Short-course high-dose rifampicin TB treatment regimens:

Recent trial results and potential outcome modifications

Daniel Grint
6-Nov-2023

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

International Statistics & Epidemiology Group

RIFASHORT – Trial results

NEJM Evidence

Published August 22, 2023

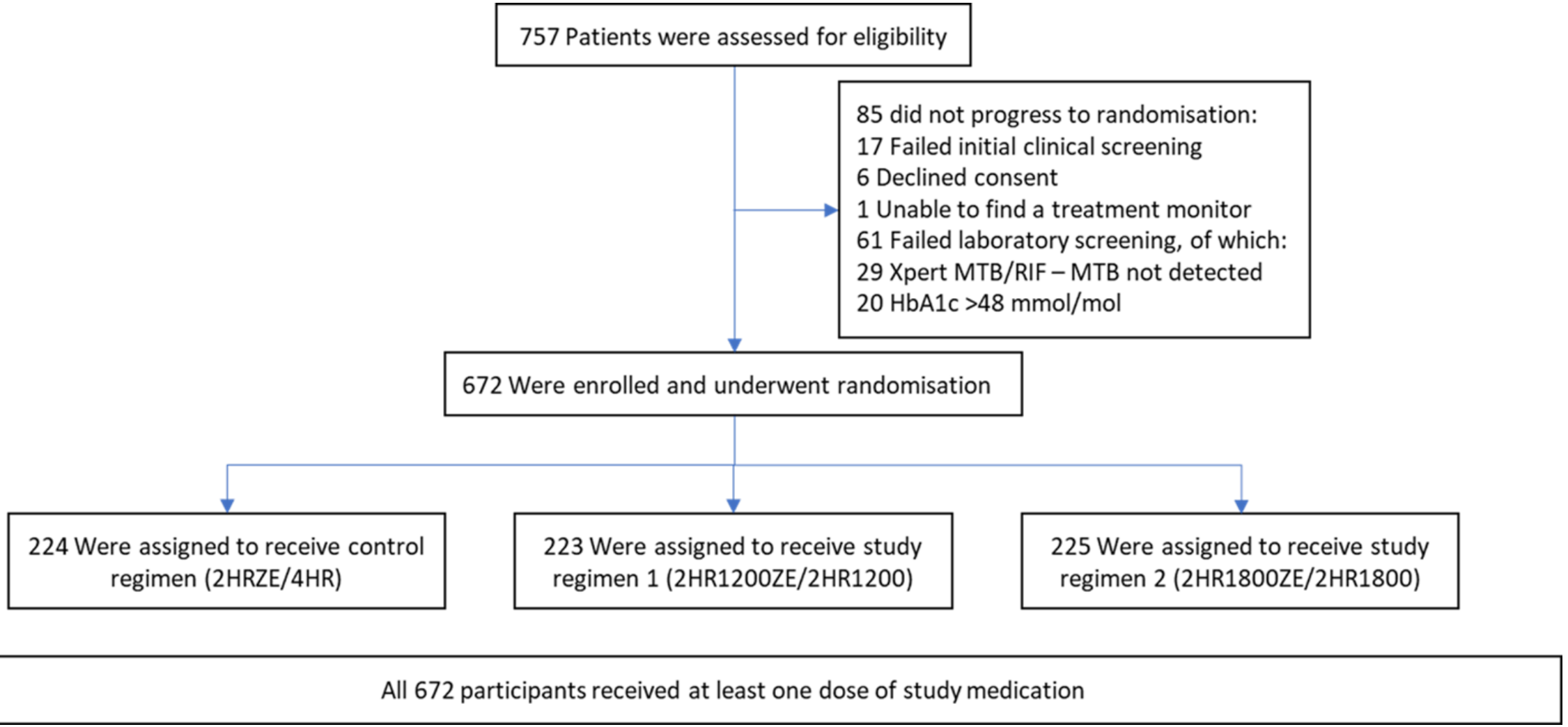
DOI: 10.1056/EVIDoa2300054

ORIGINAL ARTICLE

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

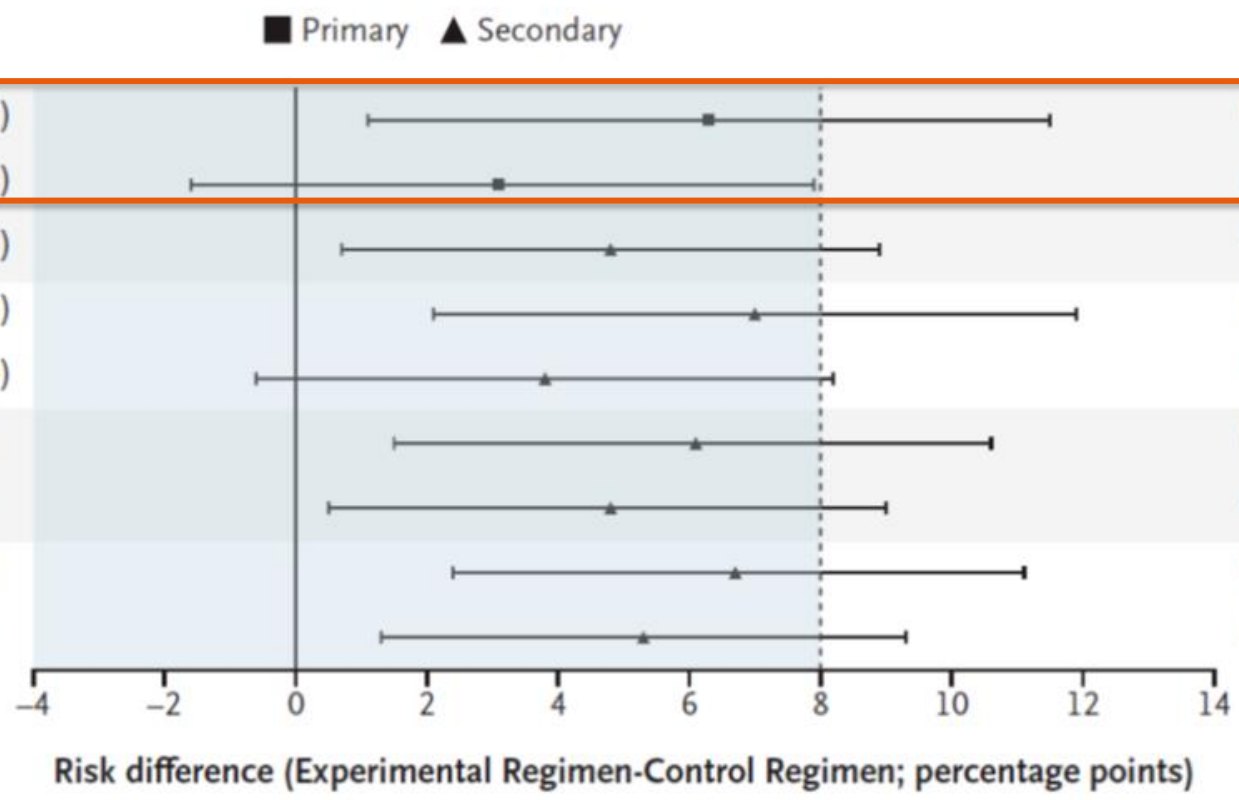
Amina Jindani, M.D.,[1] Daniel Atwine, Ph.D.,[2,3] Daniel Grint, Ph.D.,[4] Boubacar Bah, M.D.,[5] Jack Adams, B.Sc.,[1] Eduardo Rómulo Ticona, Ph.D.,[6] Bhabana Shrestha, M.D.,[7] Tefera Agizew, Ph.D.,[8] Saeed Hamid, F.R.C.P.,[9] Bushra Jamil, F.R.C.P.,[9] Adolf Byamukama, M.D.,[2] Keneth Kananura, M.Med.,[2] Ivan Mugisha Taremwa, M.Sc.,[2] Maryline Bonnet, Ph.D.,[2,10] Lansana Mady Camara, M.D.,[5] Oumou Younoussa Bah-Sow, Ph.D.,[5] Kindy Sadio Bah, M.D.,[5] Nene Mamata Bah, Ph.D.,[5] Maimouna Sow, D.M.L.T.,[5] César Eduardo Ticona Huaroto, M.D.,[6] Raquel Mugruza Pineda, B.Sc.,[6] Bijesh Tandukar, M.Sc.,[7] Bijendra Bhakta Raya, B.Sc.,[7] Neko Shrestha, M.B.B.S.,[7] Anikie Mathoma, M.P.H.,[8] Unami P. Mathebula-Modongo, Ph.D.,[8] Joyce Basotli, B.Tech.,[8] Muhammad Irfan, F.R.C.P.,[9] Dilshad Begum, M.Sc.,[9] Ammara Muzammil, D.Pharm.,[9] Imran Ahmed, M.D.,[9] Rumina Hasan, F.R.C.Path.,[9] Marcos V. Burgos, M.D.,[11] Faisal Sultan, F.R.C.P.,[12] Mariam Hassan, M.Sc.,[12] Iqra Masood, M.Phil.,[12] Claire Robb, B.Sc.,[1] Jonathan Decker, M.Sc.,[13] Sisa Grubnic, F.R.C.R.,[14] Philip D. Butcher, Ph.D.,[1] Adam Witney, Ph.D.,[1] Jasvir Dhillon, Ph.D.,[1] Tulika Munshi, Ph.D.,[1] Katherine Fielding, Ph.D.,[4] Thomas S. Harrison, M.D.,[1,14,15] and on behalf of the RIFASHORT Study Group*

RIFASHORT - CONSORT



RIFASHORT - Topline results

Study population	Study regimen	% Unfavorable	Control	aRD (90% CI)
mITT-M	SR2 (R 1800 mg)	13.4 (25/186)	7.0 (13/187)	6.3 (1.1 to 11.5)
	SR1 (R 1200 mg)	10.2 (19/186)	7.0 (13/187)	3.1 (–1.6 to 7.9)
	SR1 + SR2	11.8 (44/372)	7.0 (13/187)	4.8 (0.7 to 8.9)
mITT-All	SR2	13.4 (27/201)	6.3 (13/206)	7.0 (2.1 to 11.9)
	SR1	10.2 (21/206)	6.3 (13/206)	3.8 (–0.6 to 8.2)
PP-M	SR2	10.6 (19/180)	4.4 (8/182)	6.1 (1.5 to 10.6)
	SR1	9.3 (17/182)	4.4 (8/182)	4.8 (0.5 to 9.0)
PP-All	SR2	10.8 (21/195)	4.0 (8/201)	6.7 (2.4 to 11.1)
	SR1	9.4 (19/202)	4.0 (8/201)	5.3 (1.3 to 9.3)



RIFASHORT - Safety profile

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Table 3. Laboratory-Defined and Clinical Adverse Events According to Treatment Group.*

Participants Experiencing	Control (n=224)	Study Regimen 1 (n=223)	Study Regimen 2 (n=225)
Primary safety outcome			
Grade 3 or 4 adverse event — no. (%)	9 (4.0)	10 (4.5)	10 (4.4)
Percentage point difference from control (95% CI)		0.5 (–3.3 to 4.2)	0.4 (–3.3 to 4.2)
Secondary safety outcome			
Grade 1–4 adverse event — no. (%)	120 (53.6)	109 (48.9)	115 (51.1)
Percentage point difference from control (95% CI)		–4.7 (–13.9 to 4.6)	–2.5 (–11.7 to 6.8)
Other safety outcomes — no. (%)			
Serious adverse event	3 (1.3)	3 (1.3)	3 (1.3)
Notifiable adverse event	10 (4.5)	13 (5.8)	13 (5.8)
Notifiable adverse event, excluding pregnancy	6 (2.7)	11 (4.9)	13 (5.8)
Death	5 (2.2)	8 (3.6)	3 (1.3)

RIFASHORT – Few lack of efficacy endpoints

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Table 2. Primary and Key Secondary Outcome Analyses.*

mITT-M Primary Analysis Assessable Outcomes	Control (n=187)	Study Regimen 1 (n=186)	Study Regimen 2 (n=186)
Favorable			
Participants with outcome — no. (%)	174 (93.0)	167 (89.8)	161 (86.6)
Unfavorable			
Participants with outcome — no. (%)	13 (7.0)	19 (10.2)	25 (13.4)
Adjusted percentage point difference from control (90% CI)		3.1 (–1.6 to 7.9)	6.3 (1.1 to 11.5)
Reasons for unfavorable outcome			
Death during the treatment phase	3 (1.6)	4 (2.2)	0
Posttreatment death, TB a plausible cause	0	1 (0.5)	0
Lost to follow-up during the treatment phase	2 (1.1)	0	1 (0.5)
Withdrew from the trial during the treatment phase†	3 (1.6)	2 (1.1)	5 (2.7)
Change in treatment because of adverse event‡	1 (0.5)	2 (1.1)	7 (3.8)
Two consecutive positive cultures after completing treatment	2 (1.1)	9 (4.8)	9 (4.8)
Retreated for TB because of clinical signs and symptoms without 2 consecutive positive cultures	2 (1.1)	1 (0.5)	3 (1.6)

Not unique to RIFASHORT - TBTC Study 31

Table 2. Primary Efficacy Analysis in the Microbiologically Eligible and the Assessable Populations.*

Outcome	Microbiologically Eligible Population				Assessable Population			
	Control (N=768)	Rifapentine–Moxifloxacin (N=791)	Rifapentine (N=784)	Total (N=2343)	Control (N=726)	Rifapentine–Moxifloxacin (N=756)	Rifapentine (N=752)	Total (N=2234)
Favorable								
Participants with outcome — no. (%)	656 (85.4)	668 (84.5)	645 (82.3)	1969 (84.0)	656 (90.4)	668 (88.4)	645 (85.8)	1969 (88.1)
Adjusted difference from control — percentage points (95% CI)	NA	1.0 (–2.6 to 4.5)	3.0 (–0.6 to 6.6)	NA	NA	2.0 (–1.1 to 5.1)	4.4 (1.2 to 7.7)	NA
Participant had negative culture at month 12 — no. (%)	643 (83.7)	656 (82.9)	636 (81.1)	1935 (82.6)	643 (88.6)	656 (86.8)	636 (84.6)	1935 (86.6)
Participant was seen at month 12 but no sputum was produced or cultures were contaminated but without evidence of *M. tuberculosis* — no. (%)	13 (1.7)	12 (1.5)	9 (1.1)	34 (1.5)	13 (1.8)	12 (1.6)	9 (1.2)	34 (1.5)
Unfavorable								
Participants with outcome — no. (%)	112 (14.6)	123 (15.5)	139 (17.7)	374 (16.0)	70 (9.6)	88 (11.6)	107 (14.2)	265 (11.9)
Outcome related to tuberculosis — no. (%)	24 (3.1)	45 (5.7)	75 (9.6)	144 (6.1)	24 (3.3)	45 (6.0)	75 (10.0)	144 (6.4)
Two consecutive positive cultures at or after week 17†	11 (1.4)	34 (4.3)	63 (8.0)	108 (4.6)	11 (1.5)	34 (4.5)	63 (8.4)	108 (4.8)

RIFASHORT wasn't able to demonstrate non-inferiority

Did we pose the right question?

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Given the choice:

6 months – 2% require retreatment
or
4 months – 5% require retreatment?

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Another way? - The FDA snapshot algorithm

Primary outcome (Month 12)

TB treatment outcomes	Control	Arm A
TB cure and recurrence free survival	82%	79%
Lack of efficacy – TB recurrence, TB death	3%	3%
No month 12 assessment		
Discontinued due to death	1%	1%
Discontinued due to AE	2%	5%
Discontinued due to other reasons		
Loss to follow-up	5%	5%
Participant withdrawal	5%	5%
On study but no assessment at month 12	2%	2%