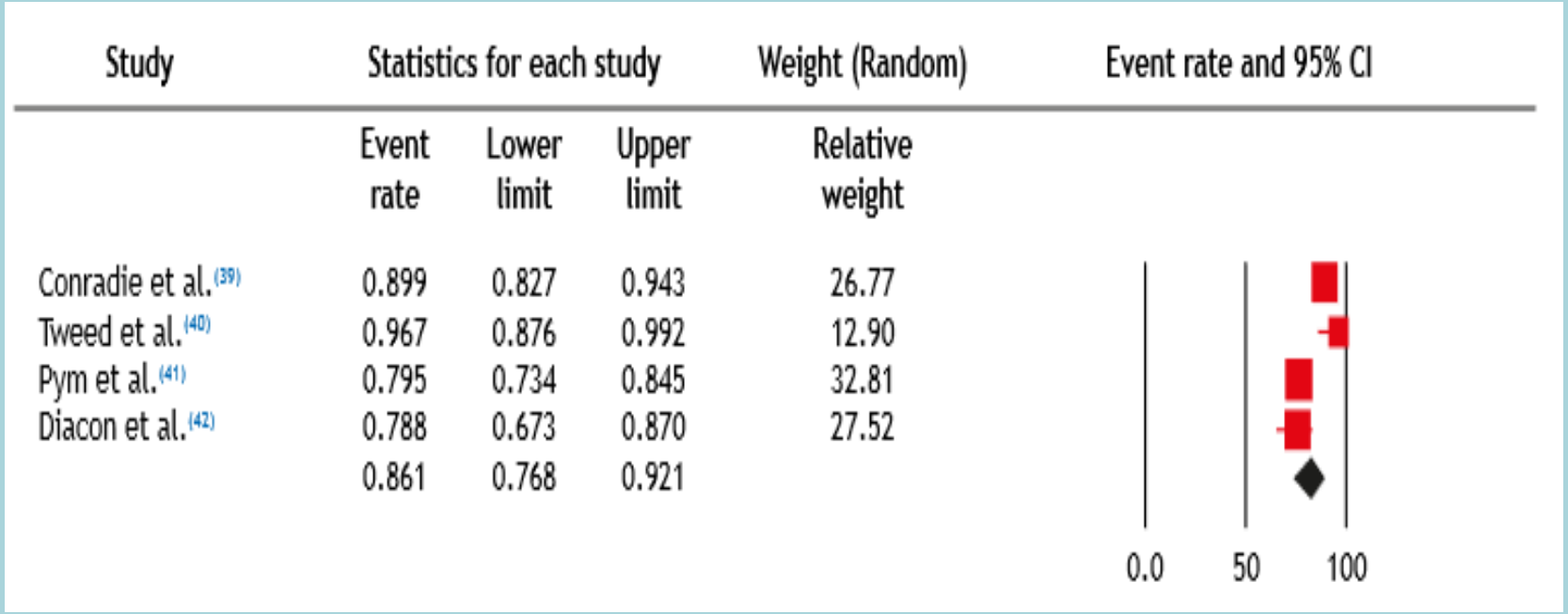
Study	Event rate	Lower limit	Upper limit	Relative weight
Koirala et al.[11]	0.742	0.695	0.783	5.16
Kwon et al.[16]	0.821	0.636	0.924	2.94
Shi et al.[17]	0.921	0.876	0.950	4.43
Gao et al.[18]	0.853	0.793	0.898	4.68
Barvaliya et al.[19]	0.803	0.725	0.863	4.61
Kashongwe et al.[20]	0.531	0.361	0.694	3.77
Das et al.[21]	0.923	0.609	0.989	1.14
Lee et al.[22]	0.568	0.453	0.675	4.54
Kim et al.[23]	0.618	0.553	0.679	5.08
Mase et al.[24]	0.857	0.573	0.964	1.79
Olayanju et al.[25]	0.648	0.559	0.727	4.81
Salhotra et al.[26]	0.827	0.796	0.855	5.20
Chesov et al.[27]	0.553	0.461	0.641	4.82
Kang et al.[28]	0.828	0.764	0.877	4.75
Sarin et al.[29]	0.595	0.443	0.731	4.03
Kempker et al.[30]	0.656	0.533	0.762	4.36
Taune et al.[31]	0.935	0.853	0.973	3.11
Ferlazzo et al.[32]	0.786	0.598	0.900	3.12
Hewison et al.[33]	0.585	0.476	0.687	4.61
Ndjeka et al.[34]	0.730	0.664	0.787	4.97
Zhao et al.[35]	0.760	0.684	0.823	4.78
Kim et al.[36]	0.615	0.456	0.753	3.93
Achar et al.[37]	0.979	0.741	0.999	0.67
Guglielmetti et al.[38]	0.800	0.658	0.893	3.65
Borisov et al.[10]	0.713	0.653	0.766	5.06
	0.747	0.698	0.790	



- ✓ The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0; I2 = 86%;
- ✓ The pooled death and treatment failure rates were 9.0% (95% CI, 6.8-12.0; I2 = 75%) and 5.7% (95% CI, 3.6-8.9; I2 = 85%), respectively.

Outcomes in the experimental studies

Treatment success rate in the experimental studies included in the meta-analysis



- ✓ The pooled treatment success rate was 86.1% (95% CI, 76.8-92.1; p = 0.00; I2 = 75%

- ✓ Mortality rates were reported in 2 studies, and the pooled death rate was 3.6% (95% CI, 0.6-9.2). Only 1 study reported a treatment failure rate, which was 1.8%

Adverse effects

Adverse effects in the studies included in the meta-analysis

Author	QTc prolongation	Liver disease/ Elevated liver enzyme	Renal failure/ Increased creatinine levels	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatological symptoms
Kwon et al.[16]	17	NR	N/R	N/R	N/R	N/R	1	N/R	N/R	N/R	N/R	N/R
Shi et al.[17]	85	59	21	13	10	24	15	16	5	3	9	2
Gao et al.[18]	39	35	9	2	6	15	11	8	11	2	6	N/R
Barvaliya et al.[19]	11	6	N/R	5	4	N/R	33	4	N/R	9	4	18
Kashongwe et al.[20]	3	1	N/R	2	5	14	15	15	N/R	N/R	N/R	15
Das et al.[21]	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Lee et al.[22]	23	N/R	1	N/R	N/R	N/R	4	N/R	N/R	N/R	N/R	N/R
Kim et al.[23]	7	28	N/R	N/R	N/R	N/R	32	N/R	N/R	34	N/R	8
Mase et al.[24]	6	N/R	N/R	N/R	2	2	4	7	4	N/R	3	3
Olayanju et al.[25]	12	36	N/R	8	59	43	30	30	N/R	20	9	N/R
Salhotra et al.[26]	14	13	4	N/R	8	22	35	26	7	N/R	15	1
Kempker et al.[30]	1	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Taune et al.[31]	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Ferlazzo et al.[32]	4	N/R	1	N/R	N/R	N/R	1	1	N/R	N/R	2	N/R
Hewison et al.[33]	12	27	5	1	9	3	34	21	N/R	N/R	N/R	6
Ndjeka et al.[34]	10	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Achar et al.[27]	0	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Guglielmetti et al.[35]	13	17	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Borisov et al.[10]	24/248	N/R	47/413	10/413	N/R	86/412	130/413	96/412	N/R	84/412	29/413	63/412
Conradie et al.[39]	0	17	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Tweed et al.[48]	0	4	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Efeito aleatório combinado	10.4 (6.2-17.0)	11.7 (6.5-20.0)	4.6 (2.3-8.9)	3.8 (2.4-6.1)	7.8 (2.3-23.0)	13.6 (7.1-24.7)	15.3 (7.5-24.1)	13.8 (9.4-24.0)	4.7 (1.3-15.2)	8.1 (4.3-14.6)	5.1 (3.3-7.9)	7.5 (3.3-16.0)
Heterogeneidade, I^2 (%)	92%	93%	85%	50%	96%	94%	94%	94%	89%	89%	68%	91%
Teste de Begg, p	0.46	0.21	0.13	0.54	0.90	0.71	0.90	0.72	0.65	0.00	0.82	0.22

QTc: corrected QT; and N/R: not reported.

Most of the adverse events potentially attributed to bedaquiline-containing regimens were gastrointestinal symptoms (15.3%), peripheral neuropathy (13.8%), and hematological disorders (13.6%)

Subgroup analysis

Pooled treatment success rates for subgroups of studies

Subgroup	No. of studies	No. of patients	Treatment success rate (%) (95% CI)	Heterogeneity I^2 (%)	Begg's test value of p
Treatment regimen:					
Regimen containing BDQ	22	3,287	74.5 (67.6-80.3)	91	0.61
Regimen containing BDQ+DLM	7	292	73.9 (62.1-83.0)	72	0.03
Type of study:					
Observational study	25	3,536	74.7 (69.8-79.0)	86	0.18
Experimental study	4	440	86.1 (76.8-92)	75	0.08

BDQ: bedaquiline; and DLM: delamanid.

- ✓ The **treatment success rate** in patients receiving bedaquiline-containing regimens was 74.5%
- ✓ For patients receiving treatment with bedaquiline and delamanid, the treatment success rate was 73.9%

- ✓ The **treatment success rates** in the observational and experimental studies included in the meta-analysis were 74.7% and 86.1%, respectively.

Thank you for your attention