CORSO AGGIORNAMENTO ECM 2018

Tubercolosi e Micobatteriosi Atipiche: un impegno globale

Ferrara, 31 Maggio 2018

Terapia delle forme multi-resistenti

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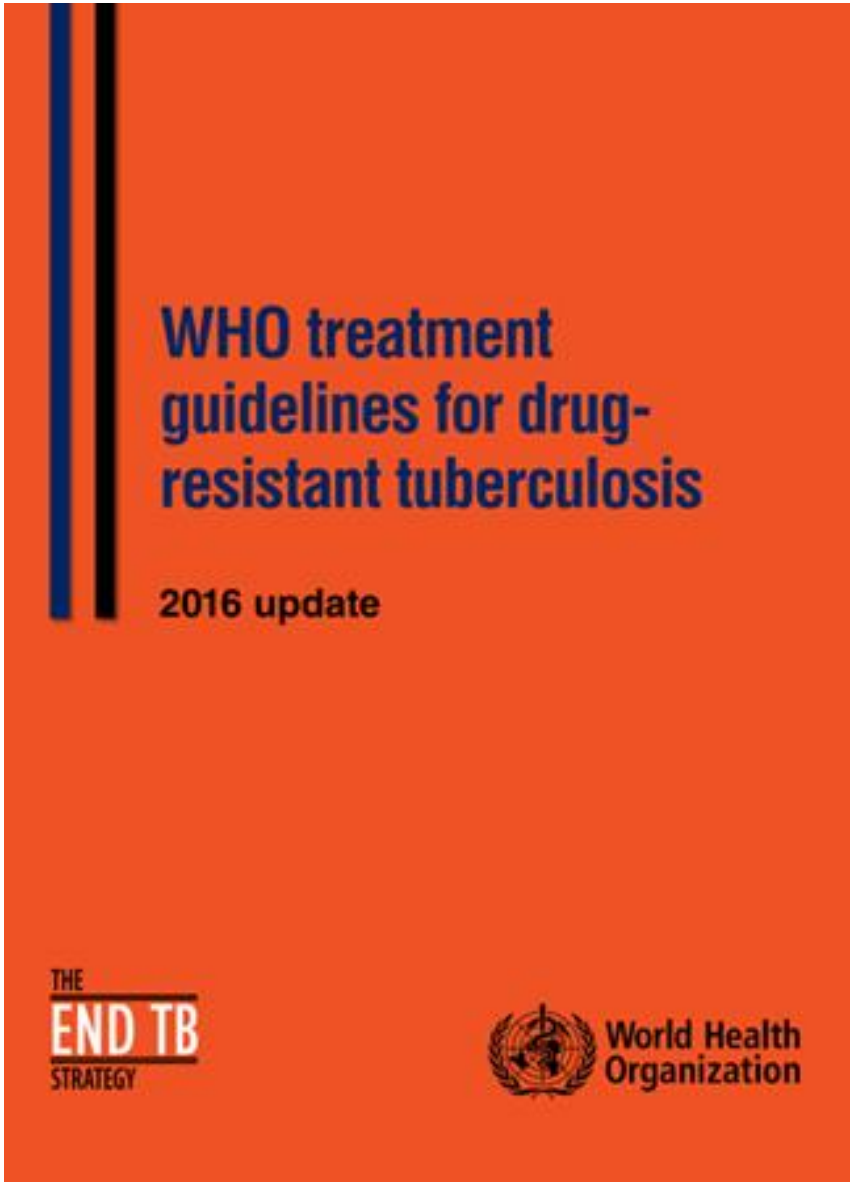
Outline

- WHO treatment guidelines for DR-TB
  - Shorter MDR-TB regimen
- Bedaquiline and delamanid – new evidences
- WHO treatment guidelines for H-resistant TB
- ERS/WHO TB Consilium



WHO guidelines for the treatment of drug-resistant tuberculosis 2016 update

WHO guidance on treatment & management of drug-resistant TB, 1996-2016

WHO guidelines for the treatment of drug-resistant tuberculosis. 2016 update

Key changes

- The design of conventional MDR-TB regimens uses a different ***regrouping of second-line medicines***
- A ***shorter MDR-TB treatment regimen*** is recommended for RR-/MDR-TB patients, under several conditions
- MDR-TB treatment is recommended for all patients with rifampicin-resistant tuberculosis, regardless if isoniazid resistance is confirmed or not
- ***Treatment of children with RR-/MDR-TB*** based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes
- Recommendation on ***partial lung resection surgery***

Regrouping of the medicines used for RR-/MDR-TB

GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP C Other Core Second-line Agents		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine
GROUP D Add-on agents *(not core MDR-TB regimen components)*	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	*p*-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

Regrouping of second line drugs

- Group D consists of **Add-on agents,** reserved for when an adequate regimen cannot be otherwise composed (replacing the old Group 5). It is split into three subgroups (D1,D2,D3): PAS belongs to D3 and bedaquiline and delamanid to D2
- Macrolides no longer have a role in MDR-TB treatment regimens
- Active TB drug safety monitoring and management (aDSM) to safeguard patient health and to contribute to global knowledge about the safety of individual medicines and drug combinations, especially in novel regimens

Longer MDR-TB regimen (1)

In patients with rifampicin-resistant TB or MDR-TB, ***a regimen with at least five effective TB medicines*** during the intensive phase is recommended, ***including pyrazinamide and*** four core second-line TB medicines – ***one chosen from Group A, one from Group B, and at least two from Group C***

Group A =
levofloxacin;
moxifloxacin;
gatifloxacin
Group B =
amikacin,
capreomycin,
kanamycin,
(streptomycin)
Group C =
ethionamide/
prothionamide,
cycloserine/ terizidone,
linezolid, clofazimine

Longer MDR-TB regimen (2)

If the minimum number of five effective TB medicines cannot be composed as given above, an ***agent from Group D2 and other agents from Group D3 may be added to bring the total to five***

The regimen may be further strengthened with high-dose isoniazid and/or ethambutol (Group D1)

Group D2
bedaquiline, delamanid
Group D3
p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone)

Treatment duration for longer MDR-TB regimen (no change from 2011 guidelines)

In the treatment of patients with MDR-TB, an intensive phase of 8 months is suggested for most patients, and the duration may be modified according to the patient's response to therapy

conditional recommendation / very low certainty in the evidence

In the treatment of patients newly diagnosed with MDR-TB, a total treatment duration of 20 months is suggested for most patients in patients, and the duration may be modified according to the patient's response to therapy

conditional recommendation / very low certainty in the evidence

Shorter MDR-TB regimen

Shorter MDR-TB regimen (1)

In patients with

- rifampicin-resistant TB or MDR-TB,
- who have not been previously treated with second-line drugs and
- in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely

a shorter MDR-TB regimen of 9–12 months may be used instead of a conventional regimen

- Conditional recommendation – very low quality of evidence

Shorter MDR-TB regimen (2)

- *Standardized regimen*;
- limited modifications are possible

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Shorter MDR-TB regimen (3)

Drug	Weight group		
	Less than 30 kg	30 kg to 50 kg	More than 50 kg
Gatifloxacin	400 mg	600 mg	800 mg
Moxifloxacin	400 mg	600 mg	800 mg ←
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg ←
Prothionamide	250 mg	500 mg	750 mg
Kanamycin†	15 mg per kilogram body weight (maximum 1 g)		

†For adults over 59 years of age, the dose will be reduced to 10 mg/kg (max dose 750 mg).

Shorter MDR-TB regimen (4)

- Recommendation *applies to adults, children, PLHIV*
- *Not recommended in case of 2nd line drug resistance, extrapulmonary disease and pregnancy*
- *Lowered costs* (<US$1,000 in drug costs/patient)
- Monitoring for effectiveness, relapse, and harms (*active TB drug safety monitoring and management (aDSM)) applies*
- *Trials* (e.g. STREAM) *expected to provide high-certainty evidence*

Choosing the treatment regimen in patients with confirmed MDR/RR-TB

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available

NO

Shorter MDR-TB regimen

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF AN EXCLUSION CRITERION

YES

Longer (individualized) MDR-TB regimens

World Health Organization

Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions

Version: 20 December 2016

These FAQs are to be read alongside the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (WHO/HTM/TB/2016.04) and their online annexes released by the Global TB Programme of the World Health Organization (WHO) in May 2016(1),(2). The 2016 guidelines provide more background about the updated WHO recommendation on the shorter MDR-TB regimen since the previous guidelines of 2011(3).

Google <WHO Treatment of drug-resistant TB resources>

http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en

Rifampicin resistant strains
(i.e. following Xpert MTB/RIF results)

- All RR-TB cases to be treated with a recommended MDR-TB regimen, regardless if isoniazid resistance is confirmed or not
- H can be added to the regimen until DST is available (and maintained if DST shows susceptibility).
- If isoniazid susceptibility cannot be tested, isoniazid may also be added to the regimen, at a dose of 15–20 mg/kg body weight/day.
- Duration of INH: INH is probably most active in first months of treatment, but if strain is susceptible it could help protect other drugs

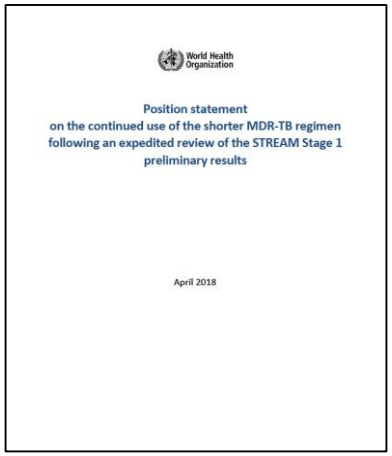
The role of surgery

Recommendation & remarks

In patients with rifampicin-resistant or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen

- Based on individual participant data (IPD) and study-level meta-analyses
- Bias to be expected (e.g. confounding by indication, publication)
- Which patients & when would benefit most? The effects in PLWH could not be evaluated
- More radical pneumonectomy does not show the same benefits
- Only to be recommended where specialist services are available

WHO Position statement on the continued use of the shorter regimen for MDR-TB following an expedited review of STREAM 1 preliminary results (April 2018)


World Health Organization

Position statement
on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results

April 2018

- Stream 1: phase III, multicentre, open-label, randomized controlled comparing shorter regimen with locally-used longer MDR-TB regimen based on WHO recommendations.
- Designed to assess the non-inferiority of shorter regimen
- Sites: Ethiopia, Mongolia, South Africa, Vietnam

WHO Position statement on shorter regimen (2)

ANNEX 1: SUMMARY OUTCOMES, STREAM STAGE 1 TRIAL[a]

Outcomes	№ of patients		Effect[b]	
	Shorter regimen (study arm)	Longer regimen (control arm)	Relative (95% CI)	Absolute (95% CI)
Time-to-culture-conversion by week 20 (ITT population)	271[c]	138[c]	HR 1.14 (0.93 to 1.40)	-
Favourable outcome at 132 weeks (follow up: 132 weeks; mITT efficacy population)[d]	164/210 (78.1%)	87/108 (80.6%)	RR 0.970 (0.862 to 1.090)	24 fewer per 1,000 (from 73 more to 111 fewer)
Died from any cause during treatment or follow-up, among all cases (follow up: 132 weeks; ITT population)[e]	24/282 (8.5%)	9/141 (6.4%)	RR 1.333 (0.637 to 2.792)	21 more per 1,000 (from 23 fewer to 114 more)
Died from any cause during treatment or follow-up, among only people living with HIV (follow up: 132 weeks; ITT population)[f]	18/103 (17.5%)	4/50 (8.0%)	RR 2.185 (0.780 to 6.115)	95 more per 1,000 (from 18 fewer to 409 more)
Lack of culture conversion, culture reversion or relapse (follow up: 132 weeks; mITT efficacy population)	19/210 (9.0%)	4/108 (3.7%)	RR 2.443 (0.852 to 7.002)	53 more per 1,000 (from 5 fewer to 222 more)
New onset QTcF interval prolongation to 500ms or more on electrocardiogram (ITT population)	28/282 (9.9%)	7/141 (5.0%)	RR 2.000 (0.896 to 4.465)	50 more per 1,000 (from 5 fewer to 172 more)
Adverse event of GRADE 3 to 5 severity (follow up: 132 weeks; assessed with ITT population)[g]	129/282 (45.7%)	63/141 (44.7%)	RR 1.024 (0.819 to 1.280)	11 more per 1,000 (from 81 fewer to 125 more)

CI: Confidence interval; HR: Hazard Ratio; ITT: intention to treat; mITT: modified intention to treat; RR: Risk ratio

WHO Position statement on shorter regimen (3)

- Favourable outcomes marginally higher for longer versus shorter treatment (80.6% vs 78.1%). Relative risk (RR) 0.970, 95%CI 0.862 – 1090; P=0.60; risk difference +2.5%, 95% CI -6.9% to +11.8%.

- Trial preliminary data **could not confirm the non–inferiority** of the shorter regimen when compared to the longer

- However, the control regimen performed much better than in programmatic conditions, and advantages of reducing treatment duration may be not adequately reflected by preliminary findings

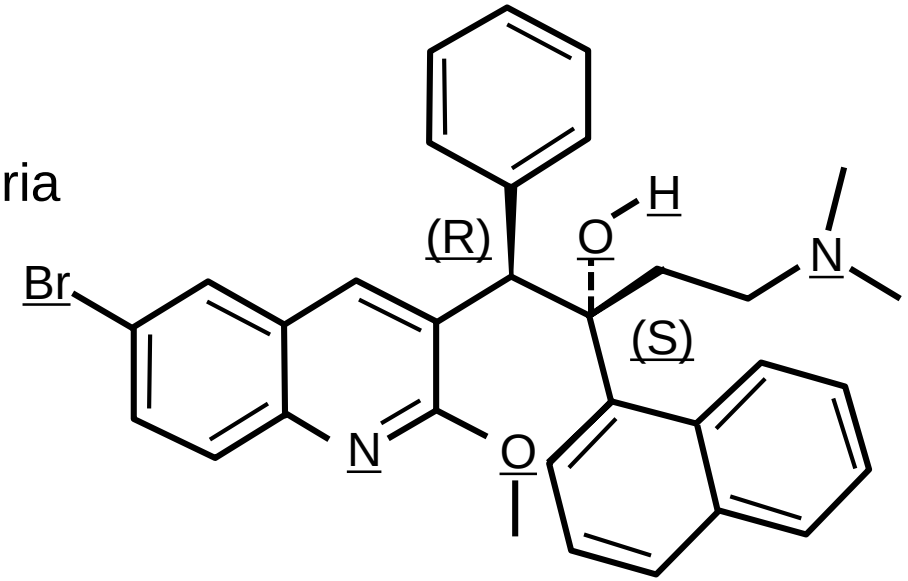
- **Conclusion: 2016 WHO recommendation on the use of the shorter MDR-TB remains in place.** The recommendation remains conditional, based on moderate certainty on the estimates of effects.

New drugs

Bedaquiline and Delamanid

Bedaquiline

- Oral diarylquinoline
- Target: ATP synthase
  - Activity specific to mycobacteria
- Bactericidal activity comparable to RIF-INH-PZA in mice
- Sterilizing activity comparable to rifampin in mice



- No cross-resistance with other antimycobacterial drugs (INH, RIF, EMB, PZA, streptomycin, amikacin, or moxifloxacin)

Andreas K, et al. Science. 2005;307:223-227. CDC. MMWR Morb Mortal Wkly Rep. 2013;62:1-12.

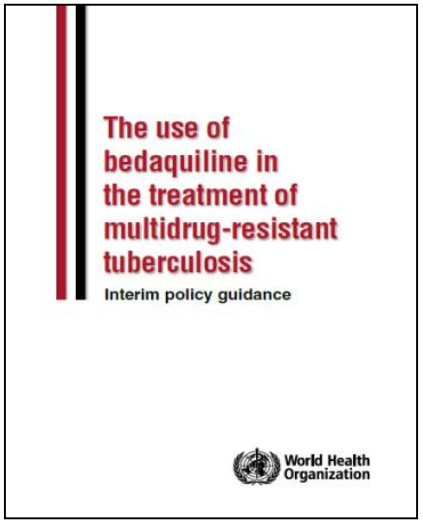
BEDAQUILINE : WHO interim policy guidance (June 2013)

"Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB"

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

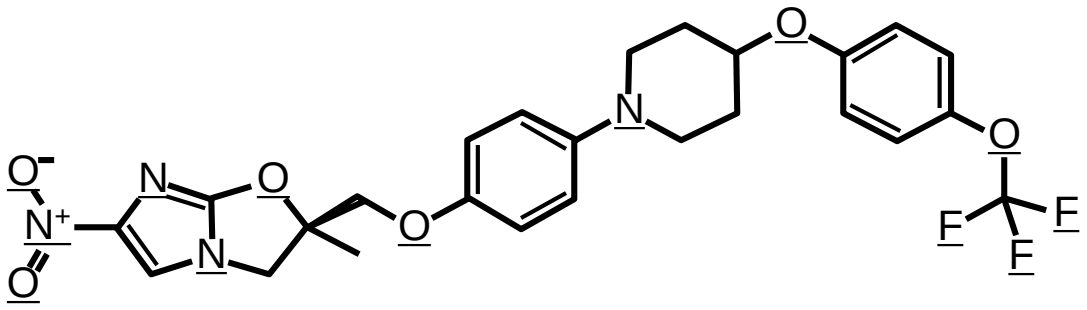
1. Treatment under close monitoring
2. Proper patient selection
3. Patient informed consent
4. Treatment as per WHO recommendations
5. Active pharmacovigilance in place



400 mg daily 2/12 200 mg 3/w 22 w added to OBR in adults

Delamanid

- Nitro-dihydro-imidazooxazole
- Derivative of metronidazole
- Inhibits mycolic acid synthesis
- Potent preclinical in vitro and in vivo activity against both drug-susceptible and drug-resistant strains of TB



Skripconoka V, et al. Eur Respir J. 2013;41:1393-1400.

DELAMANID : WHO interim policy guidance (October 2014)

"Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB"

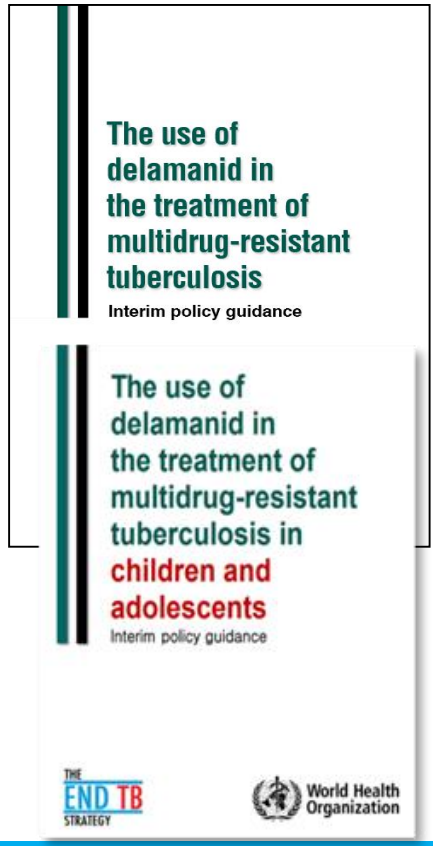
conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

1. Proper patient inclusion
2. Treatment as per WHO recommendations
3. Treatment is closely monitored
4. Active pharmacovigilance in place
5. Patient informed consent obtained

-> October 2016 : may be used in patients 6-17 years

100 mg BD added to OBR in adults



Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

A review of available evidence (2016)

28 - 29 June 2016

Geneva, Switzerland

World Health Organization

THE END TB STRATEGY

Review of available evidence on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis: Data analysis report

Prepared for:
The World Health Organization

Prepared by:
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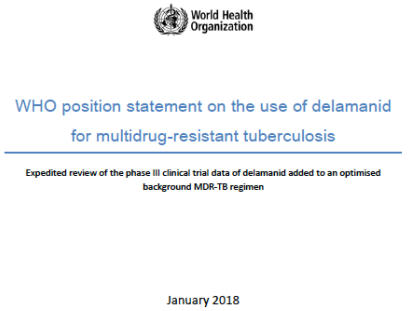
McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

MARCH 8, 2017
VERSION 6

WHO Position statement on the use of delamanid for MDR-TB (January 2018)



Trial 213: phase III, multicentre, randomized, double blind, placebo-controlled comparing:

- OBR + delamanid (for 6 months) for a total duration of 18-24 months and
- OBR + placebo (for 6 months) for a total duration of 18-24 months

No clinical relevant or statistical significant difference in treatment success, all-cause mortality, culture conversion, adverse events, QTcF prolongation

- Until then the current interim and conditional guidance on delamanid remains in place. **However, national TB programmes and other stakeholders are advised to only add delamanid to a longer MDR-TB regimen when it cannot be composed according to WHO recommendations. When an effective and well-tolerated longer MDR-TB regimen can be otherwise composed, the addition of delamanid may not be warranted.**

Can bedaquiline and delamanid be used together in the same patient?

WHO guidance stated that there are no data on the simultaneous use of bedaquiline and delamanid in the same patient and that until such data become available, no recommendation on their joint administration is possible.

Proposed conditions for the use in individual patient:

1. An effective treatment cannot be designed by adding only one new drug to the optimised background regimen
2. The clinical centre is qualified
3. Informed consent
4. Pharmacovigilance in place
5. Support of experts to the need of using the two drugs

Matteelli et al. LID 2015

First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline

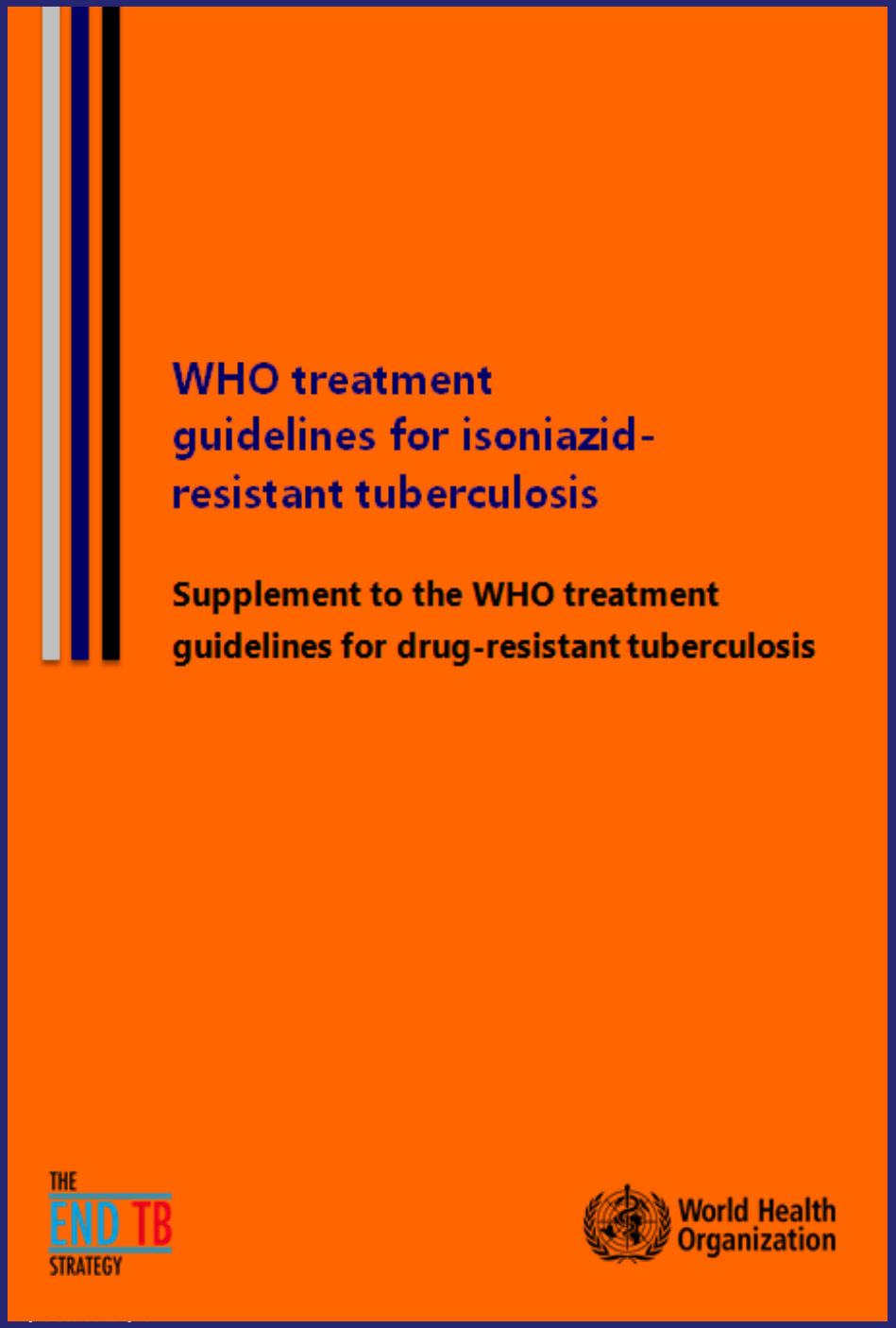
Marina Tadolini[1,7], Rangjung Dolma Lingtsang[2,7], Simon Tiberi[3,7], Martin Enwerem[4,7], Lia D'Ambrosio[5,6,7], Tsetan Dorji Sadutshang[2], Rosella Centis[5] and Giovanni Battista Migliori[5]

Eur Respir J 2016; 48: 935–938

Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study

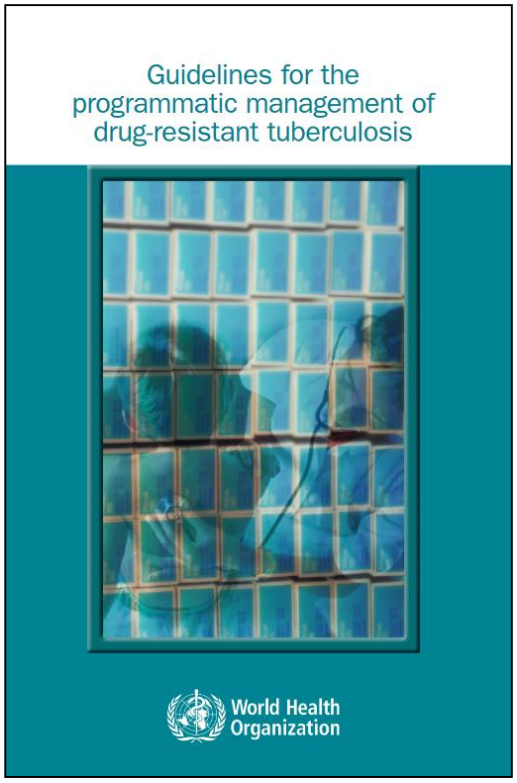
Gabriella Ferlazzo, Erika Mohr, Chinmay Laxmeshwar, Catherine Hewison, Jennifer Hughes, Sylvie Jonckheere, Naira Khachatryan, Virginia De Avezedo, Lusine Egazaryan, Amir Shroufi, Stobdan Kalon, Helen Cox, Jennifer Furin, Petros Isaakidis

Lancet Infect Dis 2018; 18: 536–44



WHO treatment guidelines for isoniazid-resistant TB

World Health Organization



since 2006…

TABLE 8.1 **Suggested regimens for mono- and poly-drug resistance[a] (when further acquired resistance is not a factor and laboratory results are highly reliable)**

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	MINIMUM DURATION OF OF TREATMENT (MONTHS)	COMMENTS
H (± S)	R, Z and E	6–9	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
H and Z	R, E and fluoro-quinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
H and E	R, Z and fluoro-quinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
R	H, E, fluoroquinolones, plus at least 2 months of Z	12–18	An injectable agent may strengthen the regimen for patients with extensive disease.
R and E (± S)	H, Z, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
R and Z (± S)	H, E, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
H, E, Z (± S)	R, fluoroquinolones, plus an oral second-line agent, plus an injectable agent for the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

WHO treatment guidelines of HR-TB, 2018

PICO question

In patients with isoniazid-resistant tuberculosis (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 or more months of REZ, leads to a higher likelihood of success with least possible risk of harm?

Evidence summary, 2018 (1)

- Individual patient data from 33 observational studies with an analysable population of 5418 Hr-TB patients
- 6-month (H)REZ regimen had a higher likelihood of treatment success and less amplification of resistance than >6 months (n.s.s)
- (H)REZ+Lfx regimens had higher success (s.s) and lower deaths and amplification of resistance (n.s.s) than (H)REZ
- Available data do not support the use of streptomycin in regimens for patients with isoniazid-resistant TB.

WHO treatment guidelines of Hr-TB, 2018

Main recommendations (1)

In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.

[conditional recommendation;
very low certainty in the evidence]

- H may be added for convenience (to use 4-drug FDC) and may increase regimen effectiveness if only low-level H resistance is present *(inhA mutation present only)*
- Dosage Levofloxacin (adults): 750 mg for BW < 49 Kg
  1000 mg for BW > 50 Kg

WHO treatment guidelines of Hr-TB, 2018

Main recommendations (2)

In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen

[conditional recommendation; very low certainty in the evidence]

WHO treatment guidelines of Hr-TB, 2018

Main remarks

The addition of levofloxacin to 6(H)REZ is recommended in all patients with Hr-TB, with the exception of the following: (i) resistance to rifampicin cannot be excluded; (ii) known or suspected resistance to levofloxacin; (iii) known intolerance to fluoroquinolones; (iv) known or risk of prolonged QT-interval; and (v) if possible, in pregnancy or during breastfeeding (not an absolute contraindication).

- In these cases: 6 (H)RZE is recommended
- Prolonging >6 months did not show to improve outcome

Frequently asked questions on the

World Health Organization

WHO treatment guidelines for isoniazid-resistant tuberculosis

Version: 24 April 2018

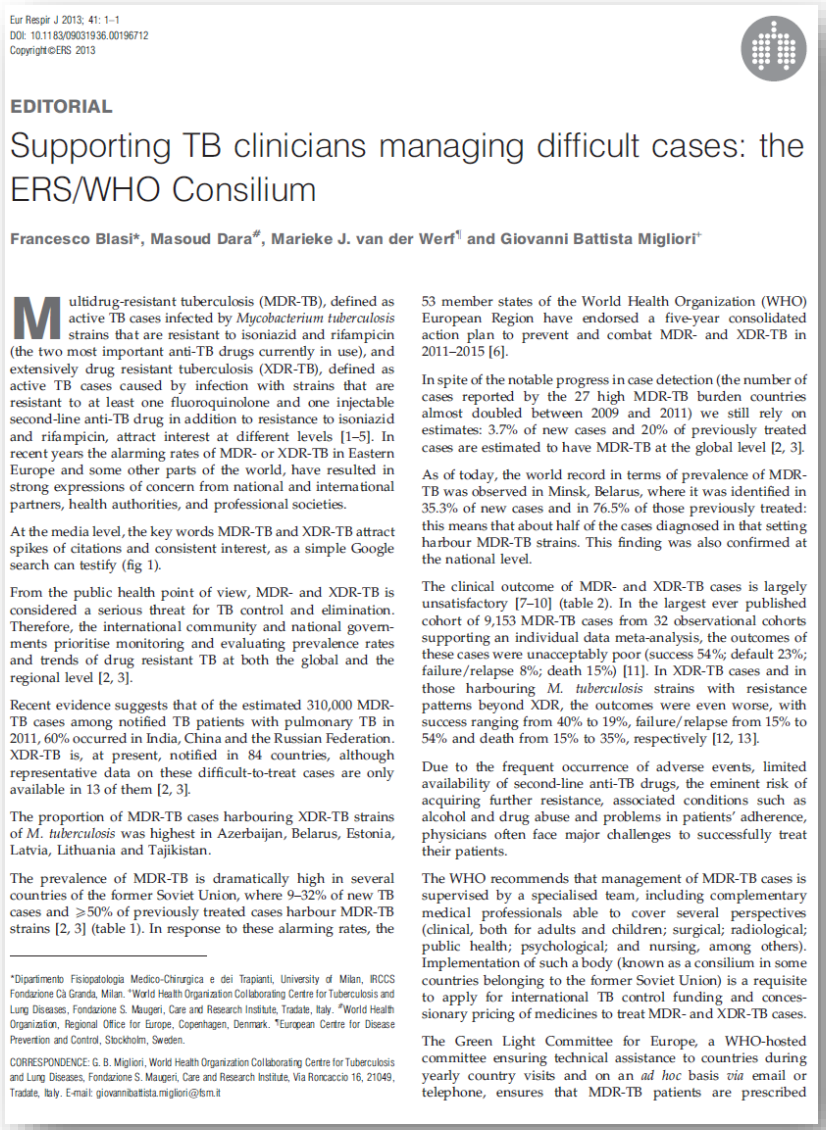
The advice in this document has been prepared by the Global TB Programme of the World Health Organization (WHO) and is to be read alongside the *WHO treatment guidelines for isoniazid-resistant tuberculosis* and its online annexes. See *Further reading* at end for additional resources.

http://www.who.int/tb/publications/2018/FAQ_TB_policy_recommendations_guidelines.pdf

Treating M/XDR-TB is difficult!

www.tbconsilium.org

ERS/WHO Consilium for M/XDR-TB



Eur Respir J 2013; 41: 1–1
DOI: 10.1183/09031936.00196712

EDITORIAL

Supporting TB clinicians managing difficult cases: the ERS/WHO Consilium

Francesco Blasi*, Masoud Dara#, Marieke J. van der Werf¶ and Giovanni Battista Migliori+

Multidrug-resistant tuberculosis (MDR-TB), defined as active TB cases infected by *Mycobacterium tuberculosis* strains that are resistant to isoniazid and rifampicin (the two most important anti-TB drugs currently in use), and extensively drug resistant tuberculosis (XDR-TB), defined as active TB cases caused by infection with strains that are resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug in addition to resistance to isoniazid and rifampicin, attract interest at different levels [1–5]. In recent years the alarming rates of MDR- or XDR-TB in Eastern Europe and some other parts of the world, have resulted in strong expressions of concern from national and international partners, health authorities, and professional societies.

At the media level, the key words MDR-TB and XDR-TB attract spikes of citations and consistent interest, as a simple Google search can testify (fig 1).

From the public health point of view, MDR- and XDR-TB is considered a serious threat for TB control and elimination. Therefore, the international community and national governments prioritise monitoring and evaluating prevalence rates and trends of drug resistant TB at both the global and the regional level [2, 3].

Recent evidence suggests that of the estimated 310,000 MDR-TB cases among notified TB patients with pulmonary TB in 2011, 60% occurred in India, China and the Russian Federation. XDR-TB is, at present, notified in 84 countries, although representative data on these difficult-to-treat cases are only available in 13 of them [2, 3].

The proportion of MDR-TB cases harbouring XDR-TB strains of *M. tuberculosis* was highest in Azerbaijan, Belarus, Estonia, Latvia, Lithuania and Tajikistan.

The prevalence of MDR-TB is dramatically high in several countries of the former Soviet Union, where 9–32% of new TB cases and ⩾50% of previously treated cases harbour MDR-TB strains [2, 3] (table 1). In response to these alarming rates, the 53 member states of the World Health Organization (WHO) European Region have endorsed a five-year consolidated action plan to prevent and combat MDR- and XDR-TB in 2011–2015 [6].

In spite of the notable progress in case detection (the number of cases reported by the 27 high MDR-TB burden countries almost doubled between 2009 and 2011) we still rely on estimates: 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB at the global level [2, 3].

As of today, the world record in terms of prevalence of MDR-TB was observed in Minsk, Belarus, where it was identified in 35.3% of new cases and in 76.5% of those previously treated: this means that about half of the cases diagnosed in that setting harbour MDR-TB strains. This finding was also confirmed at the national level.

The clinical outcome of MDR- and XDR-TB cases is largely unsatisfactory [7–10] (table 2). In the largest ever published cohort of 9,153 MDR-TB cases from 32 observational cohorts supporting an individual data meta-analysis, the outcomes of these cases were unacceptably poor (success 54%; default 23%; failure/relapse 8%; death 15%) [11]. In XDR-TB cases and in those harbouring *M. tuberculosis* strains with resistance patterns beyond XDR, the outcomes were even worse, with success ranging from 40% to 19%, failure/relapse from 15% to 54% and death from 15% to 35%, respectively [12, 13].

Due to the frequent occurrence of adverse events, limited availability of second-line anti-TB drugs, the eminent risk of acquiring further resistance, associated conditions such as alcohol and drug abuse and problems in patients' adherence, physicians often face major challenges to successfully treat their patients.

The WHO recommends that management of MDR-TB cases is supervised by a specialised team, including complementary medical professionals able to cover several perspectives (clinical, both for adults and children; surgical; radiological; public health; psychological; and nursing, among others). Implementation of such a body (known as a consilium in some countries belonging to the former Soviet Union) is a requisite to apply for international TB control funding and concessionary pricing of medicines to treat MDR- and XDR-TB cases.

The Green Light Committee for Europe, a WHO-hosted committee ensuring technical assistance to countries during yearly country visits and on an *ad hoc* basis *via* email or telephone, ensures that MDR-TB patients are prescribed

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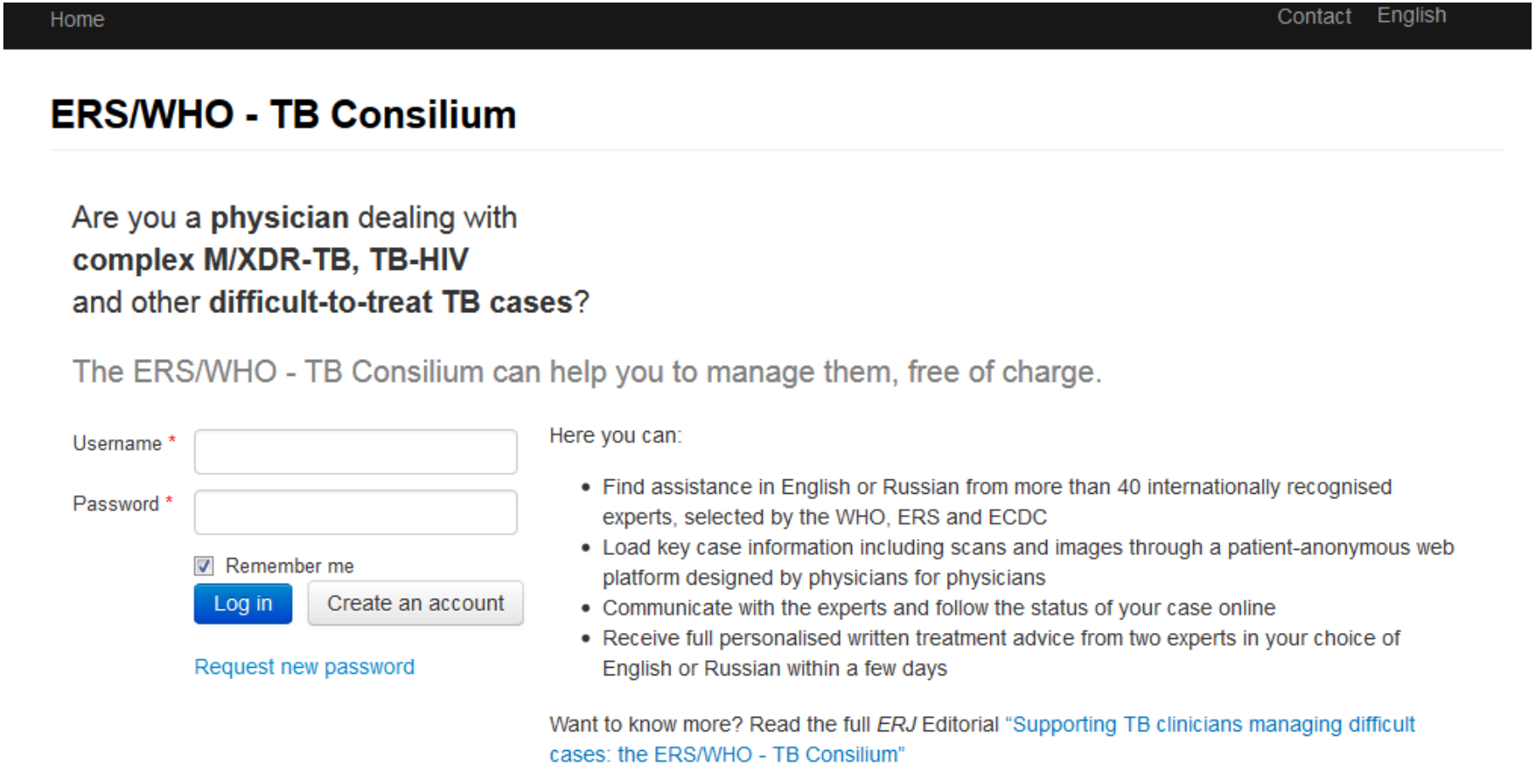
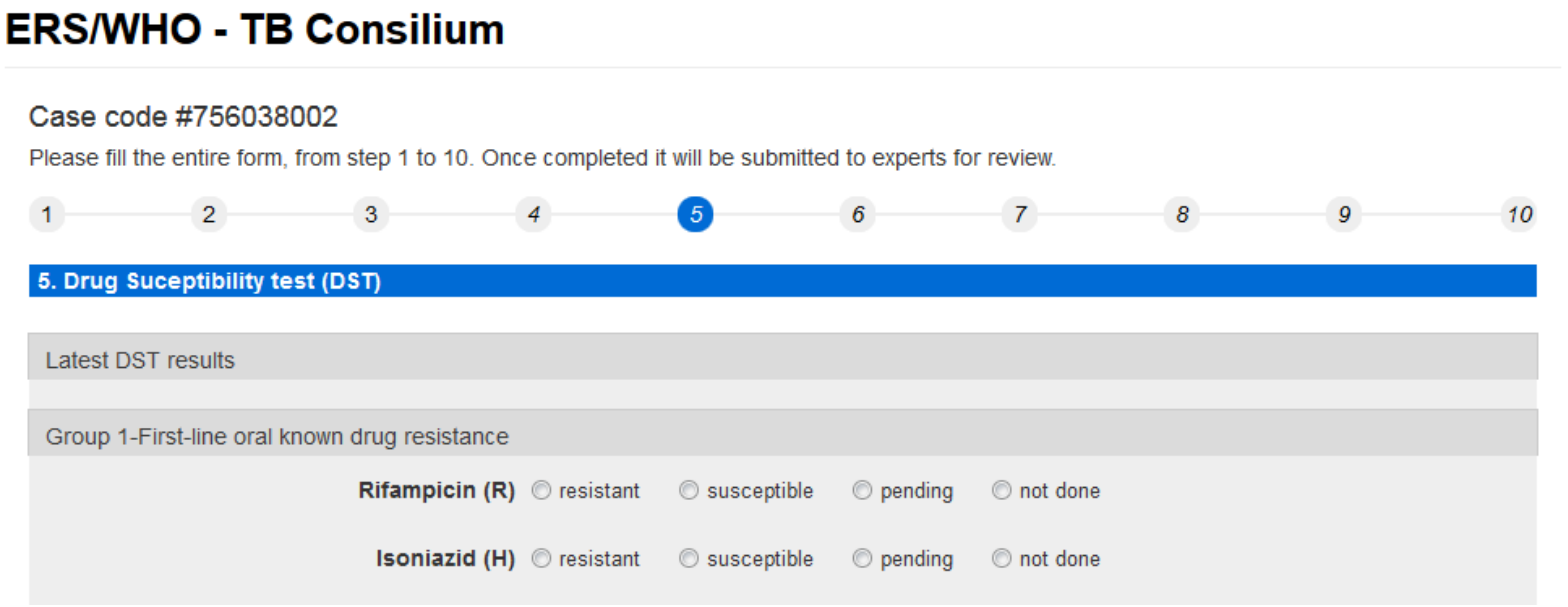
- **Objectives:**
  - To allow a European clinician, free cost, to load patient's data and receive in 1 working day suggestions by 2 experts on how to manage a difficult-to treat TB case
  - To support follow-up of TB patients travelling within Europe
- **Web-based regional platform**
- **Specialized team** able to cover several perspectives: clinical for both adults and children, surgical, radiological, public health, psychological, nursing, etc.
- **Managed by ERS, in collaboration with WHO Europe** (formal agreement) and ECDC
- 4 languages (ENG, SPA, PORT, RU)
- 20 min loading, 2 day to get the answer

www.tbconsilium.org



The platform principles: Case creation

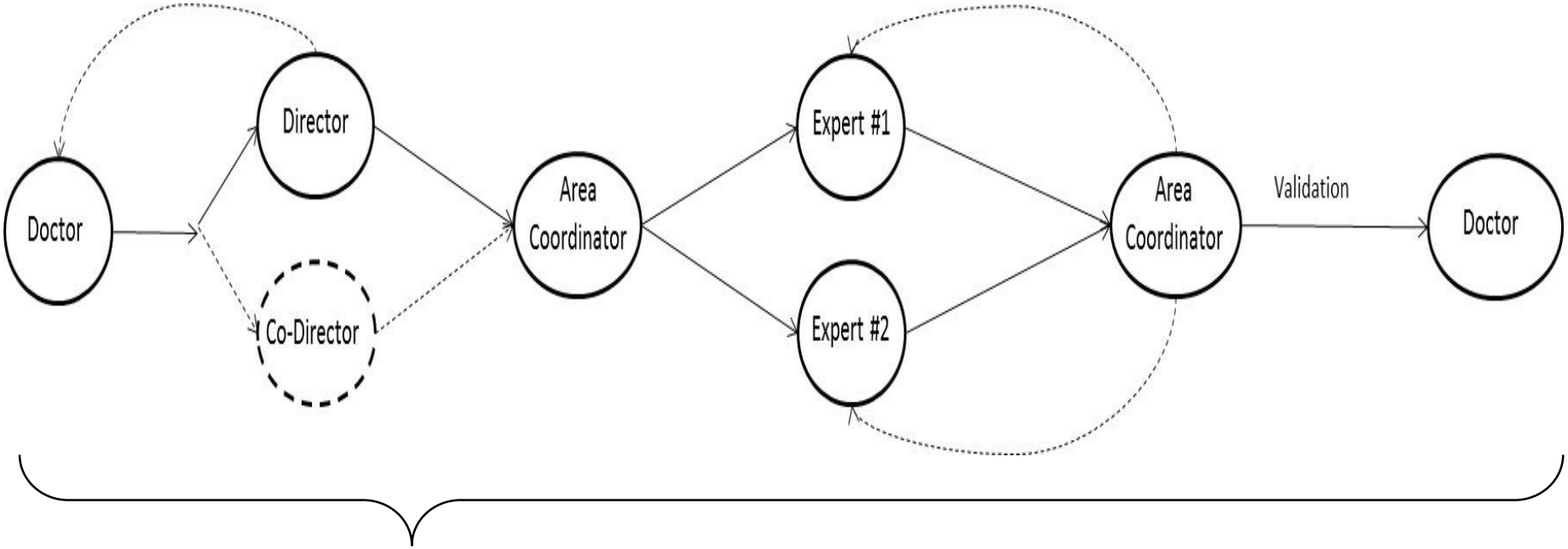
- Any physician can create an account and submit a case, through a 10 steps web form



- Estimated time: 20-45 min. Upload of pictures, imaging scans, attachments is possible.

The platform principles: Case reviewing

- Once submitted, the case is reviewed by the Area coordinator and 2 experts (chosen amongst 41 experts available today)



- **Target time for full review: 2-3 days**

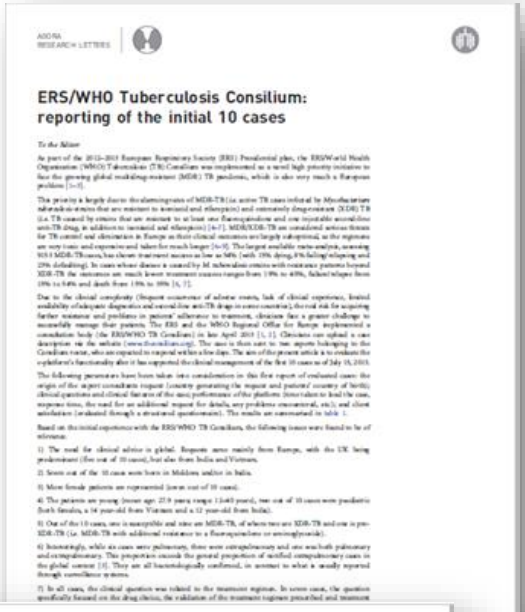
ERS/WHO TB Consilium (as of April 2018)

- **total cases: 373 cases**
- **From 42 countries (main requesting countries)**: India (61), South Africa (130), Italy (28), UK (13), Russian Federation (9), Philippines (11)
- **Mean age**: 35 years, range:1-68; 38 pediatric cases
- **Female: 40%**

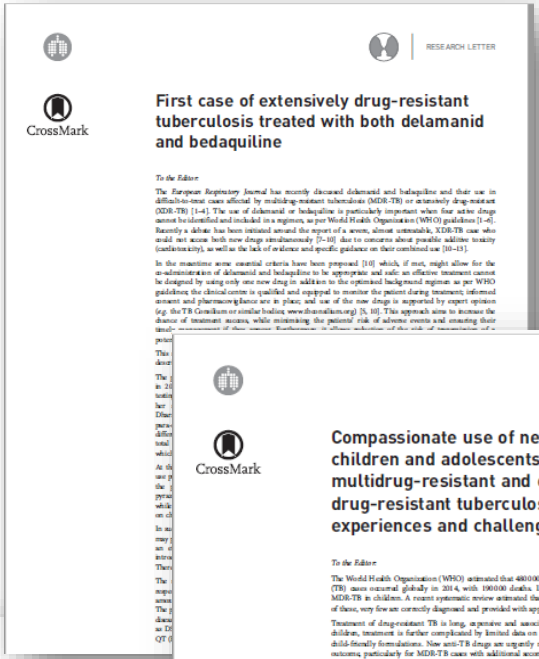
DR-TB: 264 (75,6%) (153 XDR-TB; 89 MDR-TB; 22 PRE-XDR-TB)

- **Core clinical questions**:
  - treatment regimen and/or duration
  - advice for introduction of 1 new TB drugs: Dlm or Bdq
  - advice for introduction of Dlm in compassionate use (out of 69 requests,14 not resulted eligible)
  - advice for introduction of **Dlm + Bdq**
- **Mean time to case-load**: 20 minutes
- **Average response time**: 48 hours (2 days)
- **Second opinion**: 13 cases (1 > 2 times 1 > 5 times)
- **Clinician satisfaction**: 100%

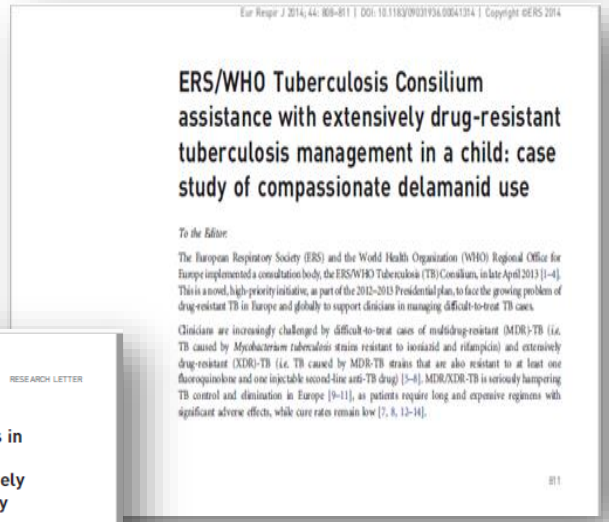
ERS/WHO TB Consilium publications



ERS/WHO Tuberculosis Consilium: reporting of the initial 10 cases

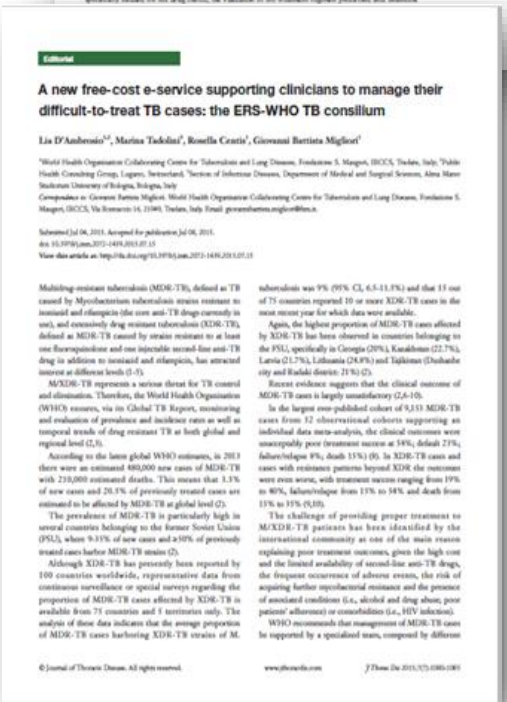


First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline

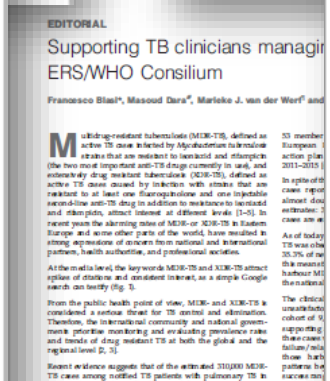


ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate delamanid use

Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges



A new free-cost e-service supporting clinicians to manage their difficult-to-treat TB cases: the ERS-WHO TB consilium



Supporting TB clinicians managi... ERS/WHO Consilium

Supporting clinical management of the difficult-to-treat TB cases: the ERS-WHO TB Consilium

If you need help

www.tbconsilium.org

Contact

gbmigliori@gmail.com

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mtadolini@hotmail.com

The cost (€) to treat TB and M/XDR is enormous: prevention is cost-effective

Costs of tuberculosis disease in the EU – a systematic analysis and cost calculation

Diel R[1], Vandeputte J[2], de Vries G[2], Stillo J[4], Wanlin M[5], Nienhaus A[6]

[1]Institute for Epidemiology, University Medical Hospital Schleswig-Holstein, Kiel, Germany

Cost per case	Susceptible	MDR-TB	XDR-TB
Estonia*	2,615	15,344	15,344
France	5,691		
Germany	7,7,51	55,003	188.466
UK	6,234	62,343	
Netherlands	8,340	46,990	148,136
Italy	9,294		
Finland	8,243		
Spain	9,384		
AVERAGE	**7,848**	**54,779**	**168,310**

EUROPEAN RESPIRATORY *journal*

Un giorno di terapia MDR-TB

“Nobody wants me around..”

Certainty of evidence

Certainty	*Definition*
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Adapted from Guyatt GH et al. BMJ. 2008 Apr 26,336(7650):924-6

Implications of the strength of a recommendation for different users

Perspective	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Adapted from Guyatt GH et al. BMJ. 2008, 336(7652):1049–1051

High dose INH

- inhA: INH normal dose
- katG: INH high dose (works on majority of strains (?)
- inhA+katG: forget INH

Implications to use drugs at high dose in case of drug resistance

Isoniazid (INH)

If *inhA* mutations only are detected, even normal doses (*e.g.* 5 mg per day per kg body weight) of INH could be used; high doses (10 $mg \cdot kg^{-1}$ or more) are likely to be effective [15, 16]. If *katG* mutations only are detected, use of high doses is an option. Most *katG* mutations (other than 315 codon) confer moderate resistance (minimum inhibitory concentration (MIC) 1–5 $\mu g \cdot mL^{-1}$) that might be treated with higher doses of the drug; even the most common S315T variant leads to a variable range of resistance [17]. In the absence of additional mutations affecting the *inhA* gene (and *ethA* gene, so far uniquely detectable by sequencing approaches), ethionamide can be considered an option for the intensive phase of the shorter regimen. If *inhA* + *katG* mutations are concurrently detected, INH drug use should be avoided, since these patterns are linked to high resistance levels.

Cabibbe AM et al. ERJ 2018

Ertapenem to treat MDR-/XDR-TB

TABLE 1 Clinical characteristics of five patients with multidrug-resistant/extensively drug-resistant tuberculosis (TB) treated with ertapenem in Sondalo, Italy

Patient	Age years	Sex	Country of birth	Previous exposure to anti-TB therapy >30 days	Total hospital admission time days	Drug resistance profile	Anti-TB regimen	Sputum smear conversion time days	Sputum culture conversion time days	Lzd exposure time days/daily dose mg	Carbapenem exposure days/daily dose mg	Erta exposure days/daily dose g	Adverse events	Outcome
1	35	F	Ukraine	3	128	H, R, E, Z, S, FQ, Eto, Amk, Cm, Km	Amx/Clv, Cfz, Trd, Mero/Erta, Eto, Bdq, Lzd, Mfx	62	88	730/900	Mero 91/3	248/1	No	Cured
2	33	M	Moldova	2	114	H, R, E, S, FQ, Eto, Trd, Amk, PAS, Km	Cm, Ipm/Cln-Erta, Mfx, PAS, Eto	Not achieved	Not achieved	No	Ipm 5/2	20/1	No	Bacteriologically positive till death
3	23	M	Moldova	2	53	H, R, E, Z, S, Eto, Trd, Amk, PAS, Km	Amk, E, Ipm/ Cln-Erta, Lzd, Mfx	Sputum positive at discharge No longer expectorating at the following controls	Culture positive at discharge No longer expectorating at the following controls	182/1200	Ipm 3/2	540/1	No	Alive, improved, treatment completed as no formal evidence of negative cultures
4	51	M	Italy	3	110	H, R, E, Z, S, Eto, Trd, Amk, PAS, Km	Amk, Trd, Ipm/Cln, Erta, Lzd, Mfx, Eto	21	39	720/1200	Ipm 2/2	690/1	Gastrointestinal, transient (Lzd restarted)	Cured
5	30	F	Romania	1	104	H, R, Z, S, FQ, Eto	Amk, Trd, E, Mero/Erta, Amx/ Clv, Lzd, Mfx, PAS	60	53	730/600	Mero 71/3	659/1	Gastrointestinal, transient (PAS restarted)	Cured
Average	35.5			2.5	96.7	9.2 drugs	6.4 drugs (5.6 active)	47.7	60	590.5	34.4	431.4		

Tiberi S, et al. ERJ 2016

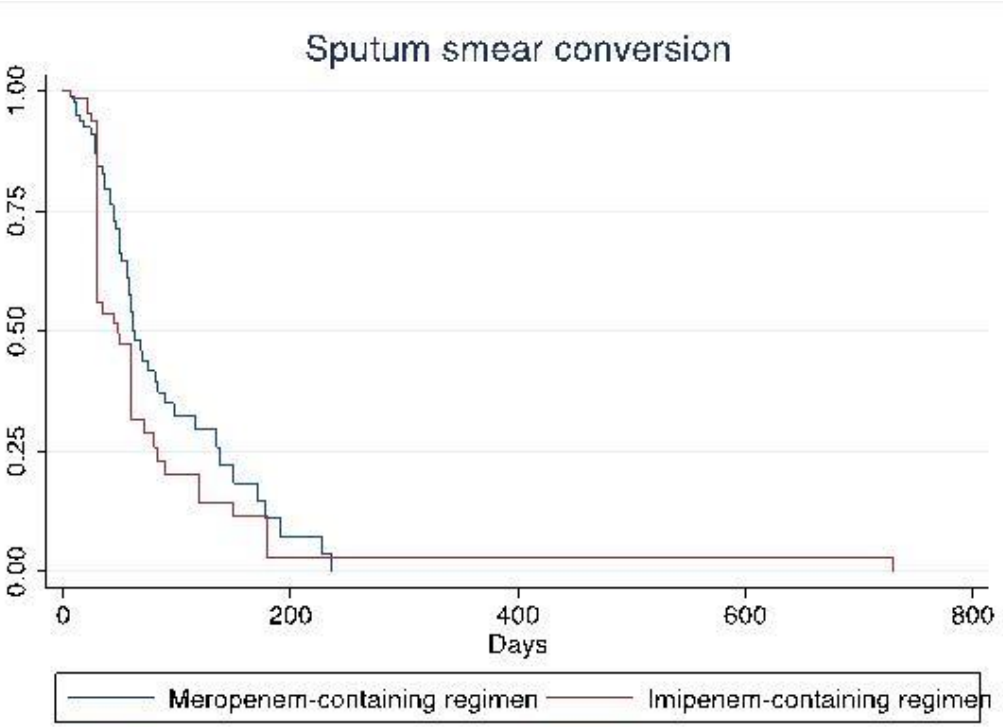
MDR-TB of the central nervous system

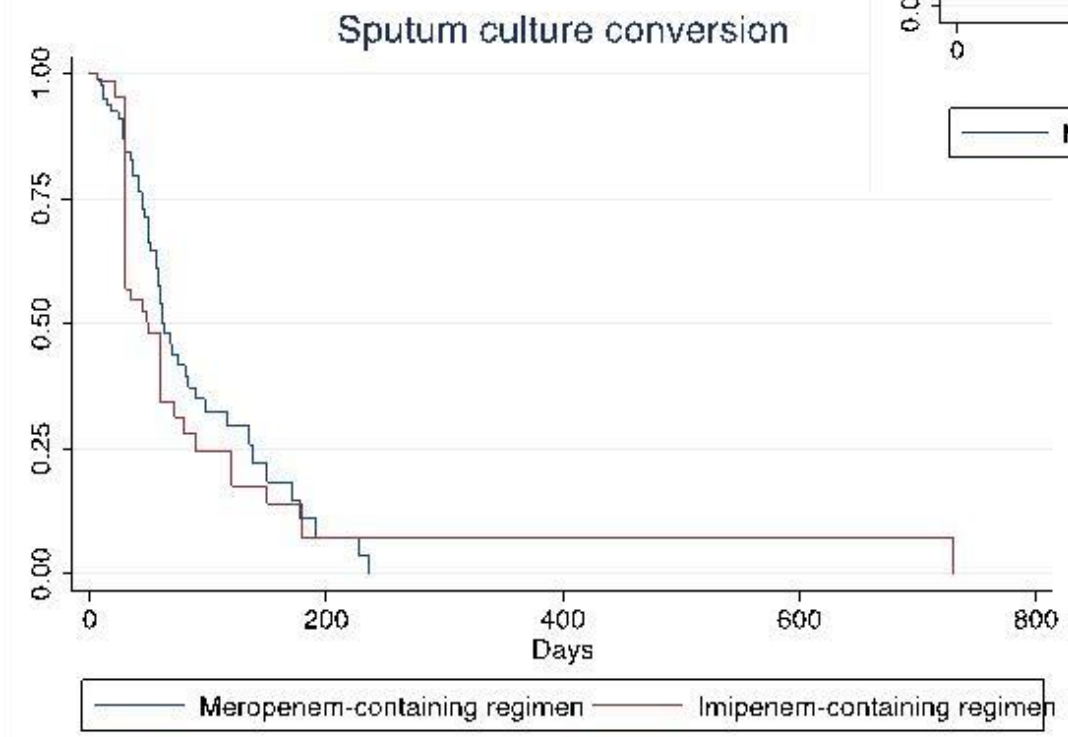
The choice of the regimen is best guided by drug susceptibility results and the known properties of TB drugs to penetrate the central nervous system.

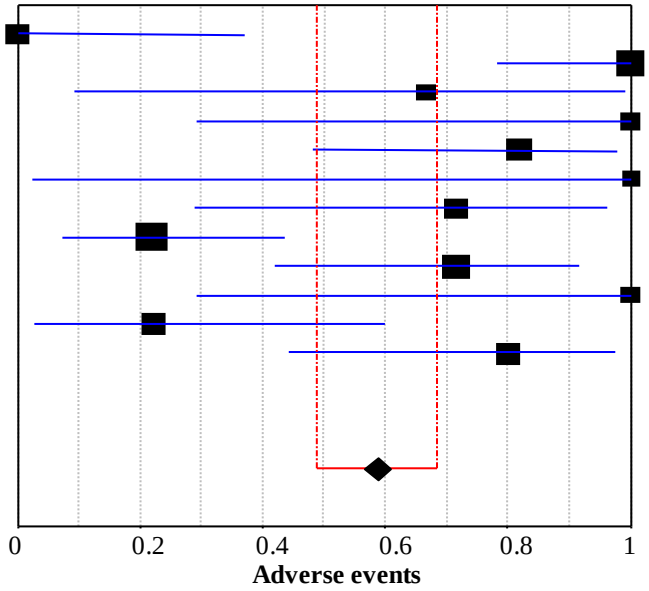
- The fluoroquinolones ethionamide (or prothionamide), cycloserine (or terizidone) and linezolid have good CNS penetration – as well as all first line drugs.
- PAS and ethambutol do not penetrate the CNS well and should not be counted upon among the number of effective drugs to treat MDR-TB meningitis.
- Kanamycin, amikacin and streptomycin only penetrate the cerebrospinal fluid in the presence of meningeal inflammation.
- There are little data on the CNS penetration of capreomycin, clofazimine, bedaquiline or delamanid.

International Carbapenems Study Group (ICSG)

	Meropenem 96 cases (49.0% XDR)	Imipenem 84 cases (67.9% XDR)
Setting	5 centres /15 countries, 4 continents	10 centrEs /15 countries, 4 continents
Age/sex M	34±10.3 yr/56.3% (76.0% migr)	36±11.2 yr/60.7% (32.1% migr)
HIV+/ART	8 HIV+ (9%)/ 6 ART	2 HIV+ (2.4%) on ART
Previous Diagnosis	Failure 79.0%; success 11.3%	Failure 87.2%; success 1.3% **P<0.05**
Previous Tx	Median 2 (IQR 1-4)	Median 2 (IQR 1-3)
Resistant to	**Median 8 drugs (IQR 6-9)**	**Median 8 drugs (IQR 7-8)** **P<0.05**
Duration	**85 d (IQR 49-156)**	**187 d (IQR 60-428)**
SS neg	**45 d (IQR 28-68)**	**30 d (IQR 30-60)**
C neg	**44 d (IQR 28-75)**	**60 d (IQR 30-90)** **P<0.05**
Outcomes	**Success 57.3%;** continue Tx 25.0%; died 11.4%; default 5.2%	**Success 40.5%;** continue Tx 27.3%; died 23.9%; adefault 7.1% **P**


Sputum smear conversion
1.00
0.75
0.50
0.25
0.00
0
200
400
600
800
Days
Meropenem-containing regimen
Imipenem-containing regimen

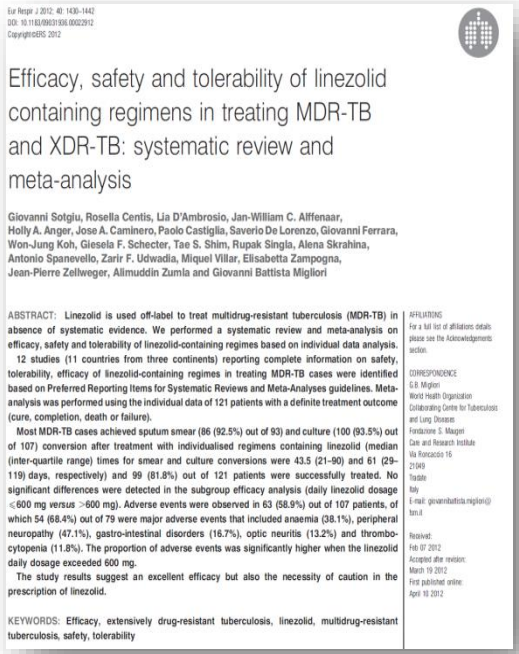

Sputum culture conversion
1.00
0.75
0.50
0.25
0.00
0
200
400
600
800
Days
Meropenem-containing regimen
Imipenem-containing regimen



Proportion of adverse events (95% CI)

Alffenaar JWC et al. [46]	0.00	(0.00 - 0.37)
Anger HA/Condos R et al. [34]	1.00	(0.78 - 1.00)
De Lorenzo S et al. [35]	0.67	(0.09 - 0.99)
Fortun J et al. [22]	1.00	(0.29 - 1.00)
Koh WJ et al. [45]	0.82	(0.48 - 0.98)
Migliori GB et al. [8]	1.00	(0.03 - 1.00)
Park IN et al. [44]	0.71	(0.29 - 0.96)
Schecter GF et al. [30]	0.22	(0.07 - 0.44)
Singla R et al. [31]	0.71	(0.42 - 0.92)
Udwadia ZF et al. [32]	1.00	(0.29 - 1.00)
Villar M et al. [33]	0.22	(0.03 - 0.60)
Von der Lippe B et al. [43]	0.80	(0.44 - 0.97)

Pooled Proportion = 0.59 (0.49 to 0.68)
Chi-square = 61.94; df = 11 (p = 0.0000)
Inconsistency (I^2) = 82.2 %



Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis

Giovanni Sotgiu, Rosella Centis, Lia D'Ambrosio, Jan-William C. Alffenaar, Holly A. Anger, Jose A. Caminero, Paolo Castiglia, Saverio De Lorenzo, Giovanni Ferrara, Won-Jung Koh, Giesela F. Schecter, Tae S. Shim, Rupak Singla, Alena Skrahina, Antonio Spanevello, Zarir F. Udwadia, Miquel Villar, Elisabetta Zampogna, Jean-Pierre Zellweger, Alimuddin Zumla and Giovanni Battista Migliori

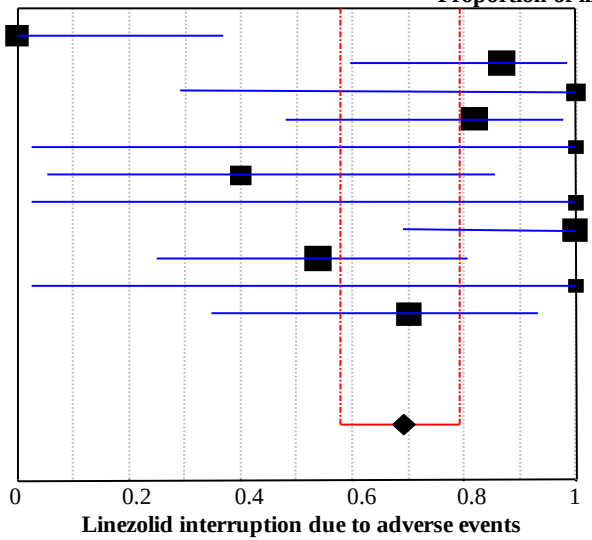
ABSTRACT: Linezolid is used off-label to treat multidrug-resistant tuberculosis (MDR-TB) in absence of systematic evidence. We performed a systematic review and meta-analysis on efficacy, safety and tolerability of linezolid-containing regimes based on individual data analysis.

12 studies (11 countries from three continents) reporting complete information on safety, tolerability, efficacy of linezolid-containing regimes in treating MDR-TB cases were identified based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Meta-analysis was performed using the individual data of 121 patients with a definite treatment outcome (cure, completion, death or failure).

Most MDR-TB cases achieved sputum smear (86 (92.5%) out of 93) and culture (100 (93.5%) out of 107) conversion after treatment with individualised regimens containing linezolid (median (inter-quartile range) times for smear and culture conversions were 43.5 (21–90) and 61 (29–119) days, respectively) and 99 (81.8%) out of 121 patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage ⩽600 mg *versus* >600 mg). Adverse events were observed in 63 (58.9%) out of 107 patients, of which 54 (68.4%) out of 79 were major adverse events that included anaemia (38.1%), peripheral neuropathy (47.1%), gastro-intestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%). The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg.

The study results suggest an excellent efficacy but also the necessity of caution in the prescription of linezolid.

KEYWORDS: Efficacy, extensively drug-resistant tuberculosis, linezolid, multidrug-resistant tuberculosis, safety, tolerability



Proportion of linezolid interruption due to adverse events (95% CI)

Alffenaar JWC et al. [46]	0.00	(0.00 - 0.37)
Anger HA/Condos R et al. [34]	0.87	(0.60 - 0.98)
Fortun J et al. [22]	1.00	(0.29 - 1.00)
Koh WJ et al. [45]	0.82	(0.48 - 0.98)
Migliori GB et al. [8]	1.00	(0.03 - 1.00)
Park IN et al. [44]	0.40	(0.05 - 0.85)
Schecter GF et al. [30]	1.00	(0.03 - 1.00)
Singla R et al. [31]	1.00	(0.69 - 1.00)
Udwadia ZF et al. [32]	0.54	(0.25 - 0.81)
Villar M et al. [33]	1.00	(0.03 - 1.00)
Von der Lippe B et al. [43]	0.70	(0.35 - 0.93)

Pooled Proportion = 0.69 (0.58 to 0.79)
Chi-square = 37.19; df = 10 (p = 0.0001)
Inconsistency (I^2) = 73.1 %

AE in Linezolid- containing regimens. Sotgiu et al, ERJ 2012

SUMMARY OF EXPERIMENTAL REGIMENS IN MDR-TB CLINICAL TRIALS UNDERWAY OR PLANNED (Source: TREAT-TB/Resist-TB)

Trial Name (funding source)	Duration of Experimental regimen (months)	Comparator	Experimental Arm(s)	GOAL			
				Shorten	All-oral	Improve tolerability	Improve cure rates
C 213 /Phase 3 Delamanid (Otsuka)	24	WHO Std	DLM+OBT				X
NeXT (MRC-SA)	6-9	SA Std	BDQ+LZD+LFX+ETA/ INH_H +PZA	X	X		X
End-TB (UNITAID)	9	None	BDQ+LZD+MXF+PZA BDQ+CFZ+LZD+LFX+PZA BDQ+CFZ+LFX+PZA DLM+LZD+MFX+PZA DLM+CFZ+LZD+LFX+PZA DLM+CFZ+LFX+PZA	X	X	X	
TB-PRACTECAL (MSF)	6	WHO Std	BDQ+PRT+LZD+MXF BDQ+PRT+LZD+CFZ BDQ+PRT+LZD	X	X	X	
STREAM Stage 1 (USAID+)	9	WHO Std	CFZ+EMB+MFX+PZA+4(KM+INH_H+PTO)	X			
STREAM Stage 2 (USAID+)	6: 9:	WHO std / 9 mo. regimen	BDQ+LFX+CFZ+PZA+2(INH_H+KM) BDQ+CFZ+EMB+LFX+PZA+4(INH_H+PTO)	X	X		
NC-005* (GATB)	2 (followed by OBT)	None for MDR Arm	BDQ+PRT+MFX+PZA *Note: this is a phase 2 study*	X	X	X	
NiX-TB (GATB)	6-9	None	BDQ+PRT+LZD *Note: pre-XDR and XDR only*	X	X	X	
STAND* (GATB)	4-6 months	None for MDR ARM	PRT+MFX+PZA	X	X	X	
Novartis	24	WHO Std	CFZ+OBT				X

Shashikant Srivastava[1], Charles A. Peloquin[2], Giovanni Sotgiu[3] and Giovanni Battista Migliori[4]

Affiliations: [1]Dept of Medicine and Office of Global Health, UT Southwestern Medical Center, Dallas, TX, [2]College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA, [3]Epidemiology and Medical Statistics Unit, Dept of Biomedical Sciences, University of Sassari–Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, [4]WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy.

Correspondence: Giovanni Battista Migliori: S. Maugeri Foundation, Via Roncaccio 16, Tradate, Varese, Italy: E-mail: giovannibattista.migliori@fsm.it

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Multidrug- and extensively drug-resistant (M/XDR) tuberculosis (TB) are emerging public health concerns [1, 2]. In 2011, the World Health Organization (WHO) estimated 12 million prevalent cases of TB globally, which is equivalent to 170 cases per 100 000 population, out of these an estimated 630 000 cases were affected by MDR *Mycobacterium tuberculosis* strains [3]. Among the newly diagnosed patients ~3.7% were infected by MDR-TB strains, but the worrisome fact is that the prevalence of MDR-TB among new cases in some Former Soviet Union countries exceeds 30% [4, 5], XDR-TB has been identied in 84 countries and the average proportion of MDR-TB cases with an XDR-TB pattern is 9.0% [3]. Further adding to the problem are the reports of "totally drug resistant" TB [6, 7], a term currently not recognised by WHO [8, 9].

Treatment of drug resistant TB is more expensive and more toxic if compared with that prescribed for drug-susceptible TB, and currently takes up to 2 years of therapy [10]. The cost per patient to treat MDR-TB cases is incredibly high [11, 12] and, in spite of international public health efforts, the treatment outcome is not very promising [13–15]. DIEL *et al.* [16] showed that direct treatment-related costs of MDR-TB patients can amount to €52 259 in Germany (table 1).

In the largest MDR-TB cohort analysed to date [13] the proportion of cases treated successfully was 62%, with 7% failing or relapsing, 9% dying and 17% defaulting; in the XDR-TB subgroup 40% achieved treatment success, 22% failed treatment or relapsed, whereas 15% died and 16% defaulted [14, 15].

In this issue of the *European Respiratory Journal* (*ERJ*) a Dutch group from Groningen [17] reported on the results of a prospective pharmacokinetic (PK) study aimed at quantifying the effect of clarithromycin on the exposure to linezolid. In simple terms they observed that clarithromycin, which has some activity against TB bacilli and is well tolerated, increases linezolid exposure (*i.e.* increases the blood levels of linezolid, which is a very expensive and toxic drug). The authors decided to quantify this phenomenon administering a fix dose of linezolid (300 mg twice a day) plus a variable one of clarithromycin (250–500 mg once a day). Using validated PK methods they demonstrated that linezolid exposure significantly increased after the co-administration of 500 mg clarithromycin by a median (interquartile range) of 44% (23–102%), when compared with baseline conditions, whereas 250 mg clarithromycin had no statistically significant effect. Co-administration was well tolerated by most patients; no patients experienced severe adverse events.

The clinical implications of these findings are as follows: 1) clarithromycin might be used as a booster for linezolid, exactly as low-dose ritonavir is used to increase protease inhibitor exposure in combined antiretroviral therapy; and 2) the relatively cheap clarithromycin could reduce the prescribed dose of the

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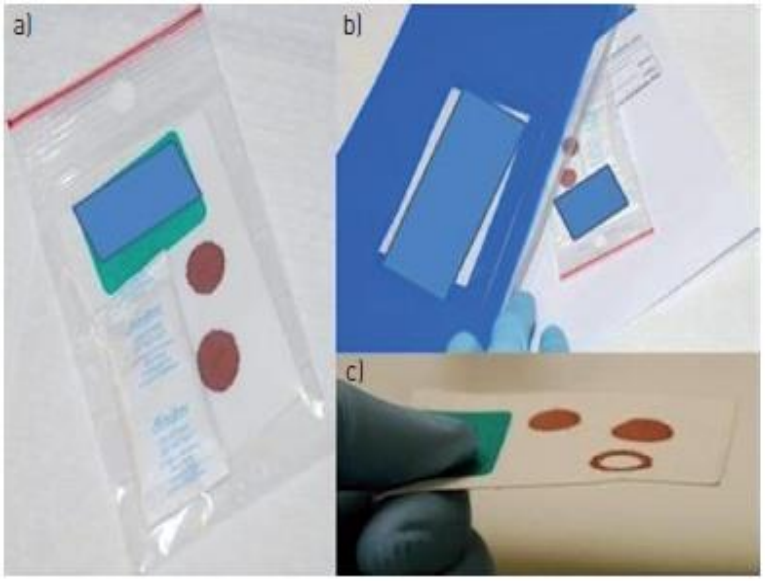
Conflict of interest: None declared

TDM: is it the future of MDR-TB treatment?



Clinical Infectious Diseases Advance Access published August 10, 2016

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

Keywords. *Mycobacterium tuberculosis*; HIV infections; antitubercular agents; case management; public health.

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These guidelines were endorsed by the European Respiratory Society (ERS) and the US National Tuberculosis Controllers Association (NTCA). It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The sponsoring and endorsing societies consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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EXECUTIVE SUMMARY

The American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) jointly sponsored the development of this guideline on the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society (ERS) and the US National Tuberculosis Controllers Association (NTCA). This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular

TDM

shipped frozen to a reference laboratory. Quality-assured laboratories in the United States and in Europe offer assays for some or all of the antituberculosis drugs [240, 241]. There are no prospective randomized trials that clearly define the role of TDM for antituberculosis drugs. As such, opinions vary regarding the utility of TDM. Experts generally use TDM as a specialized tool, providing insight into the adequacy of drug dosing [242]. For example, serum concentrations of tuberculosis drugs among children and HIV-infected patients with tuberculosis are frequently lower than those in healthy volunteers, at the same (mg/kg body weight) dose [243–246]. In some reports, lower concentrations did not have an impact on treatment response or cure [247–249]. Other reports have found an association between low drug exposure and failure, relapse, and acquired rifamycin resistance [250–252]. TDM cannot predict who will be cured, fail, or relapse; however, it does allow for timely, informed decisions regarding the need for dose adjustment when necessary. Experts suggest that TDM may be particularly helpful in situations in which drug malabsorption, drug underdosing, or clinically important drug–drug interactions are suspected (Table 9). Examples of situations in which TDM may be useful include (1) patients with delayed sputum conversion or treatment failure not explained by nonadherence or drug resistance; (2) patients with medical conditions (eg, reduced renal function) that are suspected of leading to subtherapeutic or toxic drug concentrations; and (3) patients undergoing treatment for drug-resistant tuberculosis.

Therapeutic Drug Monitoring

TDM generally consists of measurements of drug concentrations in serum specimens typically collected at 2 and 6 hours after a dose of the drug, or drugs, in question. Other sampling times may be used for selected situations. Blood samples are centrifuged; the serum is harvested and frozen, and then

Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

Poor response to tuberculosis treatment despite adherence and fully drug-susceptible *Mycobacterium tuberculosis* strain
Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption
Drug–drug interactions
Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
HIV infection
Diabetes mellitus
Treatment using second-line drugs

Abbreviation: HIV, human immunodeficiency virus.

Treatment outcome	XDR alone	XDR+2sli	XDR+sliG4†	XDR+sliG4EZ
	n = 301	*n = 68*	*n = 48*	*n =42*
Cured	**43** (27, 58)	**30** (17, 43)	**34** (-, -)	**19** (0, 48)*
Failed	**20** (15, 25)	**29** (8, 50)	**33** (-, -)	**26** (14, 38)
Died	**13** (6, 20)	**18** (7, 29)	**30** (18, 41)*	**35** (21, 50)*
Failed or died	**35** (26, 45)	**54** (40, 69)*	**48** (-, -)	**49** (37, 61)
Defaulted	15 (5, 24)	15 (3, 27)	18 (-, -)	19 (6, 32)

Treatment outcome	XDR-alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
	n = 301	*n = 68*	*n = 48*	*n =42*
Cured	1.0 (reference)	**0.4 (0.2, 0.8)**	0.6 (0.2, 1.6)	0.5 (0.2, 1.7)
Failed	1.0 (reference)	2.1 (1.0, 4.5)	1.8 (0.7, 4.7)	1.9 (0.7, 5.3)
Died	1.0 (reference)	1.6 (0.6, 4.4)	1.7 (0.6, 4.9)	1.8 (0.6, 5.3)
Failed or Died	1.0 (reference)	**2.6 (1.2, 4.4)**	**2.6 (1.1, 6.7)**	2.8 (1.0, 7.9)
Defaulted	1.0 (reference)	1.0 (0.3, 2.6)	0.5 (0.2, 1.8)	0.5 (0.1, 2.0)

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PLOS | MEDICINE

Multidrug-Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients

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ORIGINAL ARTICLE
TUBERCULOSIS

Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes

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ABSTRACT A meta-analysis for response to treatment was undertaken using individual data of multidrug-resistant tuberculosis (MDR-TB) (resistance to isoniazid and rifampicin) patients from 26 centres. The analysis assessed the impact of additional resistance to fluoroquinolones and/or second-line injectable drugs on treatment outcome.

Compared with treatment failure, relapse and death, treatment success was higher in MDR-TB patients infected with strains without additional resistance (n=4763; 64%, 95% CI 57–72%) or with resistance to second-line injectable drugs only (n=1130; 56%, 95% CI 45–66%), than in those having resistance to fluoroquinolones alone (n=426; 48%, 95% CI 36–60%) or to fluoroquinolones plus second-line injectable drugs (extensively drug resistant (XDR)-TB) (n=405; 40%, 95% CI 27–53%). In XDR-TB patients, treatment success was highest if at least six drugs were used in the intensive phase (adjusted OR 4.9, 95% CI 1.4–16.6; reference fewer than three drugs) and four in the continuation phase (OR 6.1, 95% CI 1.4–26.3). The odds of success in XDR-TB patients was maximised when the intensive phase reached 6.6–9.0 months duration and the total duration of treatment 20.1–25.0 months.

In XDR-TB patients, regimens containing more drugs than those recommended in MDR-TB but given for a similar duration were associated with the highest odds of success.

All data were from observational studies and methodologies varied between centres, therefore, the bias may be substantial. Better quality evidence is needed to optimise regimens.

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Resistance to fluoroquinolones and second-line injectable drugs have additive adverse impacts on MDR-TB outcomes http://ow.ly/kMDN8

ORIGINAL ARTICLE
TUBERCULOSIS

Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis

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ABSTRACT The broadest pattern of tuberculosis (TB) drug resistance for which a consensus definition exists is extensively drug-resistant (XDR)-TB. It is not known if additional drug resistance portends worsened patient outcomes. This study compares treatment outcomes of XDR-TB patients with and without additional resistance in order to explore the need for a new definition.

Individual patient data on XDR-TB outcomes were included in a meta-analysis comparing outcomes between XDR alone and three nonmutually exclusive XDR-TB patient groups: XDR plus resistance to all the second-line injectables (sli) and capreomycin and kanamycin/amikacin (XDR+2sli) XDR plus resistance to second-line injectables and to more than one group 4 drug, *i.e.* ethionamide/protionamide, cycloserine/terizidone or para-aminosalicylic acid (XDR+sliG4) and XDR+sliG4 plus resistance to ethambutol and/or pyrazinamide (XDR+sliG4EZ).

Of 405 XDR-TB cases, 301 were XDR alone, 68 XDR+2sli, 48 XDR+sliG4 and 42 XDR+sliG4EZ. In multivariate analysis, the odds of cure were significantly lower in XDR+2sli (adjusted OR 0.4, 95% CI 0.2–0.8) compared to XDR alone, while odds of failure and death were higher in all XDR patients with additional resistance (adjusted OR 2.6–2.8).

Patients with additional resistance beyond XDR-TB showed poorer outcomes. Limitations in availability, accuracy and reproducibility of current drug susceptibility testing methods preclude the adoption of a useful definition beyond the one currently used for XDR-TB.

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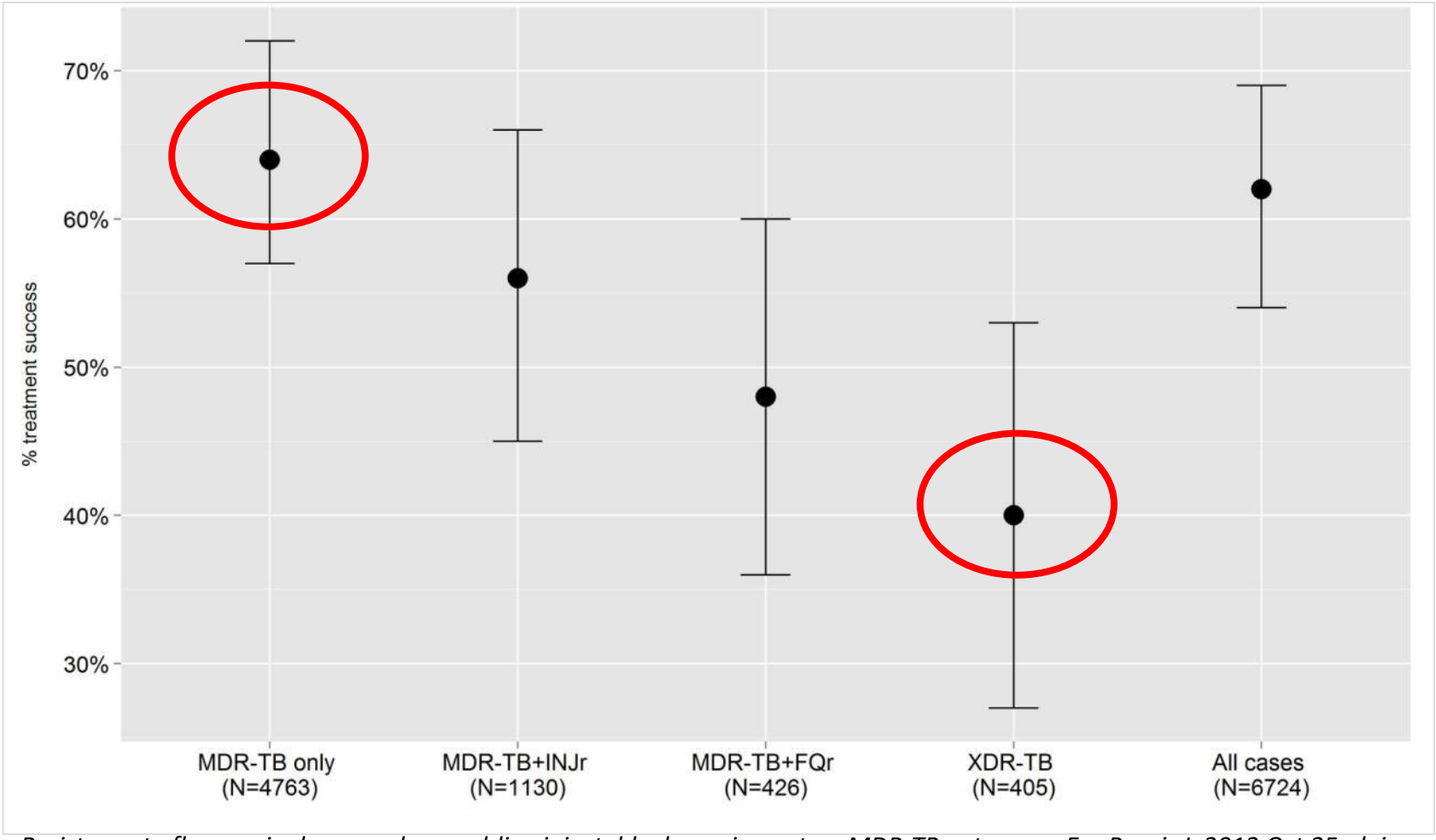
Drug resistance beyond extensively drug-resistant tuberculosis: patients with additional resistance have poorer outcomes http://ow.ly/kFUA3

Treatment success among different MDR-TB patient groups
(circles=point estimates; lines=95% confidence interval)



Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. Eur Respir J. 2012 Oct 25; doi: 10.1183/09031936.00134712

RESIST-TB

Research Excellence to Stop TB Resistance

DRUG-RESISTANT TUBERCULOSIS CLINICAL TRIALS PROGRESS REPORT

Trial Name	Description	Status	Phase	Trial Registry Identifier (link)	Expected Study Completion Date
Janssen C211	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of bedaquiline in combination with MDR-TB therapy for HIV uninfected children and adolescents	Open for participant enrollment	Phase 2	NCT02354014	2025
STREAM Stage 1	Comparison of standard WHO MDR-TB regimen with 9-month modified Bangladesh Regimen	Enrollment complete; follow up ongoing	Phase 3	ISRCTN78372190	2018
STREAM Stage 2	Comparison of 6 and 9 month bedaquiline-containing regimen against the WHO and Bangladesh regimen	Open for participant enrollment	Phase 3	NCT02409290	2021
NeXT	Open label RCT of a 6-9 month injection free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high dose isoniazid, and pyrazinamide	Currently enrolling participants in South Africa	Phase 3	NCT02454205 PACTR201409000848428	2019
NiX-TB	Study of bedaquiline, pretomanid, and linezolid in patients with XDR-TB and MDR-TB for 6 months with an option of 9 months	Currently enrolling participants in South Africa	Phase 3	NCT02333799	2021
NC-005	Study of combinations of bedaquiline, moxifloxacin, pretomanid, and pyrazinamide for 8 weeks for DS-TB and MDR-TB patients, with one arm for MDR-TB patients adding moxifloxacin to bedaquiline, PA-824 and pyrazinamide	Fully enrolled	Phase 2	NCT02193776	2018
DELIBERATE (ACTG 5343)	Study of drug-drug interactions and combined QT effects of bedaquiline and delamanid	Open for participant enrollment	Phase 2	NCT02583048	2021
Otsuka 213	Safety and efficacy study of delamanid or placebo for 6 months in combination with optimized background therapy for 18-24 months	Study completed follow-up for primary endpoint, data analysis ongoing	Phase 3	NCT01424670	2017
Otsuka 233	Safety, efficacy, and pharmacokinetic study of delamanid in pediatric patients with MDR-TB	Enrollment completed for	Phase 2	NCT01859923	2020

Last updated October 24, 2017

RESIST-TB

Research Excellence to Stop TB Resistance

DRUG-RESISTANT TUBERCULOSIS CLINICAL TRIALS PROGRESS REPORT

Trial Name	Description	Status	Phase	Trial Registry Identifier (link)	Expected Study Completion Date
		cohorts age 6+ years; enrollment open for cohort age <6 years			
Otsuka 232	Pharmacokinetic and safety trial of delamanid to determine the appropriate dose for pediatric MDR-TB HIV- patients	Enrollment completed for cohorts aged 6-11 and 12-17 years; enrollment for cohort aged 3-5 years open, dosing for patients birth to 2 years will be determined from at least 6 patients in group 3	Phase 1	NCT01856634	2018
ACTG 5312	Safety and efficacy study of different doses and generic variants of isoniazid resistant TB	Currently enrolling participants in South Africa	Phase 2	NCT01936831	2018
Opti-Q	Efficacy and safety study of increased doses of levofloxacin in combination with optimized background therapy	Follow up completed; anaylsis underway	Phase 2	NCT01918397	2017
STAND	Efficacy, safety and tolerability of a combination of moxifloxacin, pretomanid, and pyrazinamide treatments after 6 months of treatment in subjects with MDR-TB compared to combination of moxifloxacin, pretomanid, and pyrazinamide treatments in DS-TB subjects; there will be a comparator arm for MDR-TB	Currently on hold; Suspended participant enrollment	Phase 3	NCT02342886	2018
V-QUIN	Evaluating 6 months daily levofloxacin vs. placebo as preventive therapy in contacts of MDR-TB. Enrolling Children, adolescents, infants HIV+/HIV- Household randomization	Currently enrolling participants in Vietnam	Phase 3	ACTRN12616000215426	2021

RESIST-TB
Research Excellence to Stop TB Resistance

DRUG-RESISTANT TUBERCULOSIS CLINICAL TRIALS PROGRESS REPORT

Trial Name	Description	Status	Phase	Trial Registry Identifier (link)	Expected Study Completion Date
MDR-END	Comparing efficacy of treatment regimen including delamanid, linezolid, levofloxacin, and pyrazinamide for 9-12 months, with a control arm of the standard treatment regimen including injectables for 20-24 months for the treatment of quinolone sensitive MDR-TB	Currently enrolling participants in South Korea	Phase 2	NCT02619994	2019
FS-1 Trial	Safety and efficacy of FS-1 in oral dosage form in drug-resistant pulmonary tuberculosis	Currently enrolling participants in Kazakhstan	Phase 3	NCT02607449	2019
TB-CHAMP	Randomized double blind placebo-controlled, superiority multicenter trial to evaluate the efficacy of levofloxacin vs. placebo for the prevention of MDR-TB in child and adolescent household contacts	Currently enrolling	Phase 3	ISRCTN92634082	2021
Janssen Japan Trial	Open-label, single-arm, multi-center trial to explore safety, efficacy and PK of bedaquiline in Japanese participants with pulmonary MDR-TB	Currently enrolling participants	Phase 2	NCT02365623	2020
endTB	Phase III, randomized, controlled, open-label, non-inferiority, multi-country trial evaluating the efficacy and safety of new combination regimens for MDR-TB treatment	Currently enrolling participants in Georgia	Phase 3	NCT02754765	2021
TB-PRACTECAL	Multi-centre, open label, multi-arm, randomized, controlled, phase II-III trial evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and re-purposed anti-TB drugs for the treatment of biologically confirmed pulmonary MDR-TB	Currently enrolling participants in Uzbekistan	Phase 2-3	NCT02589782	2021
ZeNix	Evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB.	This study is not yet open for participant recruitment	Phase 3	NCT03086486	2022

Outcomes	№ of patients		Effect	
	Delamanid	no delamanid	Relative (95% CI)	Absolute (95% CI)
Treatment success at 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population; MGIT)[a]	263/341 (77.1%)	132/170 (77.6%)	**RR 0.993** (0.899 to 1.097)	**5 fewer per 1,000** (from 75 more to 78 fewer)
Mortality at 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population)[b]	18/341 (5.3%)	8/170 (4.7%)	**RR 1.122** (0.498 to 2.527)	**6 more per 1,000** (from 24 fewer to 72 more)
Serious Adverse Events (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population)	89/341 (26.1%) [c]	47/170 (27.6%) [c]	**RR 0.944** (0.698 to 1.276) [d]	**15 fewer per 1,000** (from 76 more to 83 fewer)
QTcF interval prolongation >60ms from baseline on electrocardiogram over 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population)[e,f]	35/341 (10.3%)	12/170 (7.1%)	**RR 1.454** (0.775 to 2.728) [g]	**32 more per 1,000** (from 16 fewer to 122 more)
QTcF interval >500ms (new onset) on electrocardiogram over 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population)[e,h]	7/341 (2.1%)	2/170 (1.2%)	**OR 1.761** (0.362 to 8.568) [g]	**9 more per 1,000** (from 7 fewer to 81 more)
Acquired resistance to delamanid up to 26 weeks (assessed with: Trial 213; ITT population; MGIT or solid media culture)[i,j]	4/341 (1.2%) [k]	0/170 (0.0%)	not estimable	
Time to sputum culture conversion by 6 months (assessed with: Trial 213; MITT population; MGIT)	198/226 (87.6%)	87/101 (86.1%)	**HR 1.17** (0.91 to 1.51)	**40 more per 1,000** (from 27 fewer to 88 more)
Primary analysis: All time points with missing culture data assumed to be positive until sputum culture conversion achieved	51 days	57 days	p=0.0562	
Last observation carried forward (LOCF): All time points with missing culture data assumed to be the same as the last observed result	44 days	57 days	p=0.0281	
Bookended: All time points with missing culture data assumed to be negative if previous and following time point negative and solid culture for time points negative, contaminated or not done	51 days	64 days	p=0.0052	
Sputum culture conversion at 2 months (assessed with: Trial 213; MITT population; MGIT)[m]	132/226 (58.4%)	54/101 (53.5%)	**RR 1.096** (0.889 to 1.352)	**51 more per 1,000** (from 59 fewer to 188 more)
Sputum culture conversion at 6 months (assessed with: Trial 213; MITT population; MGIT)[n]	198/226 (87.6%)	87/101 (86.1%)	**RR 1.017** (0.927 to 1.115)	**15 more per 1,000** (from 63 fewer to 99 more)

Classificazione precedente

Group name	Anti-TB agent	Abbreviation
Group 1. First-line oral agents	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin[a] Rifapentine[a]	H R E Z Rfb Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin[b] Kanamycin Amikacin Capreomycin	S Km Am Cm
Group 3. Fluoroquinolones (FQs)	Levofloxacin Moxifloxacin Gatifloxacin[c] Ofloxacin[d]	Lfx Mfx Gfx Ofx
Group 4: Oral bacteriostatic second-line anti-TB drugs	Ethionamide Prothionamide Cycloserine Terizidone[e] *p*-aminosalicylic acid *p*-aminosalicylate sodium	Eto Pto Cs Trd PAS PAS-Na
Group 5:Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of DR-TB. (This group includes new anti-TB agents).	Bedaquiline Linezolid Clofazimine Amoxicillin/ clavulanate Imipenem/cilastatin[f] Meropenem[f] High-dose isoniazid Thioacetazone[g] Clarithromycin[g]	Bdq Lzd Cfz Amx/Clv Ipm/Cln Mpm High dose H T Clr

First case of XDR-TB treated with DLM+BQ

	Details
Details	India, 39 years, Female, 65 kg (at diagnosis: 31/08/2015)
Case category	Retreatment case; 4 previous treatment rounds
Drugs administered in previous anti-TB treatments	Kanamycin 750 mg im (12 months) Levofloxacin 1g, PAS 10 g, Cycloserine 750 mg, Ethionamide 750 mg, Capreomycin 1g im (14months) High dose Isoniazid 900mg; Rifabutin 300mg; Clofazimine 200mg; Clarythromycin 1g; Amoxicillin-clavulanate 625mg; Terizidone 1g TDS; Imipenem 500mg iv TDS (12 months); Linezolid 600 mg then 300mg
Previous outcome	Cured (twice)
Bacteriology at baseline	Sputum smear +; Culture +; Xpert MTB/RR +
Radiology	Bilateral upper zones fibrocavitary lesions
Drug resistances	Resistant to 12 drugs: H,R, Km,Amk,Cm,Mfx,Ofx,Eto, PAS,Lzd, HdH, High dose Mfx Susceptible to: Cfz
Last treatment regimen	delamanid, bedaquiline, clofazimine (200 mg) and terizidone (1 g), all started on 25/2/2016; meropenem 1g TDS plus amoxi/clav 1g/200mg TDS iv (started 28/2/2016) BQ stopped on 07/03/2016 restarted 12/03/2016

Cardiac safety of XDR-TB regimens including bedaquiline, delamanid and clofazimine

Marina Tadolini[1,7], Rangjung Dolma Lingtsang[2,7], Simon Tiberi[3,7], Martin Enwerem[4,7], Lia D'Ambrosio[5,6,7], Tsetan Dorji Sadutshang[2], Rosella Centis[5] and Giovanni Battista Migliori[5]

	Baseline	Month 1				Month 2				Month 3				Month 4				Month 5				Month 6			
Clinical conditions	Occasional cough with expectoration	Improving Some cough with expectoration				Improving No cough, some expectoration				Improving				Improving				Improving				Improving			
Body weight kg	70	70				69				69.5				69				69				69			
Hospitalisation	October 2015	Yes				Yes				Yes				Yes				Yes				Yes			
Chest radiography	Bilateral upper zones fibro-cavitary lesions									Bilateral upper zones fibro-cavitary lesions															
Sputum smear	Positive	Positive				Negative				Negative				Negative				Negative							
Sputum culture	Positive	Positive				No growth				No growth				Ongoing				Ongoing							
		W1	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W17**	**W18**	**W19**	**W20**	**W21**	**W22**	**W23**	**W24**
Treatment	Started on 25/02/2016																								
Bedaquiline																									
Delamanid																									
Clofazimine	Hold on 2 April																								
Terizidone																									
Meropenem																									
Amoxicillin/ clavulanate																									
Verapamil	Added on 12 March																								
QTc ms	<450	476	486 481	489	491	508		500	508	491	486		512	491	510	507	520	501	489	497	492				

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Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study

Gabriella Ferlazzo, Erika Mohr, Chinmay Laxmeshwar, Catherine Hewison, Jennifer Hughes, Sylvie Jonckheere, Naira Khachatryan, Virginia De Avezedo, Lusine Egazaryan, Amir Shroufi, Stobdan Kalon, Helen Cox, Jennifer Furin, Petros Isaakidis

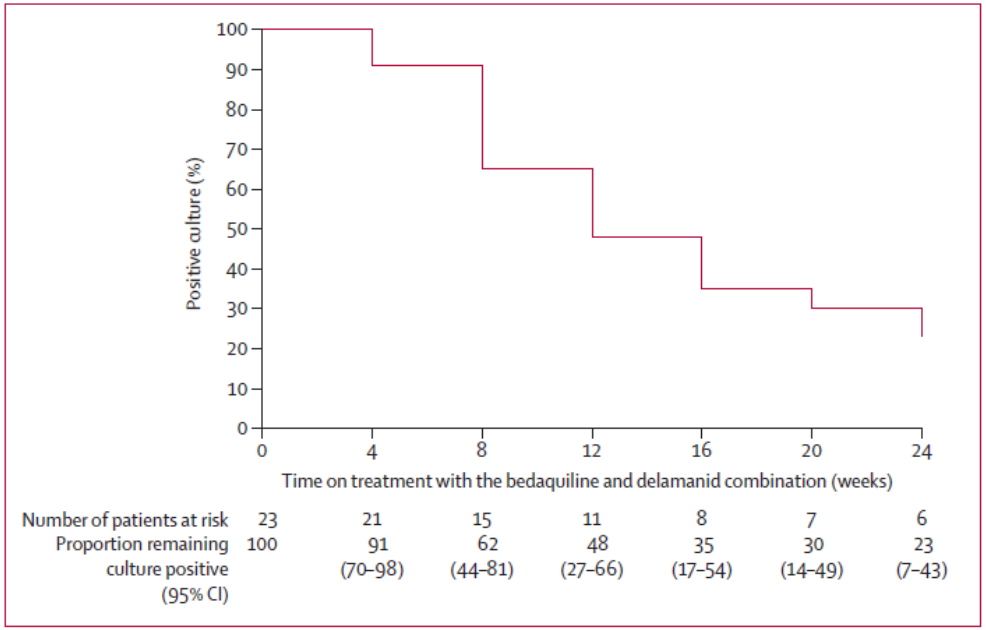

Figure 1: **Effect of combination bedaquiline and delamanid treatment on sputum cultures positive for tuberculosis**
Proportion of patients with positive sputum culture over time in patients enrolled and treated with combination bedaquiline and delamanid from January, 2016, to August, 2016, in Yerevan, Armenia; Mumbai, India; and Khayelitsha, South Africa. This figure includes only patients who had a positive culture at the time the bedaquiline and delamanid combination was initiated

17/23 (74%) who had positive baseline cultures converted to negative at month 6

No pt had an increase of more than 500 ms in their QTcF interval.

4/28 (14%) had six instances of QTcF increase of more than 60 ms from baseline but none permanently discontinued the drugs .

16 AEs reported in 7 patients

6 (H) REZ-Lfx

- If Hr is confirmed before TB treatment is started: 6 (H) REZ-Lfx is started immediately

- If Hr is dicovered after the start of treatment with 2 HRZE/4RH (patients with undiagnosed Hr or who developed Hr while on treatment) -> rapid DST for R. If RR is excluded: 6 (H) RZE-Lfx

Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence

Emanuele Pontali[1], Giovanni Sotgiu[2], Simon Tiberi[3,4], Lia D'Ambrosio[5,6], Rosella Centis[5] and Giovanni B. Migliori[5]

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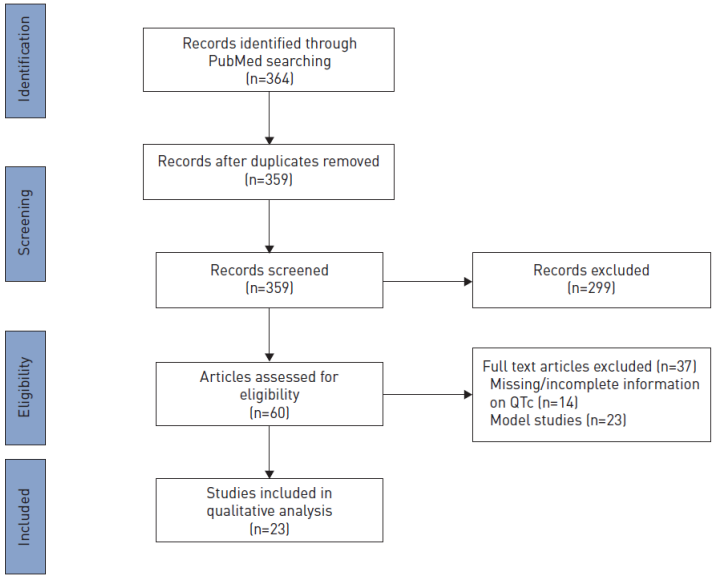

TABLE 1 Continued

First Author, year, (Ref)	Subjects exposed to BDQ	Average BDQ exposure (days) / BDQ dose	Average QTc prolongation	Concomitant drug(s) prolonging QTc	n (%) subjects with QTc >450 msec	n (%) subjects with QTc >500 msec	BDQ discontinuation due to adverse events	n (%) subjects discontinuing BDQ because of QTc prolongation
Total/median	Total: 1303 subjects	Median: 168 days			Total: 35/329 (10.6%) reporting information	Total: 42/1303 (3.2%)	Total: 44/1293 (3.4%) reporting information	Total: 8/875 (0.9%) In 2 patients out of 8 the discontinuation was temporary

In conclusion, analysis of collected information showed that bedaquiline is a relatively well-tolerated drug since its discontinuation occurred in only 3.4% and 0.6% of patients due to adverse events and QTc prolongation, respectively. Nevertheless, no complacency can be allowed, and strict ECG monitoring remains mandatory.