Newer Anti-tubercular regimens

Dr.Hariprasad

- Antitubercular drugs were first introduced in the 1950’s
- The paucity of drug classes resulted in a high relapse rate.
- This necessitated prolonged treatment regimens.

Molecular Biology of Drug Resistance

- Mtb. exhibits a low spontaneous mutation rate, as well as a doubling time (18-24 hours)
- Thick cell wall made of Mycolic acid, precludes horizontal transfer of resistance genes via plasmids or transposon.
- All currently known acquired resistances are mediated through chromosomal mutations that arise under selective pressure of antibiotic use.

Smith, Wolff et al. (2013)

Spontaneous mutation rates

Drugs	Number for a single mutation change	Number of drug resistant mutants in a Rx-naïve patient(1012)
EMB	10^7	100000
STM and INH	10^8	10,000
RMP	10^{10}	100

Two phases of chemotherapy

- Intensive phase-
  - “phase of bactericidal activity”
  - Measured by culture negativity
- Continuation phase-
  - “phase of sterilizing activity”
  - kill the more slowly growing organisms or persister’s
  - Measured by relapse rates
  - Determines the duration of a regimen

Need for newer regimens and drugs

- The standard regimen
  - Long duration of Treatment
  - Poor adherence
    - Suboptimal programmatic conditions leads to increased mortality
  - Emergence of drug resistant strains

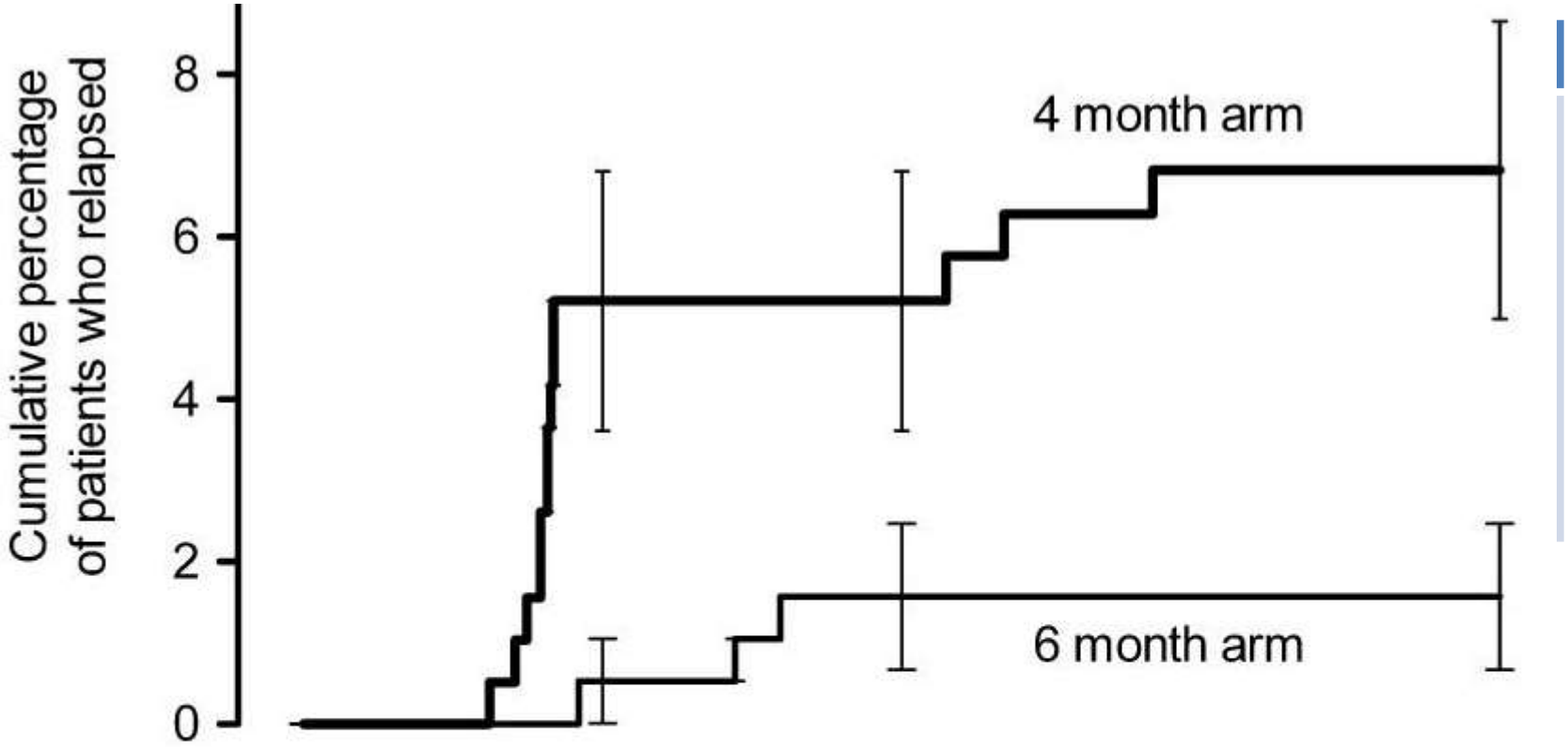
Shorter chemotherapy of tuberculosis

- The approach to shorter chemotherapy includes
  1. Use of standard drugs in higher doses
     - High dose Rifampicin, high dose INH
  2. Use of newer class of antimycobacterial drugs
     - Fluoroquinolones, Nitroimidazoles: Pretomanid, Oxazolidinone: Linezolid, Beta-lactams/Carbapenems, Diarylquinolines: Bedaquiline

- Attempts to shorten the duration of Rifampicin, by substitution of INH/Ethambutol or INH/ Thioacetazone was found to be inferior to the 6 month regimen.
- Regimens which omitted Rif in CP phase had to be extended by 2 months to prevent unacceptable relapse rates.

Duration of treatment for smear-positive pulmonary tuberculosis when rifampicin is not used in the continuation phase[a]

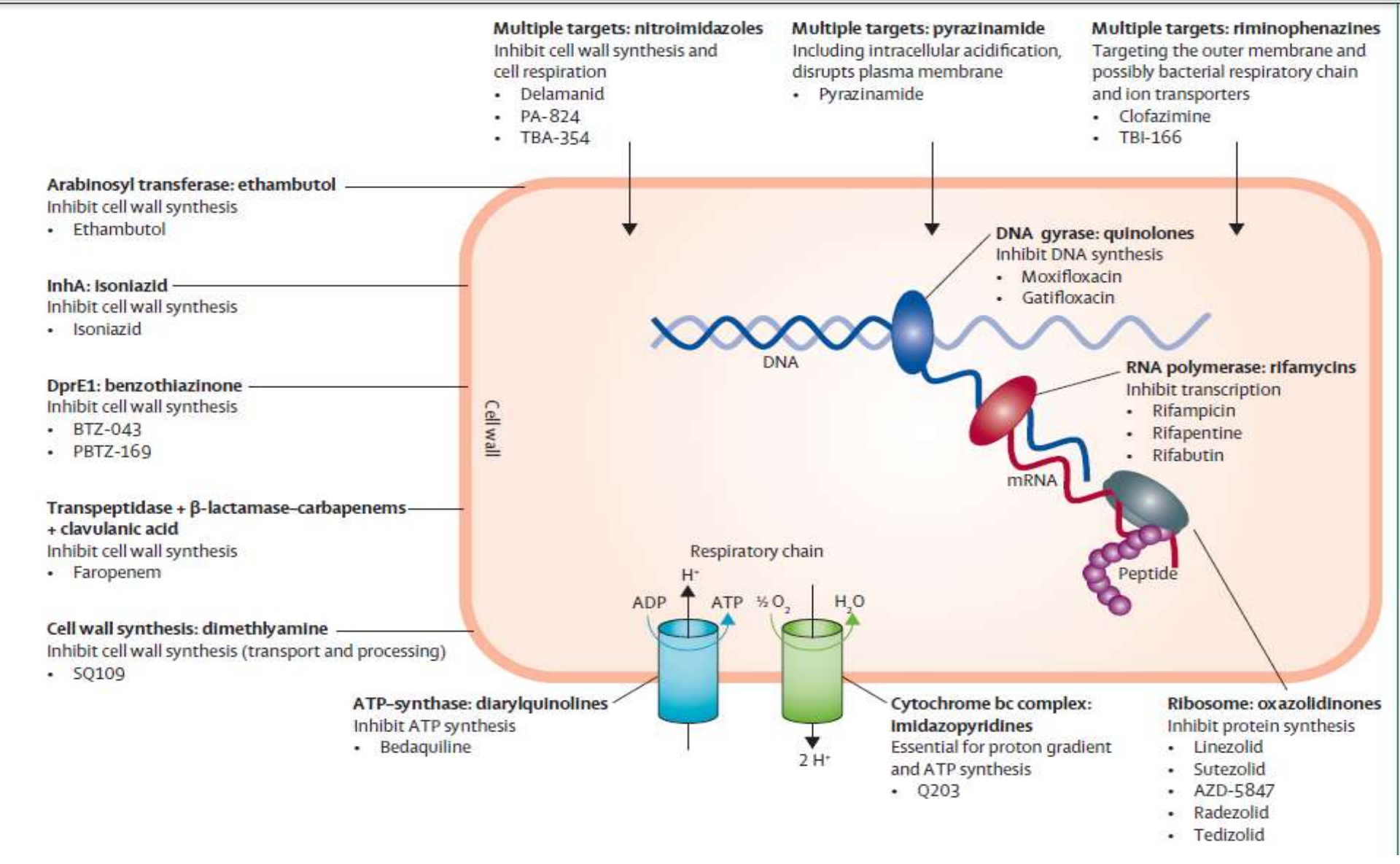
Country or area	Year of study	Regimen[b]	Duration of treatment (months)	No. of patients assessed	Relapse rate up to 2 years (%)
Africa	1972	2HRZS/4HT	6	179	7
	1974	2HRZS/4HT	6	75	13
		2HRZS/6HT	8	81	8
		1HRZS/5HT	6	79	18
		1HRZS/7HT	8	58	7
Madras[c], India	1997	2HRZE/6HE	8	305	5



•Shortening treatment from 6 to 4 months in adults with non cavitary disease and culture conversion after 2 months using current drugs resulted in a greater relapse rate.

•The combination of non cavitary disease and 2-month culture conversion was insufficient to identify patients with decreased risk for relapse.

Newer Agents



RIFAQUIN trial

The NEW ENGLAND JOURNAL of MEDICINE

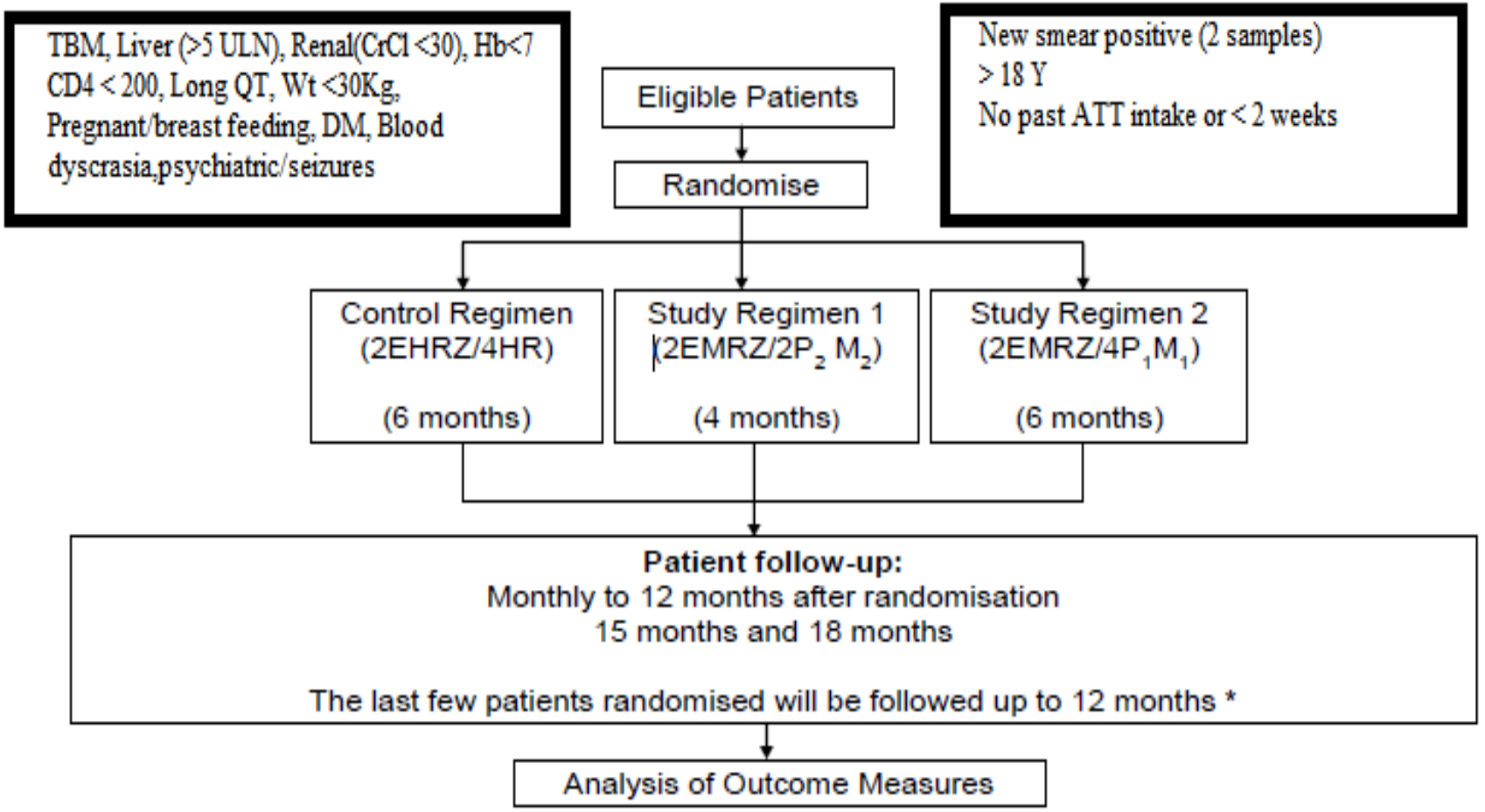
ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Hatherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Mungofa, M.P.H., Nasir A. Shah, M.B., B.S., Simukai Zizhou, M.B., Ch.B., Lloyd Magweta, M.B., Ch.B., James Shepherd, Ph.D., Sambayawo Nyirenda, M.D., Janneke H. van Dijk, Ph.D., Heather E. Clouting, M.Sc., David Coleman, M.Sc., Anna L.E. Bateson, Ph.D., Timothy D. McHugh, Ph.D., Philip D. Butcher, Ph.D., and Denny A. Mitchison, F.R.C.P., for the RIFAQUIN Trial Team*

New England Journal of Medicine **371**(17): 1599-1608.

- Evaluated the use of Moxifloxacin to shorten the duration of treatment or reduce the interval between doses.
- Conducted by **INTERTB** consortium in southern Africa.



- **Primary outcomes**

  1. The proportion of patients classified as failure/relapse by 18 months after the start of treatment expressed as the difference between the proportion in the intervention regimens and the control regimen.

  2. Number of relapses with rifamycin mono-resistance (RMR) occurring in HIV-infected patients,

  3. Grade 3 or 4 adverse events.

- **Secondary outcomes**

  1. Per protocol analysis of the first primary outcome.

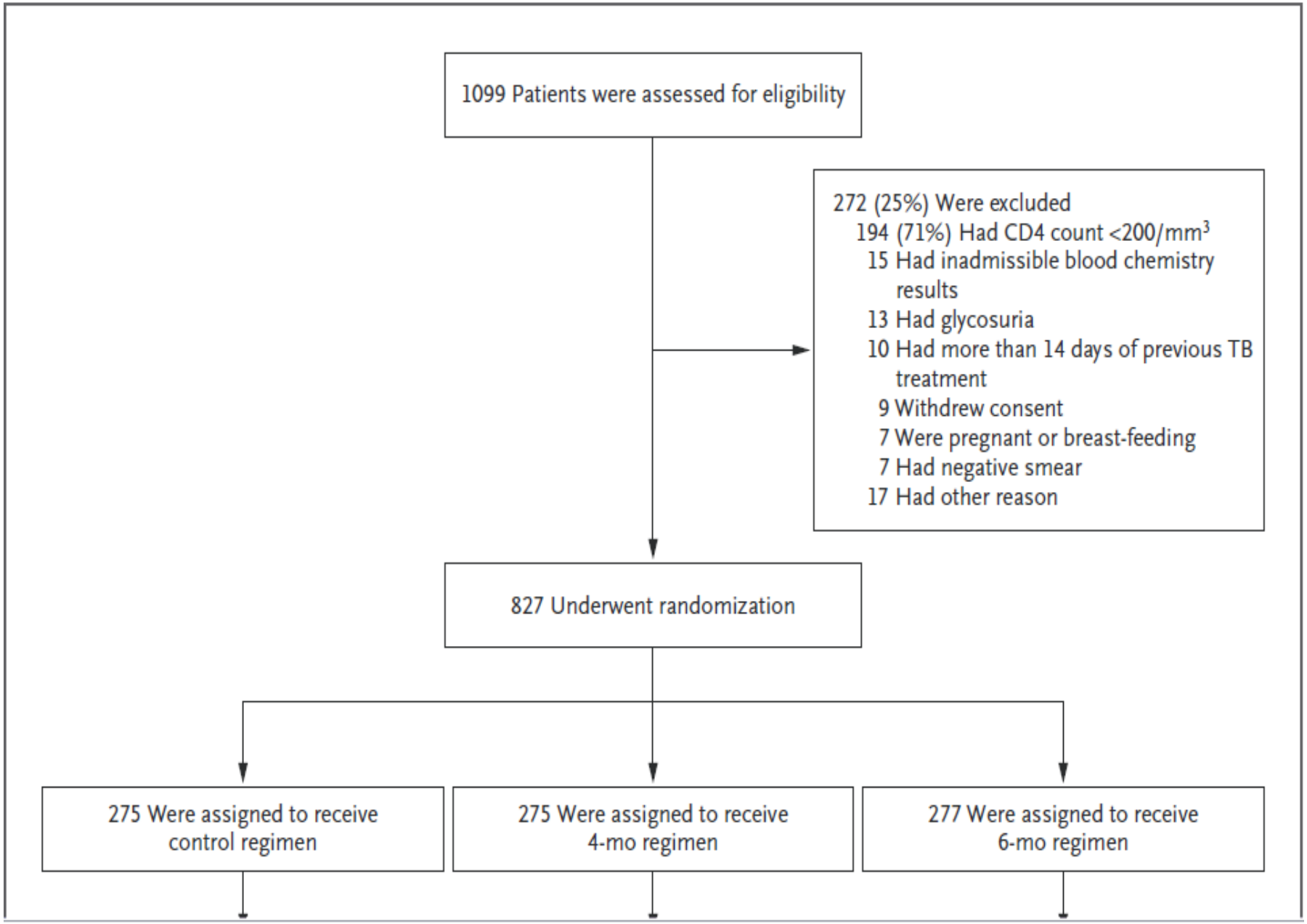
  2. Time to failure/relapse

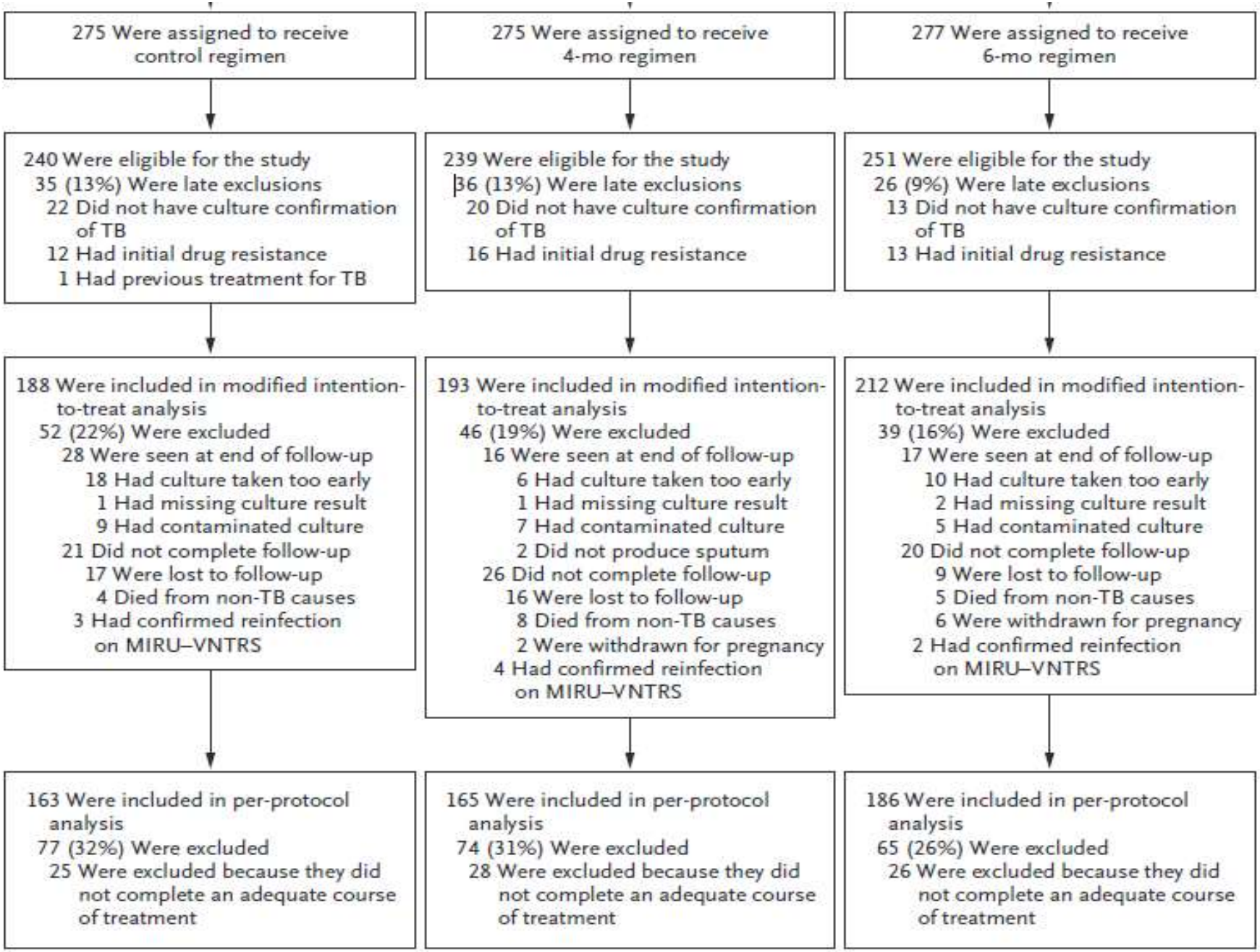
  3. Proportions of patients achieving culture negativity at 8 W

  4. Adverse events

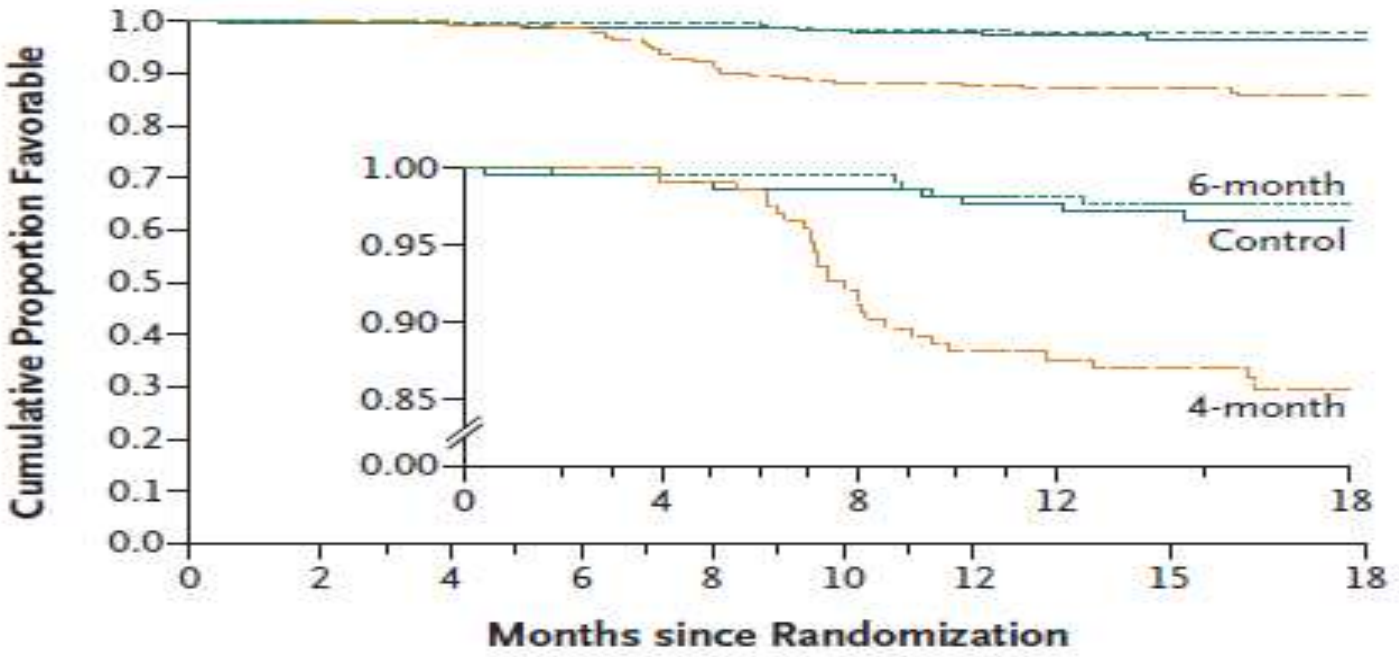
  5. Rate of completion of chemotherapy

  6. Number of observed doses of chemotherapy ingested


1099 Patients were assessed for eligibility
272 (25%) Were excluded
194 (71%) Had CD4 count <200/mm3
15 Had inadmissible blood chemistry results
13 Had glycosuria
10 Had more than 14 days of previous TB treatment
9 Withdrew consent
7 Were pregnant or breast-feeding
7 Had negative smear
17 Had other reason
827 Underwent randomization
275 Were assigned to receive control regimen
275 Were assigned to receive 4-mo regimen
277 Were assigned to receive 6-mo regimen


275 Were assigned to receive control regimen
275 Were assigned to receive 4-mo regimen
277 Were assigned to receive 6-mo regimen
240 Were eligible for the study
35 (13%) Were late exclusions
22 Did not have culture confirmation of TB
12 Had initial drug resistance
1 Had previous treatment for TB
239 Were eligible for the study
36 (13%) Were late exclusions
20 Did not have culture confirmation of TB
16 Had initial drug resistance
251 Were eligible for the study
26 (9%) Were late exclusions
13 Did not have culture confirmation of TB
13 Had initial drug resistance
188 Were included in modified intention-to-treat analysis
52 (22%) Were excluded
28 Were seen at end of follow-up
18 Had culture taken too early
1 Had missing culture result
9 Had contaminated culture
21 Did not complete follow-up
17 Were lost to follow-up
4 Died from non-TB causes
3 Had confirmed reinfection on MIRU–VNTRS
193 Were included in modified intention-to-treat analysis
46 (19%) Were excluded
16 Were seen at end of follow-up
6 Had culture taken too early
1 Had missing culture result
7 Had contaminated culture
2 Did not produce sputum
26 Did not complete follow-up
16 Were lost to follow-up
8 Died from non-TB causes
2 Were withdrawn for pregnancy
4 Had confirmed reinfection on MIRU–VNTRS
212 Were included in modified intention-to-treat analysis
39 (16%) Were excluded
17 Were seen at end of follow-up
10 Had culture taken too early
2 Had missing culture result
5 Had contaminated culture
20 Did not complete follow-up
9 Were lost to follow-up
5 Died from non-TB causes
6 Were withdrawn for pregnancy
2 Had confirmed reinfection on MIRU–VNTRS
163 Were included in per-protocol analysis
77 (32%) Were excluded
25 Were excluded because they did not complete an adequate course of treatment
165 Were included in per-protocol analysis
74 (31%) Were excluded
28 Were excluded because they did not complete an adequate course of treatment
186 Were included in per-protocol analysis
65 (26%) Were excluded
26 Were excluded because they did not complete an adequate course of treatment

Results



No. at Risk									
Control	240	232	227	213	210	203	195	175	142
4-month	239	223	211	202	185	172	169	147	127
6-month	251	234	224	217	212	207	205	180	153

Figure 3. Kaplan–Meier Failure Estimates of the Time to a Favorable Outcome in the Per-Protocol Population.

The inset shows the same data on an enlarged y axis.

- The 6-month regimen that included weekly administration of high-dose rifapentine and moxifloxacin was as effective as the control regimen.
- The 4-month regimen was not non-inferior to the control regimen.

NIRT Trial

PLoS One. 2013; 8(7): e67030.
Published online 2013 Jul 3. doi: 10.1371/journal.pone.0067030
PMCID: PMC3700922

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

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T. Mark Doherty, Editor

- 4-month Gatifloxacin or Moxifloxacin containing regimens given thrice-weekly in patients with newly diagnosed sputum-positive pulmonary TB.
- Open label RCT
- Initially planned to enroll 1200 patients, with 400 in each arm.
- Study was terminated prematurely due to higher recurrence in the non-control arms.

Inclusion criteria	Exclusion
1. Age > 18 yrs 2. New sputum smear positive on two smears	1. Previously treated for > 30 days 2. Weight < 30 Kg 3. DM 4. Severe HT 5. HIV coinfection 6. Seizures

Outcome

Favourable	3 sputum cultures were negative in the last month of Rx
	one culture was positive but cultures during the subsequent months were negative without additional Rx
Unfavorable	>1 one sputum culture was positive in the last month of treatment, one of which was ≥ 20CFU, or drug toxicity, or the patient died of TB during treatment
	Rx was changed for persistent sputum positivity, or for radiographic or clinical deterioration
Recurrence	2 positive sputum cultures in a 2-month period, one of which ≥ 20 colonies, or ii) positive sputum cultures during 4 consecutive monthly examinations, < 20 colonies b)
	Clinical/radiological recurrence, defined as clinical or persistent radiological deterioration consistent with TB in the absence of bacteriological criteria defined above.

- Study started with C and G arms due to non availability of M in 1:1 ratio
- Later on in 1:2:1 to compensate for the delayed start in M arm.

Sputum culture negativity based on three specimens each month, among 416 patients.

Month of treatment	Regimen								
	Gatifloxacin (n=136)			Moxifloxacin (n=115)			Control (n=165)		
	No. examined	Culture negative		No. examined	Culture negative		No. examined	Culture negative	
		n	%		n	%		n	%
1	135	34	25	113	37	33	165	46	28
2	133	110	83	112	98	88	164	128	78
3	130	125	96	112	111	99	162	157	97
4	129	123	95	113	112	99	163	156	96
5	–	–	–	–	–	–	162	153	94
6	–	–	–	–	–	–	163	155	95

(p = 0.04)

- 16%, 10% and 6% of patients in the G, M and control regimen arms respectively had recurrence of TB
- The differences in the TB recurrence rate between the G arm and the control arm was statistically significant (16% vs 6%; RR 0.90; 95% CI 0.83–0.98; $p = 0.02$).
- The difference in the recurrence rate between the M arm (10%) and the control arm (6%) was not statistically significant (RR 0.96; 95% CI 0.89–1.04; $p = 0.38$).
- The difference in the recurrence rate between the G and M arms was also not statistically significant. (RR 0.94; 95% CI 0.85–1.04; $p = 0.31$).

- TB recurrence rates in the gatifloxacin and moxifloxacin regimens higher necessitating the premature termination of the trial.
- Reasons for the failure of the FQ regimen :-
  - Dosage of FQ's – possibly requires higher doses than the conventional doses used to Rx bacterial disease
  - Post antibiotic effect- Moxifloxacin doesn't have a significant PAE

Chan, Au-Yeang et al. (2004)

OFLOTUB TRIAL !

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*

- Aimed to establish non- inferiority of a 4 month Gatifloxacin containing regimen compared with 6 month standard regimen.

	Gatifloxacin regimen	**Control/standard regimen**
IP Phase	HRZG	HRZE
CP Phase	HRG (2)	HR (4)

Inclusion criteria	Exclusion Criteria
18-65 yrs	TB in past 3 years
Smear positive new cases	HIV Grade III & IV
Rifampicin sensitive	DM/NIDDM
	Impaired renal, hepatic function
	Pregnant or lactating women
	QT interval > 480 , or drugs causing above
	Patients with bradycardia (<40)
	Drugs with anti-TB effects, steroids

- Primary Outcome
  - Percentage of participants with an **unfavourable outcome** by 24 months after the end of treatment

Failure	**2 positive cultures at 16 weeks and at 20 weeks in the test arm and at 24 and 28 weeks in the control arm.**
Relapse	≥ 2 positive cultures of ≥10 colonies in 2 separate monthly sputum collections during a 12 week period " after cure.
Recurrence	
Death	
Withdrawal from study	

Results

Table 2. Primary and Secondary Efficacy Analyses in the Modified Intention-to-Treat Population and Per-Protocol Population.*

Variable	Experimental Group	Control Group	Adjusted Difference, Experimental Group–Control Group† *percentage points (95% CI)*
Modified intention-to-treat analysis			
Primary outcome: unfavorable outcome 24 mo after the end of treatment — no./total no. (%)	146/694 (21.0)	114/662 (17.2)	3.5 (–0.7 to 7.7)
Secondary outcomes			
Smear-positive status at 2 mo — no./total no. (%)	118/762 (15.5)	112/759 (14.8)	0.0 (–3.0 to 2.9)
No culture conversion at 2 mo — no./total no. (%)	104/741 (14.0)	121/735 (16.5)	–2.0 (–4.9 to 1.0)
Unfavorable outcome at end of treatment — no./total no. (%)	45/781 (5.8)	67/785 (8.5)	–2.4 (–4.9 to 0.0)
Unfavorable outcome 18 mo after randomization — no./total no. (%)	139/731 (19.0)	98/744 (13.2)	5.8 (2.0 to 9.6)
No unfavorable outcome by 24 mo after the end of treatment — cumulative %‡	80.7	85.5	1.31 (1.02 to 1.67)§
No recurrence by 24 mo after the end of treatment — cumulative %¶	85.6	93.5	2.25 (1.59 to 3.18)§

Per-protocol analysis			
Primary outcome: unfavorable outcome 24 mo after the end of treatment — no./total no. (%)	115/651 (17.7)	68/601 (11.3)	5.5 (1.6 to 9.4)
Secondary outcomes			
Smear-positive status at 2 mo — no./total no. (%)	118/752 (15.7)	111/750 (14.8)	0.0 (–2.9 to 3.0)
No culture conversion at 2 mo — no./total no. (%)	103/732 (14.1)	121/726 (16.7)	–1.9 (–4.9 to 1.1)
Unfavorable outcome at end of treatment — no./total no. (%)	17/736 (2.3)	24/716 (3.4)	–1.0 (–2.7 to 0.7)‖
Unfavorable outcome 18 mo after randomization — no./total no. (%)	108/687 (15.7)	53/676 (7.8)	7.3 (3.9 to 10.7)
No unfavorable outcome by 24 mo after the end of treatment — cumulative %‡	83.7	90.6	1.73 (1.28 to 2.33)§
No recurrence by 24 mo after the end of treatment — cumulative %¶	85.7	93.7	2.32 (1.63 to 3.32)§

Table 3. Percentages of Favorable and Unfavorable Outcomes in the Primary Efficacy Analysis and of Outcomes That Could Not Be Assessed in the Modified Intention-to-Treat Population.

Variable	Experimental Group	Control Group
	no. (%)	
Favorable outcome*	548 (79.0)	548 (82.8)
Unfavorable outcome*	146 (21.0)	114 (17.2)
By end of treatment	45 (6.5)	67 (10.1)
Study dropout	19 (2.7)	33 (5.0)†
Withdrawal of consent	8 (1.2)	8 (1.2)
Adverse event other than death	1 (0.1)	1 (0.2)
Death	5 (0.7)	9 (1.4)‡
Treatment failure	12 (1.7)	16 (2.4)
After end of treatment: recurrence of tuberculosis	101 (14.6)	47 (7.1)
Two positive cultures	86 (12.4)	33 (5.0)
One positive culture	12 (1.7)	9 (1.4)
Culture-negative or unknown status§	3 (0.4)	5 (0.8)
Outcome could not be assessed¶	97 (12.3)	132 (16.6)
Protocol-defined withdrawal‖	8 (1.0)	8 (1.0)
Loss to follow-up after end of treatment**	68 (8.6)	104 (13.1)
Death after end of treatment	19 (2.4)	18 (2.3)
Withdrawal of consent after end of treatment	1 (0.1)	1 (0.1)
Other reason	1 (0.1)	1 (0.1)

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)

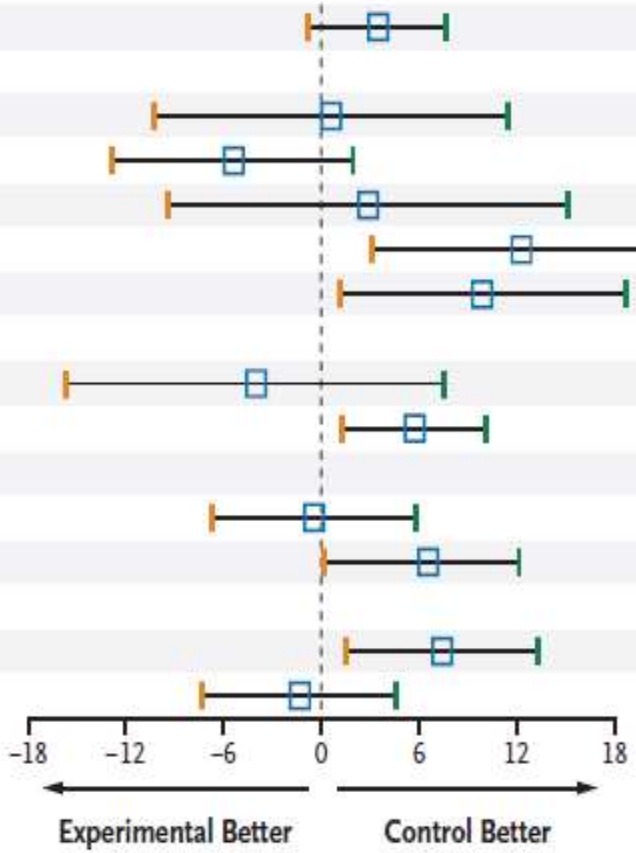


Figure 2. Unfavorable Outcomes in the Modified Intention-to-Treat Population, Overall and According to Subgroups.

Differences were adjusted according to country (except in each country). The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

REMoxTB Trial

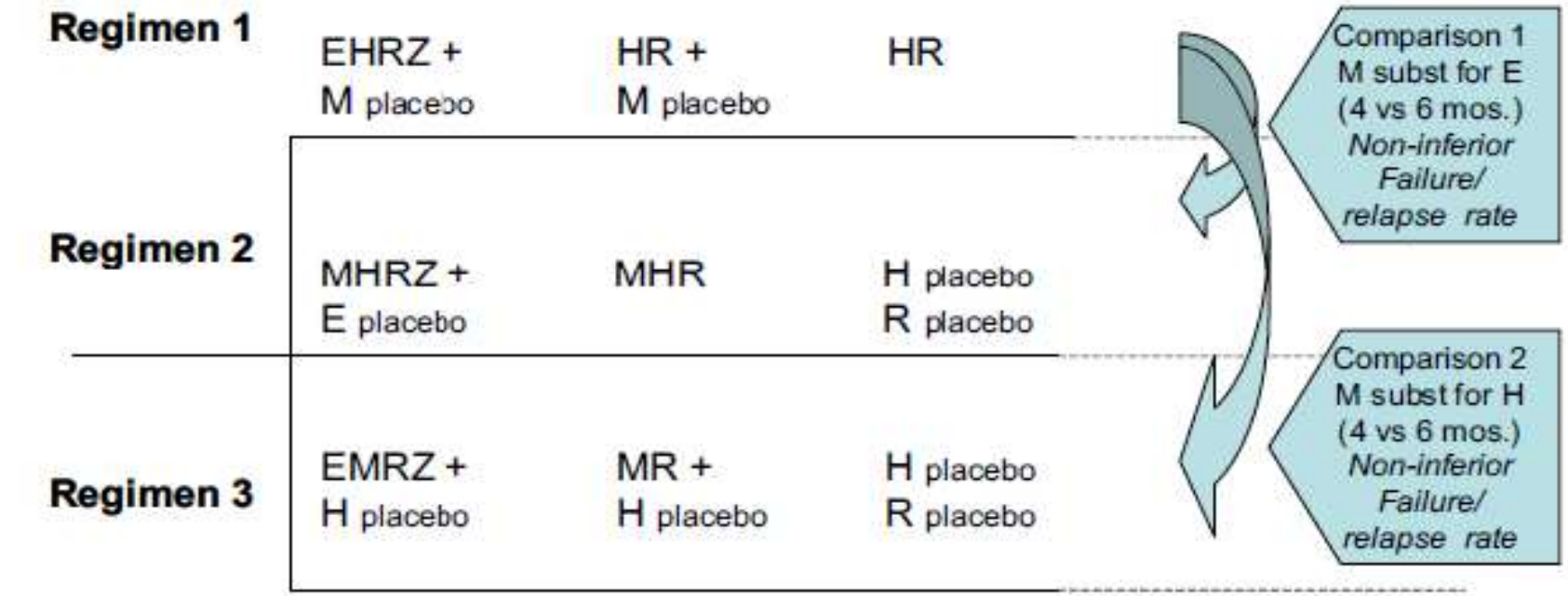
The NEW ENGLAND JOURNAL of MEDICINE

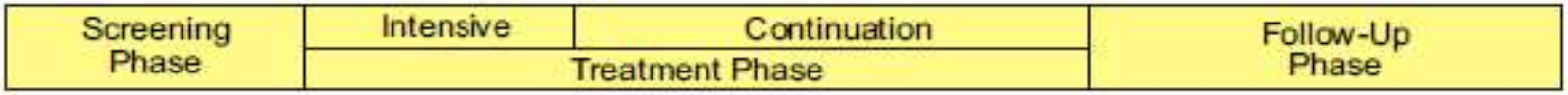
ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371 NO. 17

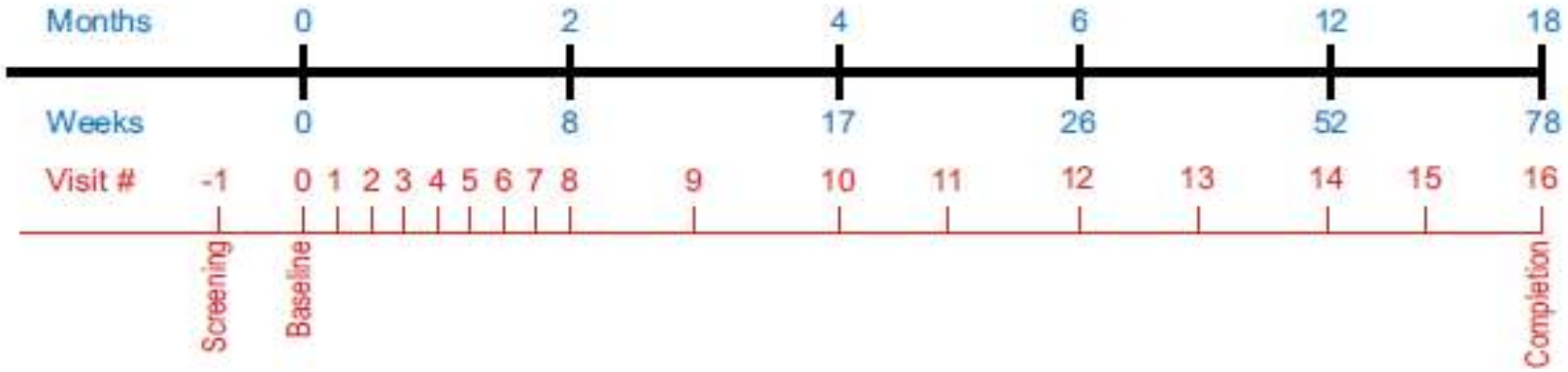
Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

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*

Inclusion	Exclusion
Two sputum specimens positive	TBM
Age > 18	DM, liver or kidney disease, blood disorders, peripheral neuritis, chronic diarrhoeal ds
AST/ALT < 3 ULN	Pregnant or breast feeding.
Bilirubin <2.5 ULN	syndromes of QT c prolongation, or on drugs causing same
Cr CL level greater than 30 ml/min	On ART or HIV infection with CD4 count less than 250 cells/µL
Haemoglobin ≥ 7.0 g/Dl Platelet count > $50x10^9$cells/L Serum potassium > 3.5 mmol/L	initial isolate is multiple drug resistant
	Weight less than 35kg


Regimen 1
EHRZ +
M placebo
HR +
M placebo
HR
Regimen 2
MHRZ +
E placebo
MHR
H placebo
R placebo
Regimen 3
EMRZ +
H placebo
MR +
H placebo
H placebo
R placebo
Comparison 1
M subst for E
(4 vs 6 mos.)
Non-inferior
Failure/
relapse rate
Comparison 2
M subst for H
(4 vs 6 mos.)
Non-inferior
Failure/
relapse rate


Screening Phase
Intensive
Continuation
Treatment Phase
Follow-Up Phase


Months
0
2
4
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Weeks
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78
Visit #
-1
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2
3
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5
6
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8
9
10
11
12
13
14
15
16
Screening
Baseline
Completion

Outcome

Favourable	two negative-culture results at different visits without an intervening positive result
Unfavorable	bacteriologically or clinically defined failure or relapse within 18 months after randomisation

Variable	Per-Protocol Analysis				Modified Intention-to-Treat Analysis			
	Control Group (N=510)	Isoniazid Group (N=514)	Ethambutol Group (N=524)	All Patients (N=1548)	Control Group (N=555)	Isoniazid Group (N=568)	Ethambutol Group (N=551)	All Patients (N=1674)
Adverse reaction	NA	NA	NA	NA	18 (3)	15 (3)	9 (2)	42 (3)
Withdrawal of consent	NA	NA	NA	NA	8 (1)	18 (3)	8 (1)	34 (2)
Relocation	NA	NA	NA	NA	2 (<1)	4 (1)	4 (1)	10 (1)
Other investigator decision	NA	NA	NA	NA	2 (<1)	5 (1)	0	7 (<1)
No completion of treatment	NA	NA	NA	NA	13 (2)	10 (2)	6 (1)	29 (2)
Follow-up								
Relapse after culture-negative status	12 (2)	46 (9)	64 (12)	122 (8)	13 (2)	46 (8)	64 (12)	123 (7)
Retreated for tuberculosis	14 (3)	17 (3)	27 (5)	58 (4)	14 (3)	18 (3)	27 (5)	59 (4)
Death from tuberculosis or respiratory distress	2 (<1)	0	0	2 (<1)	2 (<1)	0	0	2 (<1)
No culture-negative status								
Ever	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	2 (<1)	0	3 (<1)
At last visit	2 (<1)	3 (1)	2 (<1)	7 (<1)	2 (<1)	3 (1)	2 (<1)	7 (<1)
Adjusted difference from control in rate of unfavorable outcome — percentage points (97.5% CI)	NA	6.1 (1.7–10.5)	11.4 (6.7–16.1)	NA	NA	7.8 (2.7–13.0)	9.0 (3.8–14.2)	NA

- The trial showed that the substitution of moxifloxacin in 4-month regimens based on either isoniazid or ethambutol did not meet the margin for non inferiority, as compared with the 6-month control regimen.

NATURE MEDICINE | LETTER

日本語要約

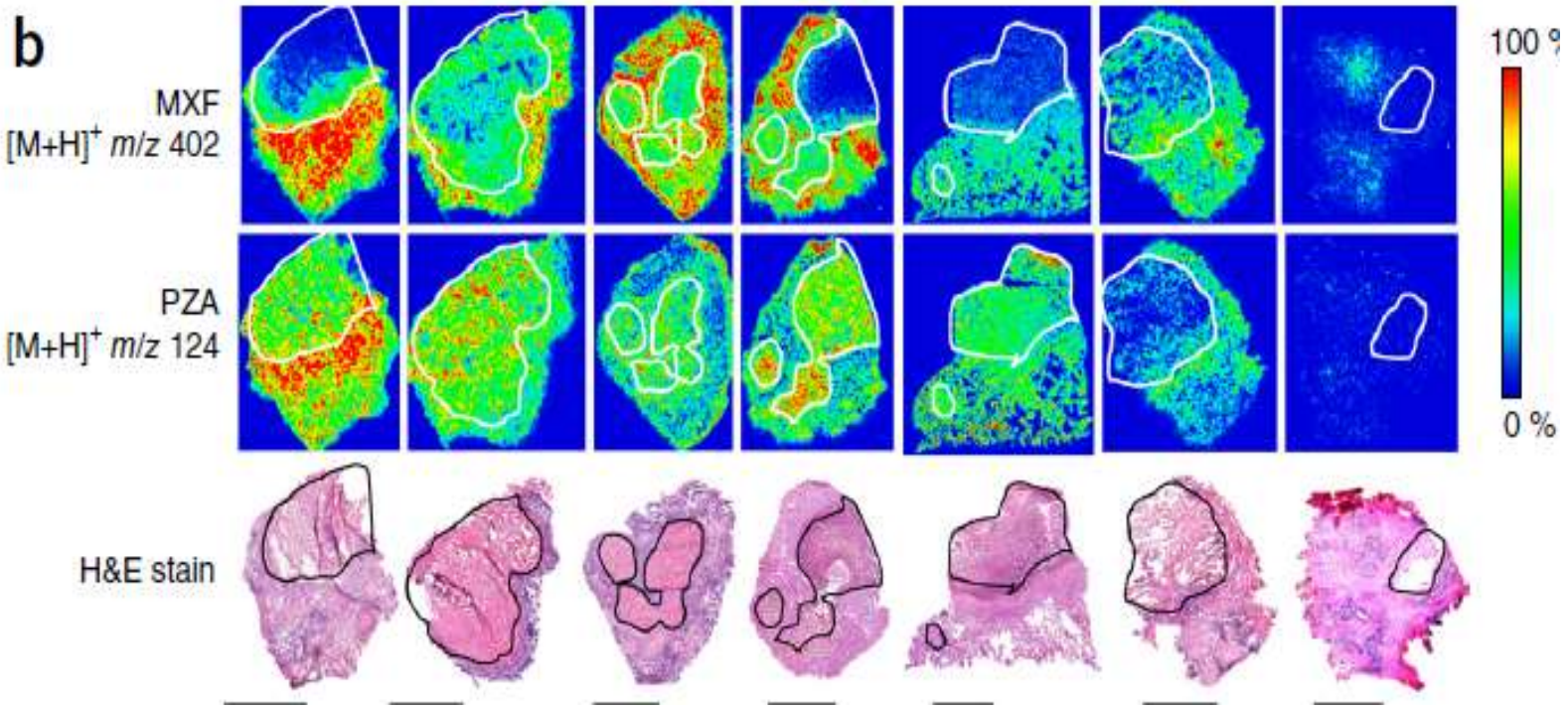
The association between sterilizing activity and drug distribution into tuberculosis lesions

Brendan Prideaux, Laura E Via, Matthew D Zimmerman, Seokyong Eum, Jansy Sarathy, Paul O'Brien, Chao Chen, Firat Kaya, Danielle M Weiner, Pei-Yu Chen, Taeksun Song, Myungsun Lee, Tae Sun Shim, Jeong Su Cho, Wooshik Kim, Sang Nae Cho, Kenneth N Olivier, Clifton E Barry III & Véronique Dartois

granulomas caseum-filled cores.

- Although preclinical trials showed a Rx shortening potential of moxifloxacin in mice, this was not replicated in human trials.
- MoxF achieved several fold lower concentration compared to Rifampicin, which itself exhibited a slow accumulation until high steady-state concentrations were achieved deep within lesions,

- Pyrazinamide alone rapidly perfused throughout the lesion.
- This inability to efficiently drug the entire lesion probably explains why shortening the course of many MoxF regimens was not successful.



(Prideaux, Via et al. 2015)

PanACEA MAMS-TB-01 trial

- High-dose (35mg/kg) rifampicin, in combination with standard dose of isoniazid, pyrazinamide and ethambutol, showed a significant shortening of time to culture conversion with a covariate-adjusted hazard ratio of 1.75, 95% confidence interval (1.21-2.55) over the 12 weeks of experimental treatment.

- Regimens using newer drugs
  1. PaMZ regimen

PaMZ regimen

- combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide was found to effective against both DS and DR Mtb in preliminary studies.
- 2b study of bactericidal activity—defined as the decrease in colony forming units (CFUs) of Mycobacterium tuberculosis in the sputum of patients with microscopy smear-positive pulmonary tuberculosis, showed superior bactericidal activity in drug-susceptible tuberculosis during 8 weeks of treatment.

	Mean Δ Log_{10} CFU	credibility interval
MPa200Z	0·155	(0·133–0·178)
	0·117 (in DR TB)	(0·070–0·174).
MPa100Z	0·133	(0·109–0·155)
HRZE	0·112	(0·093–0·131)

Shortening Treatment by Advancing Novel Drugs (STAND) Trial

- A Phase 3 Open-Label Partially Randomized Trial Study.
- Assess the efficacy, safety and tolerability of a combination of moxifloxacin, PA-824, and pyrazinamide treatments with varying doses and treatment lengths from 4 to 6 months in subjects with drug-sensitive (DS) pulmonary TB compared to standard HRZE treatment .(NCT02342886)
- Currently recruiting patients

The NEW ENGLAND JOURNAL of MEDICINE

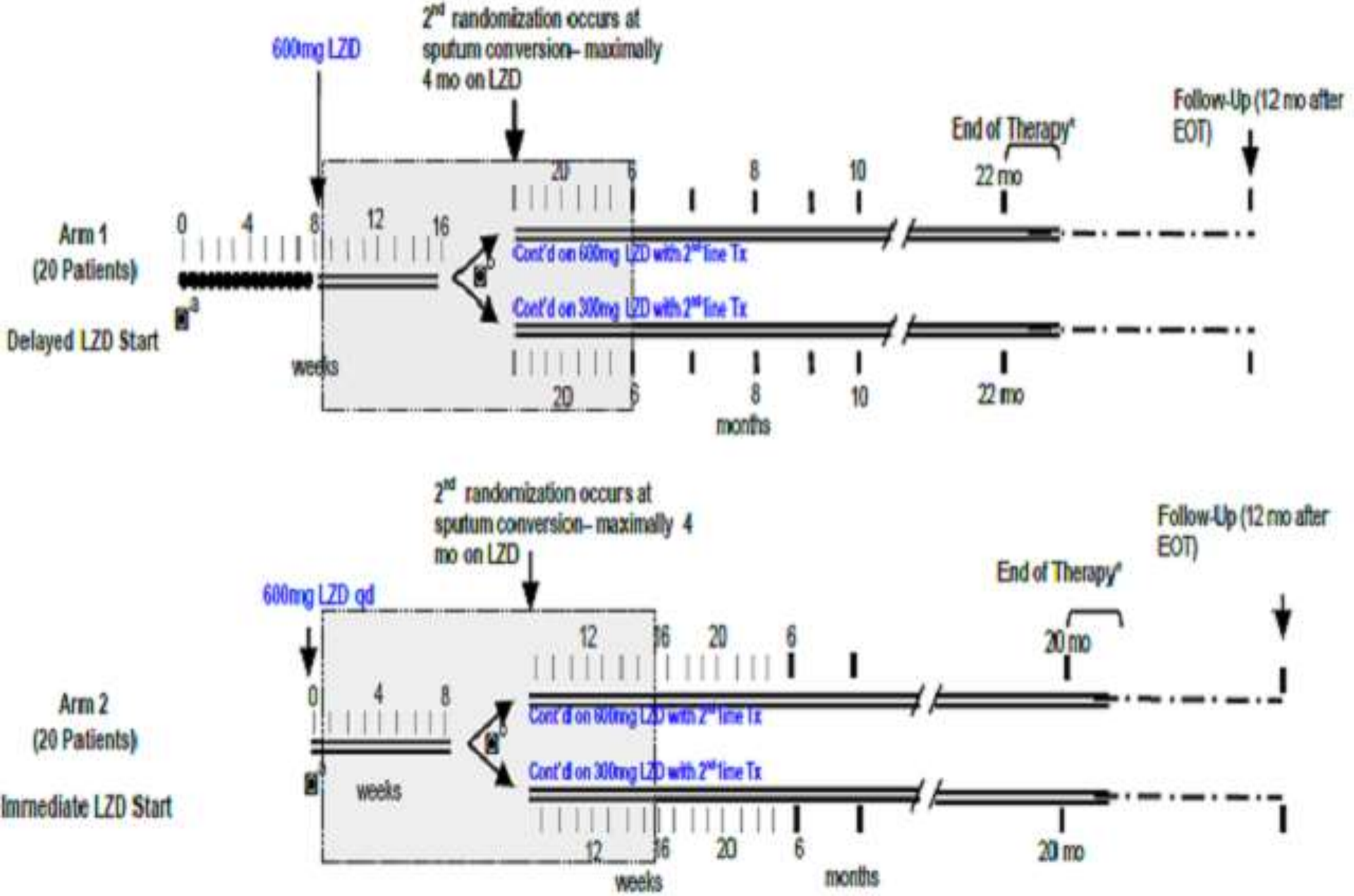
ORIGINAL ARTICLE

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.

- Oxazolidinone antibiotic class, inhibits protein synthesis by binding the 23S ribosomal RNA (rRNA) portion of the bacterial 50S ribosomal
- Mic < 1µG/ml
- A/e- peripheral neuropathy, hyper-lactatemia, and myelosuppression.
- EBA- in preclinical trials and murine models showed only a modest antimycobacterial efficacy.
- December 2008 through May 2011

Inclusion criteria	Exclusion criteria
Males and females age 20 and above	Subjects who have previously been on LZD
Documented PTB at screening	Women of childbearing potential
Radiographic evidence of tuberculous disease of the lung(s)	ANC< 1000, WBC< 3.0 X 10^3/Ml, Hb< 7.0 g/dL Platelet count < 75,000 cells/mm3
Chronic AFB positive sputum smears and culture positive	Cr > 2.0 mg/dL AST >100 IU/L/g _ALT >100 IU/L Total bilirubin > 2.0 mg/dL
MTB species identification as *Mycobacterium tuberculosis*	Moderate or severe peripheral or optical neuropathy. diabetes-related eye, foot, heart or kidney disease
resistance to INH, RIF, kana/capreomycin, rifabutin, ofloxacin, and moxifloxacin OR failure to respond to treatment despite DST susceptibility	HIV-1 or HIV-2 infection SLE or RA
Failure to respond (after at least 6 months) to a 2^{nd} line drug regimen including any known	SSRI, MAO, Chemo, systemic corticosteroids, IL, ART, within 30 days or planned for use within


600mg LZD
2nd randomization occurs at sputum conversion– maximally 4 mo on LZD
Follow-Up (12 mo after EOT)
End of Therapy*
22 mo
Arm 1
(20 Patients)
Delayed LZD Start
Cont'd on 600mg LZD with 2nd line Tx
Cont'd on 300mg LZD with 2nd line Tx
weeks
months
600mg LZD qd
2nd randomization occurs at sputum conversion– maximally 4 mo on LZD
Follow-Up (12 mo after EOT)
End of Therapy*
20 mo
Arm 2
(20 Patients)
Immediate LZD Start
Cont'd on 600mg LZD with 2nd line Tx
Cont'd on 300mg LZD with 2nd line Tx
weeks
months

1. Primary end-point
   - sputum-culture conversion, with data censored at 4 months.
   - Conversion was defined as negative sputum samples on solid (Lowenstein–Jensen) medium for 3 consecutive weeks
- 2^{nd} ry end points
   - time to discontinuation due to intolerance of LZD drug
   - occurrence of relapse with active disease at 12 months after the end of treatment

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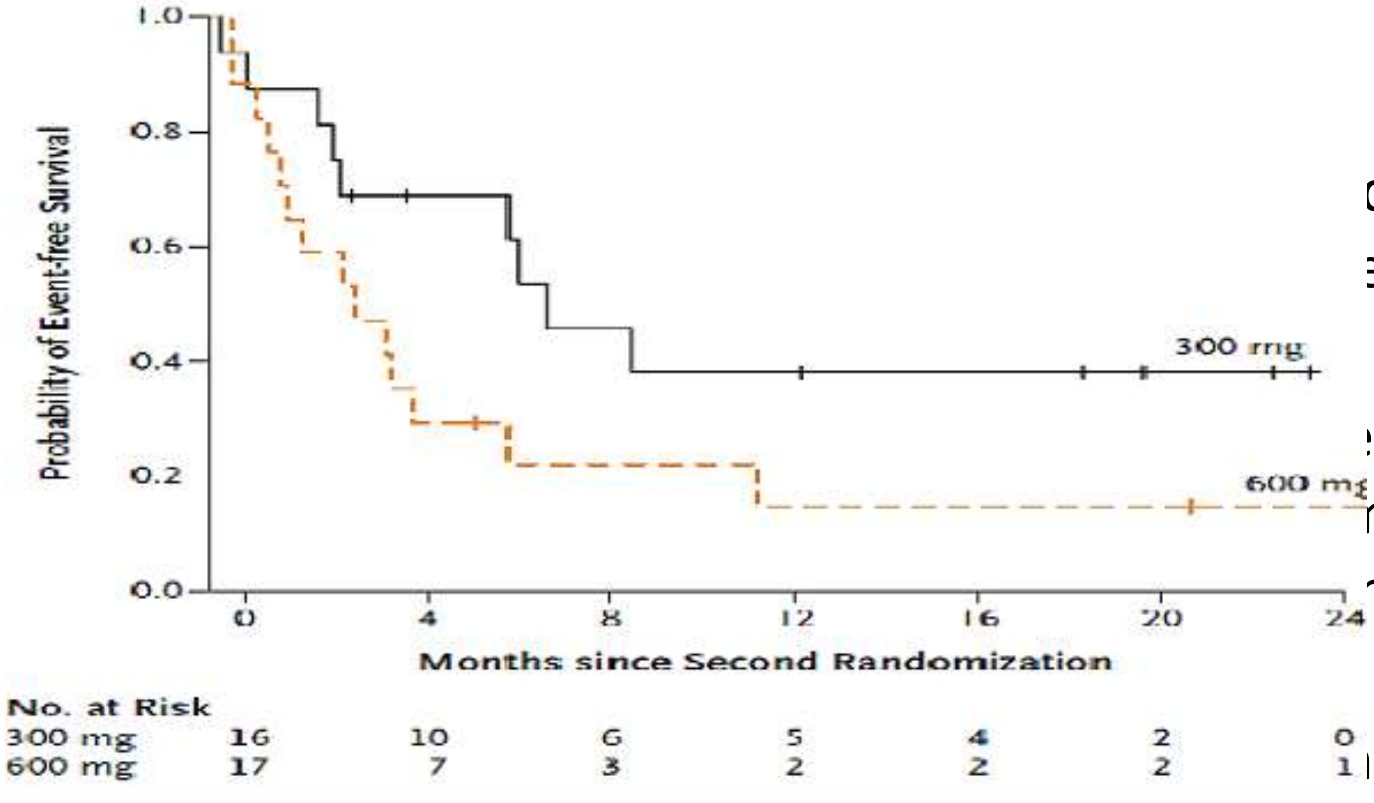

Figure 3. Probability of Event-free Survival over Time.

- 27 had negative results on sputum culture 1 year after the end of treatment, 3 were lost to follow-up, and 8 withdrew before the end of the study, including the 4 patients in whom linezolid failed, as reported previously.
- The median duration of tuberculosis treatment was 789 days overall, with 781 days of linezolid.
- Linezolid is effective at achieving culture conversion among patients with treatment refractory XDR pulmonary tuberculosis.

Drawbacks

- Linezolid a single active agent being added to a failing regimen.
- The trough level of the drug was above the MIC in all patients in 600mg group, whereas it was below MIC in 3 patients in 300mg group.
- 4 (11%)patients developed acquired resistance to Linezolid.
- Pk studies showed that, 300mg can maintain the drug level above the mutation preventing level.

Trial	Objective	Regimen	Remarks
RIFATOX Trial	Evaluate the toxicity of high dose rifampicin (15 & 20 mg/kg/d) N= 300	$2EHR_{15}Z/2HR_{15}/2HR$ $2EHR_{20}Z/2HR_{20}/2HR$ vs. 2HRZE/4HR	-20 mg/kg safe/tolerable, dose-related ↑ LFTs < gr3 - No Δ in culture conversion rates
RIFASHORT Trial	Evaluate Toxicity and Efficacy of high dose Rifampicin	2HRZE/4HR $2HR_{1200}ZE/2HR_{1200}$ $2HR_{1800}ZE/2HR_{1800}$	Not yet open for participant recruitment
HIGHRIF1	EBA N=68	2wk max tolerability dosage, Pk, EBA R to 35 mg/kg	35 mg/kg safe/tolerable, no gr4/5 events, min LFT↑(<3)
HIGHRIF2	Evaluate safety and efficacy	$2R_{1200}$ (20 mg/kg) v. $_{900}$ (15 mg/kg) v. 600 (10 mg/kg)	No serious adverse events for Rifampicin @ 10 and 15mg/Kg

Short course MDR regimen

WHO RECOMMENDATIONS

ON THE USE OF THE SHORTER MDR-TB REGIMEN

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

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

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Inclusion criteria	Exclusion criteria
Patients with proven or highly likely MDR-TB	culture identified only environmental mycobacteria and Mycobacterium tuberculosis was never isolated,
No age criteria	the patient had a history of previous treatment with second-line drugs
	Antwerp laboratory failed to confirm RMP- plus INH-resistant TB (i.e., MDR-TB).
	overt liver disease

Treatment protocol

- high-dose GFX, EMB, PZA, and clofazimine (CFZ) throughout, supplemented during the minimum 4-month intensive phase by KM, prothionamide (PTH), and INH.
- If sputum smear microscopy results at month 4 were positive, the IP was extended until sputum smears were negative or the patient was declared to have bacteriological treatment failure.
- The duration of the continuation phase was fixed at 5 months

- **Cure:** completion of treatment with five or more negative cultures over at least 12 months (follow-up period included after the last positive culture.
- **Completion:** completion of treatment with documented bacteriological conversion status persisting up to the end of treatment, but fewer than five negative cultures or < 12 months of observation after the last positive culture.
- Failure: one or more positive cultures during treatment after at least 150 days, or death or default with bacteriological evidence of active TB after the first 2 months of treatment, or a medical decision to definitively terminate treatment due to adverse drug reactions.
- Relapse: cure or treatment completion, followed by at least one positive culture during post-treatment follow-up, unless the strain was proven to be Genotypic ally different from the initial isolate.

- Reinfection disease: recurrent disease with a genotypically different strain.
- Death: death from any cause during treatment not meeting g the criteria for prior failure.
- Default: interruption of treatment for at least 2 months not meeting the criteria for prior failure.
- Conversion on culture: two negative cultures taken at least 30 days apart; time to conversion is from startnof treatment until the time the first of these two negative specimens was taken.

- **Bacteriologically favourable** –cure/treatment completed
- **Bacteriologically unfavourable** -failure/relapse

Table 1 Treatment outcome among patients with multidrug-resistant tuberculosis. Treatment success comprises cured and treatment completed; all other standard outcomes together constitute non-success

	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

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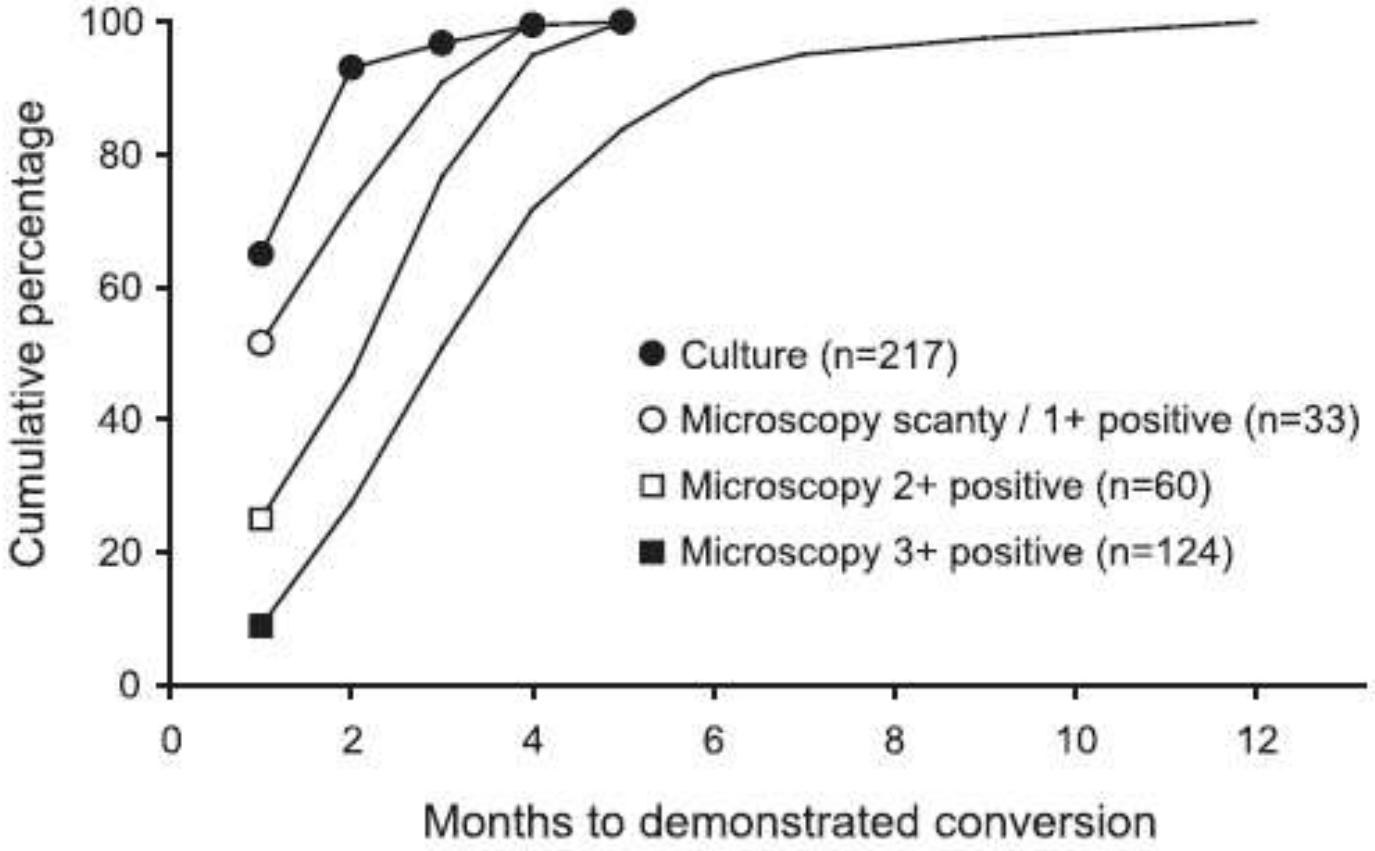

Figure 2 Sputum culture and smear conversion among 217 patients with monthly serial paired culture and microscopy result who neither died, failed nor defaulted. Microscopy results are stratified by diagnostic sputum smear grade.

Cumulative percentage of patients

95%

360

Figure 1 Number of days to treatment completion among the 439 patients who did not end treatment prematurely (due to death, default or treatment failure).

Conventional/Other MDR regimens	Bangladesh regimen
meta-analysis of 9153 MDR-TB patients from 32 observational studies conducted in 23 countries showed **a 54% treatment** success rate.	relapse-free cure rate of 87.9%
Costly, € 82 000 approx	Cheap, € 200, with generics
Duration ≥20 months	9 to 11 months
Numerous adverse effects	well tolerated, and serious events requiring a regimen change were rare.

(Ahuja, Ashkin et al. 2012)

- No RCT’s comparing the Bangladesh regimen with the current standard of care WHO regimen.
- Despite being introduced into the National programs of many countries.
- STREAM 1 trial aims to address this issue.