Newer anti-TB drugs and regimens

DM Seminar

31-10-14

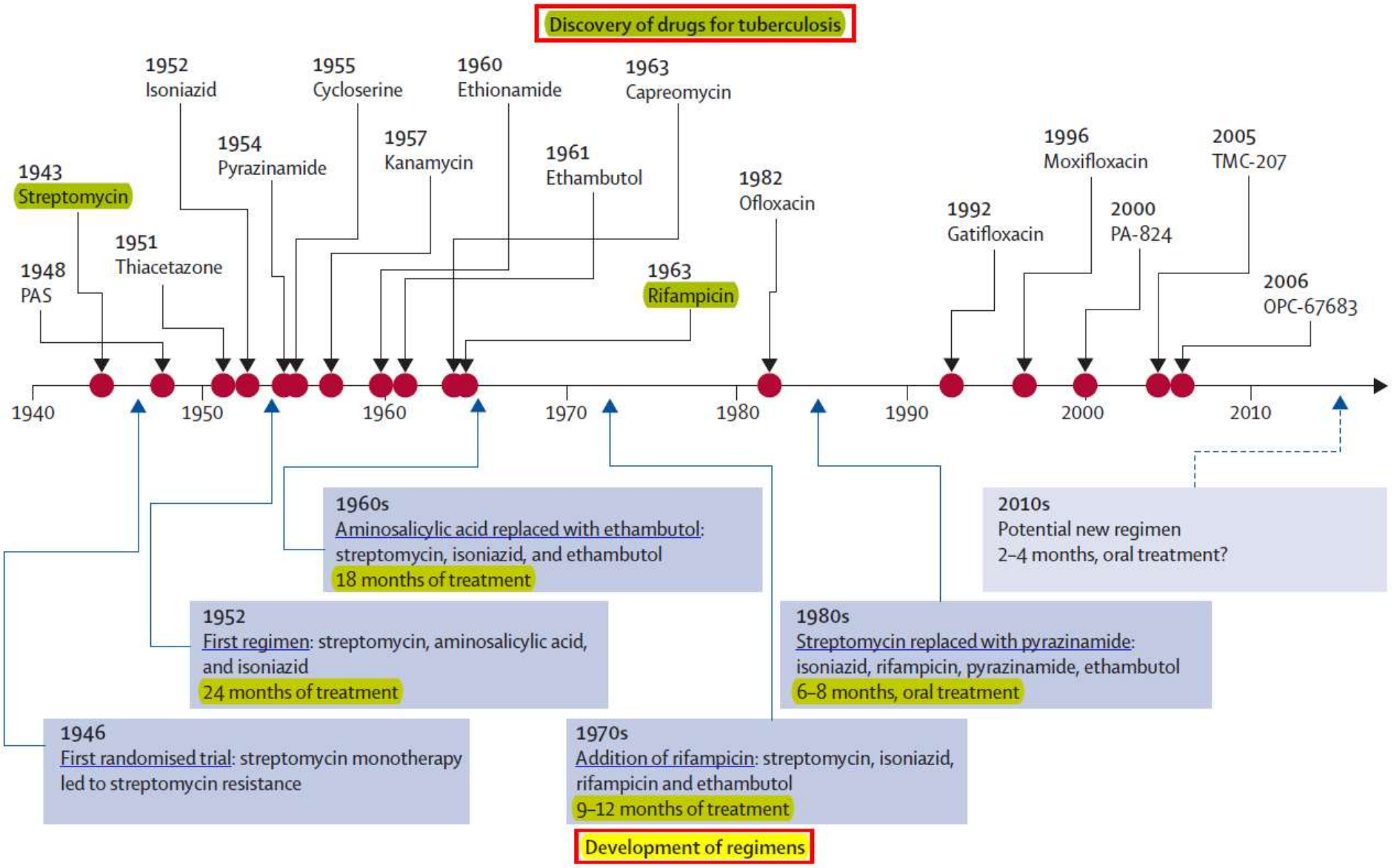
Why are newer drugs/regimens needed?

Problems with current drugs/regimens

- Drug resistance
- Drug interaction of anti-tubercular drugs with ART
- Long duration of ATT
- Long duration of Rx of latent TB

Solutions (Newer drugs/regimens)

- Novel MoA
- Less drug interaction
- More potent
- Better regimens



TMC 207 = Bedaquiline; OPC-67683 = Delamanid

Lancet 2010; 375: 2100–09

Global TB Drug Pipeline [1]

Preclinical Development | **Clinical Development**

Early Stage Development	GLP Tox.	Phase I	Phase II	Phase III
CPZEN-45	PBTZ169		AZD5847 [N]	Delamanid [NR]
BTZ043	TBA-354		Bedaquiline [NCR]	(OPC-67683)
DC-159a	Q203		(TMC-207) for DS-TB	Gatifloxacin*
SQ609			Linezolid	Moxifloxacin*
SQ641			Novel Regimens[2]	Rifapentine [R] for LTBI
TBI-166			PA-824 [Nc]	Bedaquiline [NCR]
			Rifapentine for DS-TB	(TMC-207) for MDR-TB
			SQ-109 [N]	
			Sutezolid [N]	
			(PNU-100480)	

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[2] Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186.

[C] Drug candidate currently in combination regimen in clinical testing

[R] Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

[N] New chemical entity

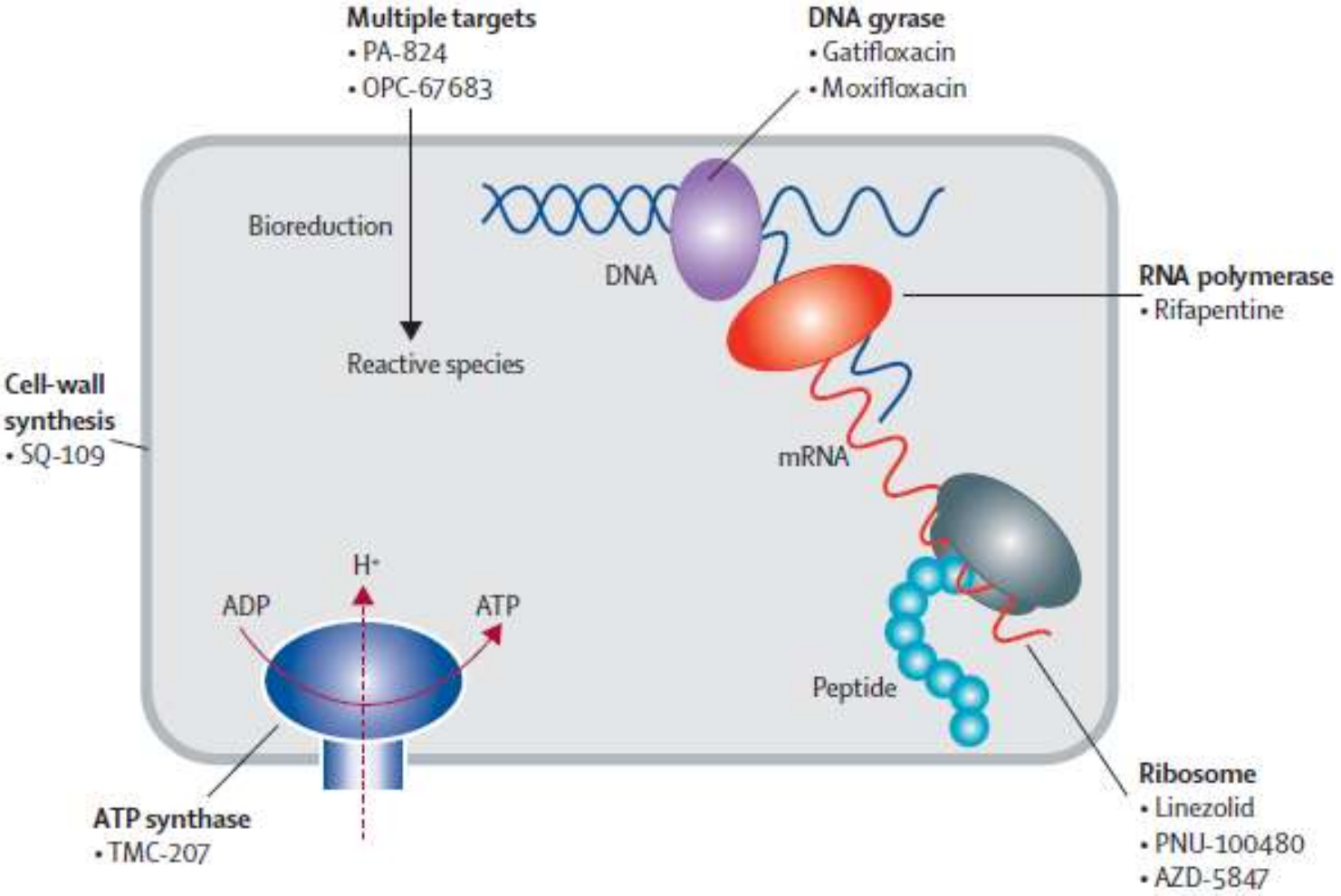
* Projects that have been completed

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: August 2014

MoA of newer drugs



TMC 207 = Bedaquiline; OPC-67683 = Delamanid

Lancet 2010; 375: 2100–09

Delamanid

Delamanid

- OPC-67683
- Nitro-dihydro-imidazooxazole derivative
- Inhibits mycolic acid synthesis and cell respiration
- Developed by Otsuka Pharmaceutical, Japan
- Marketed as DELTYBA 50mg tabs

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.

N Engl J Med 2012; 366:2151-2160

Methods

- Multinational Phase 2 trial
- 481 patients (only 4 were HIV-positive) with pulmonary MDR TB
- Patients with Karnofsky scores <50% and HIV-positive patients with CD4 count <350 or on ART were excluded
- Randomized to receive for 2 months
  - Delamanid 100 mg BD (161 patients) or
  - Delamanid 200 mg BD (160 patients) or
  - Placebo (160 patients) for 2 months
- All were given along with a background drug regimen developed according to WHO guidelines (4-5 drugs)

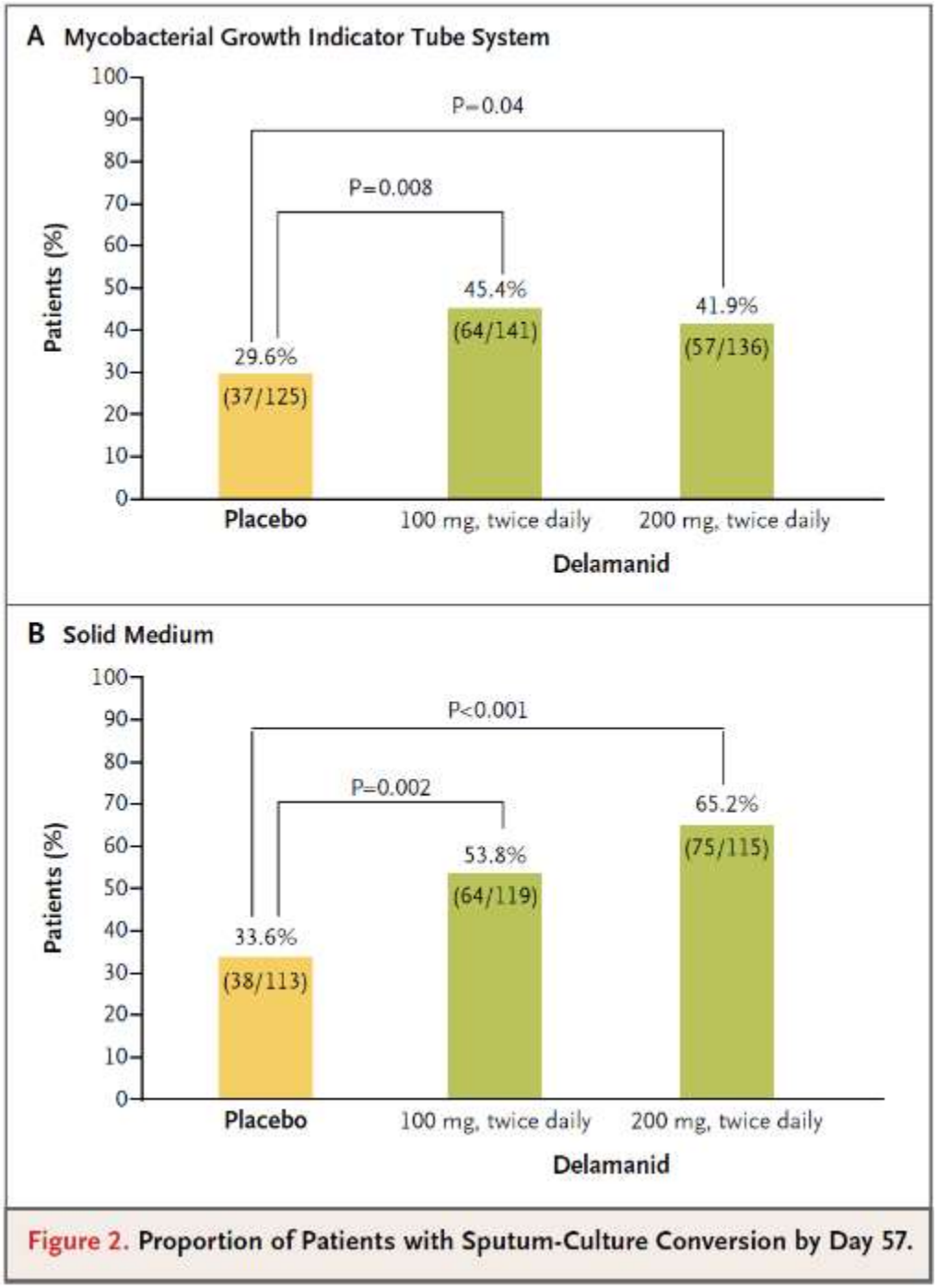
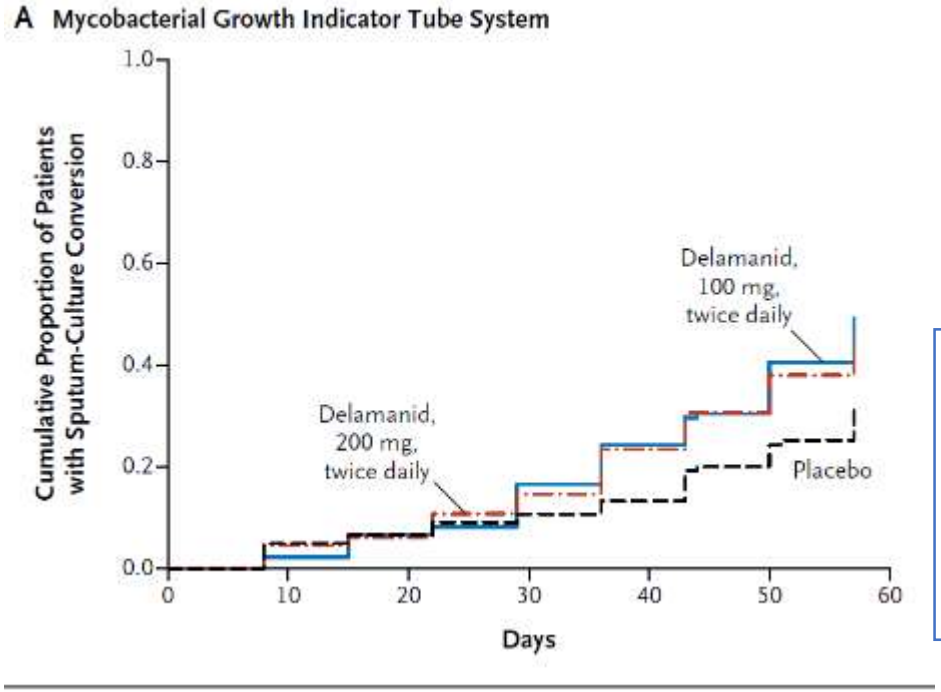
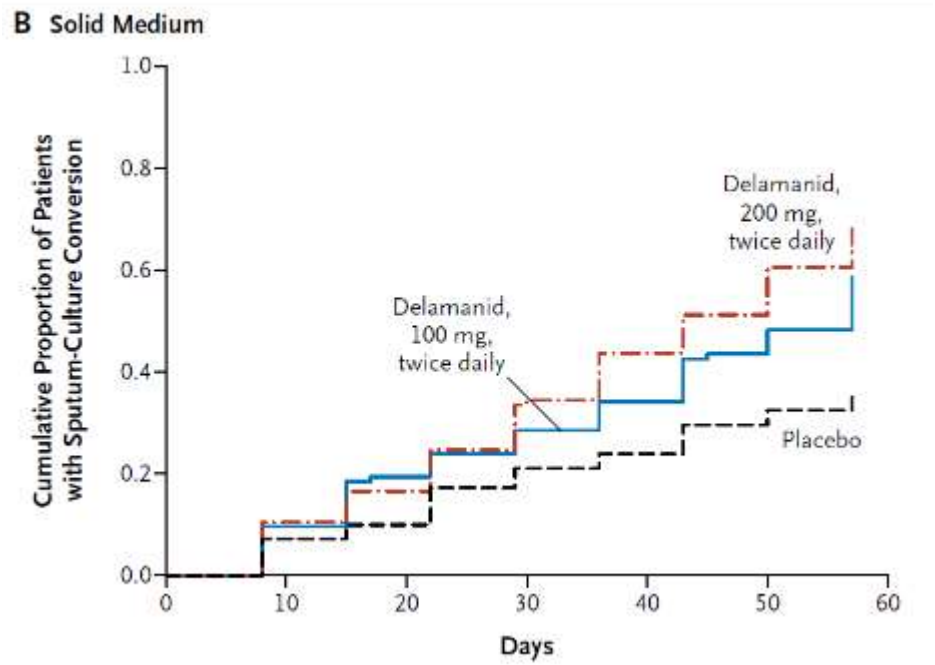


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

Sputum culture conversion (2 months)

N Engl J Med 2012; 366:2151-2160





Time to sputum culture conversion

Kaplan–Meier curves representing the time to conversion according to culture medium type showed 10% separation between the delamanid groups and the placebo group by day 36 with MGIT

N Engl J Med 2012; 366:2151-2160

Adverse events

- Prolonged QT interval
  - Delamanid 200 mg BD (13.1%)
  - Delamanid 100 mg BD (9.9%)
  - Placebo group (3.8%)
- No episodes of prolonged QT interval were associated syncope or arrhythmias

EMA Approval

- On November 22, 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) recommended granting of a conditional marketing authorisation for delamanid
- Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

Bedaquiline

Bedaquiline

- Diarylquinoline
- Inhibits mycobacterial ATP synthase
- Developed by Janssen (pharmaceuticals unit of Johnson and Johnson)
- Marketed as SIRTURO (TMC207) 100mg tabs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

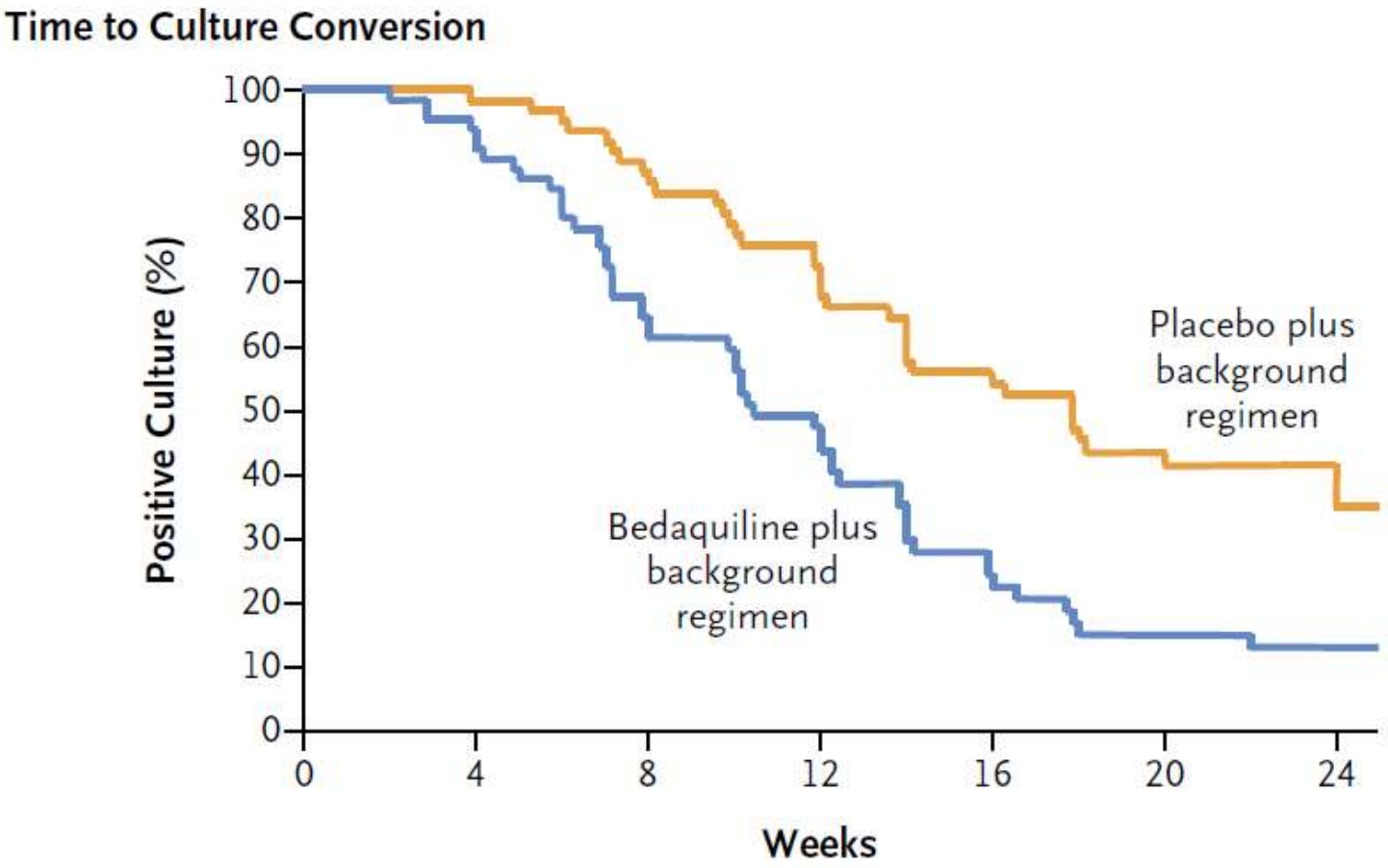
Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

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*

N Engl J Med 2014; 371:723-732

Methods

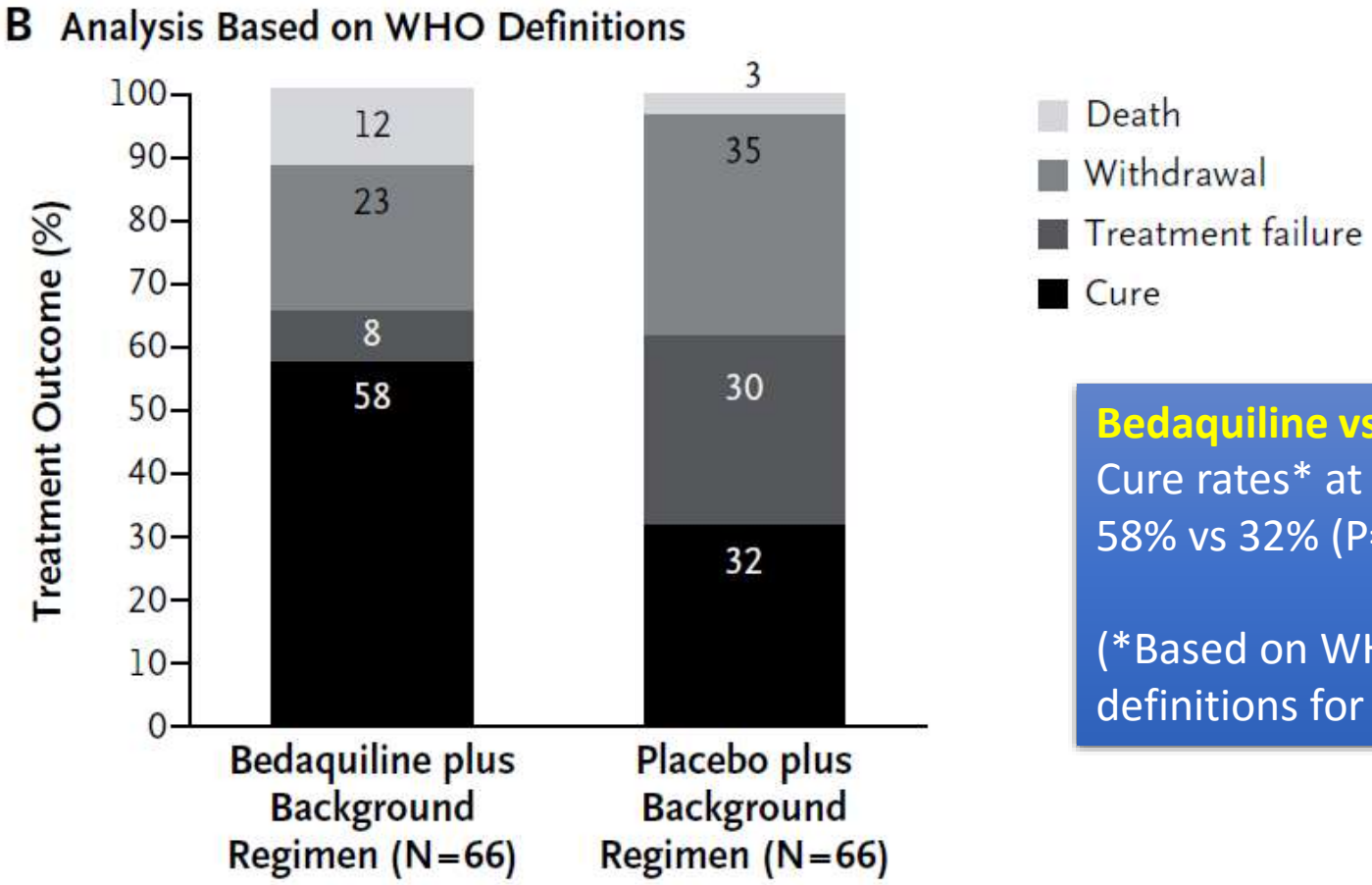
- Phase 2b, multi-national trial
- 2 sites from India: Tuberculosis research centre & National Institute for Research in Tuberculosis (Both in Chennai) & AIIMS, New Delhi
- 160 newly diagnosed, smear-positive MDR PTB patients
- HIV-positive patients with CD4 count <300 excluded
- 400 mg of bedaquiline OD for 2 weeks, followed by 200 mg thrice a week for 22 weeks, or placebo
- Both were used in combination with a 5-drug, second-line background regimen (ethionamide, pyrazinamide, ofloxacin, kanamycin, and cycloserine) consistent with WHO recommendations for Rx of MDR TB at that time



N Engl J Med 2014; 371:723-732

Bedaquiline vs Placebo

- Median time to culture conversion 83 vs 125 days (P<0.001)
- Rate of culture conversion
  - at 24 weeks (79% vs. 58%, P=0.008) and
  - at 120 weeks (62% vs. 44%, P=0.04)



Bedaquiline vs Placebo
Cure rates* at 120 weeks
58% vs 32% (P=0.003)

(*Based on WHO outcome definitions for MDR TB)

N Engl J Med 2014; 371:723-732

Bedaquiline vs Placebo: Adverse events

- Most frequent adverse events
  - Nausea (41% vs 37%)
  - Arthralgia (37% vs 27%)
  - Vomiting (29% vs 27%)
  - Most were severity grade 1 or 2
- QTc prolongation
  - Mean increase in QTc from baseline (at 24 weeks): 15.4 vs 3.3 msec ($P<0.001$)
  - Only 1 patient on bedaquiline had QTc >500ms (once)
  - No dysrhythmias

Bedaquiline vs Placebo: Deaths

Bedaquiline: 10 deaths

- 5/10 Progression of disease
- 4/10 Unrelated causes
- 1 due to motor-vehicle accident

Placebo: 2 deaths

- 2/2 Progression of disease

Subject	Treatment arm	Category	Cause of death	
Deaths while followed during trial (120 weeks)				
208–4041	BDQ	Non-responder; converted; discontinued	Alcohol poisoning	
208–4153	BDQ	Non-responder; relapse	TB-related illness	Non-compliant
208–4224	BDQ	Non-responder; relapse	TB-related illness	Non-compliant
208–5069	BDQ	Non-responder; converted; discontinued	Cirrhosis, hepatitis, anaemia	
208–4399	BDQ	Responder; converted	Cerebrovascular accident	
208–5067	BDQ	Responder; converted	Peritonitis and septic shock	
208–4120	Placebo	Non-responder; failure to convert	Haemoptysis (TB)	Compliant
Deaths during long-term survival follow-up of prematurely withdrawn subjects				
208–4127	BDQ	Non-responder; failure to convert	TB-related illness	Non-compliant
208–4145	BDQ	Non-responder; relapse	TB-related illness	Non-compliant
208–4378	BDQ	Non-responder; relapse	Motor vehicle accident	
208–4464	BDQ	Non-responder; failure to convert	TB-related illness	XDR TB
208–4155	Placebo	Non-responder; failure to convert	TB-related illness	Non-compliant XDR TB

Bedaquiline: FDA approval

- On Dec. 28, 2012 the U.S. FDA approved SIRTURO (bedaquiline) as part of combination therapy to treat adults with MDR PTB when other alternatives are not available
- SIRTURO was approved under the FDA's accelerated approval program (based on surrogate endpoints predicting clinical benefit e.g., conversion of sputum culture)
- SIRTURO carries a Boxed Warning regarding
  - Potential for QT prolongation
  - Deaths in patients treated with Sirturo

Bedaquiline: First's

- It was the first new anti-TB drug to be FDA approved after 1998 (Rifapentine was approved in 1998)
- It was the first anti-TB drug with a novel MoA to be FDA approved after 40 years (Rifampicin was approved in 1974)
- It was the first anti-TB drug to be introduced specifically for the Rx of MDR-TB in combination with other drugs

Linezolid

LRS (Delhi) experience

- 29 MDR-TB Rx failure patients (16 with XDR-TB and the remaining 13 with Pre-XDR TB [MDR-TB with resistance to any quinolone but sensitive to injectables])
- Daily unsupervised therapy with linezolid (600mg od/bd), one injectable agent, one fluoroquinolone and two or more other drugs (median of six anti-mycobacterial agents)
- Besides linezolid, capreomycin, moxifloxacin, levofloxacin and amoxycillin-clavulanic acid were used in 41.4%, 58.6%, 41.4%, and 79.3% of patients

Eur Respir J 2012; 39: 956–962

Results

TABLE 6 Treatment outcomes in 29 patients

	XDR	Pre-XDR-TB	p-value	Total
Cured	5 (31.2)	4 (30.8)	0.707[#]	9 (31.0)
Still on treatment[¶]	7 (43.7)	5 (38.5)	0.774	12 (41.4)
Failed	0	2 (15.4)	0.192[+]	2 (6.8)
Default	2 (12.5)	1 (7.7)	0.849[#]	3 (10.3)
Died	2 (12.5)	1 (7.7)	0.849[#]	3 (10.3)
Total	16 (100)	13 (100)		29 (100)

Data are presented as n (%), unless otherwise stated. XDR: extremely drug resistant; TB: tuberculosis; pre-XDR-TB: multidrug resistant-TB plus quinolone resistance without resistance against injectables. [#]: Yates' correction applied; [¶]: all patients completed >12 months of treatment and, to date, are persistently culture negative; [+]: Fisher's exact test applied.

- Interim favourable outcome (Cured + Completed >12 Mo Rx and are culture negative) = 21 (72.4%)
- 72.2% in the od group and 72.7% in the bd group achieved interim favourable outcome (P = 1)

Results

TABLE 4 Smear conversion characteristics in 29 patients

	XDR	Pre-XDR-TB	Total	p-value
Subjects	16	13	29	
Smear conversion	15 (93.7)	11 (84.6)	26 (89.7)	0.87
Median time for smear conversion months	4	4	4	0.55
Culture conversion	15 (93.7)	11 (84.6)	26 (89.7)	0.87
Median time for culture conversion months	4	4	4	1.00

Data are presented as n or n (%), unless otherwise stated. XDR: extremely drug resistant; TB: tuberculosis; pre-XDR-TB: multidrug resistant-TB plus quinolone resistance without resistance against injectables.

- Linezolid had to be stopped in 3 (10.3%) patients due to adverse reactions
- Severe anaemia, peripheral neuritis and optic neuritis; each in one patient
- All 3 were taking linezolid 600mg bd

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Myungsun Lee, M.D., Jongseok Lee, Ph.D., Matthew W. Carroll, M.D., Hongjo Choi, M.D., Seonyeong Min, R.N., Taeksun Song, Ph.D., Laura E. Via, Ph.D., Lisa C. Goldfeder, C.C.R.P., Eunhwa Kang, M.Sc., Boyoung Jin, R.N., Hyeeun Park, R.N., Hyunkyung Kwak, B.S., Hyunchul Kim, Ph.D., Han-Seung Jeon, M.S., Ina Jeong, M.D., Joon Sung Joh, M.D., Ray Y. Chen, M.D., Kenneth N. Olivier, M.D., Pamela A. Shaw, Ph.D., Dean Follmann, Ph.D., Sun Dae Song, M.D., Ph.D., Jong-Koo Lee, M.D., Dukhyoung Lee, M.D., Cheon Tae Kim, M.D., Veronique Dartois, Ph.D., Seung-Kyu Park, M.D., Sang-Nae Cho, D.V.M., Ph.D., and Clifton E. Barry III, Ph.D.

N Engl J Med 2012; 367:1508-1518

Seoul, South Korea

- 41 patients with sputum-culture–positive XDR TB (who had not had a response to any available chemotherapeutic option during the previous 6 months)
- Randomly assigned to linezolid (600mg/d) that started immediately or after 2 months, without a change in their background regimen
- After confirmed sputum-smear conversion or 4 months (whichever came first), patients underwent a second randomization to continued linezolid at a dose of 600mg/d or 300mg/d for at least an additional 18 months

N Engl J Med 2012; 367:1508-1518

Results

- 3 patients were withdrawn before initiating linezolid
- By 4 months, 15/19 patients (79%) in the immediate-start group and 7/20 (35%) in the delayed-start group had culture conversion (P=0.001)
- 34/38 (87%) had a negative sputum culture within 6 months of addition of linezolid
- 13/38 (34%) patients completed therapy without relapse
- 4 cases of acquired resistance to linezolid were observed

N Engl J Med 2012; 367:1508-1518

Clinically significant adverse events possibly or probably related to linezolid

	Total	0-4 Mo	4-8 Mo	8-12 Mo
Myelosuppression	6	**5**	1	0
Peripheral neuropathy	**20**	5	**10**	5
Optic neuropathy	6	1	2	3
Hepatic enzyme elevation	3	1	1	1
Rhabdomyolysis	1	0	1	0

- Of the 38 patients with exposure to linezolid, 31 (82%) had clinically significant adverse events that were possibly or probably related to linezolid
- 3 patients who discontinued therapy owing to adverse events (2 optic neuropathy, 1 anaemia)
- Patients who received 300 mg/d after the second randomization had fewer adverse events than those who continued taking 600 mg/d

Shorter ATT regimes

Shorter regimes: Potential candidates

- Rifapentine
  - Once weekly dosing: Half-life of rifapentine (active metabolite) vs rifampicin is 13-24 h vs 2-3 h
- Moxi/Gatifloxacin
  - Faster culture conversion rates compared to conventional regimes in animal studies and human pilot studies
  - Early bactericidal activity of moxifloxacin was comparable to that of isoniazid (Am J Respir Crit Care Med. 2003 Dec 1;168(11):1342-5; Antimicrob Agents Chemother. 2004 Mar;48(3):780-2)

NIRT, Chennai trial

OPEN ACCESS Freely available online

PLOS | ONE

Randomized Clinical Trial of Thrice-Weekly 4-Month Moxifloxacin or Gatifloxacin Containing Regimens in the Treatment of New Sputum Positive Pulmonary Tuberculosis Patients

Mohideen S. Jawahar[1]*, Vaithilingam V. Banurekha[1], Chinnampedu N. Paramasivan[1], Fathima Rahman[1], Rajeswari Ramachandran[1], Perumal Venkatesan[1], Rani Balasubramanian[1], Nagamiah Selvakumar[1], Chinnaiyan Ponnuraja[1], Allaudeen S. Iliayas[2], Navaneethapandian P. Gangadevi[2], Balambal Raman[1], Dhanaraj Baskaran[1], Santhanakrishnan R. Kumar[2], Marimuthu M. Kumar[2], Victor Mohan[2], Sudha Ganapathy[1], Vanaja Kumar[1], Geetha Shanmugam[1], Niruparani Charles[1], Murugesan R. Sakthivel[2], Kannivelu Jagannath[3], Chockalingam Chandrasekar[4], Ramavaram T. Parthasarathy[5], Paranji R. Narayanan[1]

1 National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Chennai, India, 2 National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Madurai, India, 3 Institute of Thoracic Medicine, Chennai, India, 4 Government Rajaji Hospital, Madurai, India, 5 Government Tiruvatteeswarar Hospital, Chennai, India

PLoS One. 2013 Jul 3;8(7):e67030

Patients

- 416 patients
- 2 centres: Chennai, Madurai
- Newly diagnosed, previously untreated, sputum smear +ve PTB
- HIV+ve, diabetics excluded

Regimens

- 3 groups
  - 2HRZE + 4HR (Control gp)
  - 2HRZG + 2HRG (Gatiflox gp)
  - 2HRZM + 2HRM (Moxiflox gp)
- All were thrice-weekly
- DOT

Efficacy & safety outcomes

	Control gp	Gatiflox gp	Moxiflox gp
Culture negativity at 2 months	78%	**83%**	**88%**
Culture negativity at end of Rx	**95%**	**95%**	**99%**
Unfavorable response at the end of Rx*	2%	5%	2%
Recurrence in the next 24 months†	6%	**15%**	**11%**
Acquired resistance‡	1	0	1
GI symptoms#	9%	**23%**	**22%**
Seizures (No.)	0	3	0
QTc prolongation (No.)	0	1	1
Dysglycemia	0	0	0

*Unfavourable response included Rx failure, Rx change & death
†Majority of recurrences occurred within 6 months of stopping Rx
‡Both were INH resistance
GI symptoms included nausea, vomiting, abdominal discomfort

Study was prematurely terminated by DSMB due to high TB recurrence rates in both the study arms compared to the control arm

The NEW ENGLAND JOURNAL of MEDICINE

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*

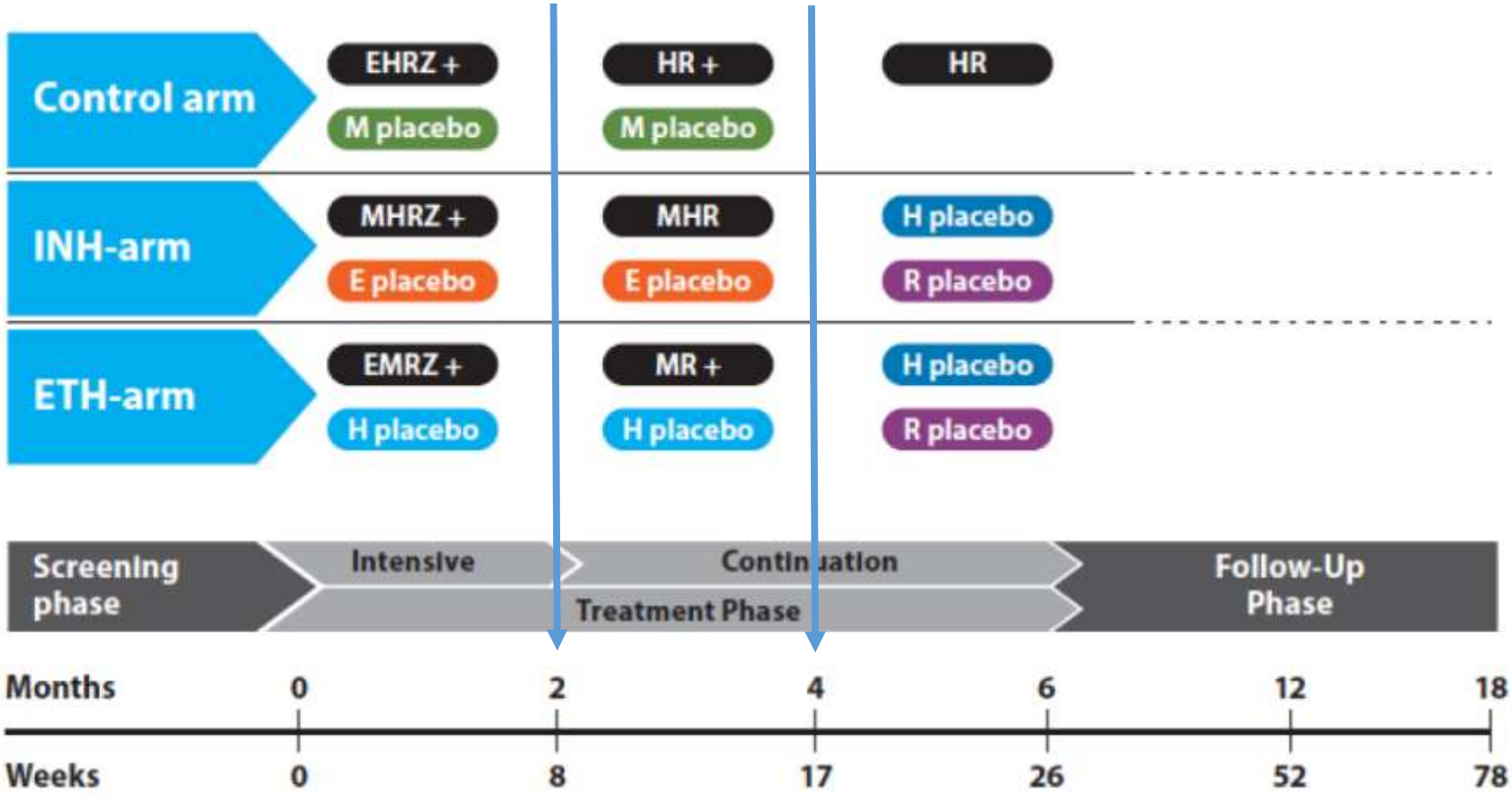
Patients

- Newly diagnosed, previously untreated, smear positive PTB patients with culture confirmed susceptibility to rifampin and fluoroquinolones
- HIV+ve with CD4 <250 or on ART excluded
- 1931 underwent randomization: 909 in South Africa, 376 in India, 212 in Tanzania, 136 in Kenya, 119 in Thailand, 69 in Malaysia, 66 in Zambia, 22 in China, and 22 in Mexico

Regimes

- Control group: HRZE (8 weeks) + HR (18 weeks)
- INH group: HRZM (8 weeks) + HRM (9 weeks)
- EMB group: MRZE (8 weeks) + MR (9 weeks)

- All drugs were given daily (DOT)
- Moxifloxacin 400mg was used
- Double-blind trial



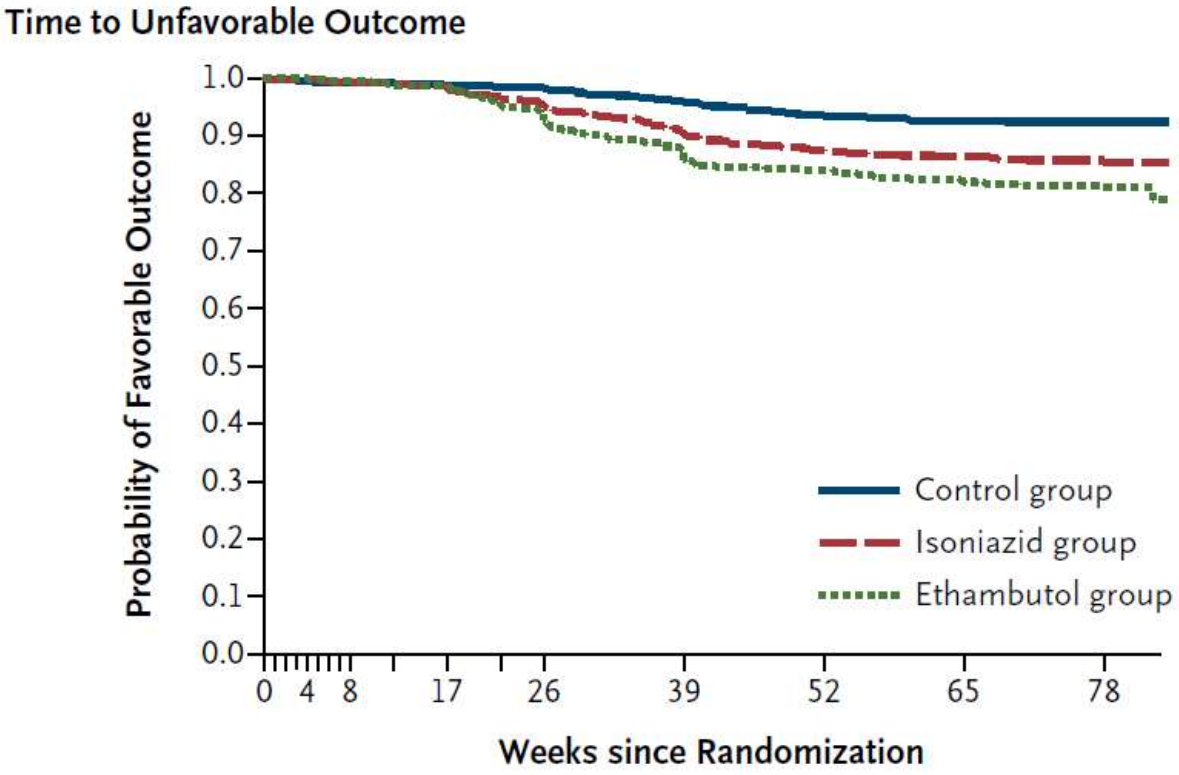
Outcomes

	Control gp	INH gp	EMB gp
Composite unfavourable outcome*: Per-protocol analysis	8%	**15%**	**20%**
Composite unfavourable outcome*: Modified ITT analysis	16%	**23%**	**24%**
Relapse**: Per-protocol analysis	2%	**9%**	**12%**
Relapse**: Modified ITT analysis	2%	**8%**	**12%**
Median time to culture negative status in weeks (95% CI): LJ solid media†	6.0 (6.0, 6.1)	**6.0 (5.1, 6.0)**	**6.0 (5.7, 6.0)**
Median time to culture negative status in weeks (95% CI): MGIT liquid media†	11.9 (8.1, 12.0)	**8.0 (8.0, 9.9)**	**8.0 (8.0, 8.1)**

* Composite unfavourable outcome (bacteriologically or clinically defined **failure or relapse** within 18 months after randomization)

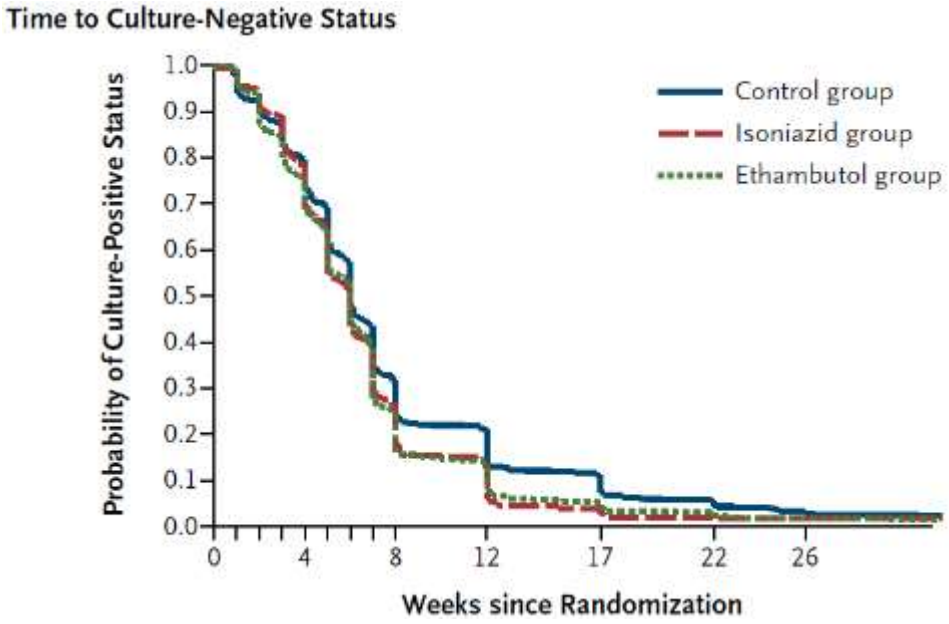
****The most common reason for an unfavorable outcome was relapse** after conversion to culture-negative status after the end of active treatment

Time to unfavourable outcome



In the per-protocol analyses, the time to an unfavorable outcome was shorter in the isoniazid group than in the control group (hazard ratio, 1.87; 97.5% CI, 1.07 to 2.67) and was further reduced in the ethambutol group (hazard ratio, 2.56; 97.5% CI, 1.51 to 3.60)

Time to culture-negativity



Median time to culture negative status in weeks (95% CI)

- LJ solid media
  - Control group: 6.0 (6.0, 6.1)
  - INH group: 6.0 (5.1, 6.0)
  - Ethambutol group: 6.0 (5.7, 6.0)
- MGIT liquid media
  - Control group: 11.9 (8.1, 12.0)
  - INH group: 8.0 (8.0, 9.9)
  - Ethambutol group: 8.0 (8.0, 8.1)

In Kaplan–Meier analyses, patients in the isoniazid group and the ethambutol group had **conversion to culture-negative status sooner than those in the control group** in sputum analyses with the use of Lowenstein–Jensen solid medium and MGIT medium

Adverse events

- No significant difference in the incidence of grade 3 or 4 adverse events.
- No significant between-group differences in tendinopathy, seizure, clinically significant cardiac toxicity, hepatic dysfunction, hypoglycemia or hyperglycemia, and peripheral neuropathy.

Resistance

- 4 cases of resistance:
  - Control group: 3 (two for rifampin and one for isoniazid)
  - INH group: None
  - Ethambutol group: 1 (for moxifloxacin)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

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Patients

- Newly diagnosed, previously untreated, smear positive PTB patients
- HIV+ patients with CD4 <200 or on ART were initially excluded. However, later, those with CD4 >150 or starting ART at screening were included
- 827 patients from South Africa, Zimbabwe, Botswana, and Zambia were enrolled
- 28% of patients were coinfected with HIV

RIFAQUIN: Regimens

- Moxifloxacin 400mg was used
- 2HRZE (daily) + 4HR (daily) (Control regimen)
- 2MRZE (daily) + 2MRp (twice weekly) (Rp 900mg)
- 2MRZE (daily) + 4MRp (once weekly) (Rp 1200mg)
- Intensive phase was directly observed at the health facility (DOT)
- Continuation phase
  - Control regimen was supervised by a relative or another person
  - Study regimens were directly observed at the health facility
- Open label

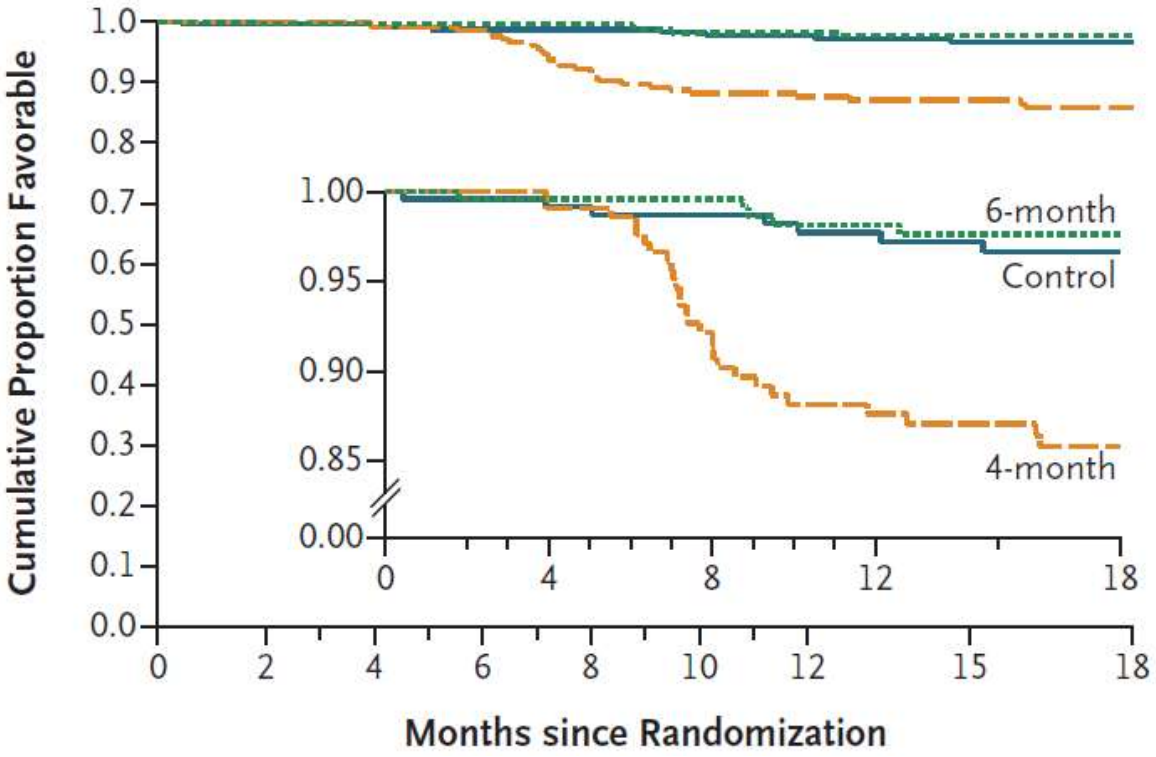
Outcomes

	Control gp	4M gp	6M gp
Composite unfavourable outcome*: Per-protocol analysis	4.9%	**18.2%**	3.2%
Composite unfavourable outcome*: Modified ITT analysis	14.4%	**26.9%**	13.7%
Relapse (Culture-confirmed)	2.4%	**11.5%**	2.2%

*Composite unfavourable outcome included **failure, relapse or death**

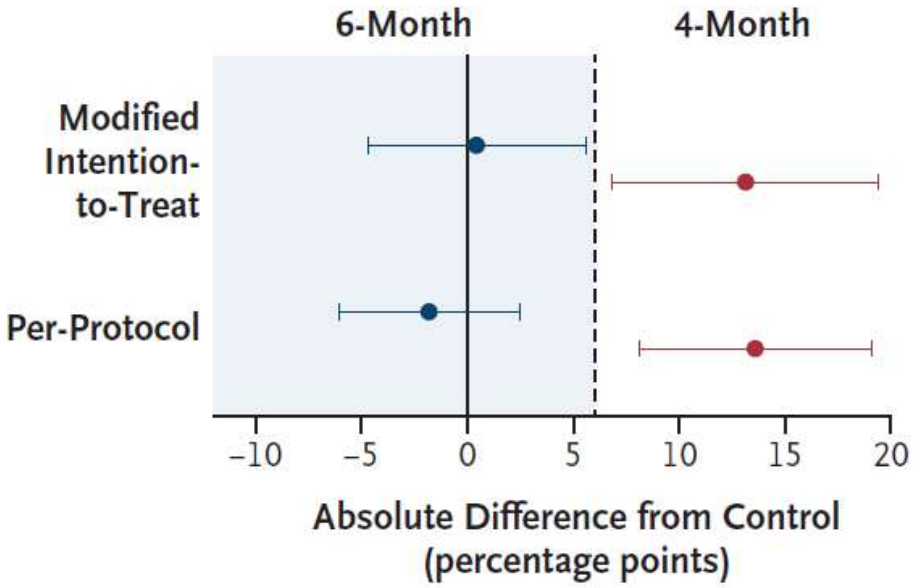
Moxifloxacin substitution for INH in the intensive phase reduced the proportion of patients with positive cultures at 2 months from 14.6% to 9.6%

Time to unfavourable outcome (Per-protocol population)



With the 4-month regimen, 24/30 unfavorable outcomes (80%) occurred <6 months after the end of Rx

Non-inferiority analysis



The dashed line represents the 6 percentage-point margin of noninferiority (as compared to control)

Compared to the control regimen:

- 4-month MOX-RPT regimen was inferior
- 6-month MOX-RPT regimen was non-inferior

Adverse events & deaths

	Control gp	4M gp	6M gp
Grade 3 or 4 adverse events possibly or probably related to study drug (No.)	6	6	4
Death due to any cause (No.)	6	**12**	7
Death possibly related to TB (No.)	1	2	1

Adherence

	Control gp	4M gp	6M gp
Proportions of patients with adherence rates ≥89%	75.3%	**81.4%**	**80.9%**
Proportions of patients with adherence rates ≥95%	48.7%	**76.7%**	**76.9%**

*Adherence during first 2 months was similar between all groups

Acquired resistance

- Only 1 case in control group to rifampicin (HIV+ve, Poor adherence)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

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Patients

- Newly diagnosed sputum-positive PTB
- 1836 patients from five sub-Saharan African countries: Benin, Guinea, Kenya, Senegal, and South Africa were enrolled
- Patients with prior history of ATT within last 3 years, diabetics, HIV stage 3 & 4 patients were excluded

Regimes

- 2HRZE + 4HR
- 2HRZG + 2HRG
- Gatifloxacin 400mg/d was used irrespective of body weight
- All drugs were administered 6 days a week (DOT)
  - Intensive phase: daily DOT by health centre staff
  - Continuation phase: Boxes provided to supervisor every 2 weeks who would ensure their daily intake
- Open label trial

Outcomes

	Control gp	Gatiflox gp
Composite unfavourable outcome*: Per-protocol analysis†	11.3%	**17.7%**
Composite unfavourable outcome*: Modified ITT analysis††	17.2%	**21%**
Rx failure	2.4%	1.7%
Recurrence (relapse or reinfection)	7.1%	**14.6%**
Dropouts	5%	2.7%

*Composite unfavourable outcome (at 24 months) included **failure**, **recurrence** (relapse or reinfection), **death or study dropout** during Rx

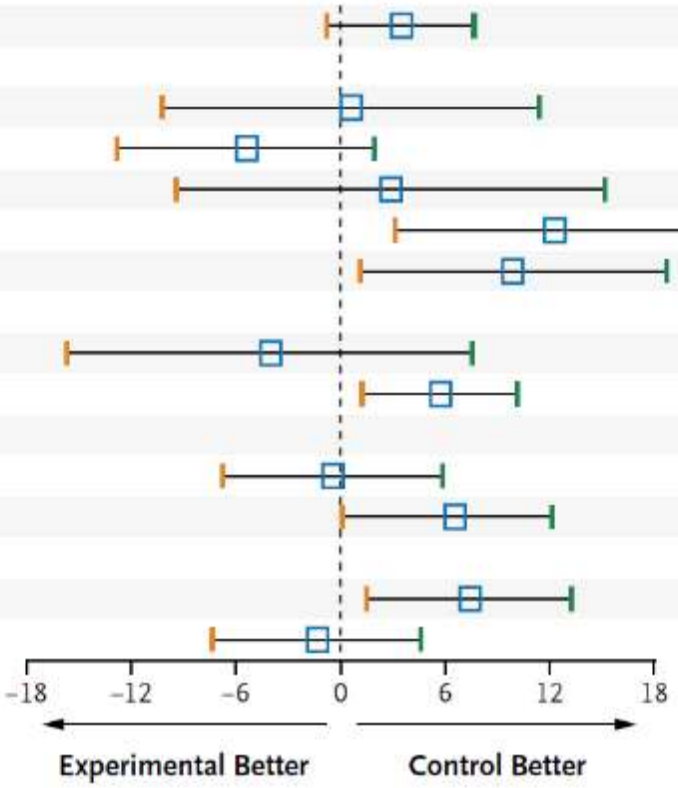
† Adjusted Difference, Experimental Group−Control Group: 5.5 (1.6 to 9.4)

†† Adjusted Difference, Experimental Group−Control Group: 3.5 (−0.7 to 7.7)

No significant difference in smear positivity or culture positivity at 2 months

Subgroup analysis: Unfavourable outcomes in modified ITT population

Subgroup	No. of Patients	Percentage with Unfavorable Outcome		Percentage-Point Difference, Experimental–Control (95% CI)
		Experimental Group	Control Group	
Overall	1356	21.0	17.2	3.5 (–0.7 to 7.7)
Country				
Benin	232	23.6	22.9	0.6 (–10.2 to 11.5)
Guinea	375	13.1	18.5	–5.4 (–12.8 to 2.0)
Kenya	166	22.0	19.0	2.9 (–9.4 to 15.2)
Senegal	268	23.8	11.6	12.3 (3.2 to 21.3)
South Africa	315	25.6	15.6	9.9 (1.1 to 18.8)
HIV status				
Positive	238	27.0	31.7	–4.0 (–15.7 to 7.6)
Negative	1111	19.8	13.8	5.8 (1.3 to 10.2)
BMI				
<16	602	19.3	19.2	–0.4 (–6.7 to 5.9)
≥16	754	22.4	15.6	6.6 (0.1 to 12.2)
Cavitary disease				
Yes	692	22.8	15.1	7.5 (1.7 to 13.3)
No	657	18.9	19.8	–1.3 (–7.3 to 4.6)



Rate of cavitary disease was 20% in Benin, Guinea, and Kenya and 90% in Senegal and South Africa

Adverse events

- No difference in serious adverse events, QTc interval, hyperglycemia

	REMoxTB, Gillespie NEJM 2014	RIFAQUIN, Jindani NEJM 2014	OFLOTUB, Merle NEJM 2014
Regimen	•Control group: HRZE (8 weeks) + HR (18 weeks) •INH group: HRZM (8 weeks) + HRM (9 weeks) •EMB group: MRZE (8 weeks) + MR (9 weeks)	•2HRZE (daily) + 4HR (daily) •2MRZE (daily) + 2MRp (twice weekly) •2MRZE (daily) + 4MRp (once weekly)	•2HRZE + 4HR •2HRZG + 2HRG
Efficacy outcomes			
Composite unfavourable outcome	8% vs **15%** vs **20%**	4.9% vs **18.2%** vs 3.2%	11.3% vs **17.7%**
Relapse	2% vs **9%** vs **12%**	2.4% vs **11.5%** vs 2.2%	7.1% vs **14.6%**
Time to culture negativity (weeks)	11.9 vs **8** vs **8**‡	N/A	N/A
Culture positivity at 2 months	N/A	14.6% (Control) vs **9.6%** (Moxiflox)	No difference
Safety outcomes			
Adverse events	No difference	No difference	No difference
Death (Any cause)	2% vs 2% vs 1%	2.2% vs 4.4% vs 2.5%	1.4% vs 1.2%
Adherence	N/A	Similar in initial 2 months. Thereafter, **better in both MOX-RPT groups**.	N/A
Resistance	3 vs 0 vs 1	1 vs 0	N/A

Concerns raised

- Extrapolation of data from mouse models:
  - Mice studies predicted that the inclusion of moxifloxacin would result in shortening of Rx duration by 1-2 months
  - Dormant bacilli less common in mice compared to humans
- Poor predictability of culture conversion when used as a surrogate for long-term outcomes

Rifapentine

Substitution of Rifapentine for Rifampin During Intensive Phase Treatment of Pulmonary Tuberculosis: Study 29 of the Tuberculosis Trials Consortium

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Method

- Multicentre phase 2 trial
- 531 adults with sputum smear-positive PTB
- Rifapentine 10 mg/kg/dose vs Rifampin 10 mg/kg/dose
- Both administered 5 days per week for 8 weeks (intensive phase) along with HZE
- Open label
- DOT
- Continuation phase INH + RMP in both groups

Results

Table 2. Percentages of Participants with Negative Sputum Cultures at Completion of Intensive Phase Treatment, by Treatment Group

Treatment group	Rifampin	Rifapentine	Difference (95%CI)	*P*
Protocol correct analysis group				
Liquid media	110/169 (65.1%)	133/196 (67.9%)	2.8 (–6.9, 12.4)	.65
Solid media	145/174 (83.3%)	171/198 (86.4%)	3.0 (–4.3, 10.5)	.50
Modified intention-to-treat group				
Liquid media	122/195 (62.6%)	152/228 (66.7%)	4.1 (–5.0, 13.2)	.44
Solid media	167/211 (79.2%)	193/233 (82.8%)	3.7 (–3.6, 11.0)	.38

No difference in adverse events or drug discontinuation

Rifapentine for LTBI: RCTs

	Patients	Intervention	Results
Schechter AJRCCM 2006	399 household contacts of patients with pulmonary TB Only 1 HIV infected Brazil	RPT 900 mg + INH 900 mg once wkly for 12 wk Vs RMP 450–600 mg + PZA 750–1,500 mg daily for 8 wk Follow-up: 2 years	**TB incidence**: 4 cases of TB occurred. 3 in RMP+PZA arm and 1 in RPT+INH arm (1.46 vs. 0.52%; difference, 0.94%; 95% CI, −1.6 to 3.7%) **Hepatotoxicity**: 20/193 (10%) receiving RMP+PZA experienced grade 3 or 4 hepatotoxicity, compared with 2/206 (1%) on RPT+INH ($p < 0.001$) hence study prematurely halted
Martinson NEJM 2011	1148 adults with HIV infection (Not on ART) and a positive TST [Median CD4 484] South Africa	RPT (900 mg) + INH (900 mg) wkly for 12 wks, RMP (600 mg) + INH (900 mg) twice weekly for 12 wks, INH (300 mg) daily for up to 6 yrs (continuous INH), or INH (300 mg) daily for 6 months (control group) Median follow-up: 4 years (approx.)	**Incidence rates of active TB or death** were (per 100 person-years): 3.1 in RPT+INH gp, 2.9 in RMP+INH gp, and 2.7 in the continuous-INH gp, as compared with 3.6 in control group (P>0.05 for all comparisons) **SAEs** more common in continuous-INH gp than in other gps (18.4 vs 8.7 to 15.4 per 100 person-years)
Sterling NEJM 2011 (PREVENT TB)	7731 persons (≥2 years, close contact with TB, TST positive) 2.6% HIV positive (Not on ART) USA, Canada, Brazil, Spain Open label, Phase III	3 months of directly observed once-weekly RPT (900 mg) + INH (900 mg) (combination-therapy gp) Vs 9 months of self-administered daily INH (300 mg) (isoniazid-only group) Follow-up: 33 months	**TB development & cumulative TB rate**: Combination 7/3986 (0.19%) vs INH 15/3745 (0.43%). **Rx completion rates**: Combination 82.1% vs INH 69.0% (P<0.001) **Permanent drug discontinuation owing to an adverse event**: Combination 4.9% vs INH 3.7% (P=0.009) **Possible hypersensitivity**: Combination 3.8% vs INH 0.5% (P <0.001) **Hepatotoxicity**: Combination 0.4% and INH 2.7% (P<0.001) **Resistance**: 2 INH resistance in INH gp vs 1 RMP resistance in combination gp

LTBI Rx: CDC 2011

Drugs	Duration	Interval	Minimum doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	6 months	Daily	180
		Twice weekly*	52
Isoniazid and Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

*DOT

Conclusions

Drug-resistant TB

- MDR TB
  - Delamanid and bedaquiline are useful when added to the standard MDR ATT regimen
    - Both decrease the time required for culture conversion and improve culture conversion rates
    - Bedaquiline improves cure rates
- XDR TB
  - Linezolid may improve cure rates

Shorter ATT regimes

- Drug-sensitive TB
  - Quinolone based 4-month ATT regimens are inferior to conventional 6-month ATT regimens (higher relapse rates, despite equal or more rapid culture conversion)
  - Substitution of rifampicin with rifapentine during IP unlikely to help
- LTBI
  - Once weekly INH + Rifapentine (3 months) is the shortest regimen available for LTBI