TB – New Drugs, Shorter Courses

Brian Chong

John Hunter Hospital, Newcastle NSW

Talk supervisor: Chris Coulter

Disclosures

Unfortunately none

Current Situation

- In 2013, Australia had:
  - 1,263 notified TB cases (including 43 relapses)
  - 22 MDR-TB cases
  - No XDR-TB cases
- Global treatment outcomes:

	All TB (n = 5.9 million in 2014)	MDR-TB (n = 86,936 in 2013)	XDR-TB (n = 4,086 in 2013)
Successful	83%	52%	28%
Died	-	17%	27%
Failed	-	9%	21%
Lost	-	22%	23%

Toms C, Stapledon R, Waring J, Douglas P (2015). Tuberculosis Notifications in Australia 2012 and 2013. *CDI*
WHO (2016). *Global Tuberculosis Report*

Current WHO Guidelines for MDR-TB

Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

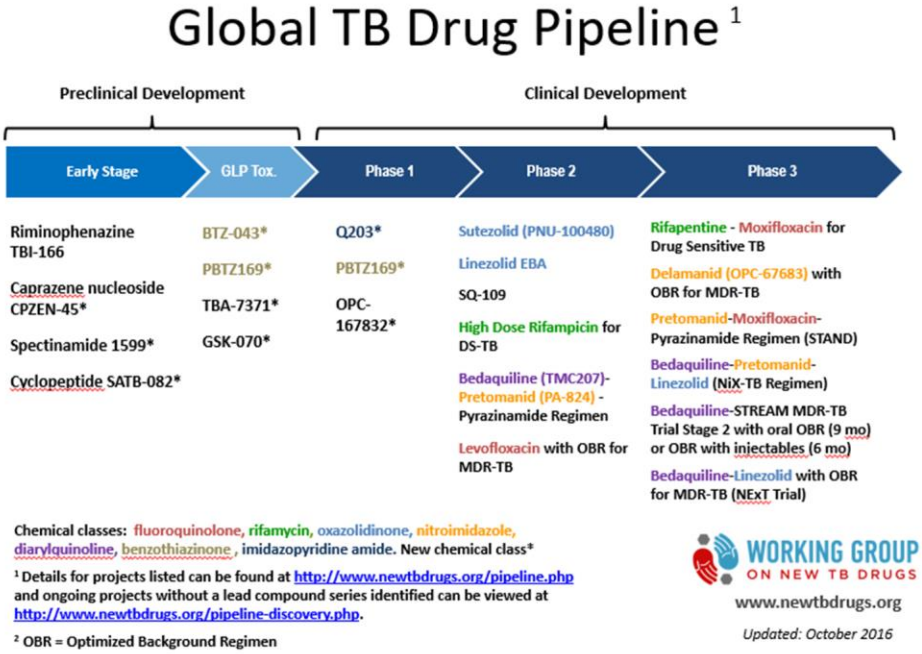
[a] This regrouping is intended to guide the design of longer regimens; the composition of the recommended shorter MDR-TB regimen is standardized (see Section A).
[b] Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text).
[c] Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of XDR-TB *(26)*.
[d] Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.
[e] HIV-status must be confirmed to be negative before thioacetazone is started.

Duration of longer MDR-TB treatment regimens

In the treatment of patients with MDR-TB, an intensive phase of eight months is suggested for most patients; the duration may be modified according to the patient's response to therapy (conditional recommendation, very low quality evidence).

In the treatment of patients newly diagnosed with MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most; the duration may be modified according to the patient's response to therapy (conditional recommendation, very low quality evidence).

WHO (2016). *WHO Treatment Guidelines for Drug-Resistant Tuberculosis*



New (and New-ish) Drugs

Bedaquiline (TMC207)

- Class – diarylquinoline
- Mechanism of action – inhibition of ATP synthase
- Half-life – 164 days
- Dosing – 400mg daily for 2 weeks, followed by 200mg three times weekly (total duration 24 weeks)
- Adverse effects – QT prolongation, hepatotoxicity
- Known drug interactions – CYP3A4 inducers/inhibitors (rifampicin, efavirenz)


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.&H., Ramonde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pistorius, M.D., Rene Krause, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.Tech.(Micro), Jenny Allen, B.Sc., Juan Carlos Palomino, Ph.D., Tine De Marez, Ph.D., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Johan Verbeeck, D.V.M., Ph.D., Wim Parys, M.D., Karel de Beule, Pharm.D., Koen Andries, D.V.M., Ph.D., and David F. Mc Neeley, M.D., M.P.H.T.M.

Bedaquiline (n=23) vs placebo (n=24) for 8 weeks, in addition to background regimen

Sputum culture conversion rate at 8 weeks – 48% (bedaquiline) vs 9% (placebo)

Two Year Follow-up

AAC
Journals.ASM.org

Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance

A. H. Diacon,[a] P. R. Donald,[a] A. Pym,[b] M. Grobusch,[c] R. F. Patientia,[a] R. Mahanyele,[b] N. Bantubani,[c] R. Narasimooloo,[c] T. De Marez,[d] R. van Heeswijk,[e] N. Lounis,[e] P. Meyvisch,[e] K. Andries,[e] and D. F. McNeeley[d]
Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa[a]; Medical Research Council, Durban, South Africa[b]; Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa[c]; Tibotec, Inc., Yardley, Pennsylvania, USA[d]; and Tibotec BVBA, Mechelen, Belgium[e]

Safe
MAY reduce risk of resistance on treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

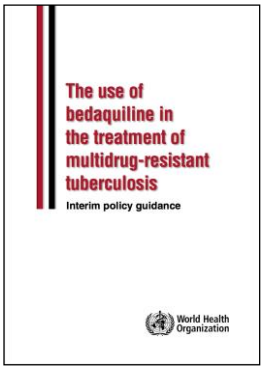
Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*

Bedaquiline (n=79) vs placebo (n=81) for 24 weeks, in addition to background regimen
Median time to culture conversion - 83 days (bedaquiline) vs 125 days (placebo)
Cure rates - 58% (bedaquiline) vs 32% (placebo) at 120 weeks
10 deaths in bedaquiline group, 2 in placebo group (cause unclear)

WHO Recommendation 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)'



Bedaquiline x Clofazimine

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Cross-Resistance between Clofazimine and Bedaquiline through Upregulation of MmpL5 in *Mycobacterium tuberculosis*

Ruben C. Hartkoorn, Swapna Uplekar,* Stewart T. Cole
Ecole Polytechnique Fédérale de Lausanne, Global Health Institute, Lausanne, Switzerland

Mutations in *pepQ* Confer Low-level Resistance to Bedaquiline and Clofazimine in *Mycobacterium tuberculosis*

Deepak Almeida[a], Thomas Ioerger[b], Sandeep Tyagi[a], Si-Yang Li[a], Khisimuzi Mdluli[c], Koen Andries[d], Jacques Grosset[a], Jim Sacchettini[e] and Eric Nuermberger[a,f#]

Delamanid (OPC-67683)

- Class – nitro-dihydro-imidazooxazole
- Mechanism of action – inhibition of mycolic acid synthesis
- Half-life – 30 to 38 hours
- Dosing – 100mg BD for 6 months
- Adverse effects – QT prolongation
- Known drug interactions – none significant (metabolised by albumin)

Gupta R et al (2016). Delamanid in the Treatment of Multidrug-Resistant Tuberculosis. *The International Journal of Tuberculosis and Lung Disease*

Trial 204

The NEW ENGLAND JOURNAL of MEDICINE

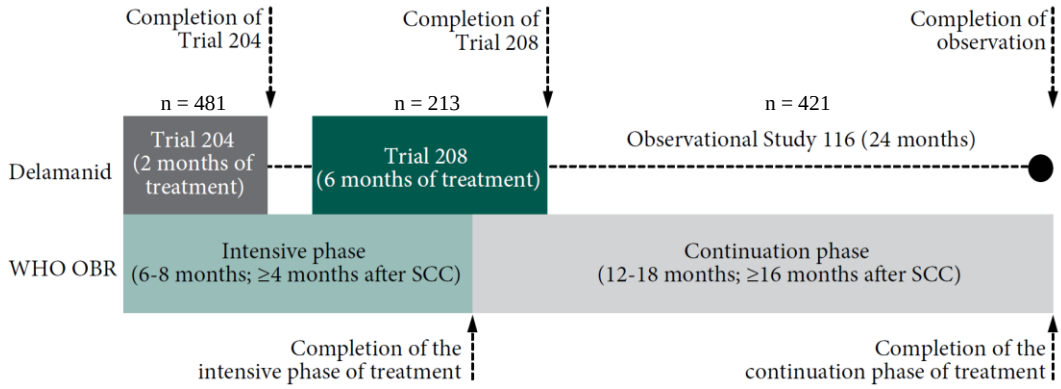
ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

Delamanid 100mg BD (n=161) vs delamanid 200mg BD (n=160) vs placebo (n=160) for 8 weeks, in addition to background regimen
Sputum conversion at 8 weeks – 45.4% (D100) vs 41.9% (D200) vs 29.6% (placebo)

Figure 1: Design of delamanid Trial 204, Trial 208 and Study 116 (Modified from Skripconoka et al, 2013) *(10)*



- WHO OBR refers to the optimised background regimen designed according to WHO recommended treatment for multidrug-resistant tuberculosis (MDR-TB)
- SCC: Sputum Culture Conversion
- Note: the time period between completion of Trial 204 and initiation of Trial 208 was variable

WHO (2014). *The Use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis*

Observational Study 116

TABLE 2 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

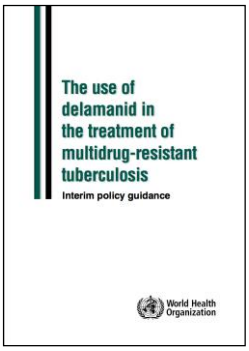
Treatment outcome	Long-term treatment[#]	Short-term treatment[¶]	All patients[+]
Favourable	143 (74.5; 67.7–80.5)[§]	126 (55.0; 48.3–61.6)[§]	269 (63.9; 59.1–68.5)
Cured	110 (57.3; 50.0–64.4)	111 (48.5; 41.8–55.1)	221 (52.5; 47.6–57.4)
Completed	33 (17.2; 12.1–23.3)[§]	15 (6.6; 3.7–10.6)[§]	48 (11.4; 8.5–14.8)
Unfavourable	49 (25.5; 19.5–32.3)[§]	103 (45.0; 38.4–51.7)[§]	152 (36.1; 31.5–40.9)
Died	2 (1.0; 0.1–3.7)[§]	19 (8.3; 5.1–12.7)[§]	21 (5.0; 3.1–7.5)
Failed	32 (16.7; 11.7–22.7)	26 (11.4; 7.6–16.2)	58 (13.8; 10.6–17.4)
Defaulted	15 (7.8; 4.4–12.6)[§]	58 (25.3; 19.8–31.5)[§]	73 (17.3; 13.8–21.3)

Data are presented as n (%; 95% CI). MDR: multidrug-resistant; TB: tuberculosis; XDR: extensively drug-resistant. [#]: 192 patients received delamanid (100 mg and/or 200 mg twice a day) for at least 6 months; [¶]: 229 patients received delamanid (100 mg or 200 mg twice a day) or placebo for 2 months; [+]: n=421; [§]: differences between the long-term and the short-term treatment groups for the corresponding treatment outcome were statistically significant ($p<0.001$), all other differences did not reach statistical significance ($p \geqslant 0.05$).

Skripconoka V et al (2013). Delamanid Improves Outcomes and Reduces Mortality in Multidrug-Resistant Tuberculosis. *European Respiratory Journal*

WHO Recommendation 2014

'Delamanid may be added on to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation; very low confidence in estimates of effect)'



NCT01424670 (clinicaltrials.gov)

- Phase III, double-blind, placebo-controlled
- 511 patients aged 18 to 69 with pulmonary MDR-TB
- 2:1 ratio of delamanid vs placebo, in addition to background regimen
- Delamanid dosed at 100mg BD for 2 months, then 200mg daily for 4 months
- Includes a HIV-positive cohort (n = 48)
- 121 patients on moxifloxacin
- Follow-up complete as of June 2016

Gupta R et al (2016). Delamanid in the Treatment of Multidrug-Resistant Tuberculosis. *The International Journal of Tuberculosis and Lung Disease*

Pretomanid (PA-824)

- Class – nitro-imidazo-oxazine
- Mechanism of action – inhibition of mycolic acid synthesis; generation of reactive nitrogen species
- Half-life – 16 to 20 hours
- Dosing – 200mg daily (tentative)
- Adverse effects – ↑ serum creatinine (dose-dependent, reversible, no definite effect on true renal function a la trimethoprim)

Ginsberg A et al (2009). Safety, Tolerability, and Pharmacokinetics of PA-824 in Healthy Subjects. *Antimicrobial Agents and Chemotherapy*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2010, p. 3402–3407 Vol. 54, No. 8
0066-4804/10/$12.00 doi:10.1128/AAC.01354-09

Early Bactericidal Activity and Pharmacokinetics of PA-824 in Smear-Positive Tuberculosis Patients▽†

Andreas H. Diacon,[1,2]* Rodney Dawson,[3] Madeleine Hanekom,[1,2] Kim Narunsky,[3] Stefan J. Maritz,[1] Amour Venter,[1] Peter R. Donald,[1] Christo van Niekerk,[4] Karl Whitney,[5] Doris J. Rouse,[5] Martino W. Laurenzi,[4] Ann M. Ginsberg,[4] and Melvin K. Spigelman[4]

TABLE 2. Early bactericidal activity for days 0 to 14, 0 to 2, and 2 to 14 measured by fall in CFU on solid medium[a]

Dosage[c]	PA-824 group										Standard treatment group[b]	
	200 mg		600 mg		1,000 mg		1,200 mg		All groups			
	Mean $\log_{10}$ CFU/ml	*n*	Mean $\log_{10}$ CFU/ml	*n*	Mean $\log_{10}$ CFU/ml	*n*	Mean $\log_{10}$ CFU/ml	*n*	Mean $\log_{10}$ CFU/ml	*n*	Mean $\log_{10}$ CFU/ml	*n*
EBA(0–14)	0.106 (0.049)	12	0.107 (0.053)	14	0.091 (0.083)	15	0.088 (0.084)	11	0.098 (0.072)	52	0.148 (0.055)	7
EBA(0–2)	0.109 (0.487)	15	0.096 (0.226)	13	0.025 (0.340)	15	−0.035 (0.420)	15	0.047 (0.373)	58	0.403 (0.290)	8
EBA(2–14)	0.106 (0.063)	12	0.113 (0.079)	12	0.095 (0.062)	14	0.113 (0.099)	11	0.106 (0.077)	49	0.112 (0.050)	7

[a] Values are mean $\log_{10}$ CFU/ml sputum/day (±SD). *n*, number of participants with results; EBA, early bactericidal activity.
[b] For a definition of standard treatment, see the text.
[c] Note that EBA(0–14) can deviate from the arithmetic sum of EBA(0–2) and EBA(2–14) due to missing data points.

Sutezolid (PNU-100480)

- Class – oxazolidinone
- Mechanism of action – inhibition of protein synthesis
- Half-life – 4 hours
- Dosing – 600mg BD (tentative)
- Adverse effects – promises to be better than linezolid (n.b. the tedizolid story)

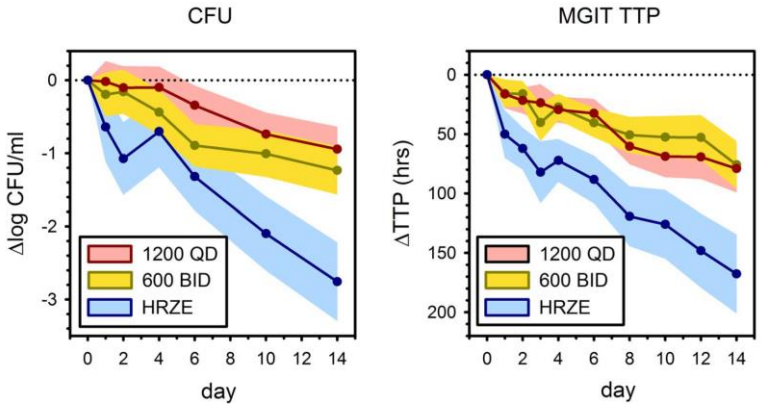
Wallis R et al (2011). Biomarker-Assisted Dose Selection for Safety and Efficacy in Early Development of PNU-100480 for Tuberculosis. *Antimicrobial Agents and Chemotherapy*

OPEN ACCESS Freely available online

PLOS ONE

Mycobactericidal Activity of Sutezolid (PNU-100480) in Sputum (EBA) and Blood (WBA) of Patients with Pulmonary Tuberculosis

Robert S. Wallis[1*¤a], Rodney Dawson[2], Sven O. Friedrich[3], Amour Venter[4], Darcy Paige[5], Tong Zhu[5], Annette Silvia[5], Jason Gobey[5], Craig Ellery[5], Yao Zhang[5], Kathleen Eisenach[6], Paul Miller[1¤b], Andreas H. Diacon[3]



In Limbo

SEQUELLA Incorporated

Sutezolid for the Treatment of Tuberculosis

Clinical Development Status: Phase 2

21 February 2017

Request for open access to all existing clinical data on sutezolid

Dear Dr. Nacy,

We write to call your attention to the licensing agreement reached between the Medicines Patent Pool (MPP) and Johns Hopkins University (JHU) regarding the clinical development of tuberculosis (TB) treatment candidate sutezolid[1], and to formally request that Sequella join these efforts by openly providing access to all existing clinical data necessary to further facilitate sutezolid's development and future patients' access.

Sincerely,

The Sutezolid coalition, including Doctors Without Borders/Médecins Sans Frontières (MSF) Access Campaign, Treatment Action Group (TAG), Universities Allies for Essential Medicines (UAEM), the Global TB Community Advisory Board (TB CAB) and Public Citizen.

http://www.doctorswithoutborders.org/sites/usa/files/msf_sutezolid_letter_to_sequella.pdf

Short(er) Courses

Rapid Evaluation of Moxifloxacin in Tuberculosis (REMoxTB)


ORIGINAL ARTICLE

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

- Adults with newly-diagnosed TB and confirmed sensitivity to rifampicin + quinolones
- Control – HRZE for 8 weeks, then HR for 18 weeks
- Isoniazid group – moxifloxacin instead of ethambutol for 17 weeks
- Ethambutol group – moxifloxacin instead of isoniazid for 17 weeks

Variable	Per-Protocol Analysis			
	Control Group (N=510)	Isoniazid Group (N=514)	Ethambutol Group (N=524)	All Patients (N=1548)
Favorable outcome — no. (%)				
Patients with outcome	467 (92)	436 (85)	419 (80)	1322 (85)
Culture-negative status at 18 mo	409 (80)	389 (76)	367 (70)	1165 (75)

RIFAQUIN

Status and Outcome	Control Regimen	4-Month Regimen	6-Month Regimen	Total
Per-protocol analysis — no.	163	165	186	514
Favorable — no. (%)	155 (95.1)	135 (81.8)	180 (96.8)	470 (91.4)
Unfavorable				
Failure (culture confirmed) — no.	2	2	0	4
Death during treatment — no.	1	0	1	2
Relapse (culture confirmed) — no.	4	19	4	27
Relapse (limited bacteriology) — no.	1	7	1	9
Culture positive when last seen — no.	0	2	0	2
Total — no. (%)	8 (4.9)	30 (18.2)	6 (3.2)	44 (8.6)
Difference from control in unfavorable rate (adjusted for study center)		13.6	−1.8	

Control – HRZE for 2 months, then HR for 4 months
4-Month – moxifloxacin + rifampicin + pyrazinamide + ethambutol daily for 2 months; then moxifloxacin + rifapentine 900mg twice weekly for 2 months
6-Month – moxifloxacin + rifampicin + pyrazinamide + ethambutol daily for 2 months; then moxifloxacin + rifapentine 1200mg weekly for 4 months

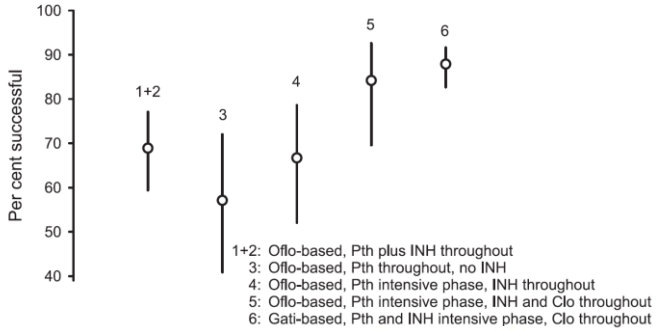
Jindani A et al (2014). High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis. *NEJM.*

Bangladesh Regimen

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

[1]International Union Against Tuberculosis and Lung Disease, Paris, France; [2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Damien Foundation Bangladesh, Dhaka, Bangladesh; and [4]Institute of Social and Preventive Medicine, University of Zurich, Switzerland



Regimen (sequence)	Intensive Phase	Continuation Phase 1	Continuation Phase 2	Patients Enrolled Number	Col %
1	3* KCOEHZP	12 OEHZP	6 EP	59	13.8
2	3(+) KCOEHZP	12 OHEZP		44	10.3
3	3(4) KCOEZP	12 OEZP		35	8.2
4	3(+) KCOEHZP	12 OHEZ		45	10.5
5	3(+) KCOEHZP	12 OHEZC		38	8.9
6	4(+) KCGEHZP	5 GEZC		206	48.2
Total number of patients enrolled				427	100.0

Definition of abbreviations: C = clofazimine; Col % = column percent; E = ethambutol; G = gatifloxacin; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; Z = pyrazinamide.

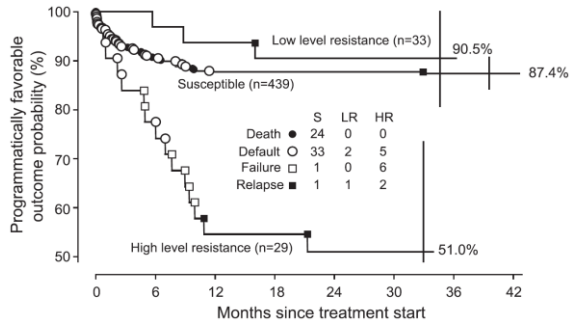
INT J TUBERC LUNG DIS 18(10):1180–1187

http://dx.doi.org/10.5588/ijtld.14.0100

Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients

K. J. M. Aung,* A. Van Deun,†‡ E. Declercq,§ M. R. Sarker,* P. K. Das,* M. A. Hossain,* H. L. Rieder‡

	n (%)	95%CI
Total (*n* = 515)		
Success (*n* = 435, 84.5%)		
Completion	17 (3.3)	2.1–5.2
Cure, 0 months follow-up	4 (0.8)	0.3–2.0
Cure, 6 months follow-up	7 (1.4)	0.7–2.8
Cure, 12 months follow-up	11 (2.1)	1.2–3.8
Cure, 18 months follow-up	36 (7.0)	5.1– 9.5
Cure, 24 months follow-up	358 (69.5)	65.4–73.3
Cured, reinfection disease	2 (0.4)	0.1–1.4
Non-success (*n* = 80, 15.5%)		
Failure	7 (1.4)	0.7–2.8
Death, first 60 days	14 (2.7)	1.6–4.5
Death, after 60 days	15 (2.9)	1.8–4.7
Default, first 60 days	19 (3.7)	2.4–5.7
Default, after 60 days	21 (4.1)	2.7–6.2
Relapse	4 (0.8)	0.3–2.0



Cure rate in relation to quinolone resistance

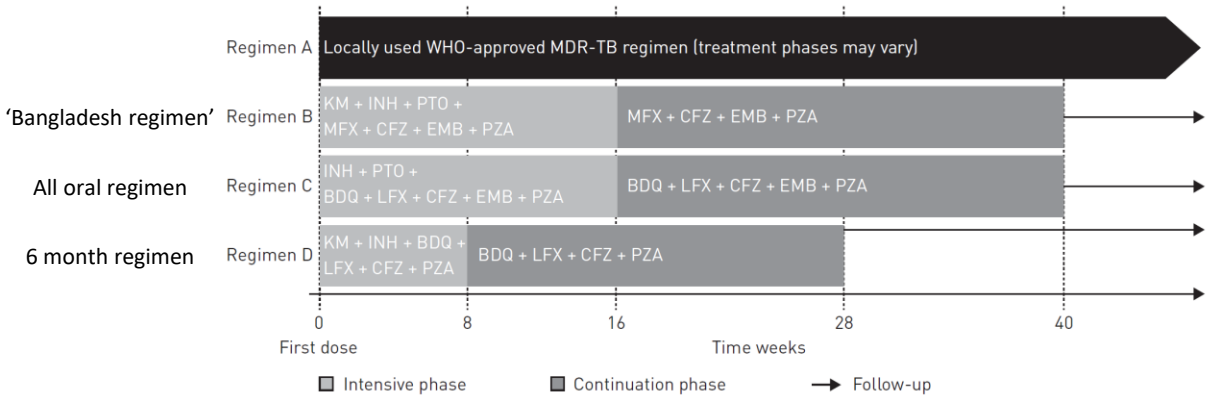
WHO Recommendation 2016

'In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs – and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely – a shorter MDR-TB regimen of 9–12 months may be used (conditional recommendation, very low certainty in the evidence)'

Additional exclusion criteria – pregnant; extra-pulmonary TB

Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials

Riya Moodley[1] and Thomas R. Godec[1] on behalf of the STREAM Trial Team[2]



STREAM

- Adults with pulmonary MDR-TB + no initial quinolone/injectable resistance line probe assay
- Phase 1 – non-inferiority trial of B (Bangladesh regimen) vs A (standard WHO regimen)
  - 424 patients enrolled
  - Results expected 2018
- Phase 2 – patients randomised to any of the listed regimens
  - Primary outcomes are non-inferiority of C (all oral) and D (6 month regimen) vs B (Bangladesh regimen)
  - First patient enrolled March 2016

Rusen ID (2016). STREAM Trial Update, accessible at http://www.cptrinitiative.org/wp-content/uploads/2016/05/5.7-Rusen.pdf

Nix-TB

- Open label trial in South Africa
- Bedaquiline + pretomanid + linezolid 1200mg daily for 6 months (with an option for 9 months if culture positive at 4 months)
- XDR-TB or MDR-TB with treatment intolerance/failure
- Exclusion criteria – HIV with CD4 count <50; QTC >500ms; significant peripheral neuropathy
- Primary endpoint – failure or relapse within 6 months of completing treatment

Conradie F (2017). The Nix-TB Trial of Pretomanid, Bedaquiline and Linezolid to Treat XDR-TB, accessible at http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb

Nix-TB Early Results

- 72 patients enrolled (37 HIV positive, 47 XDR-TB)
  - 4 deaths on treatment (all within 2 months)
  - 31 completed treatment and 6-month follow-up:
    - 2 relapses/reinfections:
      1. XDR-TB on line probe assay – awaiting whole genome sequencing
      2. Drug-sensitive TB – likely reinfection
  - All surviving patients were culture-negative at 4 months (74% negative at 2 months)
- Adverse events:
  - 49 patients had at least one linezolid dose interruption
  - ~10 patients had transaminitis – all resolved after a pause in treatment

Conradie F (2017). The Nix-TB Trial of Pretomanid, Bedaquiline and Linezolid to Treat XDR-TB, accessible at http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb

More Coming!

Nickname	Sponsor	TB Type	Trial Drugs	Status
MDR-END	Seoul National University Hospital	Quinolone-sensitive MDR	Delamanid + linezolid + levofloxacin + pyrazinamide for 9 to 12 months	Enrolling
STAND	TB Alliance	DS	Moxifloxacin + pretomanid + pyrazinamide for 4 to 6 months	Suspended for NC-005
NC-005	TB Alliance	DS or MDR	3 arms with bedaquiline + pretomanid + pyrazinamide +/- moxifloxacin vs HRZE	Recruitment completed
endTB	MSF	MDR	5 arms (containing bedaquiline or delamanid) vs standard regimen for 39 weeks	Enrolling
NeXT	University of Cape Town	MDR or XDR	Linezolid + bedaquiline + levofloxacin + pyrazinamide + ethionamide/isoniazid for 6 to 9 months	Enrolling

Resist-TB (2016). DR-TB Clinical Trials Progress Report, accessible at http://www.resisttb.org/?page_id=1602
Specific information on individual trials accessible at http://clinicaltrials.gov

In Summary

NEW DRUGS

- Bedaquiline - WHO approved
- Delamanid - WHO approved
- Pretomanid - active phase III trials
- Sutezolid - progress stagnant

SHORTER COURSES

- ReMoxTB - negative trial
- RIFAQUIN - negative trial for shorter course
- 'Bangladesh Regimen' - WHO approved, ongoing trial vs standard of care (in STREAM)
- STREAM - ongoing
- Nix-TB - early results appear promising

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