New and repurposed drugs to figh against M/XDR-TB

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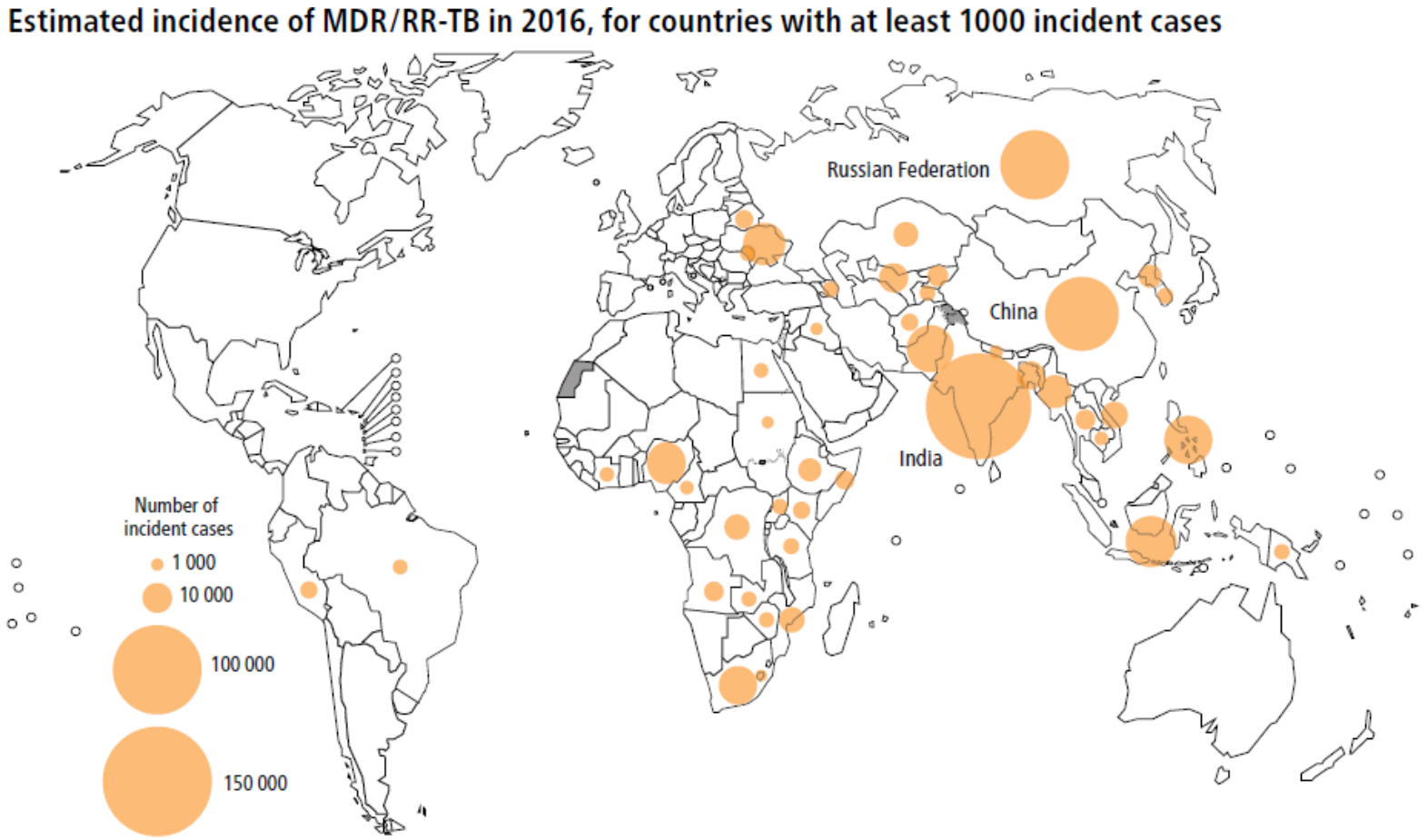
Introduction

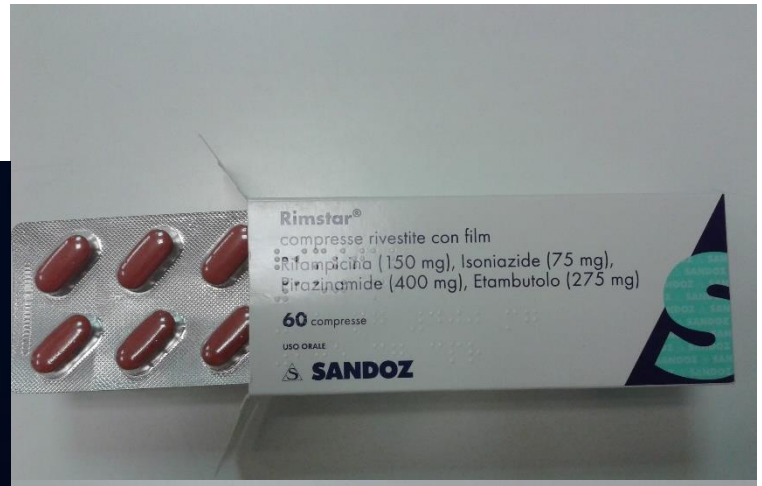
Aims: to discuss

- The need for new drugs
- The clofazimine study
- The carbapenem studies
- The linezolid studies
- The delamanid paediatric study
- The bedaquiline study
- Combining BQ+DLM
- Conclusions

MDR/RR-TB: 3 COUNTRIES, ALMOST 50% CASES

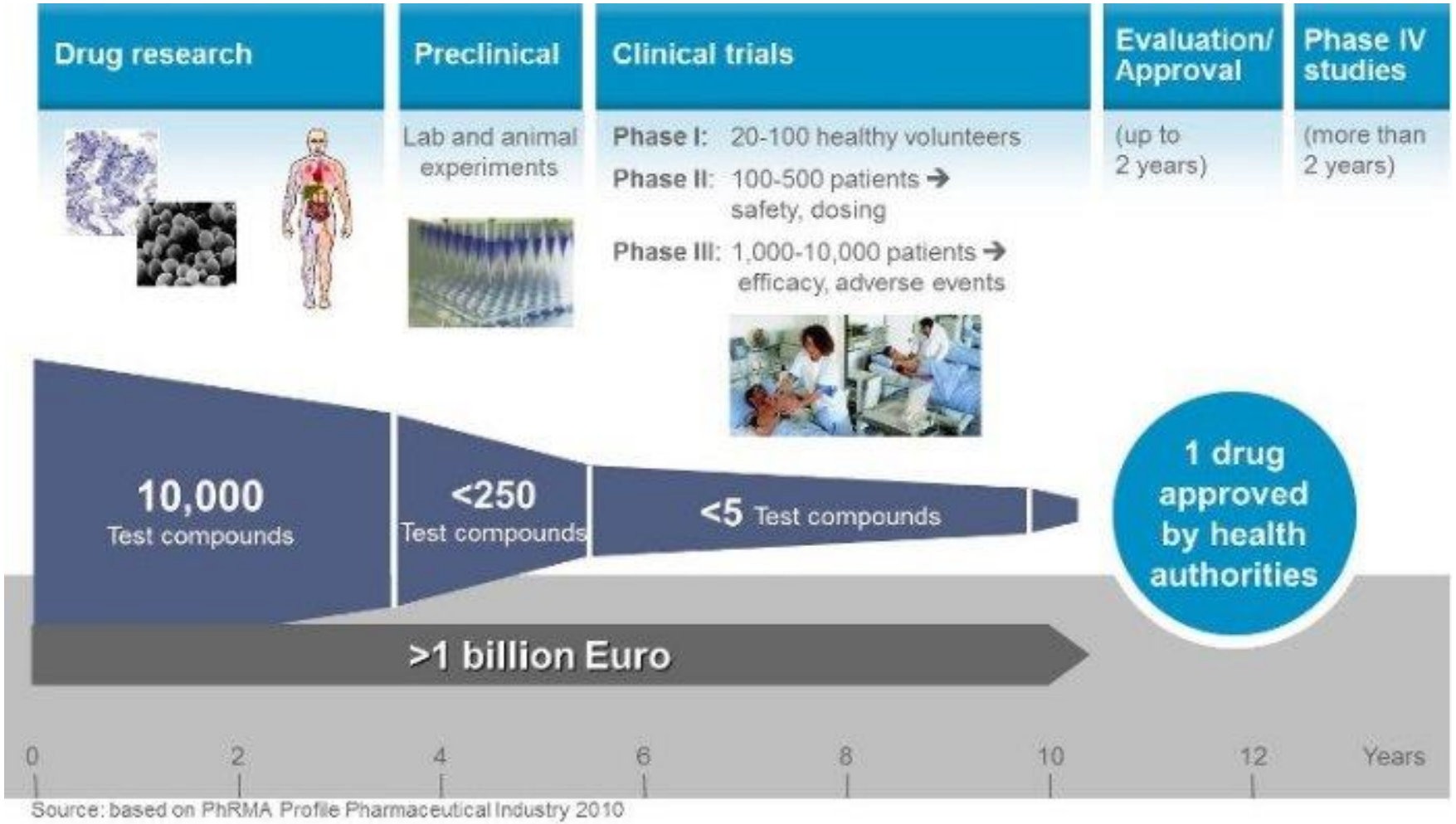


A day of treatment: drug-susceptible TB



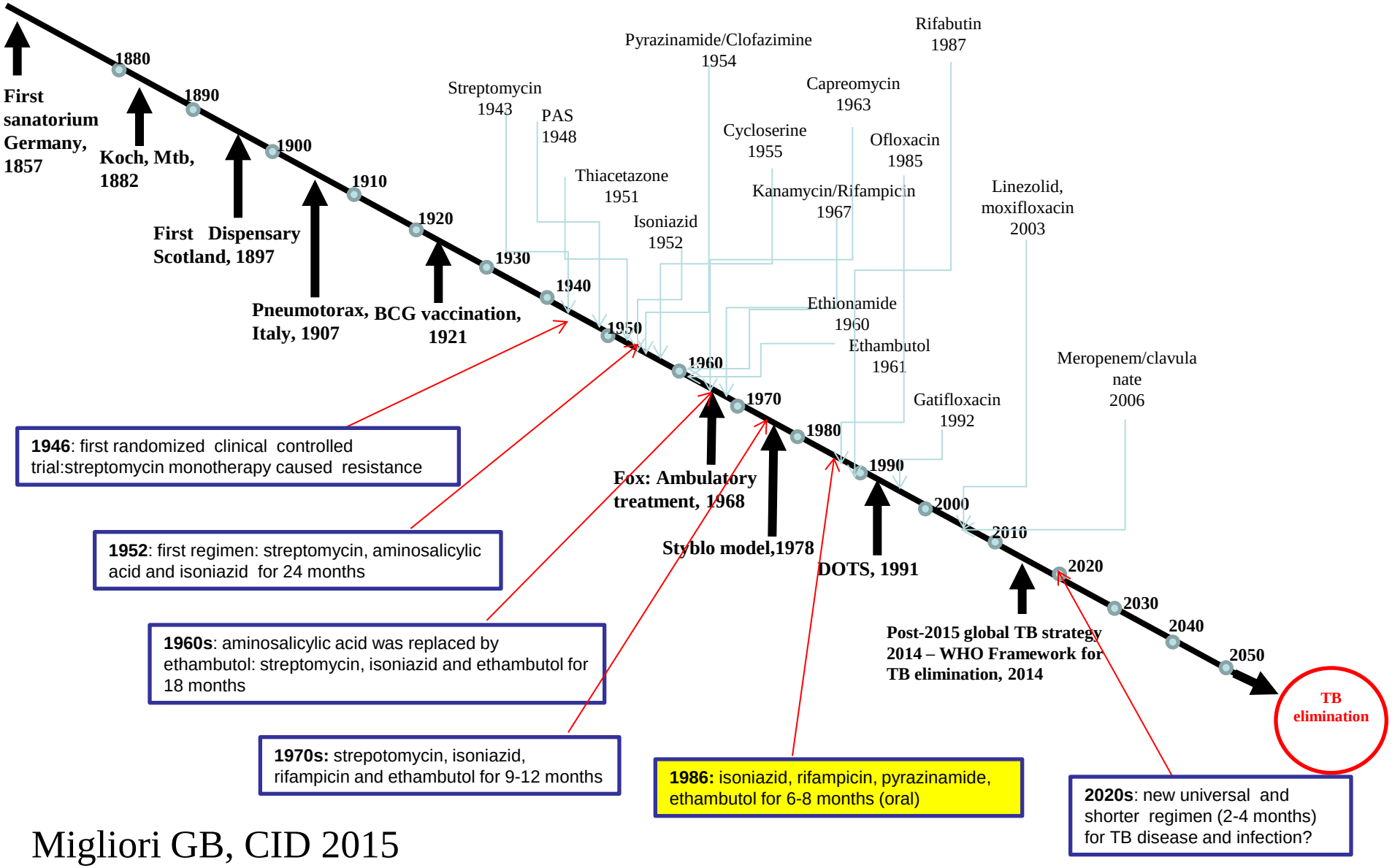
A day of treatment: MDR-TB

Developing a new drug



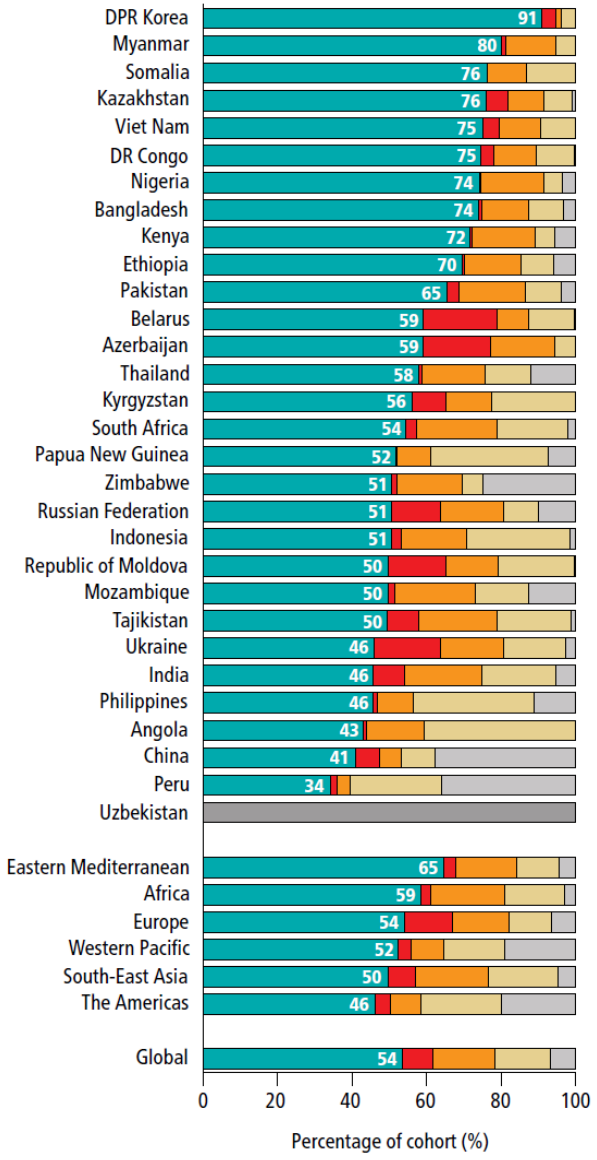
Source: based on PhRMA Profile Pharmaceutical Industry 2010

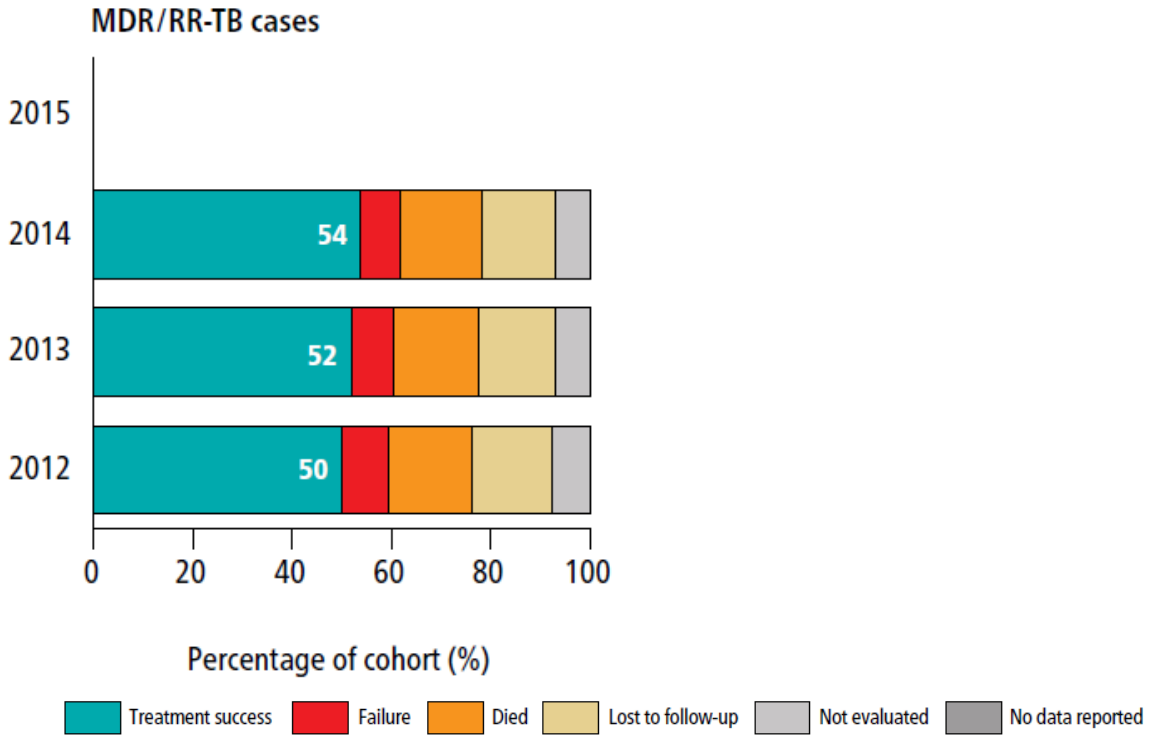
History of anti-TB treatment



Migliori GB, CID 2015

Treatment outcomes for pt diagnosed with MDR-TB by WHO Region, 2012-2014 cohorts





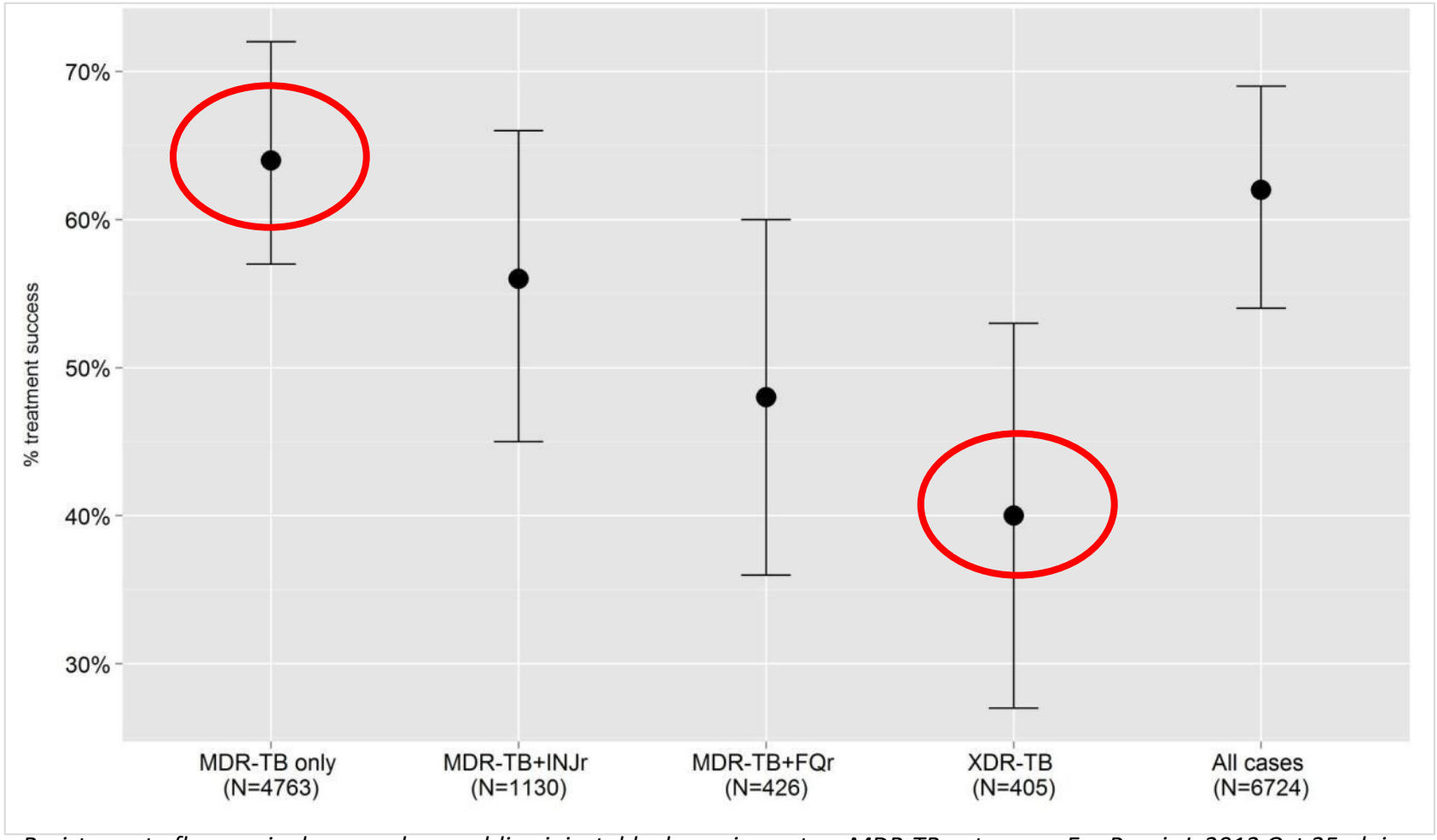
Success IPD global analysis:
Longer 76% (30 studies; ~1400 pts)
Shorter 78% (3 studies, <500 pts, double failures/relapses)

GLOBAL TB PROGRAMME

World Health Organization

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

Shorter MDR-TB regimen (2) - *Main remarks*

- *Standardized regimen*; limited modifications are possible
- 4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E
- Recommendation *applies to adults, children, PLHIV*
- Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; *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*

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Choosing the treatment regimen for RR-/MDR-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?

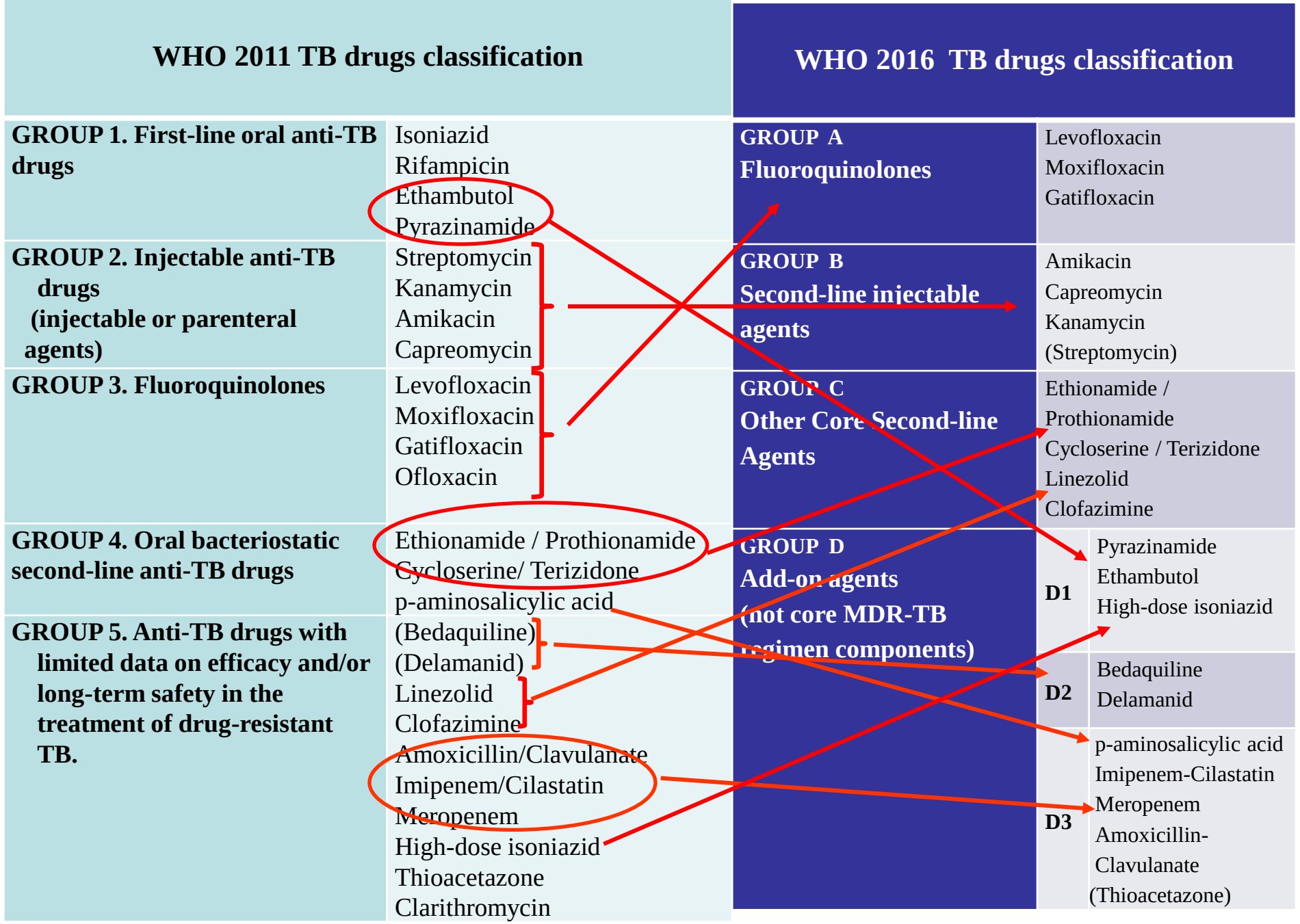
NO

Shorter MDR-TB regimen

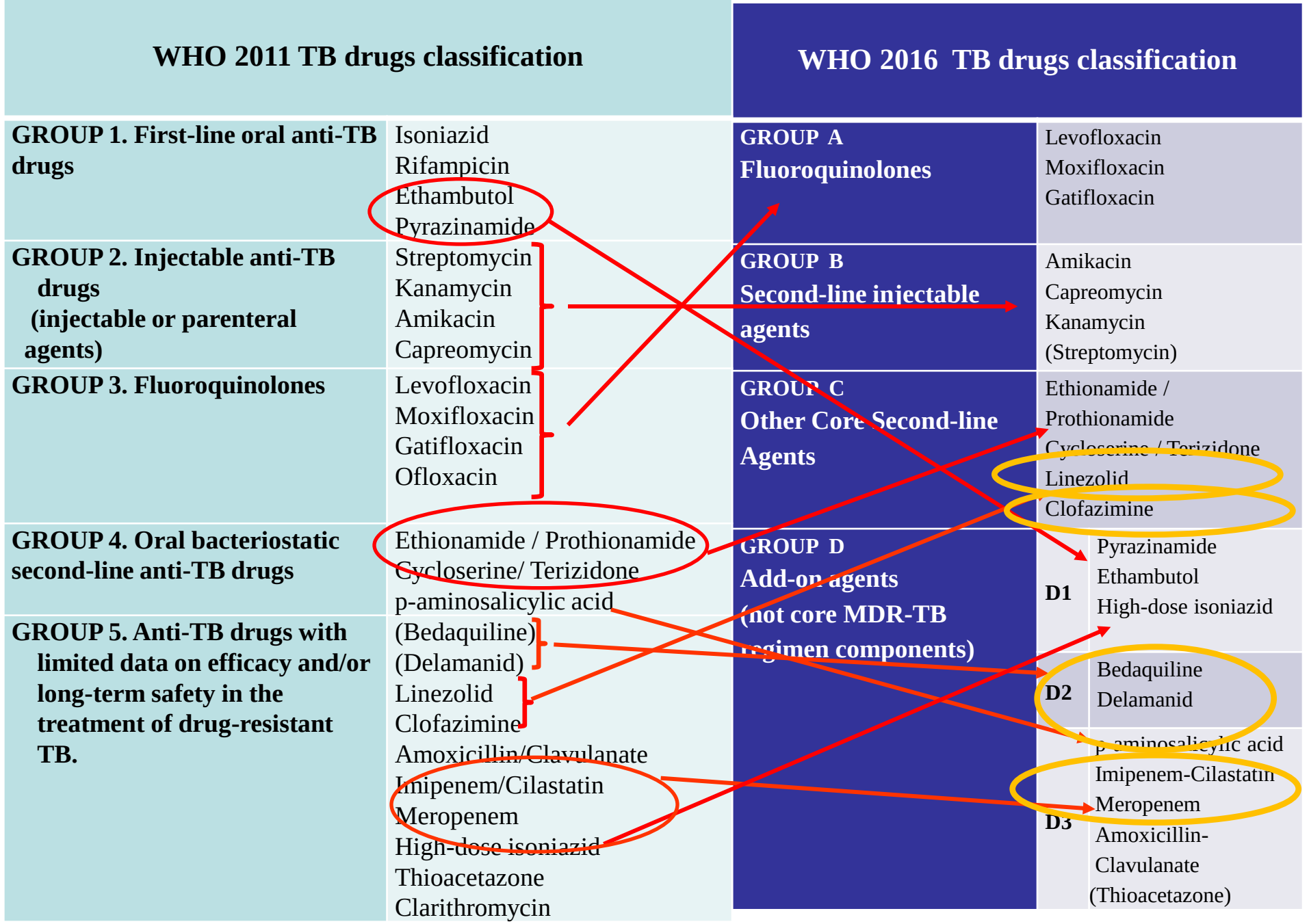
FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Longer MDR-TB regimens



Drugs with potential for further scale-up of the hiearchy: linezolid, delamanid, bedaquiline, carbapenémicos



Drugs with potential for further scale-up of the hiearchy: linezolid, delamanid, bedaquiline, carbapenems

Effectiveness and safety of clofazimine-containing or clofazimine-free regimens in multidrug-resistant tuberculosis patients in Brazil: a first nationwide report on over 2,500 cases

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What know before? Not much

- A single meta-analysis based on cases from the Bangladesh study (selected group)
- Correct dose unknown
- No info on HIV+

Questions:

1. Clofa: does it work with MDR-TB?
2. In HIV co-infected?
3. Which outcomes at programme level?
4. What is the correct dose?
5. Is it really safe?

TABLE 1 Dosage and drug administration details that comprised the treatment regimens for multidrug-resistant tuberculosis (MDR-TB) in Brazil, 2000–2010

Drug	Daily dose ($mg \cdot kg^{-1}$)		
	Body weight ⩽45 kg		Body weight >45 kg
Clofazimine-containing regimen (2000–2006)			
Amikacin	500	‘Young Programme’	750–1000#
Ofloxacin	400		800
Clofazimine	50		100
Terizidone	500		750
Ethambutol	800		1200
Streptomycin	500	Oflo	750–1000#
Pyrazinamide-containing regimen (2006–2010)			
Amikacin	500	‘Mature Programme’	750–1000#
Levofloxacin¶	750		1000
Pyrazinamide	1000		1500
Terizidone	500		750
Ethambutol	800		1200
Streptomycin	500	Levo	750–1000#

#At a body weight of ⩾60 kg a dosage of 1000 $mg \cdot kg^{-1}$ was used; ¶levofloxacin was introduced in 2010.

Both regimens are not super-strong: 3 drugs (probably) active

TABLE 2 Demographic, epidemiological and clinical characteristics of the multidrug-resistant tuberculosis (MDR-TB) cohort in Brazil, 2000–2010

Variable	Clofazimine regimen	Pyrazinamide regimen	p-value
Male	952/1446 (65.8)	714/1096 (65.2)	0.72
Age years	38 (29–47)	39 (28–49)	0.45
Job			
Housewife	33/1446 (2.3)	146/1096 (13.3)	<0.0001
Unemployed	38/1446 (2.6)	200/1096 (18.3)	
Retired	7/1446 (0.5)	58/1096 (5.3)	
Self-employed	66/1446 (4.6)	277/1096 (25.3)	
Other	1302/1446 (90.0)	415/1096 (37.9)	
Period of education years			
0	116/1130 (10.3)	78/1019 (7.7)	<0.0001
1–3	313/1130 (27.7)	235/1019 (23.1)	
4–7	496/1130 (43.9)	374/1019 (36.7)	
8–11	126/1130 (11.2)	251/1019 (24.6)	
>11	79/1130 (7.0)	81/1019 (7.9)	
Resistance pattern			
MDR-TB	1425/1446 (98.6)	1087/1096 (99.2)	0.16
pre-XDR-TB	18/1446 (1.2)	8/1096 (0.7)	0.21
XDR-TB	3/1446 (0.2)	1/1096 (0.1)	0.53
Clinical presentation			
Pulmonary	1429/1446 (98.8)	1058/1096 (96.5)	<0.0001
Extra-pulmonary	14/1446 (1.0)	7/1096 (0.6)	
Pulmonary and extra-pulmonary	3/1446 (0.2)	31/1096 (2.8)	
Pulmonary involvement			
Normal	3/1435 (0.2)	0/1089 (0.0)	<0.0001
Unilateral, cavitary	191/1435 (13.3)	214/1089 (19.7)	
Unilateral, not cavitary	92/1435 (6.4)	85/1089 (7.8)	
Bilateral, cavitary	961/1435 (67.0)	683/1089 (62.7)	
Bilateral, not cavitary	188/1435 (13.1)	107/1089 (9.8)	
Extra-pulmonary involvement			
Lymph nodes	8/16 (50.0)	10/25 (40.0)	0.27
Bones	4/16 (25.0)	3/25 (12.0)	
Pleurae	2/16 (12.5)	2/25 (8.0)	
Other	2/16 (12.5)	10/25 (40.0)	
Weight at baseline kg	50.0 (48.0–58.0)	54.0 (47.0–62.0)	<0.0001
Weight at end of treatment kg	53.0 (48.0–63.5)	58.5 (50.0–68.0)	<0.0001

Some differences emerging over time

Variable	Clofazimine regimen	Pyrazinamide regimen	p-value
DOT	500/1446 (34.6)	738/1096 (67.3)	<0.0001
HIV testing	86/1444 (6.0)	84/ 1085(7.7)	0.08
Risk factors			
Exposure to corticosteroids	3/1445 (0.2)	3/1096 (0.3)	1.0
Transplantation	0/1445 (0.0)	0/1096 (0.0)	–
Drug abuse	24/1445 (1.7)	107/1096 (9.8)	<0.0001
Alcohol user	52/1445 (3.6)	210/1096 (19.2)	<0.0001
Tobacco user	3/1445 (0.2)	35/1096 (3.2)	<0.0001
Exposure to TNF-α	0/1445 (0.0)	0/1096 (0.0)	–
Diabetes mellitus	57/1445 (3.9)	132/1096 (12.1)	<0.0001
Silicosis	3/1445 (0.2)	2/1096 (0.2)	1.0
Co-morbidities			
Neoplasia	6/1445 (0.4)	9/1096 (0.8)	0.19
Renal failure	3/1445 (0.2)	5/1096 (0.5)	0.30
Hepatitis	5/1445 (0.4)	9/1096 (0.8)	0.17
Mental disorder	16/1445 (1.1)	30/1096 (2.8)	0.002
AIDS	79/1445 (5.5)	76/1096 (7.0)	0.13
Other diseases	42/1445 (2.9)	128/1096 (11.7)	<0.0001
Seizures	0/1445 (0.0)	0/1096 (0.0)	–
Drug-resistance			
Pyrazinamide	614/1123 (54.7)	139/466 (29.8)	<0.0001
Ethambutol	586/1368 (42.8)	341/1047 (32.6)	<0.0001
Aminoglycosides	639/1384 (46.2)	398/1031 (38.6)	<0.0001
Amikacin	6/39 (15.4)	3/31 (9.7)	0.72
Kanamycin	1/6 (16.7)	2/16 (12.5)	1.0
Streptomycin	638/1381 (46.2)	397/1030 (38.5)	<0.0001
Fluoroquinolones	18/46 (39.1)	8/35 (22.9)	0.12
Ofloxacin	16/44 (36.4)	6/32 (18.8)	0.10
Levofloxacin	2/3 (66.7)	0/4 (0.0)	0.14
Moxifloxacin	–	1/1 (100.0)	–
Ciprofloxacin	1/6 (16.7)	1/15 (6.7)	0.50
Ethionamide	342/1015 (33.7)	72/323 (22.3)	<0.0001
Clofazimine	–	–	–
Terizidone	1/1 (100.0)	–	–
n of resistance	3 (3–4)	3 (2–3)	<0.0001
N of resistance ⩾3	1238/1446 (85.6)	676/1096 (61.7)	<0.0001

Prevalence of resistances lowering over time

TABLE 3 Treatment outcomes for the multidrug-resistant tuberculosis (MDR-TB) cohort in Brazil, 2000–2010

Treatment outcome	Clofazimine regimen	Pyrazinamide regimen	p-value
Outcome			
Cured	421/1446 (29.1)	384/1096 (35.0)	<0.0001
Treatment completed	459/1446 (31.7)	324/1096 (29.6)	
Died	314/1446 (21.7)	120/1096 (11.0)	
Died (non-TB cause)	29/1446 (2.0)	22/1096 (2.0)	
Lost to follow-up	144/1446 (10.0)	151/1096 (13.8)	
Failed	78/1446 (5.4)	95/1096(8.7)	
Treatment success	880/1446 (60.9)	708/1096 (64.6)	0.054
n of resistance <3			
Cured	46/208 (22.1)	141/420 (33.6)	0.003
Treatment completed	75/208 (36.1)	141/420 (33.6)	0.54
Died	51/208 (24.5)	36/420 (8.6)	<0.0001
Died (non-TB cause)	4/208 (1.9)	13/420 (3.1)	0.38
Lost to follow-up	17/208 (8.2)	55/420 (13.1)	0.07
Failed	15/208 (7.2)	34/420 (8.1)	0.69
n of resistance ⩾3			
Cured	375/1238 (30.3)	243/676 (36.0)	0.01
Treatment completed	384/1238 (31.0)	183/676 (27.1)	0.07
Died	263/1238 (21.2)	84/676 (12.4)	<0.0001
Died (non-TB cause)	25/1238 (2.0)	9/676 (1.3)	0.27
Lost to follow-up	127/1238 (10.3)	96/676 (14.2)	0.01
Failed	63/1238 (5.1)	61/676 (9.0)	0.001

- More deaths in the ‘young’ programme
- Success (not significantly) minor

Effectiveness

- **Success: 60.9%**

A bit lower than using Z (in other studies: ~65%) because:

1. Regimen with Z better
2. More resistences (FQs) with the ‘young’ programme
3. More re-treatments with the ‘young’ programme
4. Less DOT with the ‘young’ programme

- Clofa works well with HIV-co-infected (6% here; in other studies 1 case only)

TABLE 4 Adverse events notified in the multidrug-resistant tuberculosis (MDR-TB) cohort in Brazil, 2000–2010

Adverse event	Clofazimine regimen	Pyrazinamide regimen	p-value
Hyperpigmentation	725/1445 (50.2)	63/1096 (5.8)	<0.0001
Arthralgia	194/1445 (13.4)	231/1096 (21.1)	<0.0001
Gastrointestinal intolerance	151/1445 (10.5)	102/1096 (9.3)	0.34
Hearing impairment	133/1445 (9.2)	86/1096 (7.9)	0.23
Insomnia	104/ 1445 (7.2)	73/1096 (6.7)	0.60
Headache	88/1445 (6.1)	70/1096 (6.4)	0.76
Mental disorder	85/1445 (5.9)	51/1096 (4.7)	0.17
Visual impairment	56/1445 (3.9)	38/1096 (3.5)	0.59
Renal impairment	27/1445 (1.9)	13/1096 (1.2)	0.17
Neuropathy	0/1445 (0.0)	0/1096 (0.0)	–
Haematologic abnormality	0/1445 (0.0)	0/1096 (0.0)	–
Allergic reaction	0/1445 (0.0)	2/1096 (0.2)	0.19
Electrolyte disorder	0/1445 (0.0)	0/1096 (0.0)	–
Hypothyroidism	0/1445 (0.0)	0/1096 (0.0)	–
Hyperuricemia	0/1445 (0.0)	0/1096 (0.0)	–
Haematuria	0/1445 (0.0)	0/1096 (0.0)	–
Nystagmus	2/1445 (0.1)	1/1096 (0.1)	1.0
Seizure	0/1445 (0.0)	1/1096 (0.1)	0.43
Other	0/1445 (0.0)	2/1096 (0.2)	0.19

Tolerability

In terms of safety, the global evidence available before our study consisted of the previously mentioned systematic review and a clinical trial [17, 18]. The systematic review [18] concluded that although the optimal clofazimine dose is not yet known (being 100 mg·day^{-1} in the majority of available studies), adverse events are in general minor and rarely life-threatening. Although important, the review is affected by relevant between-study heterogeneity and by the epidemiological observational nature, with potential selection biases. Gastro-intestinal intolerance was observed in 40–50% of cases, with 75–100% reporting brownish skin pigmentation while ichthyosis and skin darkness were notified in 8–20% of patients. In the Chinese trial [17], 94.3% of cases reported adverse events of the skin and 47.2% reported ichthyosis, while 11.3% had gastro-intestinal disturbances and, overall, <4% had neurological complaints. In our study, adverse events were even lower: gastro-intestinal complaints were recorded in 10.5% of cases and hyper-pigmentation in 50.2% of patients. Neurological disturbances were reported in 9–13% of cases.

- The dose working well is 100 mg/day
- AE are minor: gastrointestinal 10.5%, pigmentation 50.2%, neurological 9-13% of cases
- AE less than in other studies

Conclusions from the Brazil study

To our knowledge, this is the largest ever cohort treated with clofazimine and the first study reporting all cases from a major country. The results of the therapeutic performance of clofazimine within a standardised regimen indicate that the drug is effective at the programmatic level (ensured success rates above 60%), safe [17, 18] and, as discussed elsewhere [13], does not increase the prevalence of drug resistance. The take-home message for the clinician is that: 1) clofazimine can be added to an optimised background regimen, designed as per WHO recommendations, within both individualised or standardised regimens (which include the newly recommended "shorter" regimen) [5, 34]; and 2) the tolerability of the drug seems to be confirmed. Furthermore, the study results confirm that the 100 $mg \cdot day^{-1}$ dose of clofazimine is probably adequate, as recently demonstrated both *in vitro* and *in vivo* in a murine model [28]. In conclusion, clofazimine seems to have the potential to further contribute to the successfully treatment of more TB cases affected by multidrug-resistance, although results from randomised, controlled clinical trials are necessary to provide a definite answer [30].

- Larger study in the literature
- Clofa works well (success >60%) at programme level
- Dose: 100 mg/ day
- Minor AE
- Does not increase resistance to other drugs

What known before on Carbapenems?

- Good activity in vitro
- Almost nothing in clinical studies on humans

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	6o	590.5	34.4	431.4		

Tiberi S, et al. ERJ 2016

New evidence on Carbapenems: ICSG

Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB

Simon Tiberi[1,31], Marie-Christine Payen[2,31], Giovanni Sotgiu[3,31], Lia D'Ambrosio[4,5,31], Valentina Alarcon Guizado[6], Jan Willem Alffenaar[7], Marcos Abdo Arbex[8,9], Jose A. Caminero[10,11], Rosella Centis[4], Saverio De Lorenzo[12], Mina Gaga[13], Gina Gualano[14], Aurora Jazmín Roby Arias[15], Anna Scardigli[11,16], Alena Skrahina[17], Ivan Solovic[18], Giorgia Sulis[19], Marina Tadolini[20], Onno W. Akkerman[21], Edith Alarcon Arrascue[11,22], Alena Aleska[23], Vera Avchinko[17], Eduardo Henrique Bonini[8,9], Félix Antonio Chong Marín[15], Lorena Collahuazo López[15], Gerard de Vries[24], Simone Dore[3], Heinke Kunst[25], Alberto Matteelli[19], Charalampos Moschos[13], Fabrizio Palmieri[14], Apostolos Papavasileiou[13], Antonio Spanevello[26,27], Dante Vargas Vasquez[28], Pietro Viggiani[12], Veronica White[29], Alimuddin Zumla[30] and Giovanni Battista Migliori[4]

ABSTRACT No large study has ever evaluated the efficacy, safety and tolerability of clavulanate to treat multidrug- and extensively drug-resistant tuberculosis (MDR- and XDR of this observational study was to evaluate the therapeutic contribution, effectiveness, safety a profile of meropenem/clavulanate added to a background regimen when treating MDR- and

Patients treated with a meropenem/clavulanate-containing regimen (n=96) showed a resistance profile than those exposed to a meropenem/clavulanate-sparing regimen (n=168): group XDR-TB was more frequent (49% *versus* 6.0%, p<0.0001) and the median (inter (IQR)) number of antibiotic resistances was higher (8 (6–9) *versus* 5 (4–6)). Patients were meropenem/clavulanate-containing regimen for a median (IQR) of 85 (49–156) days.

No statistically significant differences were observed in the overall MDR-TB cohor subgroups with and without the XDR-TB patients; in particular, sputum smear and cultu rates were similar in XDR-TB patients exposed to meropenem/clavulanate-containing reg *versus* 100.0%, p=1.00 and 88.0% *versus* 100.0%, p=1.00, respectively). Only six cases re events attributable to meropenem/clavulanate (four of them then restarting treatment).

The nondifferent outcomes and bacteriological conversion rate observed in cases who we than controls might imply that meropenem/clavulanate could be active in treating MDR- and X

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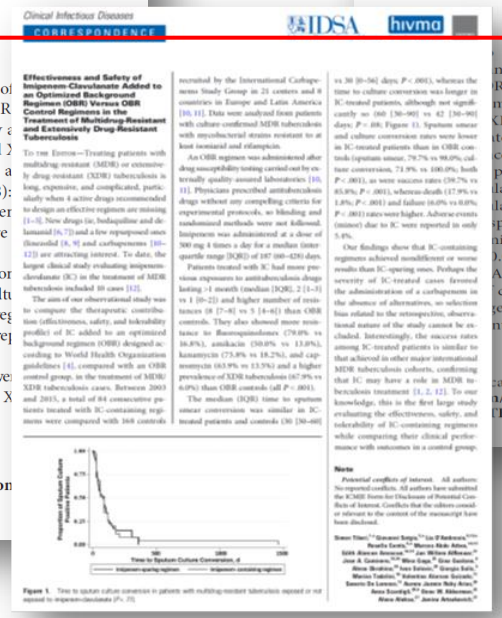
Meropenem/clavulanate is effective and safe to treat MDR- and XDR-TB in con controls http://ow.ly/XG75j

Eur Respir J. 2016;
47: 1235-43.


Clinical Infectious Diseases
CORRESPONDENCE
IDSA hivma

Effectiveness and Safety of Imipenem-Clavulanate Added to an Optimized Background Regimen (OBR) Versus OBR Control Regimens in the Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

Clin Infect Dis. 2016
May 1;62(9):1188-90

Comparison of effectiveness and safety of imipenem/clavulanate- *versus* meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB

Simon Tiberi[1,30], Giovanni Sotgiu[2,30], Lia D'Ambrosio[3,4,30], Rosella Centis[3,30], Marcos Abdo Arbex[5,6], Edith Alarcon Arrascue[7,8], Jan Willem Alffenaar[9], Jose A. Caminero[8,10], Mina Gaga[11], Gina Gualano[12], Alena Skrahina[13], Ivan Solovic[14], Giorgia Sulis[15], Marina Tadolini[16], Valentina Alarcon Guizado[17], Saverio De Lorenzo[18], Aurora Jazmín Roby Arias[19], Anna Scardigli[8], Onno W. Akkerman[20], Alena Aleksa[21], Janina Artsukevich[21], Vera Avchinko[13], Eduardo Henrique Bonini[5,6], Félix Antonio Chong Marín[19], Lorena Collahuazo López[19], Gerard de Vries[22], Simone Dore[2], Heinke Kunst[23], Alberto Matteelli[15], Charalampos Moschos[11], Fabrizio Palmieri[12], Apostolos Papavasileiou[11], Marie-Christine Payen[24], Andrea Piana[2], Antonio Spanevello[25,26], Dante Vargas Vasquez[27], Pietro Viggiani[18], Veronica White[28], Alimuddin Zumla[29] and Giovanni Battista Migliori[3]

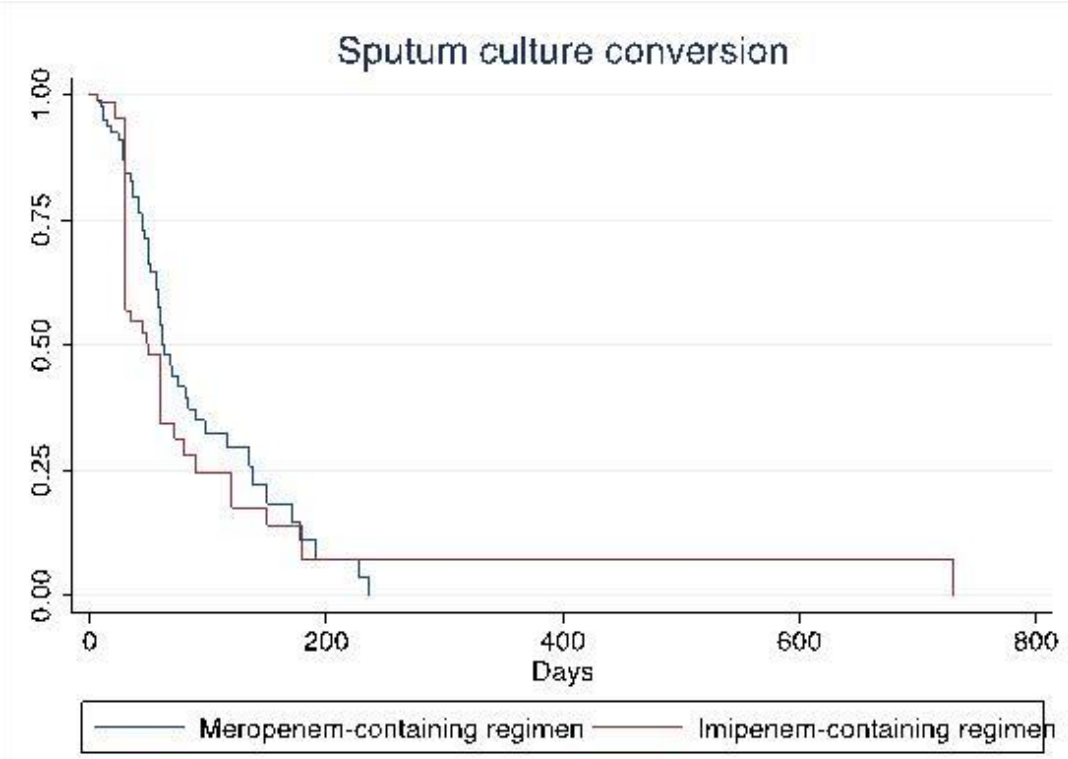
large study to date has ever evaluated the effectiveness, safety and tolerability of
nate *versus* meropenem/clavulanate to treat multidrug- and extensively drug-resistant
R- and XDR-TB). The aim of this observational study was to compare the therapeutic
mipenem/clavulanate *versus* meropenem/clavulanate added to background regimens to
DR-TB cases.
ted with imipenem/clavulanate-containing regimens showed a similar median number of
ces (8 *versus* 8) but more fluoroquinolone resistance (79.0% *versus* 48.9%, p<0.0001) and
prevalence (67.9% *versus* 49.0%, p=0.01) in comparison with 96 patients exposed to
lanate-containing regimens. Patients were treated with imipenem/clavulanate- and
lanate-containing regimens for a median (interquartile range) of 187 (60–428) *versus* 85
spectively.
nificant differences were observed on sputum smear and culture conversion rates (79.7%
.02 and 71.9% *versus* 94.8%, p<0.0001, respectively) and on success rates (59.7% *versus*
Adverse events to imipenem/clavulanate and meropenem/clavulanate were reported in
cases only.
gests that meropenem/clavulanate is more effective than imipenem/clavulanate in treating
nts.

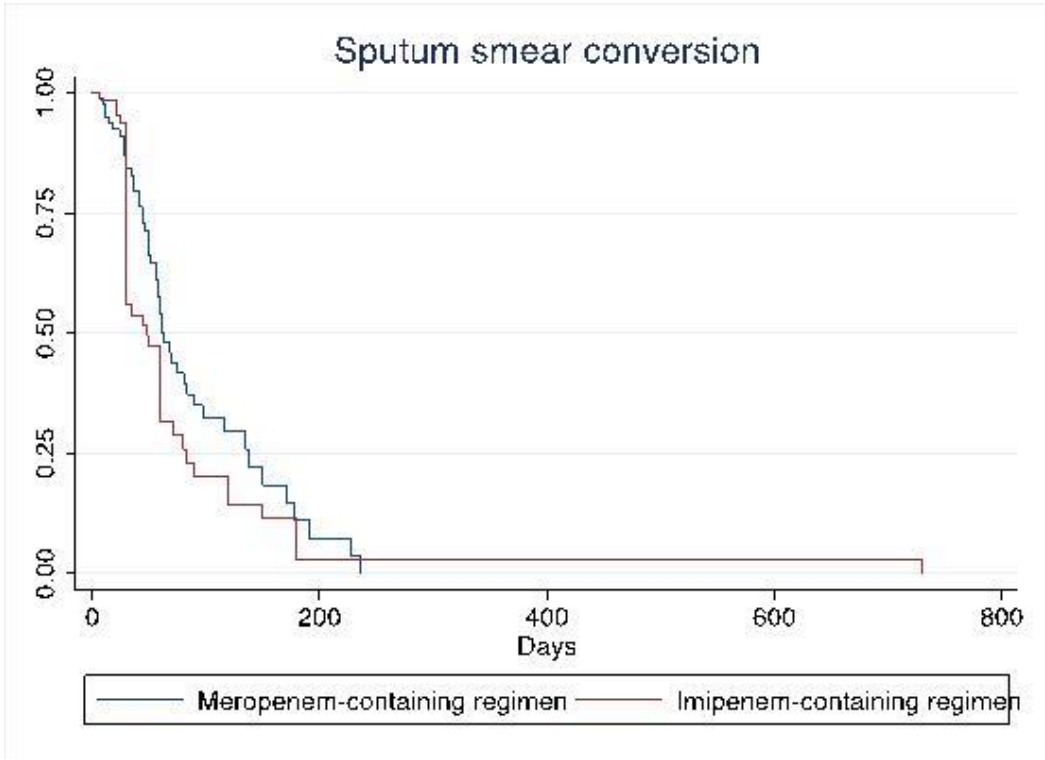
cations
n/clavulanate is safe and more effective than imipenem/clavulanate in treating MDR B patients http://ow.ly/Z4S2o

Eur Respir J. 2016;
47:1758-1766

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 <0.0001**
Interruptions AE	Linezolid 17.1%; Meropenem 8.5%	Linezolid 22.5%;Imipenem 7.3%	
New drugs	1 Delamanid, 9 BQ	0 Delamanid, 7 BQ	





Conclusions:

- Clinical efficacy, but parenteral use!
- Well tolerated
- But expensive!
- Switch option with Ertapenem

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REVIEW
TUBERCULOSIS

New anti-tuberculosis drugs and regimens: 2015 update

Lia D'Ambrosio[1,6], Rosella Centis[1,6], Giovanni Sotgiu[2], Emanuele Pontali[3], Antonio Spanevello[4,5] and Giovanni Battista Migliori[1]

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Linezolid: what was known

- 600 mg << toxic than 1,200 mg (ERJ 2019)
- 300 mg: might create resistances
- Clarithromycin: >> blood levels of LNZ
- Ideal dose: 300-600 mg/die

Linezolid, a first-generation oxazolidinone, demonstrated clinical effectiveness in most difficult-to-treat drug-resistant cases, although the frequency and severity of adverse events (*i.e.* peripheral neuropathy, optic neuropathy, gastrointestinal disorders and myelosuppression) limit its long-term use [23]. A recent prospective randomised trial enrolling XDR-TB patients failing previous chemotherapy demonstrated the efficacy of a reduced linezolid dosage (300–600 mg per day), confirming previous findings [21]: 87% of all enrolled patients achieved bacteriological conversion within 6 months [24]. As four patients acquired resistance during treatment (three of them receiving 300 mg per day), additional evidence is necessary to assess the optimal dose and adequate duration of treatment. Interesting studies have been conducted to prevent adverse events while maintaining the efficacy of linezolid using intermittent dosing and of increasing linezolid concentration in combination with clarithromycin (table 5) [28, 29]. An innovative study from the Netherlands [29] suggested that clarithromycin can boost the blood levels of linezolid, allowing administration of lower doses with fewer adverse events and economic savings. A recent individual-data meta-analysis [23] provided updated evidence on efficacy, safety and tolerability of linezolid, and indirect evidence that a proper treatment drug monitoring (TDM)) approach to drug dosage can reduce linezolid toxicity (fig. 3) [31].

Recently, although not yet approved by regulatory authorities, another oxazolidinone drug (sutezolid) is attracting interest, being better tolerated [32].

As of today, a daily linezolid dose ranging between 300 and 600 mg seems to be adequate to treat MDR/XDR-TB when added to OBR [21–29, 31–35].

very breath counts

TABLE 1 Safety and tolerability of linezolid in patients treated for multidrug-resistant/extensively drug-resistant tuberculosis in Belarus, Germany, Italy and Switzerland, 2001–2007

	Total	600 mg *q.d.*	600 mg *b.i.d.*	p-value#
Patients				
Total n	85	28	57	
No adverse event	50 (58.8)	24 (85.7)	26 (45.6)	0.0004
Any adverse event	35 (41.2)	4 (14.3)	31 (54.4)	0.0004
Minor	8 (9.4)	0	8 (14)	
Major	27 (31.8)	4 (14.3)	23 (40.4)	0.01
Episodes				
Total n	52	5	47	
Anaemia	23 (44.2)	3 (60)	20 (42.5)	0.44
Thrombocytopenia	7 (13.5)	0 (0)	7 (14.9)	
Nausea/vomiting	4 (7.7)	1 (20)	3 (6.4)	0.25
Polyneuropathy	3 (5.8)	1 (20)	2 (4.3)	0.13
Others	15 (28.8)	0 (0)	15 (31.9)	

Data are presented as n (%), unless otherwise stated. #: comparison between 600 mg *q.d.* group and 600 mg *b.i.d.* group.

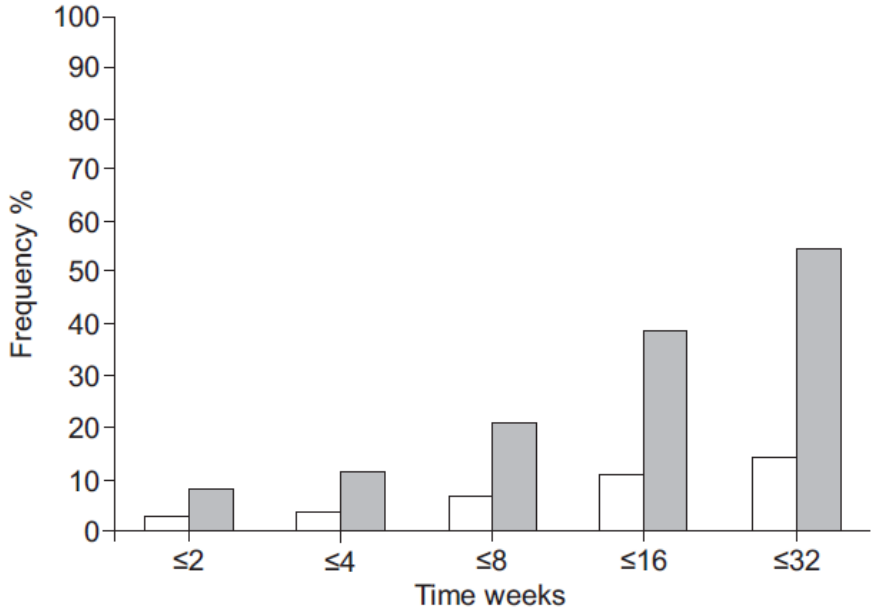
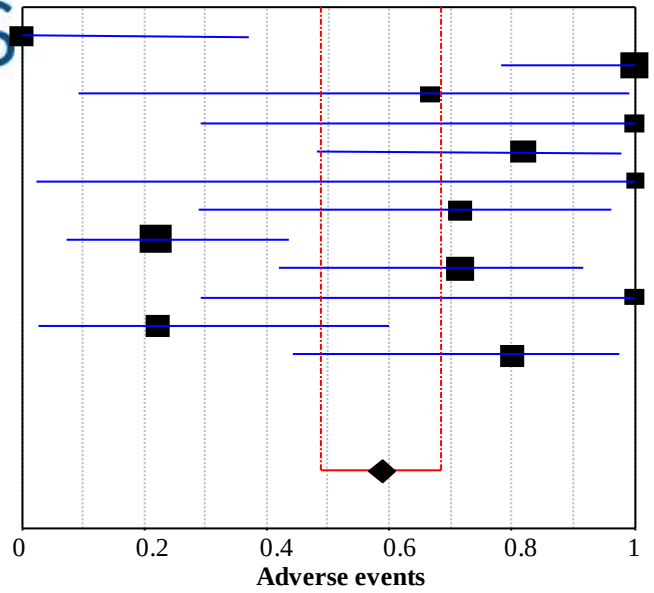


FIGURE 1. Frequency of adverse effects attributed to linezolid during combined treatment against multidrug-resistant/extensively drug-resistant tuberculosis at different time-points after treatment initiation with a 600 mg *q.d.* or a 600 mg *b.i.d.* regimen (denominator is the total number of individuals per group). □: 600 mg *q.d.*, n=28; ■: 600 mg *b.i.d.*, n=57.

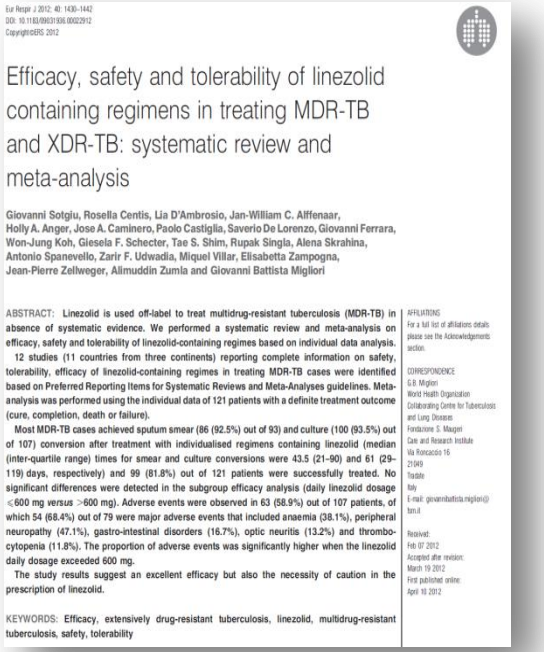
First evidence that 600 mg produces << AE than 1,200
Major AE: 14.3 vs. 40.4% (ERJ 2009)



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)
FortunJ 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.

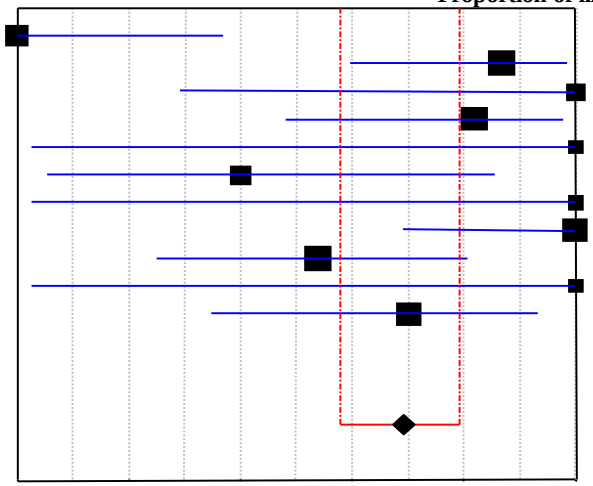
12 studies (11 countries from three continents) reporting complete information on safety, tolerability, efficacy of linezolid-containing regimes in treating MDR-TB cases were identified based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Meta-analysis was performed 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)
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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

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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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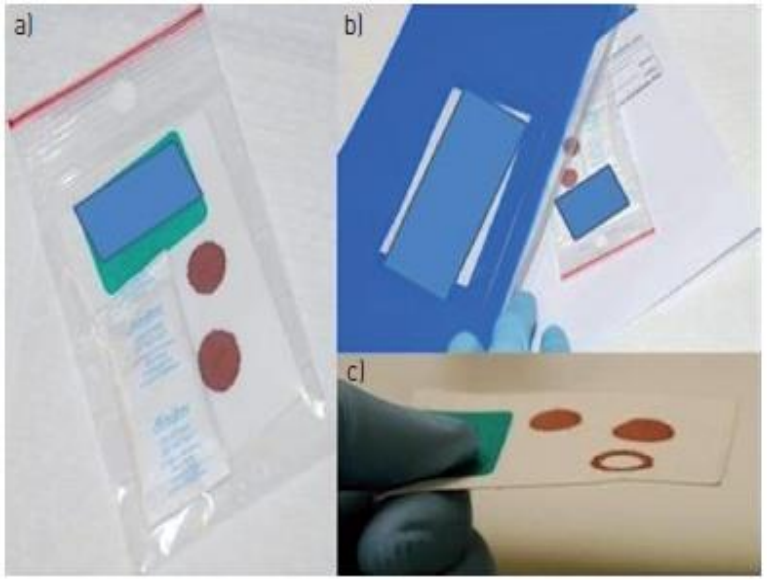
Conflict of interest: None declared

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

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

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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.

Received 4 June 2016; accepted 6 June 2016.

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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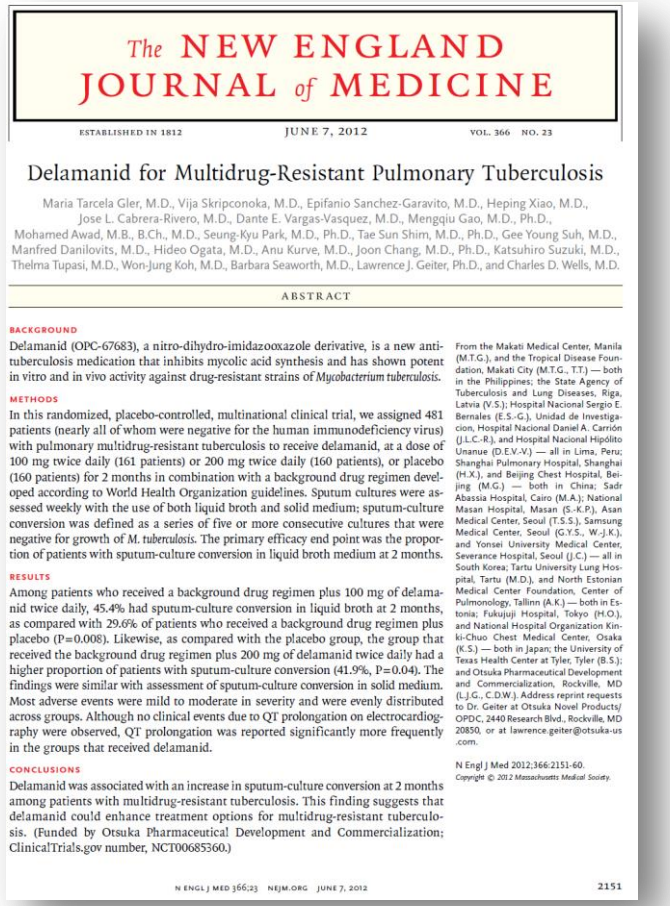
EXECUTIVE SUMMARY

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

Delamanid: what known?



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Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

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ABSTRACT

BACKGROUND

Delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, is a new antituberculosis medication that inhibits mycolic acid synthesis and has shown potent in vitro and in vivo activity against drug-resistant strains of *Mycobacterium tuberculosis*.

METHODS

In this randomized, placebo-controlled, multinational clinical trial, we assigned 481 patients (nearly all of whom were negative for the human immunodeficiency virus) with pulmonary multidrug-resistant tuberculosis to receive delamanid, at a dose of 100 mg twice daily (161 patients) or 200 mg twice daily (160 patients), or placebo (160 patients) for 2 months in combination with a background drug regimen developed according to World Health Organization guidelines. Sputum cultures were assessed weekly with the use of both liquid broth and solid medium; sputum-culture conversion was defined as a series of five or more consecutive cultures that were negative for growth of *M. tuberculosis*. The primary efficacy end point was the proportion of patients with sputum-culture conversion in liquid broth medium at 2 months.

RESULTS

Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo (P=0.008). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, P=0.04). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.

CONCLUSIONS

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

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ERJ Open

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

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ABSTRACT: Multidrug-resistant and extensively drug-resistant tuberculosis (TB) are associated with worse treatment outcomes for patients, including higher mortality, than for drug-sensitive tuberculosis. Delamanid (OPC-67683) is a novel anti-TB medication with demonstrated activity against multidrug-resistant disease.

Patients who participated in the previously reported randomised, placebo-controlled trial of delamanid and the subsequent open-label extension trial were eligible to participate in a 24-month observational study designed to capture treatment outcomes. Treatment outcomes, as assessed by clinicians and defined by the World Health Organization, were categorised as favourable and unfavourable. Delamanid treatment groups were combined for analysis, based on their duration of treatment. In total, for 421 (87.5%) out of 481 patients from the original randomised controlled trial, consent was granted for follow-up assessments.

Favourable outcomes were observed in 143 (74.5%) out of 192 patients who received delamanid for ⩾6 months, compared to 126 (55%) out of 229 patients who received delamanid for ⩽2 months. Mortality was reduced to 1.0% among those receiving long-term delamanid *versus* short-term/no delamanid (8.3%; p<0.001). Treatment benefit was also seen among patients with extensively drug-resistant TB.

This analysis suggests that treatment with delamanid for 6 months in combination with an optimised background regimen can improve outcomes and reduce mortality among patients with both multidrug-resistant and extensively drug-resistant TB.

KEYWORDS: **Extensively drug-resistant, mycobacterium, pulmonary infection, treatment outcomes**

Multidrug-resistant tuberculosis (MDR-TB), or tuberculosis (TB) caused by strains of *Mycobacterium tuberculosis* (MTB) resistant to at least isoniazid and rifampicin, the two most effective bactericidal agents currently available for TB treatment, has emerged as a global public health emergency [1]. It requires treatment with combination therapy consisting of four to six medications including a fluoroquinolone and an injectable anti-TB agent, as well as bacteriostatic agents administered for up to 2 years [2]. Additionally, the treatment is generally more toxic and far more expensive than the standardised treatment regimen used to treat drug-susceptible TB [3, 4]. Moreover, the inability to use isoniazid and rifampicin for treatment results in a lower likelihood of patients achieving treatment success (bacteriologic cure and treatment completion) and higher mortality than for patients with drug-susceptible TB. In contrast to drug-susceptible TB patients, for whom ⩾85% can readily achieve treatment success and generally <5% die [1], three large meta-analyses of MDR-TB treatment cohorts have shown favourable outcomes in the range of 54% to 67% while mortality ranges from 9% to 15% [5–7]. Further analyses have shown that if patients fail to achieve sputum culture conversion (SCC) from growth of MTB to no growth of MTB early in the course of MDR-TB treatment, they have a much higher likelihood of a poor outcome at the end of treatment, including death [8, 9]. Even in high resource settings such as the European Union (EU), surveillance data showed that treatment success averaged from 30–49% for 2007–2008 MDR-TB cohorts [10, 11], although under reporting of treatment outcomes may have affected these results [12].

Extensively drug-resistant (XDR)-TB, or MDR-TB that is also resistant to a fluoroquinolone and an injectable anti-TB agent, has emerged as a more

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- No info on children
- No info on combined use with BQ
- Not much known on the effect on QT

Delamanid improves SS-C conversion at month 2 (45.4 vs 29.6%)

- Favourable outcomes: 74.5%).
- Mortality reduced to 1.0%
- Works also among XDR-TB pts

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

Marina Tadolini[1,21], Anthony J. Garcia-Prats[2,21], Lia D'Ambrosio[3,4,21], Catherine Hewison[3,21], Rosella Centis[3,21], H. Simon Schaaf[2,21], Ben J. Marais[6], Hannetjie Ferreira[7], Jose A. Caminero[8,9], Sylvie Jonckheere[10], Animesh Sinha[11], Krzysztof Herboczek[12], Zarema Khaidarkhanova[13], Armen Hayrapetyan[14], Naira Khachatryan[15], Ia Urtkmelidze[16], Carolina Loreti[17], Susanna Esposito[18], Alberto Matteelli[19], Jennifer Furin[20], Francis Varaine[5] and Giovanni Battista Migliori[3]

Patient	Country of origin	Age years	Sex	TB form	Test results at time of delamanid request	Resistance profile	Expert panel consulted and indication for delamanid	Drugs used prior to delamanid	Started delamanid	Treatment outcome or interim treatment response
1	Italy	13	M	P and EP	SS+/C+ (MGIT), Xpert+	XDR-TB: H, R, Z, E, S, Rfb, Amk, Cm, Km, Lfx, Mfx, Ofx, Eto, Pto, HdH	TB Consilium: extensive resistance to SLDs, drug toxicity and limited options for treatment	H, Z, E, Amk, Mfx, Eto, PAS, Tzd, Amx/Clv, Clr, Cfz, Lzd, Mpm	Yes	Cured
2	South Africa	17	F	P	SS+/C+, Xpert+	XDR-TB: H, R, Amk, Km, Ofx, Eto	TB Consilium: extensive resistance to SLDs and severe clinical presentation	H, Z, E, Cm, Km, Mfx, Eto, PAS, Tzd, Cfz, HdH	No[#]	
3	South Africa	13	M	P	SS+/C+, Xpert+	XDR-TB: H, R, Amk, Ofx	TB Consilium: extensive resistance to SLDs and severe clinical presentation	Z, E, Cm, Km, Mfx, Eto, PAS, Tzd, Amx/Clv, Clr, Cfz, Lzd	Yes	Currently culture negative, good clinical response, delamanid completed
4	South Africa	13	F	P	SS−/C+ (MGIT), Xpert+	XDR-TB: H, R, Amk, Ofx	TB Consilium: extensive resistance to SLDs and severe clinical presentation	E, Z, Cm, Mfx, Eto, PAS, Tzd, Cfz, HdH, Lzd	Yes	Currently culture negative, good clinical response, delamanid ongoing
5	South Africa	8	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	Pre-XDR: H, R, Amk, Cm, Km, Eto	TB Consilium: extensive resistance to SLDs and severe clinical presentation	Z, Amk, Mfx, Eto, Tzd	Yes	First culture not yet available
6	Namibia	9	M	P and EP	SS−/C−, lymph C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Cm, Km, Lfx, Mfx, Ofx, Eto, PAS, Cs, HdH	TB Consilium: extensive resistance to SLDs and severe clinical presentation	Z, Cm, Mfx, PAS, Cs, Amx/Clv, Clr, Cfz, HdH	No[¶]	
7	South Africa	12	F	P	SS−/C+ (MGIT), Xpert indeterminate	XDR-TB: H, R, S, Amk, Cm, Km, Ofx, Eto, Pto, HdH	TB Consilium: extensive resistance to SLDs and severe clinical presentation	H, R, Z, E, Eto, Tzd, Lfx	Yes	Currently culture negative, good clinical response, delamanid ongoing
8	India	12	F	P	SS+/C+ (MGIT)	XDR-TB: R, H, Z, E, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS, Cs, Lzd	TB Consilium: extensive resistance to SLDs and severe clinical presentation	E, Z, Cm, Mfx, PAS, Cs, Amx/Clv, Clr, Cfz, Lzd, Mpm	Yes	First culture not yet available
9	India	17	F	P	SS+/C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS	endTB committee: extensive resistance to SLDs	H, R, Z, E, S, Km, Mfx, Pto, PAS, Cs, Amx/Clv, Clr, Cfz, Lzd	Yes	Currently culture negative, good clinical response, delamanid completed
10	India	15	F	P	SS+/C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Km, Ofx, Eto, PAS, Cfz	endTB committee: extensive resistance to SLDs	H, R, Z, E, Km, Mfx, Eto, PAS, Cfz, Lzd	Yes	Currently culture negative, good clinical response, delamanid completed
11	India	16	M	P	SS−/C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS	endTB committee: failure of previous treatment and extensive resistance to SLDs	H, R, Z, E, Rfb, Cm, Km, Lfx, Mfx, Eto, PAS, Cs, Amx/Clv, Cfz, HdH, Lzd	Yes	Culture negative, good clinical response, delamanid completed
12	India	13	F	P and EP (lymph node)	SS+/C+ (MGIT), Xpert MTB+, R resistant	XDR-TB: H, R, E, Z, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS, Cs	endTB committee: extensive resistance to SLDs	H, R, Z, E	No[+]	
13	Georgia	16	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	MDR-TB: H, R, E, Z	endTB committee: no improvement with SLDs (still smear positive after 3 months of treatment)	E, Z, Cm, Mfx, Cs, PAS, Lzd	Yes	Currently culture negative, good clinical response, delamanid ongoing

19 children, 16 treated, 3 HIV+
Resistant to 5-15 drugs
Adult dose (100 mg x 2/day), one- 22kg, half dose
6 completed 24 weeks DLM
10 continuing treatment

DLM in children

All patients showed good tolerability to delamanid with no or mild adverse events, except one patient from India. This patient was receiving a combination of delamanid-capreomycin-ethionamide-cycloserine-clofazimine-imipenem-amoxicillin/clavulanate-pyrazinamide, and experienced severe vomiting, renal impairment and severe electrolyte disturbances (hypokalaemia and hypomagnesaemia) that led to QTcF (QT interval in the ECG corrected according to Fredericia formula) prolongation (>500 ms) requiring temporary delamanid discontinuation (albumin was normal). After management of vomiting and electrolyte imbalance correction, the patient was able to complete delamanid treatment without further QTcF prolongation.

1 child had QTcF >500 ms; after short interruption able to continue DLM without further problems

As shown in table 1, the interim treatment response is good: 13 (81.2%) out of 16 were *Mycobacterium tuberculosis* culture-negative at the time of this report (three patients were recently started on delamanid, so the interim treatment responses are not yet available). Except for one patient who has successfully completed MDR-TB treatment, the remaining patients are continuing treatment and do not have final treatment outcomes yet.

13/16 (81.2%) culture neg at month 2

Delamanid Trial 2013: EFFICACY		
Outcomes	**N° cases**	**% favorable outcomes**
Trial 204/208/116 Phase 2 ERJ 2013	192	74.5%
Trial 213 Phase 2	339	81.4%
Latvia Programamtic use ERJ 2017	19	84.2%

Delamanid Trial 2013: SAFETY

	DLM+OBR N: 341	Placebo + OBR N: 170	Total N: 511
AE on Tx	4 (1.2%)	5 (2.9%)	9 (1.8%)
Discontinuation for AE	8 (2.3%)	3 (1.8%)	11 (2.2%)
Serious AE	89 (26.1%)	47 (27.6%)	136 (26.6%)
Hepatotoxicity	22 (6.5%)	12 (7.1%)	34 (6.7%)
QT prolongation	18 (5.3%)	5 (2.9%)	23 (4.5%)

Delamanid QTcF (95% CI)

Week	Trial 204 (100 mg BID) Moxi excluded	Trial 213 Moxi included (24% cases)
4	7.6 msec (5.3-9.8)	4.7 msec (2.2-7.2)
8	12.1 msec (9.6-14.7)	5.3 msec (2.7-9.9)
26	N/A	2.5 msec (-0.3-5.3)

No amplification of resistance

DLM+OBR vs PLC+OBR (%) : **FLD** 1.9 vs 6.5; **Z** 1.2 vs 5.1; **SLD** 3.1 vs 4.5; **FQ** 1.8 vs 3.6

Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study

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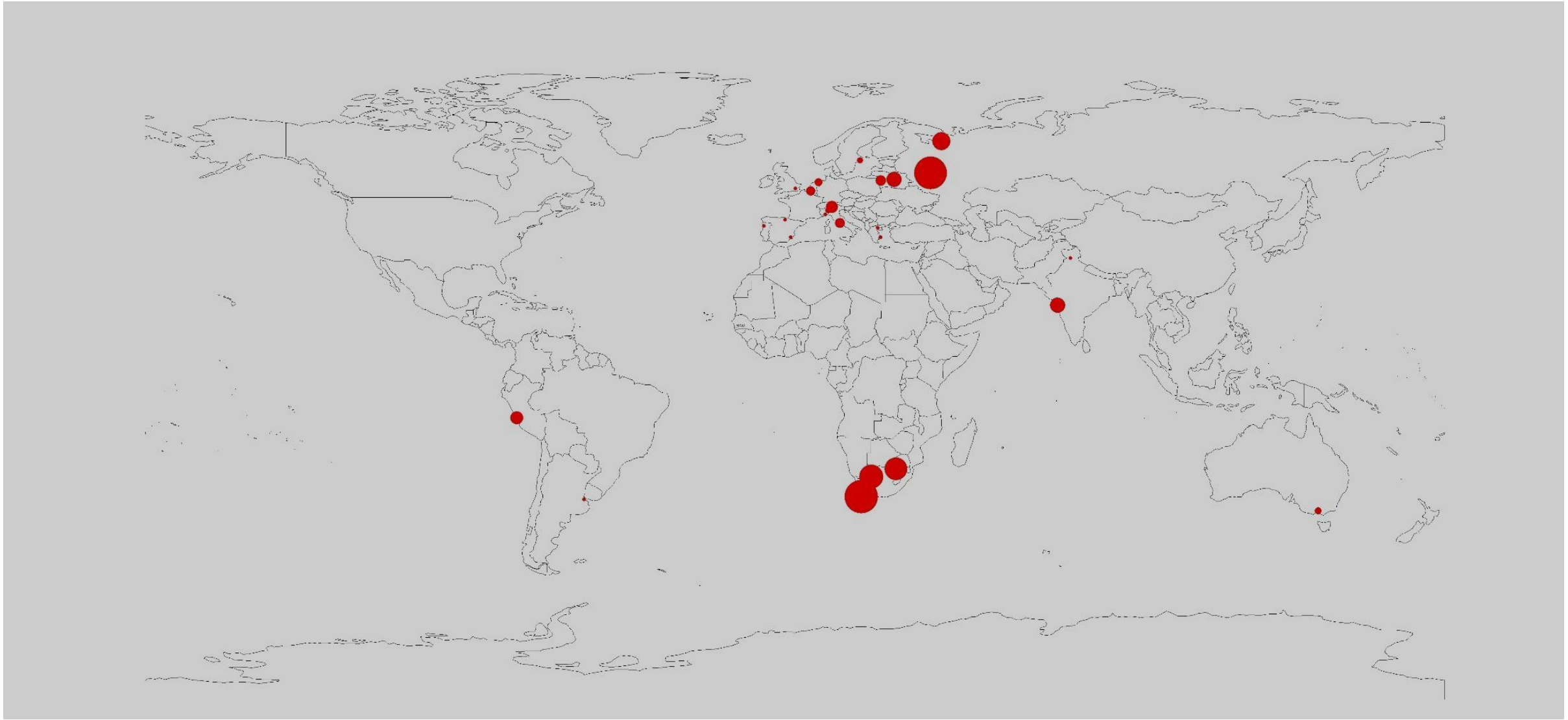
International BQ Study Group

@ERSpublications
Bedaquiline is safe and effective in treating MDR- and XDR-TB patients http://ow.ly/6MWK30adHkw

Cite this article as: . Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017; 0: 1700387 [https://doi.org/10.1183/13993003.00387-2017].

Distribution of MDR-/XDR-TB treated with BQ, 2008-2016

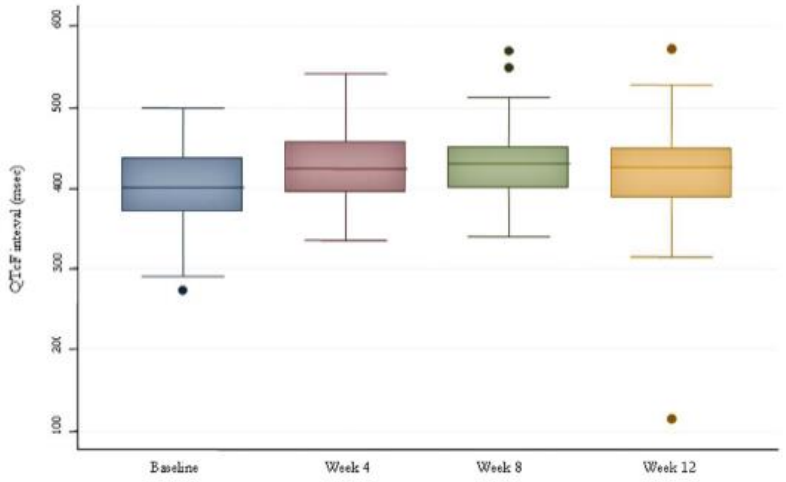


Borisov S. et al. Efficacy of BQ, ERJ 2017

Interruption of bedaquiline, n (%)	51/428 (11.9)
Interruption of bedaquiline due to adverse events, n (%)	25/428 (5.8)
Adverse events presumably due to bedaquiline, n (%)	80/213 (19.4)
Bedaquiline restarted if interrupted, n (%)	25/69 (36,2)
Median (IQR) total bedaquiline exposure, days	168 (86-180)
Creatinine >1.4x ULN, n (%)	91/411 (22.1)
Lipase >1.6x ULN, n (%)	1/239 (0.4)
ALT >3x ULN, n (%)	92/413 (22.3)
Bilirubin >2x ULN, n (%)	47/413 (11.4)
Median (IQR) albumin, gr/dl	36 (30-40)
Potassium <3.4 or >5.6 mmol/L, n (%)	98/412 (23.8)
Magnesium <0.59 mmol/L, n (%)	21/199 (10.6)
Calcium <1.75 mmol/L, n (%)	23/302 (7.6)
Nausea, n (%)	130/413 (31.5)
Neuropathy peripheral, n (%)	96/412 (23.3)
Oto-vestibular toxicity, n (%)	96/412 (23.3)
Vomiting, n (%)	87/411 (21.2)
Anaemia, n (%)	86/412 (20.9)
Arthralgia, n (%)	84/412 (20.4)
Skin rash, n (%)	63/412 (15.3)
Diarrhoea, n (%)	56/412 (13.6)
Renal failure, n (%)	47/413 (11.4)
Thrombocytopenia, n (%)	41/413 (9.9)
Neutropenia, n (%)	40/413 (9.7)
Lymphocytopenia, n (%)	40/413 (9.7)
QT prolongation, n (%)	24/248 (9.7)
Hypothyroidism, n (%)	38/410 (9.3)
Psychiatric disorder, n (%)	29/413 (7.0)
Tendinopathy, n (%)	18/413 (4.4)
Optic neuropathy, n (%)	10/413 (2.4)
Deep vein thrombosis, n (%)	7/412 (1.7)
Pancreatitis, n (%)	4/318 (1.3)
Hallucinations, n (%)	2/411 (0.5)
Stroke, n (%)	1/318 (0.3)

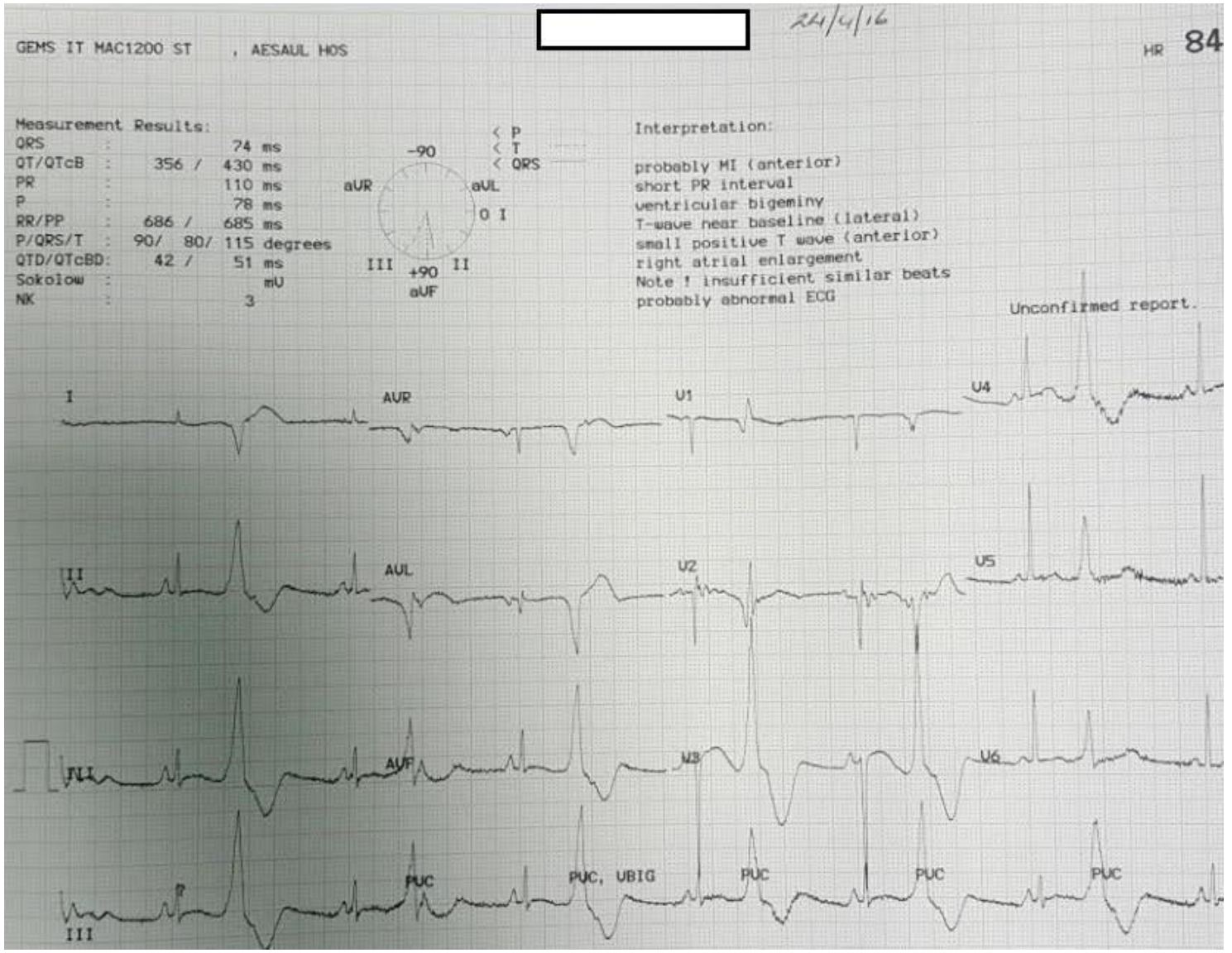
Borisov S. et al.
Safety and tolerability of BQ
ERJ 2017 in press

With 168 days of exposure (median), only 11% interrupted tretament (6% with AE)
Median values of QT tend to stabilise after week 12



Median values and trends of QTcF

Does BQ kill? Premature ventricular complex bigeminy



Cause of death: hypokalaemia

Treatment outcomes by Region: Africa has 10% lower success

Overall success rate: 77%
Overall smear conversion rate, end treatment: 90.0%
Overall, culture conversion rate, end of treatment: 91.8%

Treatment outcome	Africa	Eastern Europe	Other settings
Total cohort	**(n=113)**	**(n=85)**	**(n=49)**
Treatment success	**73 (64.6)**	**65 (76.5)**	**38 (77.6)**
Cured	73 (64.6)	54 (63.5)	27 (55.1)
Completed	-	11 (12.9)	11 (22.5)
Died	**27 (23.9)**	**3 (3.5)**	**3 (6.1)**
Defaulted	9 (8.0)	8 (9.4)	1 (2.0)
Failure	3 (2.7)	9 (10.6)	7 (14.3)
Transferred out	1 (0.9)	-	-

EDITORIAL
RESPIRATORY INFECTIONS AND TUBERCULOSIS

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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@ERSpublications
Bedaquiline is well tolerated: evidence indicates a minority of patients discontinue use due to QT extension http://ow.ly/9NRT30fNv4y

Cite this article as: Pontali E, Sotgiu G, Tiberi S, *et al.* Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. *Eur Respir J* 2017; 0: 1701462 [https://doi.org/10.1183/13993003.01462-2017].

Is BQ safe on QT?

<0.9% of cases treated had problems

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	macrolides −19 msec With MFX and CFZ +55 msec	40%); Macrolides (1/10; 10%)	No information reported 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

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

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

TABLE 1 Clinical characteristics of the first case treated with both delamanid and bedaquiline

	Details	Comments
Country of birth	India	
Age	39 years	
Sex	Female	
Body weight at diagnosis	65 kg	
Case category	Retreatment case	
Number of previous anti-TB treatments	4	
Drugs administered in previous anti-TB treatments	Kanamycin 750 mg *i.m.* (12 months) Levofloxacin 1 g, PAS 10 g, cycloserine 750 mg, ethionamide 750 mg, capreomycin 1 g *i.m.* (14 months) High-dose isoniazid 900 mg, rifabutin 300 mg, clofazimine 200 mg, clarithromycin 1 g, amoxicillin/clavulanate 625 mg, terizidone 1 g three times daily, imipenem 500 mg *i.v.* three times daily (12 months), linezolid 600 mg then 300 mg	
Previous outcome	Cured (twice)	
Body mass index at baseline	26.9 $kg \cdot m^{-2}$	
Bacteriology at baseline	Sputum smear positive Culture positive Xpert positive	At Day 18: smear negative Culture taken after 28 days of treatment: ongoing (negative on the 14th day of MGIT culture)
Radiology	Bilateral upper zones fibrocavitary lesions	
Drug resistances	Resistant to 12 drugs: Isoniazid, rifampicin, kanamycin, amikacin, capreomycin, moxifloxacin, ofloxacin, ethionamide, PAS, linezolid, high-dose isoniazid, high-dose moxifloxacin Susceptible to: clofazimine	
Last treatment regimen	Delamanid, bedaquiline, clofazimine (200 mg), terizidone (1 g) and meropenem 1 g three times daily plus amoxicillin/clavulanate 1 g/200 mg three times daily *i.v.*, all started on February 25, 2016	Bedaquiline stopped on March 7, 2016, restarted March 12, 2016

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

Researchers have described the first case of severe extensively drug-resistant tuberculosis (XDR-TB) treated with both delamanid and bedaquiline. The findings, published as a letter in the *European Respiratory Journal*, reports the rationale for prescribing both delamanid and bedaquiline in an XDR-TB case and describes the difficulties encountered in the early phase of treatment.

Read the full study

Access the ERS/WHO TB Consilum

First case treated with DLM+BQ

Variable	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 + At Day 18: SS -; C: ongoing
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; and meropenem 1g TDS plus amoxi/clav 1g/200mg TDS iv (started 28/2/2016) BQ stopped on 07/03/2016 restarted 12/03/2016

UPDATE ON THE CASE

Table 1: Follow-up clinical information on the first case undergoing joint treatment with delamanid and bedaquiline

	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	70 Kg	70 Kg				69 Kg				69.5 Kg				69 Kg				69 Kg				69 Kg			
Hospitalization	October 2015	Yes				Yes				Yes				Yes				Yes				Yes			
Chest radiography	Bilateral upper zones fibro-cavitary lesions	-				-				Bilateral upper zones fibro-cavitary lesions				-				-							
Sputum Smear	+	+				Negative				Negative				Negative				Negative				-			
Sputum Culture	+	+				No growth				No growth				Ongoing				Ongoing							
		W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	W 19	W 20	W 21	W 22	W 23	W 24
Treatment	Started on 25/02/2016																								
Bedaquiline																									
Delamanid																									
Clofazimine	Hold on 2 April																								
Terizidone																									
Meropenem																									
Amoxi/Clavulanate																									
Verapamil	Added on 12 March																								
QTc (ms)	< 450 msec	476	486 481	489	491	508	-	500	508	491	486	-	512	491	510	507	520	501	489	497	492				

W: week; Qtc: corrected QT or the measure of time between the start of Q wave and the end of Tb wafe in the heart's electrical cycle; ms: milliseconds

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Dispatch

Bedaquiline and Delamanid Combination Treatment of 5 Patients with Pulmonary Extensively Drug-Resistant Tuberculosis

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MINIMUM REQUIREMENTS COMBINED USED DLM+BQ – LANCET ID 2015

	Requisite	Comment
1	Clinical centre qualified	The clinical centre is highly qualified in terms of clinical expertise, number of cases managed and laboratory services. The eligibility criteria for these centres should comply with national regulation, and, ideally, to international ones to be developed
2	Informed consent	The patient should sign it, as recommended by the World Health Organization separately for delamanid[5] and bedaquiline
3	Pharmaco-vigilance	Pharmacivigilance to be seen as both a guarantee for the patient and an additional source of information complementing existing trials
4	Expert opinion on rational use of drugs	The use of the drugs is considered rationale by an independent and qualified body such as the ERS TB Consilium (available at: www.tbconsilium.org in different languages and free of charge). This step is also an essential component of the Otsuka's delamanid compassionate use programme

PREVALENCE OF RESISTANCE TO THE DRUGS COMPOSING THE BANGLADESH REGIMEN (ERJ 2016)

Cohort	FQ (95% CI)	Clofa (95% CI)	E (95% CI)	Z (95% CI)	Prothio (95% CI)	Kana (95% CI)
Intern Carbap Study Group (ICSG)	137/336, 40.8% (35.6-46.1)	-	232/339, 68.4% (63.5-73.4)	195/300, 65.0% (59.6-70.4)	174/314, 55.4% (49.9-60.9)	100/225, 44.4% (37.9-50.9)
ICSG Europe	91/283, 32.2% (26.8-37.6)	-	195/284, 68.7% (63.3-74.1)	165/255, 64.7% (58.8-70.6)	150/279, 53.8% (48.0-59.7)	64/172, 37.2% (30.0-44.4)
ICSG S. America	46/53, 86.8% (77.7-95.9)	-	37/55, 67.3% (54.9-79.7)	30/45, 66.7% (52.9-80.5)	24/35, 68.6% (53.2-84.0)	36/53, 67.9% (55.3-80.5)

COMPARISON OF THE RESULTS ON PHENOTYPIC AND GENOTYPIC RESISTANCE TO ANTI-TB DRUGS, MEXICO, 2010-2017

	Phenotypic results N=112*		Genotypic results N=57*		Kappa value (95% CI)
	N	(%)	N	(%)	
Fluoroquinolones Resistant	26/111	23.42	12/57	21.05	0.894 (0.751 - 1.000)
Ofloxacin Resistant	26/111	23.42			
Moxifloxacin Resistant	8/49	16.33			
Injectables Resistant	13/111	11.71	1/57	1.75	0.226 (-0.145 - 0.597)
Amikacin Resistant	9/111	8.11			
Kanamycin Resistant	10/92	10.87			
Capreomycin Resistant	6/50	12.00			
Ethambutol Resistant	38/112	33.93	19/57	33.33	0.763 (0.585 - 0.942)
Isoniazid Resistant	97/112	86.61	31/57	54.39	0.597 (0.402 - 0.793)
katG + *inhA* genes			1/57	1.78	
katG gene only			18/57	31.58	
inhA only			14/57	24.56	
Pyrazinamide Resistant	46/110	41.82			
ELIGIBLE FOR THE SHORTER REGIMEN	Crit 1: 80 Crit 2: 56 Crit 3: 50	71.42% 50% 44%			

* The denominators varies as not necessarily all 112 strains underwent the tests for all the drugs

Criterion 1: eligible if NO resistance to fluoroquinolones AND injectables AND NO *katG* + *inhA* mutations

Criterion 2: eligible as per Criterion 1 AND NO resistance to ethambutol

Criterion 3: elegible as per Criterion 2 but NO *katG* mutation (see text for details)

Impact (1)
The cohort studies by Dick Menzies

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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

Impact 2

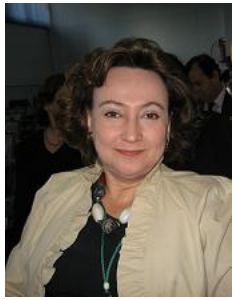
- IPD (Dick Menzies's cohort II) of 12,156 M/XDR-TB cases (effectiveness) and 13,641 for tolerability
- Major source of evidence for ATS/ISDA/CDC/ERS guidelines and future WHO ones
- Contribution of ERS TB Collaborative projects:

- Carbapenems: 145/191 cases (75.9%)
- Clofazimine: 149/790 cases (18.9%) for efficacy, all 1,485 for tolerability analysis
- BQ: 140/411 cases (34.1%)
- All Clofazimine data send to FDA for approval of TB indication

Conclusions

- After 40 years we have 2 new drugs
- BQ and DLM seem to be effective and well tolerated
- Under non-trial conditions BQ achieved 77% success!! With large regional differences
- We need quality studies, also in programmatic conditions, in both adults and children
- Important to monitor the QT interval and implement aDSM
- Clofazimine: new evidence support is effectiveness and safety; FDA is evaluating to include the TB indication
- Carbapenems: although expensive and needing parenteral administration, they can be useful
- The ERS effort will continue with the aDSM project and the severe cases

Thanks to the members of the ERS/ALAT and ERS/SBPT collaborative projects: this framework made possible to perform the studies presented



Ευχαριστίες!!

Thanks!!