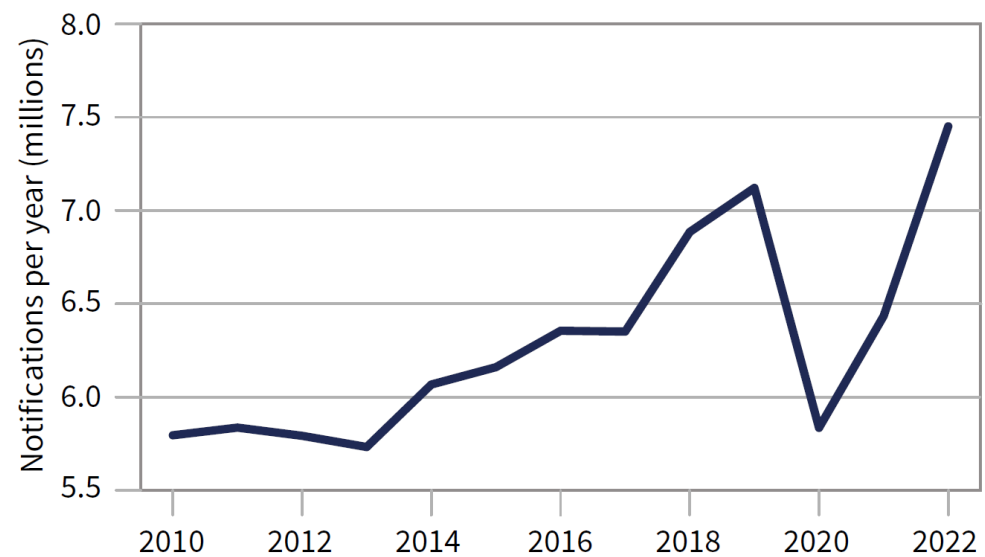


Treatment shortening of Drug-susceptible TB

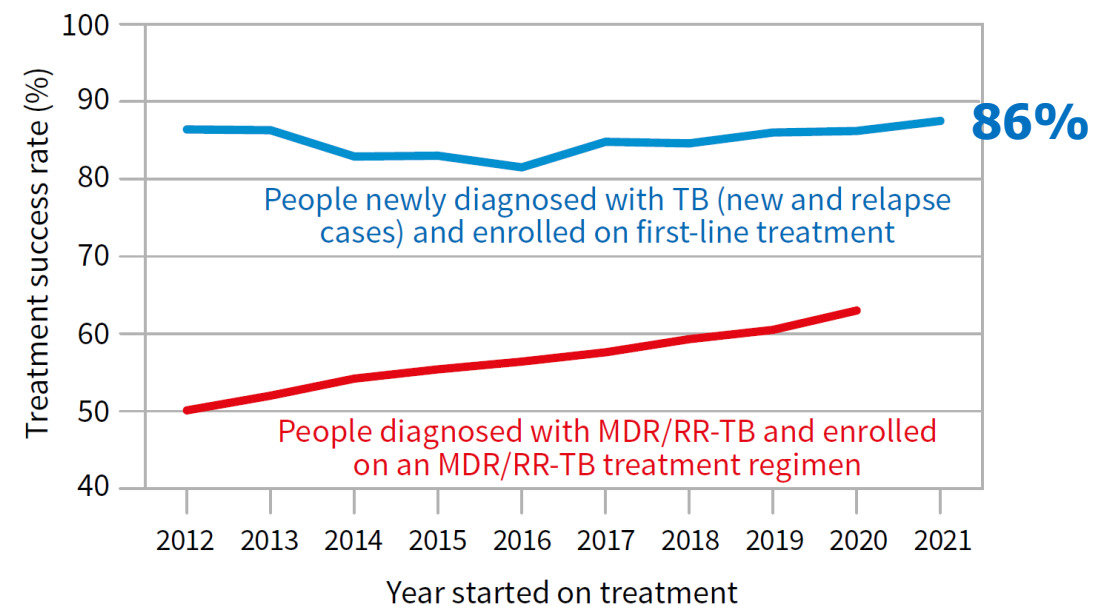
19/OCT/2024

4th KATRD TB/NTM International Symposium
Jeongha Mok, Pusan National University Hospital

Global trend in case notifications of people newly diagnosed with TB, 2010–2022



Global success rates for people treated for TB, 2012–2021^a



Tx outcome of DS-TB, Korea, 2020

Table 3. Treatment outcomes among patients with TB in 2020

Characteristic	Treatment outcomes								
	Treatment success			Treatment interruption	Treatment failed	Death			Still on treatment
	Sub-total	Cured	Completed			Sub-total	TB-related	Others	
Total (24,000) ^{a)}	19,212 (80.1)	3,519 (14.7)	15,693 (65.4)	522 (2.2)	7 (0.0)	3,550 (14.8)	640 (2.7)	2,910 (12.1)	709 (3.0)
Sex									
Male (14,505)	11,469 (79.1)	2,230 (15.4)	9,239 (63.7)	330 (2.3)	7 (0.0)	2,230 (15.4)	403 (2.8)	1,827 (12.6)	469 (3.2)
Female (9,495) ^{a)}	7,743 (81.5)	1,289 (13.6)	6,454 (68.0)	192 (2.0)	0 (0.0)	1,320 (13.9)	237 (2.5)	1,083 (11.4)	240 (2.5)
Age (yr)									
<65 (12,162)	10,833 (89.1)	1,948 (16.0)	8,885 (73.1)	291 (2.4)	5 (0.0)	571 (4.7)	138 (1.1)	433 (3.6)	462 (3.8)
0-19 (281)	263 (93.6)	41 (14.6)	222 (79.0)	2 (0.7)	0 (0.0)	3 (1.1)	1 (0.4)	2 (0.7)	13 (4.6)
20-49 (5,753) ^{a)}	5,262 (91.5)	879 (15.3)	4,383 (76.2)	142 (2.5)	3 (0.1)	128 (2.2)	42 (0.7)	86 (1.5)	218 (3.8)
50-64 (6,128)	5,308 (86.6)	1,028 (16.8)	4,280 (69.8)	147 (2.4)	2 (0.0)	440 (7.2)	95 (1.6)	345 (5.6)	231 (3.8)
≥65 (11,838) ^{a)}	8,379 (70.8)	1,571 (13.3)	6,808 (57.5)	231 (2.0)	2 (0.0)	2,979 (25.2)	502 (4.2)	2,477 (20.9)	247 (2.1)



Pre-drug era

Sanatorium with fresh air and sunlight

Progress of DS-TB treatment

Date	Regimen	Duration
1944	SM + PAS	
1952	INH + SM + PAS	24M
1960s	INH + SM + EMB	18M
1970s	INH + SM + EMB + RIF	9M
1980s	INH + EMB + RIF + PZA	6M

Korean guidelines for TB

1966

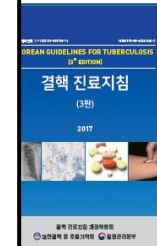
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화학요법
지침

폐결핵
진료의
기준

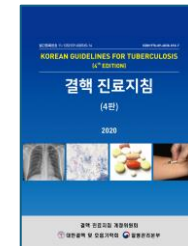
폐결핵
진료의
기준

- Microbiologically negative patient
- Economically disadvantaged patient
 - INH (mono therapy)
- New patient
- Patient with no cavity / minimal symptom
- Economically affluent patient
 - INH + PAS (or) INH + SM
- Patient with cavity / severe disease
 - INH + PAS + SM

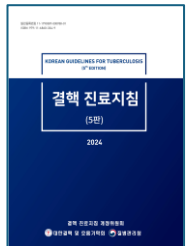
2017



2020



2024



Why should we shorten the Tx duration?

EDITORIAL

The New Antibiotic Mantra—“Shorter Is Better”

Brad Spellberg, MD

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

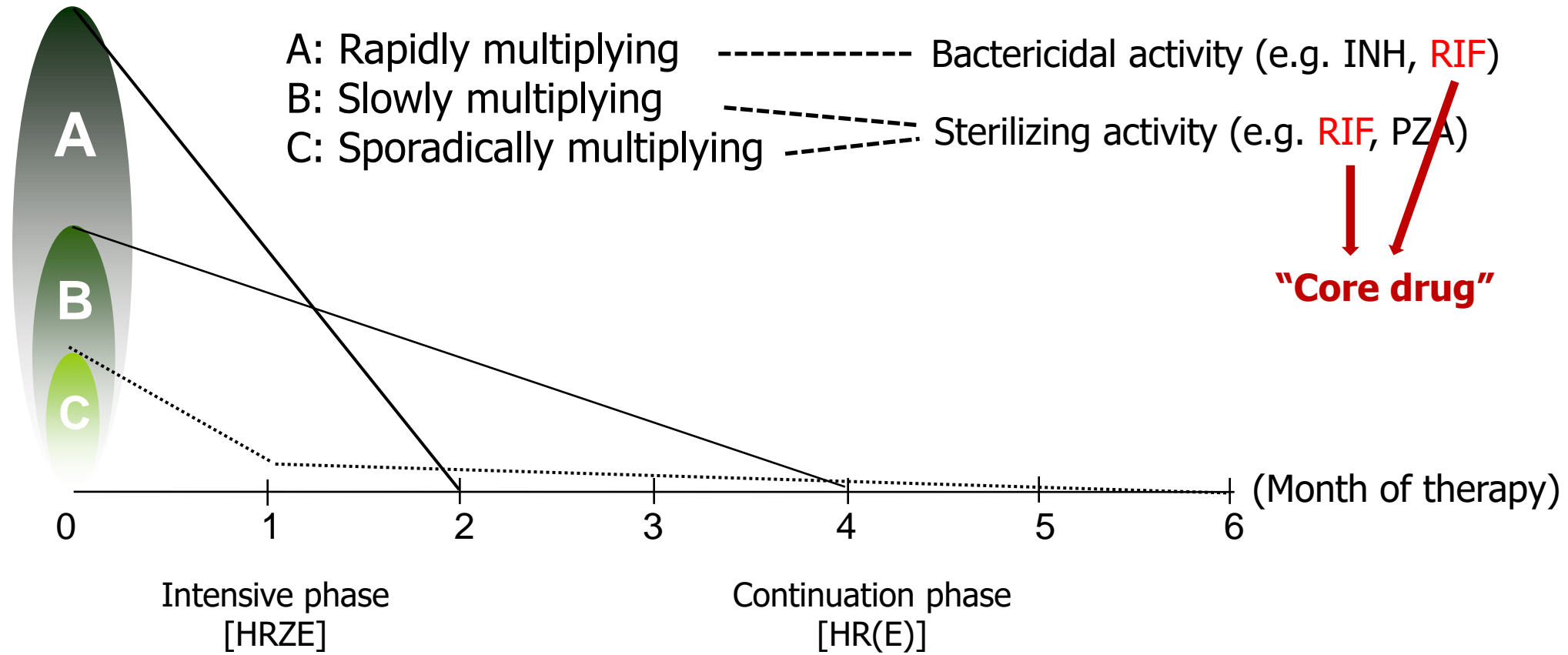
Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia ¹⁻³	3-5	7-10
Nosocomial pneumonia ^{6,7}	≤8	10-15
Pyelonephritis ¹⁰	5-7	10-14
Intraabdominal infection ¹¹	4	10
Acute exacerbation of chronic bronchitis and COPD ¹²	≤5	≥7
Acute bacterial sinusitis ¹³	5	10
Cellulitis ¹⁴	5-6	10
Chronic osteomyelitis ¹⁵	42	84

TABLE 1

The advantages of TB treatment-shortening

	Problem	Solution
Public health		
Improved treatment completion rates	Longer treatment regimens often lead to a high patient dropout rate, resulting in incomplete treatment and the emergence of drug resistance	Shorter regimens are more likely to be completed, thus reducing transmission and improving public health outcomes
Reduced treatment costs	Several pills per day Long engagement of healthcare personnel and facility	Shorter regimens require fewer medications and less healthcare provider time, leading to significant cost savings for healthcare systems
Enhanced control of TB outbreaks	Longer treatment impacts transmission control	Shorter regimens can be rapidly deployed during outbreaks to quickly contain and control the spread of the disease
Improved patient quality of life	Longer treatment requires extensive time-commitment	Shorter regimens reduce the burden on patients by requiring less time commitment and potentially fewer side effects
Clinical		
Improved drug efficacy	Longer treatment is associated with the risk of relapse	Newer, more-potent drugs can be used in shorter regimens, potentially increasing treatment effectiveness and reducing the risk of relapse
Reduced drug resistance	Longer treatment is associated with drug tolerance and mutations	Shorter regimens allow less time for mutations to occur and lead to drug resistance
Improved tolerability	Longer TB treatment is associated with various drug-related side effects	Shorter regimens can have fewer side effects, leading to better patient adherence and treatment outcomes
Social and economic		
Increased productivity	Longer TB treatment affects productivity negatively	Shorter regimens allow patients to return to work and other activities sooner, leading to increased economic productivity
Reduced stigma	TB as a disease brings a stigma in underdeveloped communities	Shorter regimens can help to reduce the stigma associated with TB by allowing patients to complete treatment more quickly and discreetly
Improved equity	TB treatment is often not available to marginalized populations, including homeless people, refugees and drug users	Shorter regimens can improve access to treatment for marginalized populations who can have difficulty adhering to longer regimens

Theoretical basis of TB treatment



Approach to shortening DS-TB treatment

1. Addition/reinforcement of core drug
 - High dose rifampin
 - Rifapentine
 - New or repurposed drug
2. Stratified/precision medicine
3. Others

Approach to shortening DS-TB treatment

1. Addition/reinforcement of core drug

- High dose rifampin
- Rifapentine
- New or repurposed drug

2. Stratified/precision medicine

3. Others

Landmark studies in 2010s

The NEW ENGLAND
JOURNAL of MEDICINE

NEJM 2014;371.

REMOxTB	Control group	2HREZ / 4HR
	INH group	2HR MZ / 2HR M
	EMB group	2 M REZ / 2 M R
OFLOTUB	Control group	2HREZ / 4HR
	GFX group	2HR GZ / 2HR G
RIFAQUIN	Control group	2HREZ / 4HR
	4M group	2 M REZ / 2 M + P (twice weekly)
	6M group	2 M REZ / 4 M + P (once weekly)

Failed to achieve non-inferiority
vs. 6M standard regimen
(high relapse rate)

High dose rifampin

- Current recommended dose of RIF : 10mg/kg/day (up to 600mg/day)
 - Chosen in the 1960s, primarily due to concerns about **cost** and the **fear of ADR**

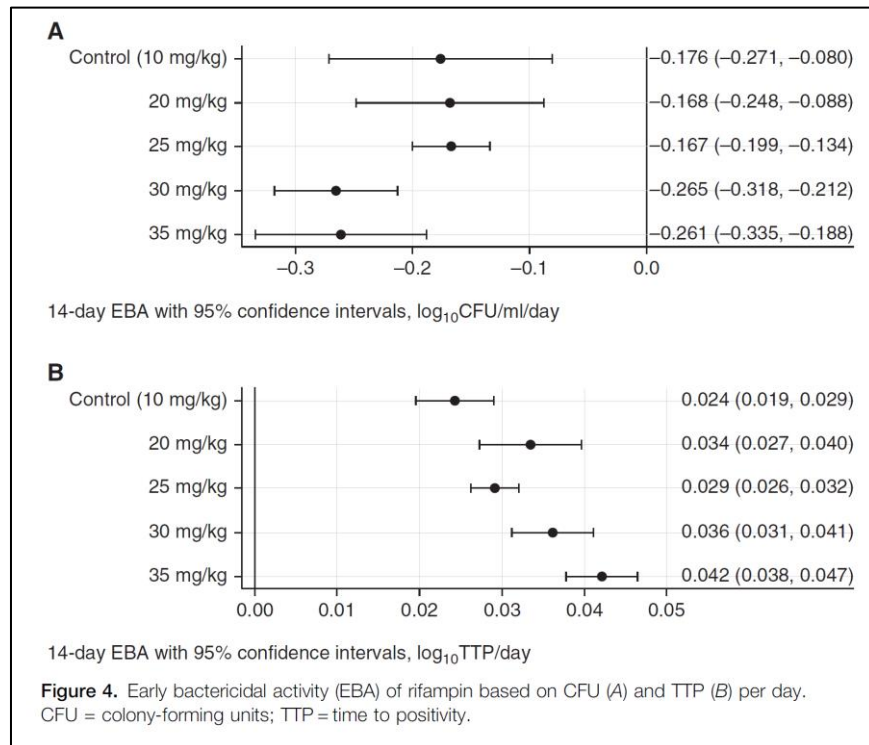


Table 2. Possibly Related and Definitely Related Adverse Events per Grade and per Dose Group

Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

RIFASHORT trial

- Phase 3, randomized, non-inferiority trial

- 2M HR_{10mg/kg}EZ / 4M HR_{10mg/kg}
 2M HR_{1200mg}EZ / 2M HR_{1200mg}
 2M HR_{1800mg}EZ / 2M HR_{1800mg}

- Primary outcome : unfavorable outcome at 18M

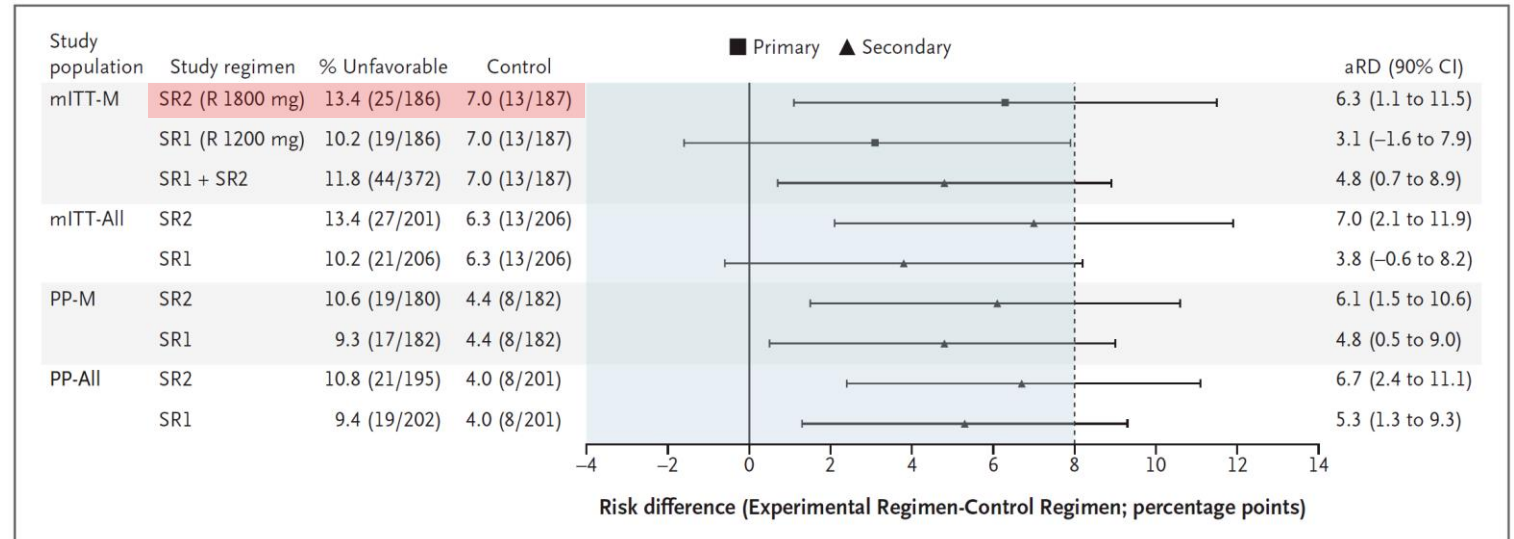
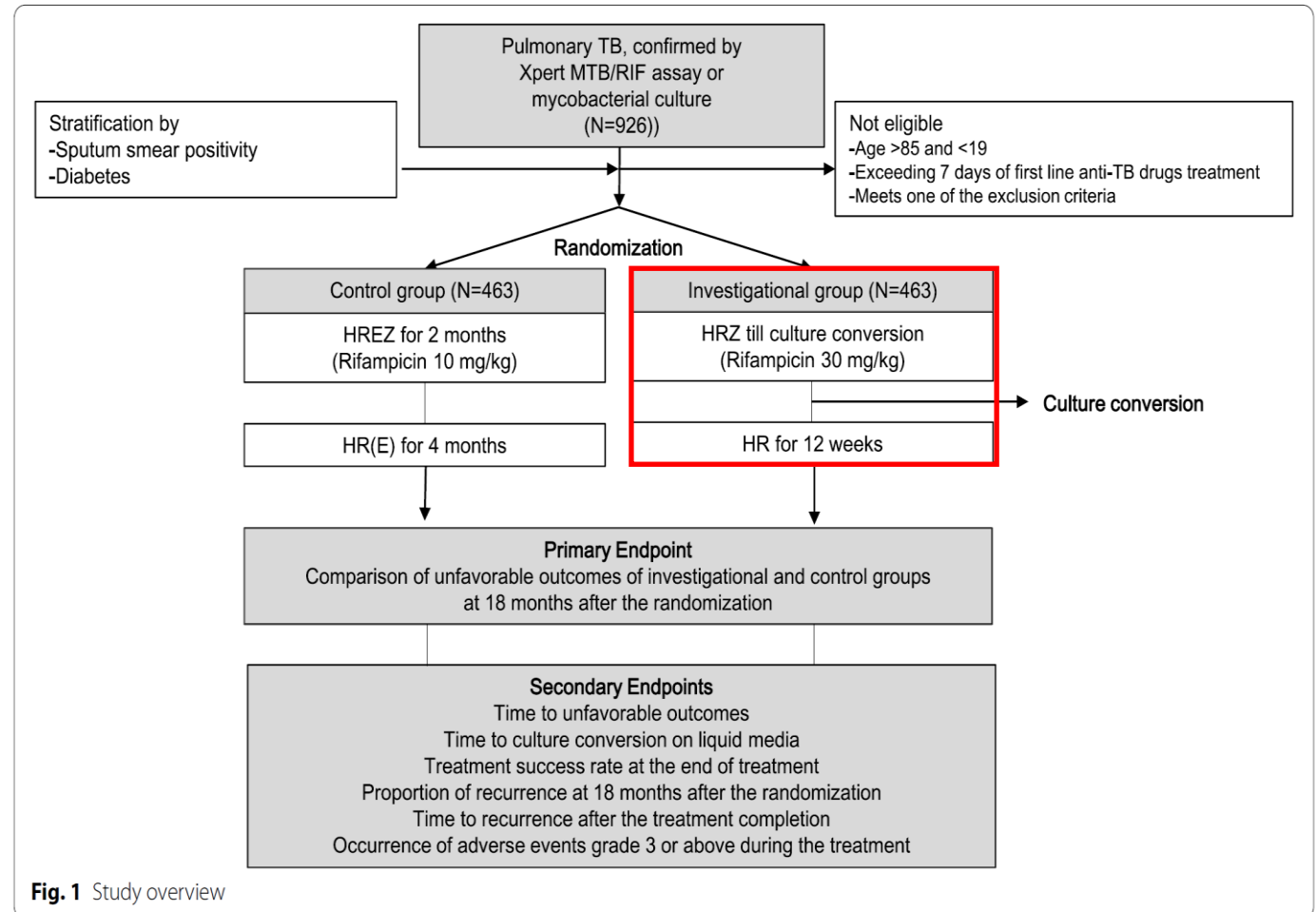


Table 2. Primary and Key Secondary Outcome Analyses.*

mITT-M Primary Analysis Assessable Outcomes	Control (n=187)	Study Regimen 1 (n=186)	Study Regimen 2 (n=186)
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)

Hi-DoRi-3 trial

- Phase 3, randomized, non-inferiority trial
- Primary outcome : unfavorable outcome at 18M



Hi-DoRi-3 trial

Early termination

- Slow patient enrollment (COVID-19 pandemic)
- Issue on MMP in RIF

	Modified intention-to-treat population		Per-protocol population	
	Control group	Investigational group	Control group	Investigational group
Disposition of the participants				
Underwent randomization	38	38	38	38
Included in the population	32	26	21	17
Not assessable	6	12	6	7
- Investigational drugs not administered*	-	10	-	10
- Randomization error, drug resistance confirmed after enrolment	5	2	5	2
- Treatment completed and discontinued, but no evidence of relapse or failure	1	-	1	-
Outcomes				
Unfavorable outcomes at 18 months after randomization	10 (31.25%)	10 (38.46%)	0 (0%)	1 (5.88%)
Difference versus the control group (95% confidence interval)	NA	7.21% [∞ to 31.86]	NA	5.88% [∞ to 17.07]
Failed to obtain negative conversion of sputum culture	0	0	0	0
Use of secondary anti-TB drugs or discontinuation of rifampicin for more than 4 weeks	5	2	0	0
Relapse after treatment completion (including clinical relapse)	0	2	0	1
Died during treatment	0	0	0	0
Loss to follow-up during treatment	0	0	0	0
Withdrawal	4	4	0	0
Other investigations' decision	1	2		0

* Subject taking rifampicin prior to issue for detection of 1-methyl-4-nitrosopiperazine detection

Substitution of EMB with LZD

- Phase 2 RCT in Korea
- 2M HRZ + 2M EMB
2M HRZ + 2W Lzd
2M HRZ + 4W Lzd
- Primary outcome
: 8W culture conversion

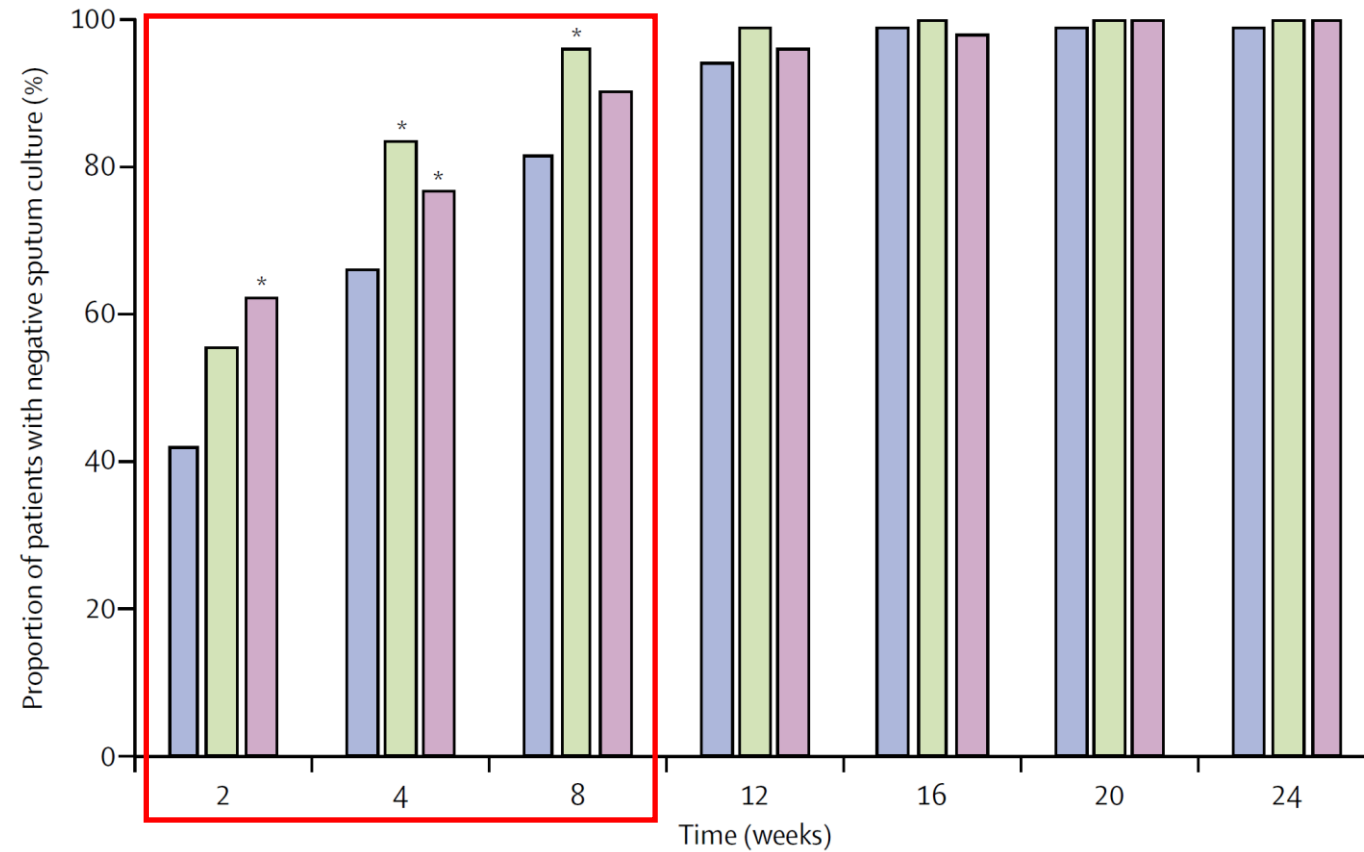
	Control group	Linezolid 2 weeks group	Linezolid 4 weeks group
Modified intention-to-treat analysis			
Patients with culture conversion	103/134 (77%)	111/135 (82%)	100/132 (76%)
Difference (95% CI)	ref	5.4 (-4.3 to 15.0)	-1.1 (-11.3 to 9.1)
p values	ref	0.28*	0.83*
Per-protocol analysis			
Patients with culture conversion	90/110 (82%)	106/111 (96%)	94/104 (90%)
Difference (95% CI)	ref	13.7 (5.5 to 21.9)	8.6 (-0.6 to 17.7)
p values	ref	0.001*	0.07*

* χ^2 test. Data are n/N (%) or difference (95% CI), unless otherwise stated.

Table 2: Primary outcome (sputum culture negativity on liquid media at completion of 8 weeks of treatment) classification according to treatment group for modified intention-to-treat and per-protocol analyses

Substitution of EMB with LZD

Post-hoc analysis (PP population)



SimpliciTB trial

- Phase 2, partially randomized, non-inferiority trial
- DS-TB
 - : 6M HR(EZ) vs. 4M BPaMZ
- DR-TB (Hr, RR, MDR)
 - : 6M BPaMZ (single arm)
 - pan-TB regimen
- Primary outcome
 - : 8W culture conversion

DS-TB

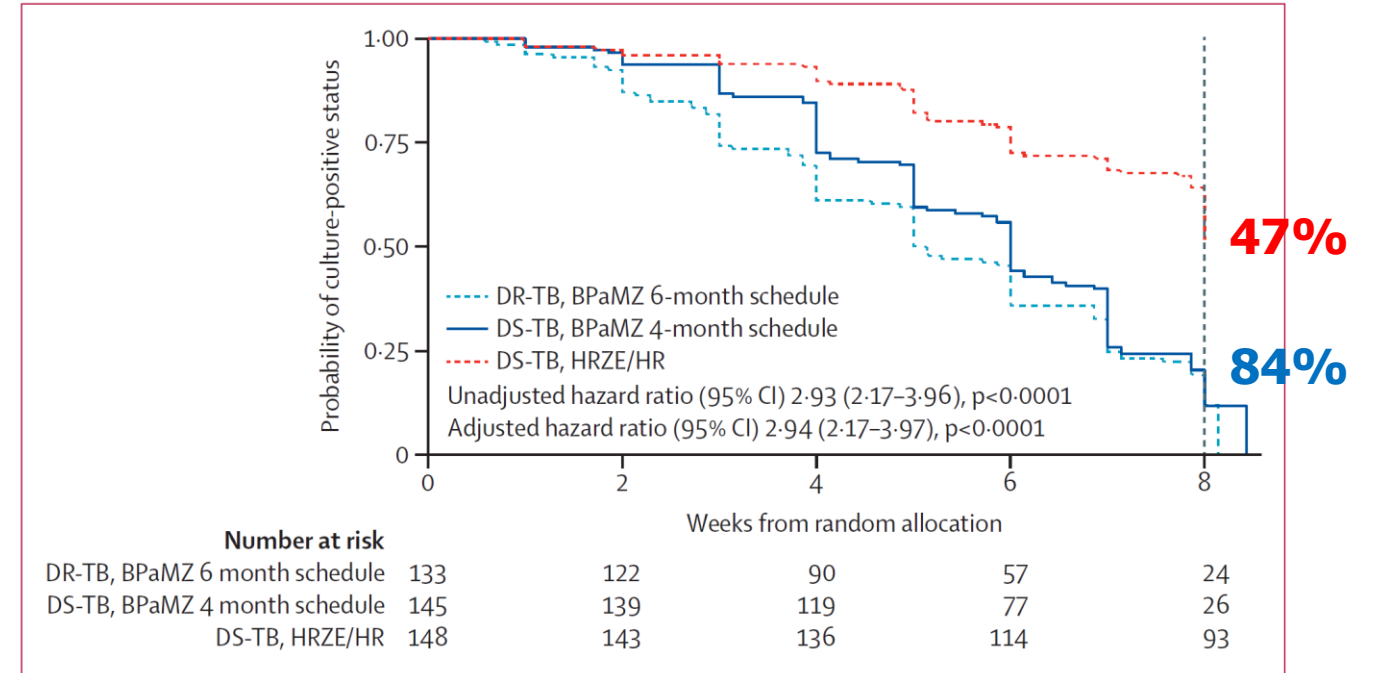
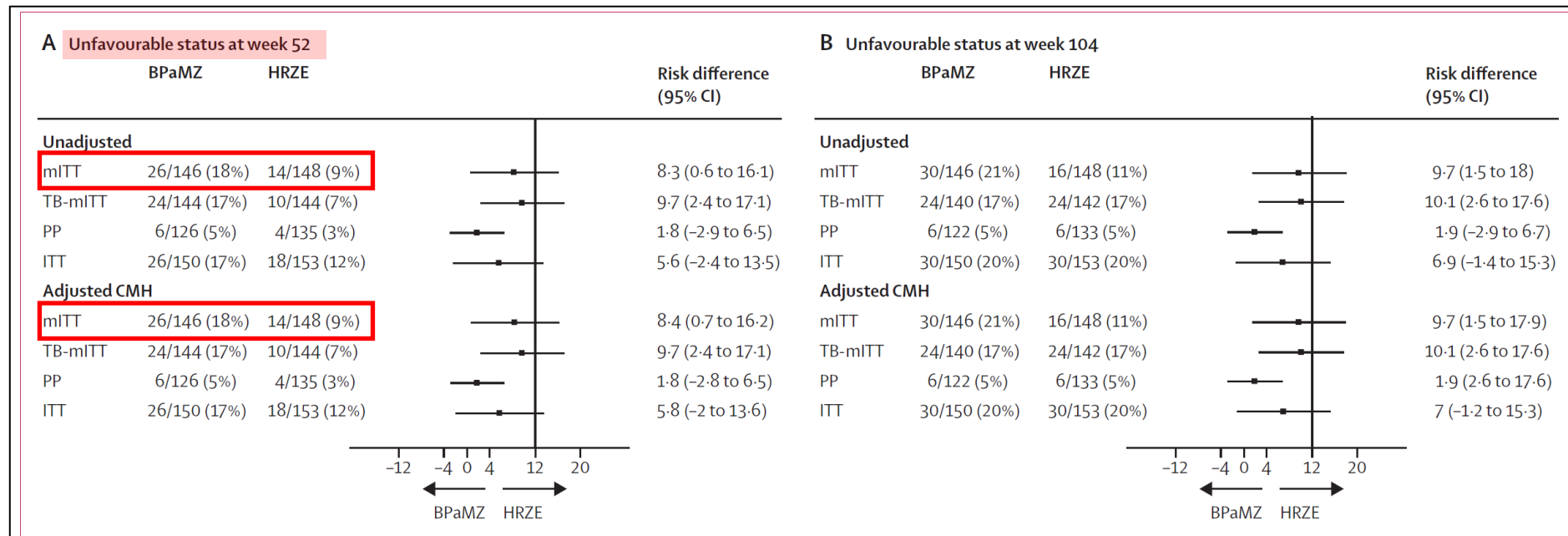


Figure 2: Primary efficacy analysis in the mITT population—time to culture-negative status by 8 weeks

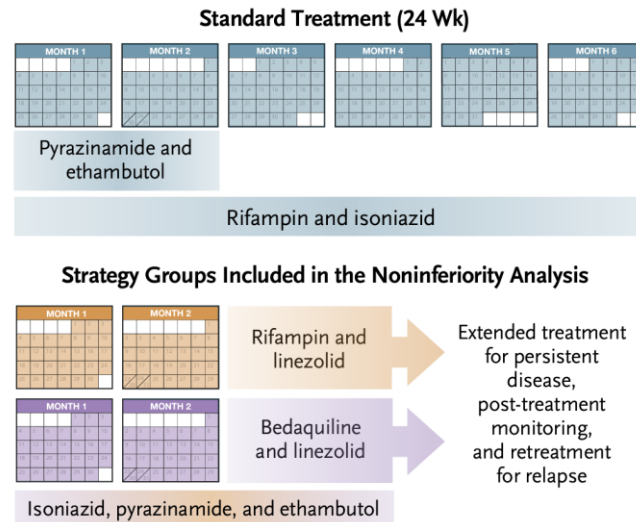
SimpliciTB trial

DS-TB

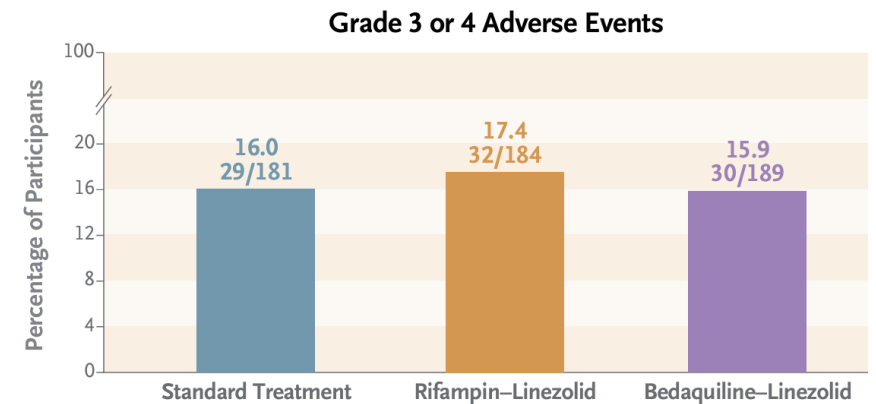
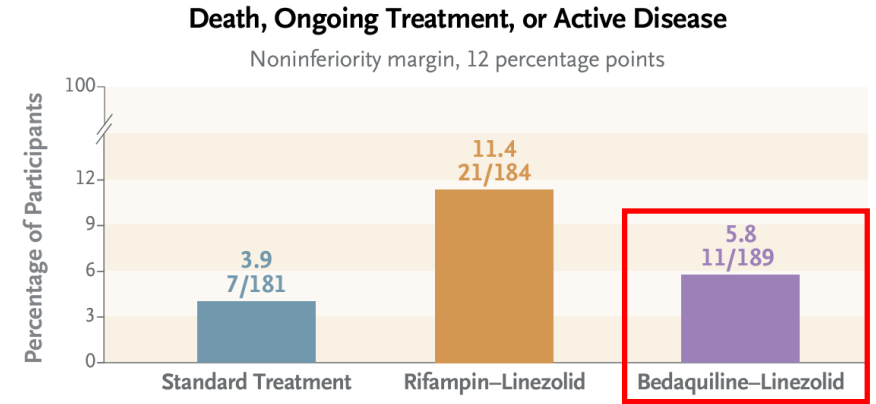


TRUNCATE-TB trial

- Phase 2–3, randomized, non-inferiority trial
- Primary outcome : death before W96 (or) ongoing TB treatment/ active TB at W96



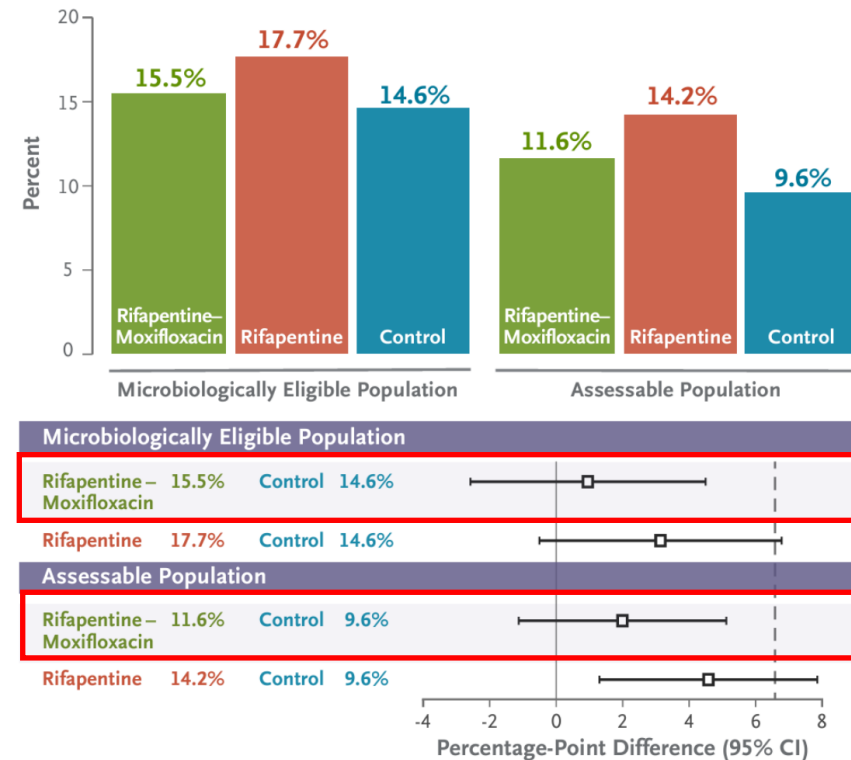
Total treatment duration (Bdq + Lzd arm)
= 84.8 days (mean)



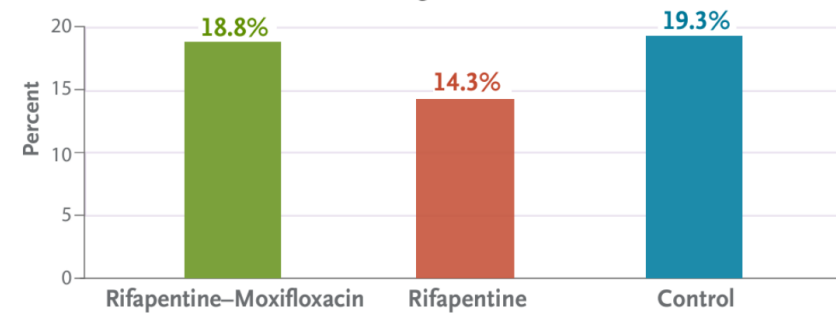
Study 31/A5349

- Phase 3, randomized, non-inferiority trial
- 2M HREZ / 4M HR
 2M HP_{daily}EZ / 2M HP_{daily}
 2M HP_{daily}MZ / 2M HP_{daily}M
- Primary outcome
 : survival free of TB at 12M

Absence of tuberculosis disease-free survival at 12 months after randomization



Grade 3 or higher adverse events



Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide⁸ (conditional recommendation, moderate certainty of evidence) – new recommendation.

Subgroups excluded from the recommendation

However, there were also subgroups for which there was no evidence (as they were not eligible for inclusion in the trial) and therefore the use of the shorter regimen outside the research environment is not indicated in these populations. These groups include:

- people weighing less than 40 kg;
- people with certain forms of extra-pulmonary TB (such as TB meningitis, disseminated TB, osteoarticular TB, abdominal TB);
- persons living with HIV infection with a CD4 count less than 100 cells/mm³ (NB: The trial did not include persons living with HIV infection if they had a CD4 count of less than 100 cells/mm³ and the GDG panel expressed concerns at an increased risk of relapse in this group (also because this group is at a higher risk of disseminated TB);
- children less than 12 years of age (NB: The trial aimed to recruit people aged 12 years and above. The youngest participant was 13 years of age. Therefore, no children were included in the trial. In the microbiologically-eligible population, there were 70 and 56 participants who were under 20 years of age in the rifapentine-moxifloxacin and control arms respectively); and
- pregnant, breastfeeding and postpartum women (NB: Pregnant or breast-feeding women were excluded from the study because of uncertainties about the safety of rifapentine, moxifloxacin, and pyrazinamide in these groups. Women who became pregnant while receiving study regimens were deregistered from the study and were treated according to national TB programme or local guidelines. The women continued to receive scheduled study follow-up, were classified as being on a non-study regimen, and did not receive study radiographs. Women who became pregnant while on study follow-up (but not on study treatment) continued to receive scheduled study follow-up and did not receive study radiographs. In all cases – i.e. whether pregnant during treatment or during follow up – the outcome of the pregnancy was reported on study forms).

Approach to shortening DS-TB treatment

1. Addition/reinforcement of core drug

- High dose rifampin

- Rifapentine

- New or repurposed drug

2. Stratified/precision medicine

3. Others

Back to the past...

REMoxTB	Control group	2HREZ / 4HR
	INH group	2HRMZ / 2HRM
	EMB group	2MREZ / 2MR
OFLOTUB	Control group	2HREZ / 4HR
	GFX group	2HRGZ / 2HRG
RIFAQUIN	Control group	2HREZ / 4HR
	4M group	2MREZ / 2M + P (twice weekly)
	6M group	2MREZ / 4M + P (once weekly)

Failed to achieve non-inferiority vs. 6M standard regimen

20% of patients were failed with 4M regimens !! ☹️

vs.

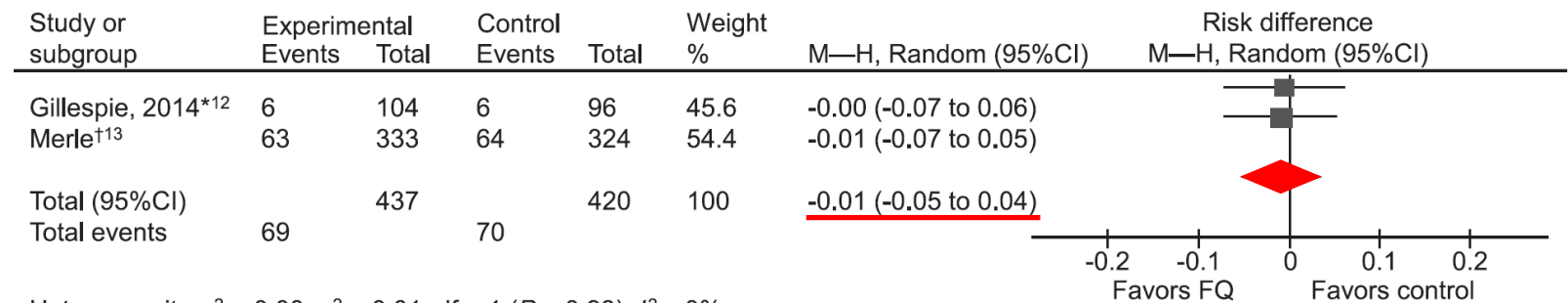
80% of patients were cured with 4M regimens !! 😊



One-size-fits-all ?

- Meta-analysis of
 - REMoxTB trial
 - RIFAQUIN trial
 - OFLOTUB trial

Daily 4M regimens (EMB → FQ) for non-cavitary TB

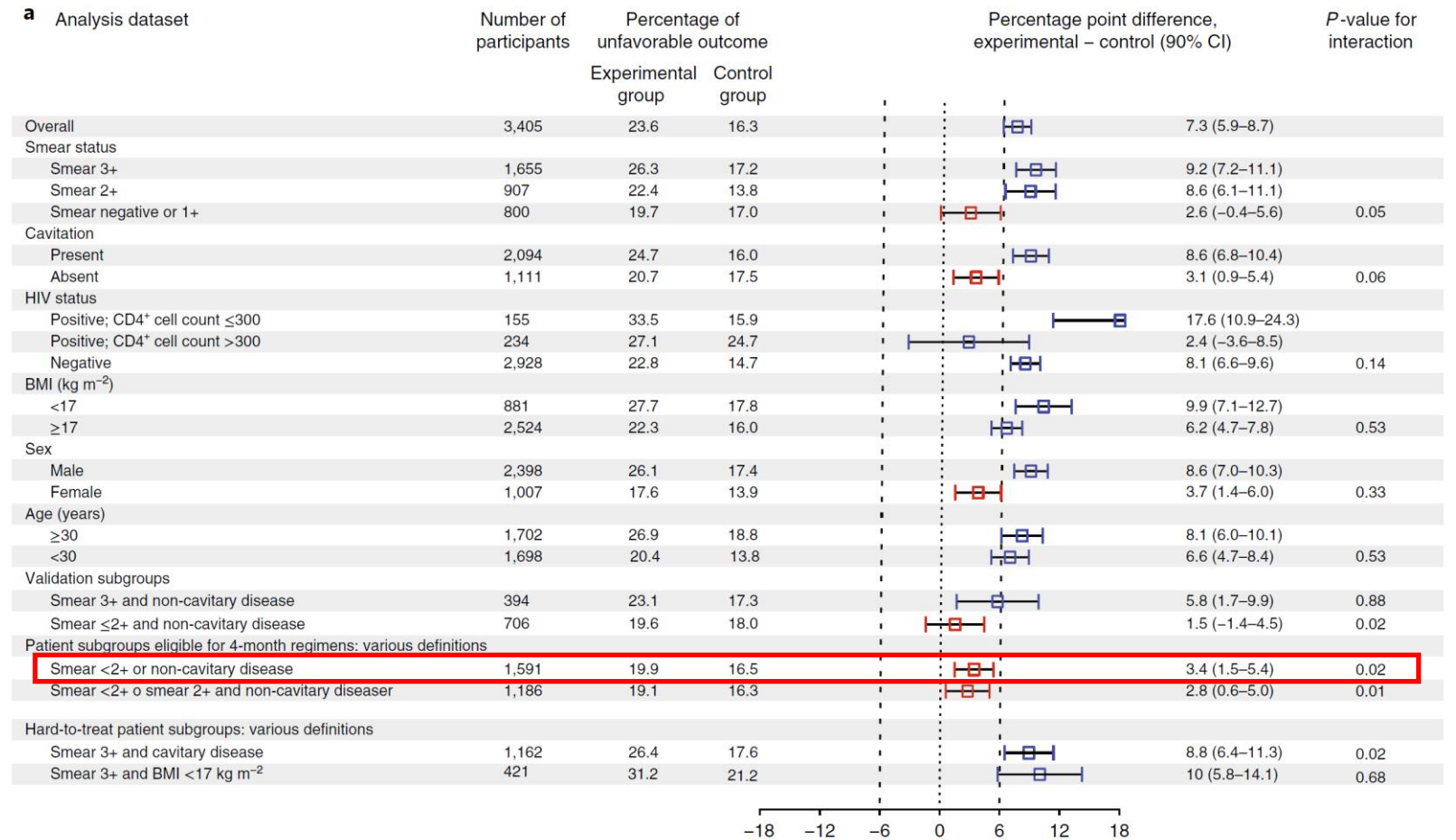


Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.01$, $df = 1$ ($P = 0.93$); $I^2 = 0\%$
 Test for overall effect: $Z = 0.30$ ($P = 0.77$)

One-size-fits-all ?

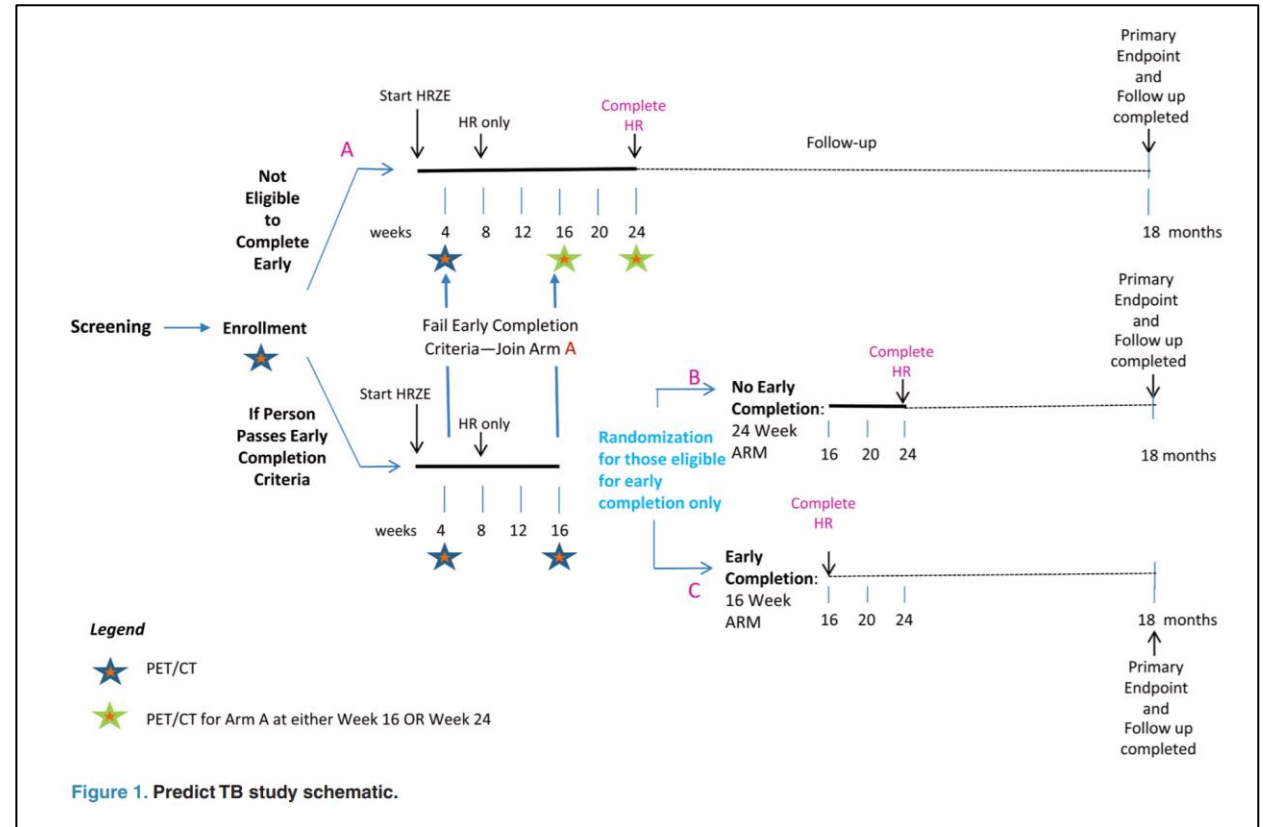
- Pooled analysis (IPD) of
 - REMoxTB trial
 - RIFAQUIN trial
 - OFLOTUB trial

Easy-to-treat phenotype

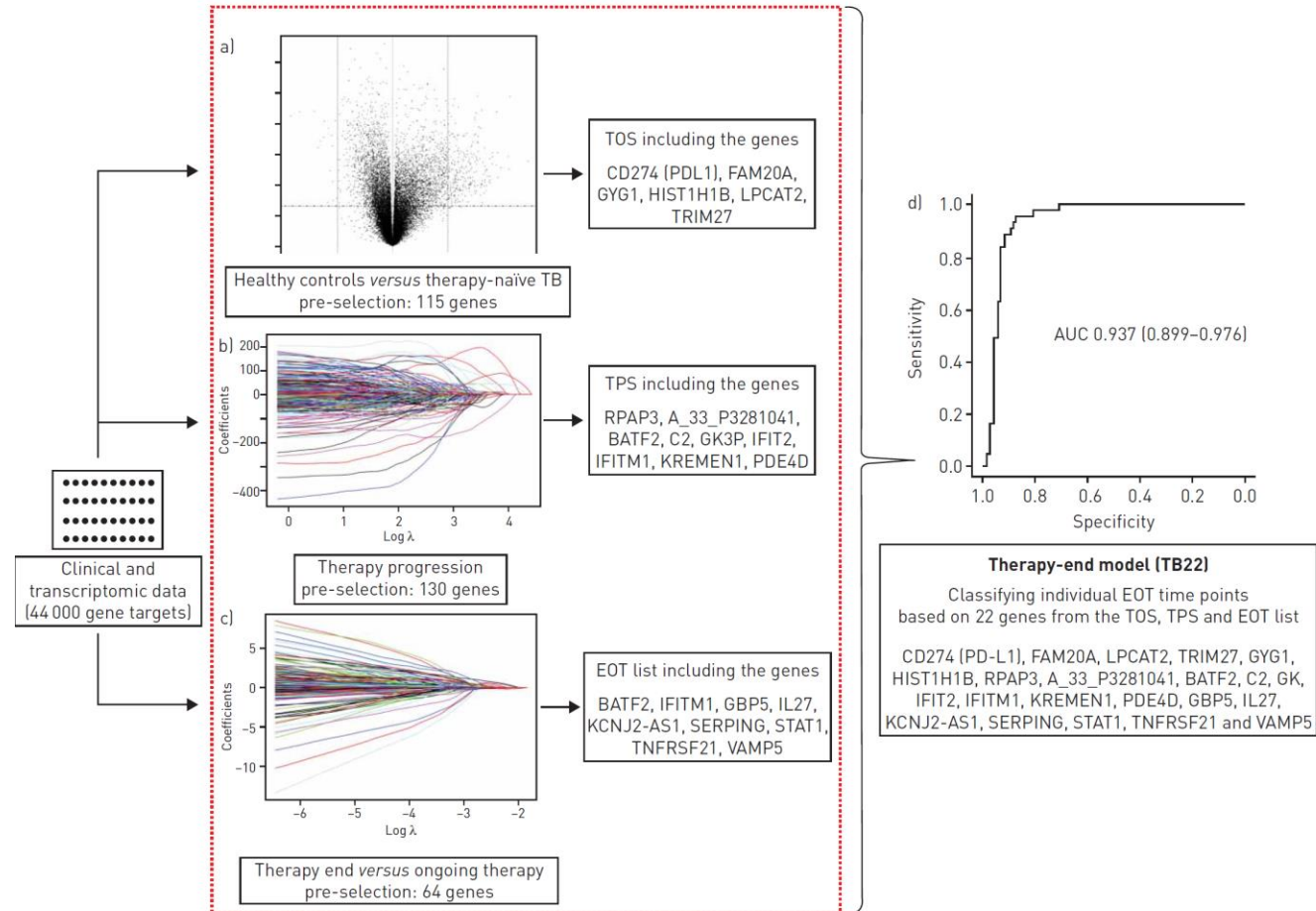


PredictTB trial

- Phase 2, randomized, non-inferiority trial
- 2HREZ/4HR vs. 2HREZ/2HR
- Stratification by disease severity
 - PET-CT scan
 - Xpert cycle threshold



RNA signature-guided individualized Tx



RNA signature-guided individualized Tx

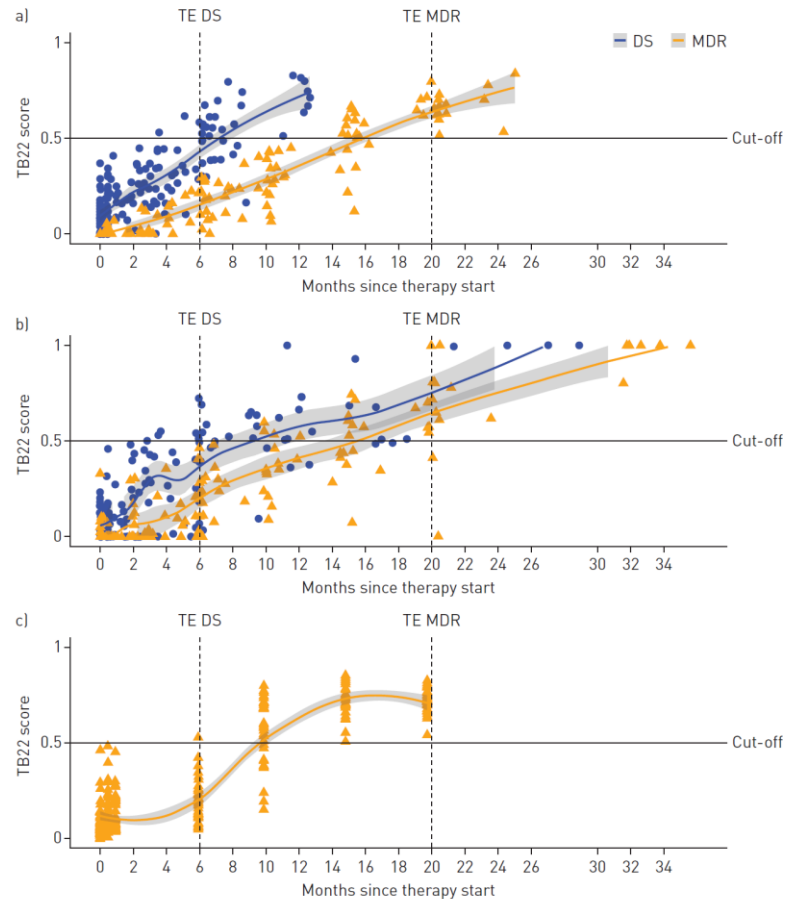
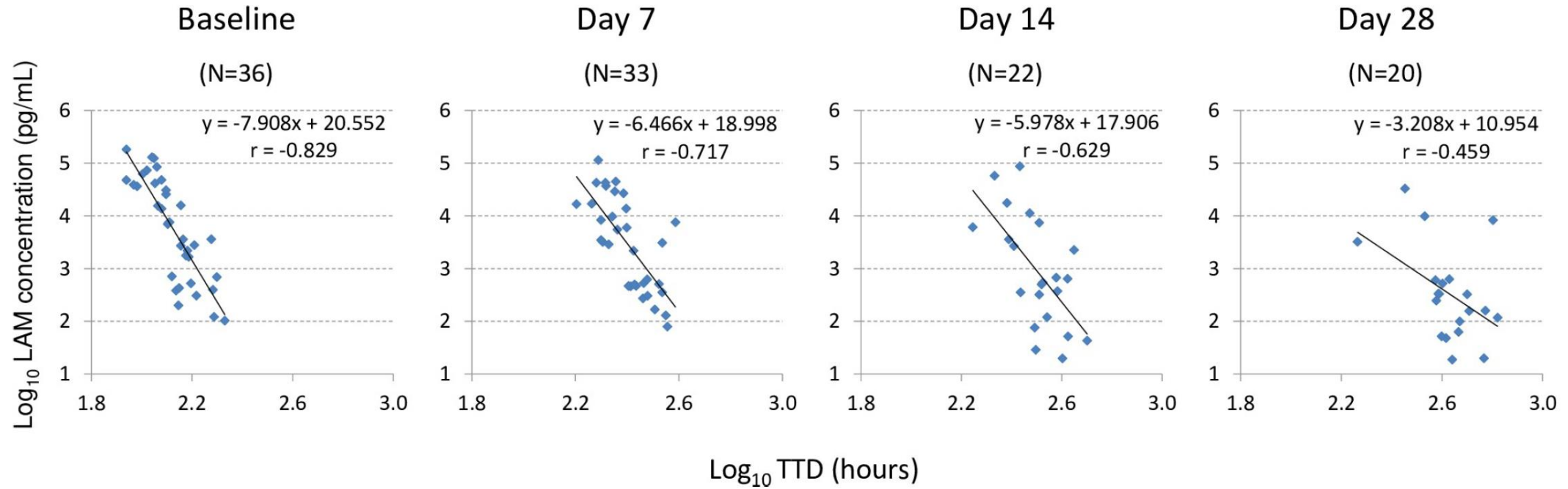


TABLE 1 Clinical characteristics of tuberculosis (TB) patients including the observed and predicted therapy durations in drug-susceptible (DS)- and multidrug-resistant (MDR)-TB patients from the German identification cohorts (GIC), the German validation cohorts (GVC) and the Romanian validation cohort (RVC)

	DS-TB (n=78)		MDR-TB (n=114)			p-value
	GIC	GVC	GIC	GVC	RVC	
Patients	50	28	30	32	52	
Baseline age years	48.2 (40.0–60.2)	34.6 (22.1–49.3)	36.2 (32.0–41.6)	33.2 (24.5–44.7)	37.0 (28.3–46.7)	0.083
Baseline TTP* days	21.0 (16–32.3)	10 (8–13.0)	22.0 (11.8–32.5)	22.0 (11.8–32.5)	40.0 (27.5–56.0)	>0.001
Time to culture conversion days	47.5 (25.8–75.0)	46.0 (24.5–55.0)	38.0 (33.0–215.5)	50.0 (30.5–59.8)	32.0 (27.0–60.0)	0.861
Therapy outcome[#]						
Cure	29 (58.0)	20 (71.4)	17 (56.7)	20 (62.5)	34 (65.4)	
Failure	7 (14.0)	1 (3.6)	3 (10.0)	1 (3.1)	4 (7.7)	
Death	1 (2.0)	1 (3.6)	2 (6.6)	1 (3.1)		
Lost to follow-up/undeclared	13 (26.0)	6 (21.4)	8 (26.7)	10 (31.3)	14 (26.9)	
Observed therapy duration days	184.0 (182.5–246.0)	273.0 (202.6–365)	638.0 (612.6–682.3)	641.0 (608.0–656.5)	611.0 (597.5–631.5)	<0.001
Predicted therapy duration days	175.0 (152.5–233.8)	225.0 (176.0–310.0)	420.0 (340.0–520.0)	430 (427.5–510.0)	450.0 (325.0–0.5)	<0.001

Sputum LAM as biomarker

Correlation of sputum LAM concentration and MGIT TTD



Approach to shortening DS-TB treatment

1. Addition/reinforcement of core drug

- High dose rifampin
- Rifapentine
- New or repurposed drug

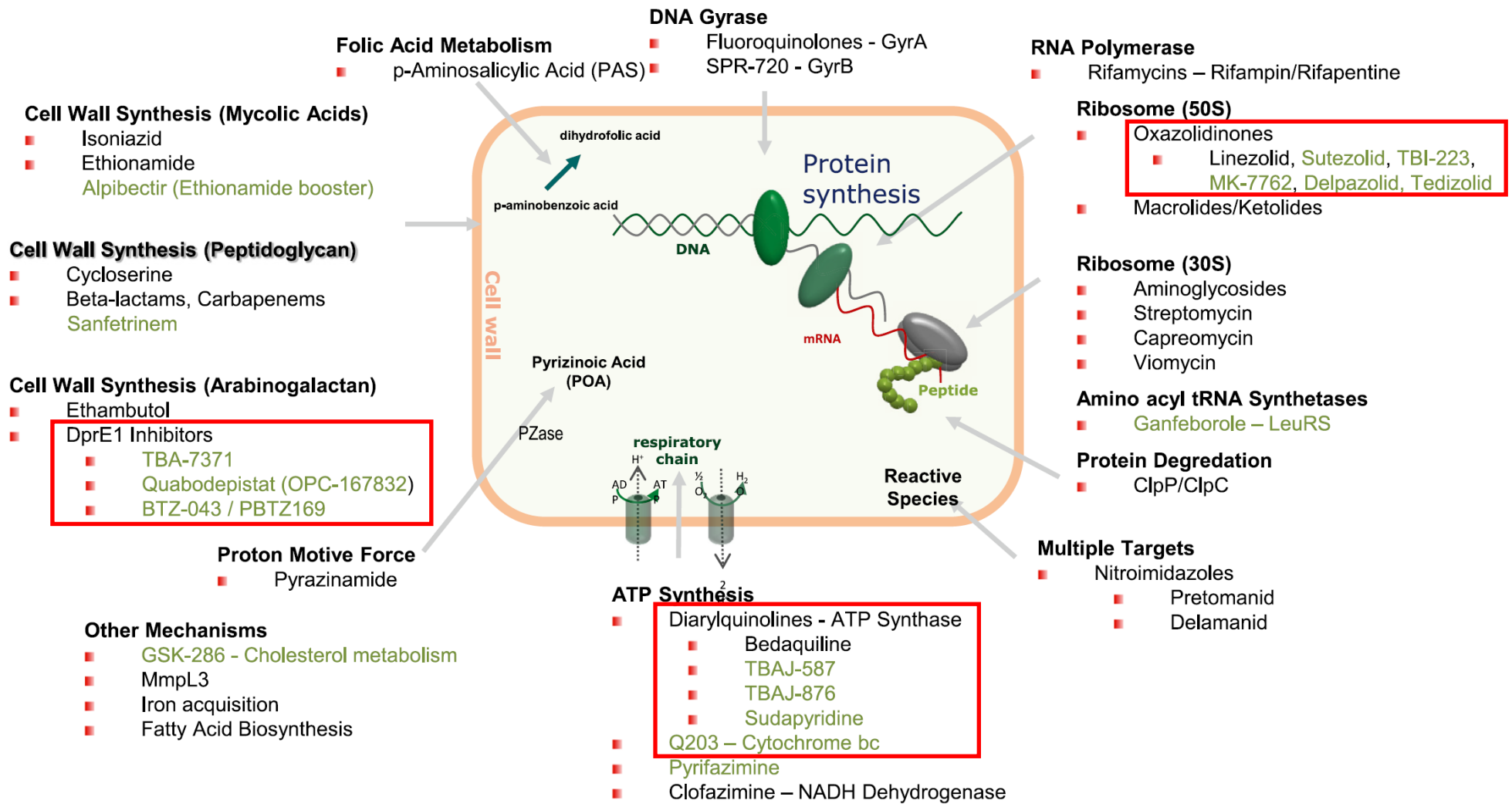
2. Stratified/precision medicine

3. Others

Host-directed therapy

Table 1. Host-directed therapy candidates and their current status

S.no.	Candidate	Cellular processes	References	Current status
1	Trehalose	Remove protein aggregates Activates the cascade of proteins involving PIKfyve, TRPML1 and TFEB to activate long-term autophagy responses Autophagy regulator AMPK regulator	Sarkar <i>et al.</i> (2007) Sharma <i>et al.</i> (2021)	Under consideration (proof of concept is available in many studies)
2	Metformin	Regulator of ROS production Agonist of AMPK pathway and regulator of autophagy Educated the adaptive immune T-cells	Singhal <i>et al.</i> (2014) Bohme <i>et al.</i> (2020) Padmapriyadarsini <i>et al.</i> (2022)	Clinical trial
3	Vitamin D	Induces the production of AMP like cathelicidins and defensins Facilitates the disruption of bacterial membranes Induces immune responses like autophagy and chemokine secretion	Kaufmann <i>et al.</i> (2014) Liu <i>et al.</i> (2006)	Clinical trials
4	Statins	Controls cholesterol metabolism Maintains the lipid levels	Su <i>et al.</i> (2021)	Phase II clinical trial
5	Celecoxib	Inhibitor of COX2 Block PGE2 biosynthesis	Sorgi <i>et al.</i> (2020) Jain <i>et al.</i> (2020) Naftalin <i>et al.</i> (2018)	Clinical trial
6	Everolimus	Everolimus is an inhibitor of mTOR Induces autophagy	Cerni <i>et al.</i> (2019)	Phase II clinical trial
7	CC-11050	Anti-inflammatory role Phosphodiesterase-4 inhibitor	Subbian <i>et al.</i> (2016a), Wallis <i>et al.</i> (2021)	Phase II clinical trial
8	Valproic acid	HDAC1 inhibitor Increase the acetylation of histones	Moreira <i>et al.</i> (2020) Nieto-Patlan <i>et al.</i> (2019)	Under consideration (proof of concept is available in many studies)
9	Imatinib	SRC kinase inhibitor Decrease intracellular bacterial survival	Napier <i>et al.</i> (2011)	Phase II clinical trial



TB Research Tracker

Use the table below to access the most up-to-date information on clinical trials, operational research and other studies on TB and MDR-TB

Filters

[Reset](#)
 Clinical Trials

 Operational Research

Name	Indication	Theme	Type of Study	Research Topic	Location	Cohort Size	End Date	Select
M72/AS01E	TB vaccines	New vaccine	Phase 3	Phase III Randomized, Double-blind, Placebo-controlled, Multicenter, Clinical Trial to Assess the Prophylactic Efficacy, Safety, and Immunogenicity of the Investigational M72/AS01E-4 Mycobacterium Tuberculosis (Mtb) Vaccine	South Africa	26000	Aug 2029	🔍
MTBVAC	TB vaccines	New vaccine		Phase III study to evaluate the efficacy safety and immunogenicity of MTBVAC administered in healthy HIV unexposed and HIV exposed uninfected newborns in TB-endemic regions of Sub-Saharan Africa	South Africa	6960	Aug 2029	🔍
Optimizing(O) Rifapentine-based(RI) Regimen and shortENing(EN) the Treatment of Drug-sensitive Tuberculosis(T) (ORIENT)	DS-TB	Dose optimization	Phase 2	To evaluate Efficacy and Safety of Short-course Treatment for Drug-sensitive Tuberculosis	China	2442	Nov 2027	🔍
Treatment Shortening of Drug-Sensitive Pulmonary Tuberculosis Using High Dose Rifampicin (Hi-DoRI-3) (Hi-DoRI-3)	DS-TB	Dose optimization	Phase 3	High dose rifampicin and treatment shortening	Republic of Korea	926	Dec 2026	🔍
PHOENIX MDR-TB	TPT MDR-TB	New regimen research	Phase 3	Delamanid and Isoniazid as TPT in contacts of people with multidrug-resistant TB	Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Tanzania, Thailand, Uganda	5610	Sep 2026	🔍
TB YOUTH - Tuberculosis sYstemic Management Using One-month, Ultra-short Tuberculosis Preventive Treatment Regimen for sChool Contacts	TPT DS-TB	New regimen research		A prospective, multicenter, open-label, cluster randomized controlled trial conducted in school settings to explore if 1 month isoniazid and rifapentine given three times a week as TPT is non inferior to 3 months of daily isoniazid and rifampicin	China	3520	Sep 2026	🔍
H107e/ CAF 10b	TB vaccines	New vaccine		A Phase 1a, Dose-finding, Open-label Trial Followed by a Phase 1b, Double-blind, Randomised, Placebo-controlled Trial to Evaluate the Safety, Reactogenicity, and immunogenicity of the Tuberculosis Subunit Vaccine H107e/CAF10b in Adults	South Africa	140	May 2026	🔍
BNT164	TB vaccines	New vaccine	Phase 1	Phase I safety and immunogenicity of two investigational RNA-based vaccines against TB	Germany	96	Feb 2026	🔍
DOT-LTBI	TPT DS-TB	Health services research		Adherence, efficacy and safety of two delivery models of standard TPT regimens in socially marginalised individuals	Denmark	150	Jan 2026	🔍
Introduction of concomitant management for MDR/RR-TB and HCV infections	DR-TB	Efficacy and safety		Safety and effectiveness of a concomitant management of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) and hepatitis C virus (HCV) infection	Belarus, Georgia, Moldova, Republic of Armenia, Ukraine, Kyrgyzstan, Kazakhstan	200	Jan 2026	🔍
Ultra-Short Course Bedaquiline, Clofazimine, Pyrazinamide and Delamanid Versus Standard Therapy for Drug-Susceptible TB (PRESCIENT)	DS-TB	New regimen research	Phase 2	A Phase IIc, Open-Label, Randomized Controlled Trial of Ultra-Short Course Bedaquiline, Clofazimine, Pyrazinamide and Delamanid Versus Standard Therapy for DS-TB	Haiti, South Africa	156	Jan 2026	🔍
Rifapentine and Isoniazid TB Preventive Therapy (3HP) for Children Taking Dolutegravir-based Antiretroviral Treatment (DOLPHIN KIDS)	TPT DS-TB	Safety and tolerability		Safety, Tolerability and Drug-drug Interactions of Short-course Treatment of LTBI With High-dose Once-weekly Rifapentine and Isoniazid (3HP) Among Infants, Children and Adolescents Living With HIV Taking Dolutegravir-based Antiretroviral Treatment	South Africa	92	Dec 2025	🔍
RUTI	TB vaccines	New vaccine	Phase 2	Phase IIb study to investigate therapeutic vaccine RUTI against tuberculosis	India, Argentina	140	Nov 2025	🔍
VPM1002 - infants	TB vaccines	New vaccine	Phase 3	Phase III evaluation of efficacy and safety of VPM1002 in prevention of TB infection among infants in comparison to BCG	Gabon	6940	Oct 2025	🔍
GamTBvac	TB vaccines	New vaccine	Phase 3	Phase III safety and efficacy study of the subunit recombinant TB vaccine GamTBvac to prevent TB	Russian Federation	7180	Oct 2025	🔍

Key considerations for reducing the treatment duration

Real-world applicability

- Programmatic use of 4M HPMZ
- SF, USA (2021-2023)

Adverse events	
Any adverse event	18/22 (81.8)
Mild (CTCAE grade 1) ^f	7/22 (38.9)
Gastrointestinal (nausea and/or vomiting)	4/22 (18.2)
Rash	2/22 (9.0)
Myalgias	1/22 (4.5)
Moderate (CTCAE grade 2) ^f	10/22 (45.5)
Gastrointestinal (nausea and/or vomiting)	5/22 (22.7)
Nausea and/or vomiting with liver function test values >3x upper limit of normal	2/22 (9.1)
Dermatologic	2/22(9.1)
Dizziness, flushing, palpitations, anxiety	1/22 (4.5)
Severe (CTCAE grade 3) ^f	1/22 (4.5)
Syncope, weakness, nausea, electrolyte abnormality	1/22 (4.5)
HPMZ treatment discontinued due to adverse event(s)	11/22 (50.0)
Median time to first adverse event occurrence (range), d	4.3 (1–63)
Median time to HPMZ cessation (range), d	10.5 (3–70)
Cases who completed HPMZ treatment	9/22 (40.9)
Median time to HPMZ treatment completion (range), d	126 (120–198)

Hyperbilirubinemia = 63.6%

Real-world applicability

- RCT in Korea
- HCWs with LTBI
- 3HR vs. 3H₁P₁

Table 2

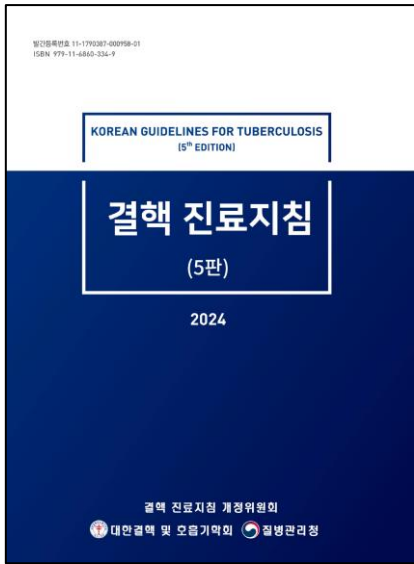
Adverse events and treatment completion rates of subjects by treatment regimen.

	Total subjects (n = 406)	3H ₁ P ₁ group (n = 226)	3HR group (n = 180)	P value
Adverse events				
No. of subjects with any adverse events	272 (67.0)	170 (75.2)	102 (56.7)	<0.001
No. of subjects with any grade 3 or 4 adverse events	10 (2.5)	8 (3.5)	2 (1.1)	0.074
No. of subjects with any grade 1 or 2 adverse events	262 (64.5)	162 (71.7)	100 (55.6)	0.001

Table 3

Detailed adverse events of study subjects according to the grade and symptoms.

	Total subjects (n = 406)	3H ₁ P ₁ group (n = 226)	3HR group (n = 180)	P value
Grade 3 or 4 adverse events*				
Anaphylaxis	4 (1.0)	4 (1.8)	0	0.133
Hepatotoxicity	3 (0.7)	2 (0.9)	1 (0.6)	>0.99
Urticaria	2 (0.5)	1 (0.4)	1 (0.6)	>0.99
Dizziness	1 (0.2)	1 (0.4)	0	>0.99



Currently, rifapentine has not been introduced in S. Korea, and concerns about its safety have not been resolved, making it difficult to adopt the 4M HPMZ regimen recommended by the WHO

라. 단기 치료 처방

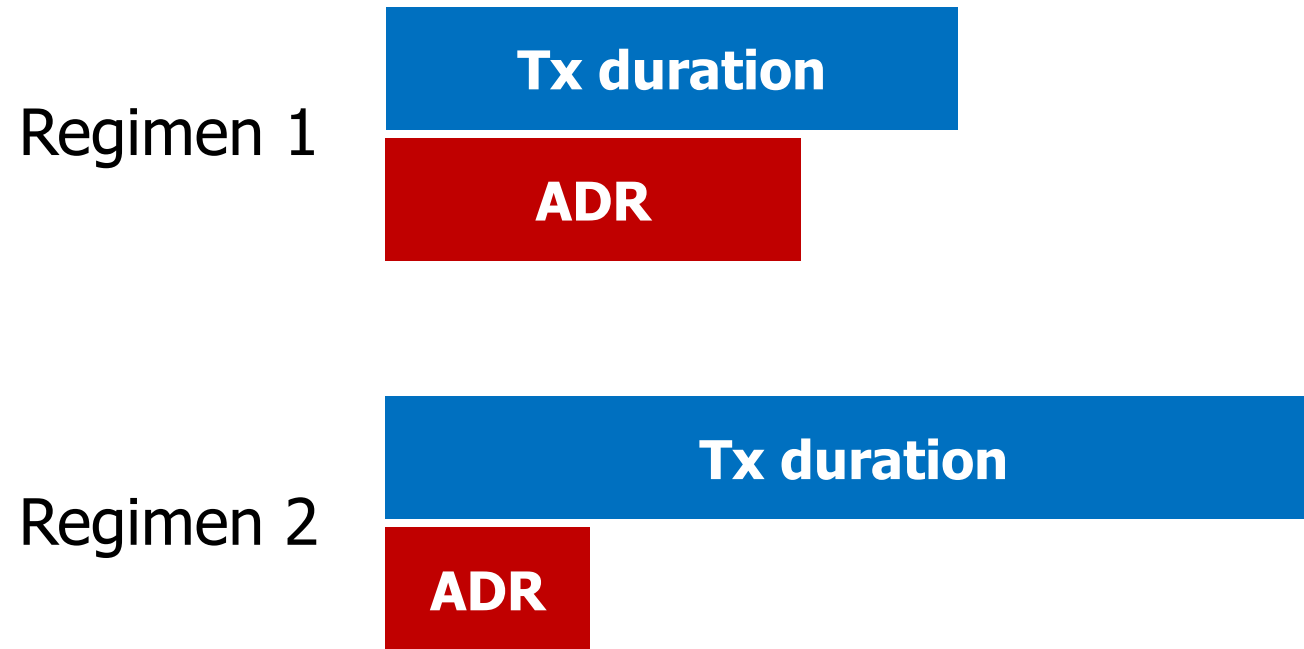
약제감수성 결핵 치료에 사용되는 리팜핀을 포함한 표준요법은 오랜 기간 동안 사용되어 효과와 안전성이 입증되었다. 하지만, 여러가지 항결핵제를 6개월 이상 장기간 복용해야 하기 때문에 치료 기간 중 발생하는 부작용과 비순응도와 같은 문제점들이 있다. 이를 극복하기 위해 6개월 표준요법과 새로운 4개월 단지요법을 비교하는 제3상 임상시험(REMoxTB, OFLOTUB, RIFAQUIN)이 과거에 진행이 되었으나, 4개월 단지요법들의 비열등성은 입증하지 못하였다.

하지만, 최근에는 폐결핵 환자(12세 이상의 청소년과 성인)를 대상으로 리파펜틴을 근간으로 한 4개월 단지요법의 효과와 안전성을 평가한 제3상 다기관 비열등성 무작위배정 임상시험인 Study 31/A5439의 결과가 발표되었다.⁸ 이 연구의 일차 목적은 무작위 배정 후 12개월 동안 결핵 완치였으며, 4개월 간 리파펜틴과 목시플록사신을 사용한 단기치료요법(2HPMZ/2HPM)이 6개월 표준요법과 비교하여 효과에 있어 열등하지 않음이 입증되었고, 사망률과 부작용 발생의 빈도는 유사하였다. 이에 따라 세계보건기구는 2022년 치료 지침에 4개월 단기치료요법을 조건부 권장사항으로 권고하였다.

리파펜틴은 리파마이신(rifamycin) 계통의 약물로 리팜핀과 항결핵 효과는 유사하다고 알려졌으나 반감기가 길어 주1회 복용이 가능한 약제이다. 국내에서는 2016년 잠복결핵감염 치료제로 도입하기 위한 임상연구가 시행되었으나, 리파펜틴에 의한 아나필락시스 사례가 보고되어 조기 종료되었다.⁹ 현재 국내에서는 리파펜틴이 도입되지 않았고 안전성에 대한 우려가 해소되지 않아 세계보건기구에서 권고한 4개월 단지요법을 수용하기 어렵다. 리파펜틴을 근간으로 하는 4개월 단지요법의 국내 수용을 위해서는 추가 연구와 검토가 필요하다.

Patient-centered outcome

If you were the TB patient, what would you choose?



Patient-centered outcome

Shorter TB treatment regimens should be safer as well

O. Rucsineanu,^{1,2} P. Agbassi,² R. Herrera,² M. Low,³ L. McKenna,^{2,4} J. Stillo,^{2,5} P. Winarni,² A. Acharya,⁶ A. H. Sari²

'Shorter' in terms of overall therapeutic duration is not always better, especially when the drugs used to shorten treatment may be associated with increased risk of toxicity or require more intensive monitoring to assess for possible toxicity.

TABLE 2 Additional considerations in treatment shortening trials

- Time spent engaging in the activities of treatment (such as monitoring, regimen adjustment, time spent feeling unwell);
- Time out of work or school, or unable to meet household or other responsibilities and their economic implications;
- Type of adverse events and qualitative experience of them (such as pain, reversibility, impact on other social roles);
- Predictability of adverse event, including predisposing risk factors;
- Preferences of person being treated;
- Factors driving loss to follow-up

Considerations for clinical trials

1. Surrogate marker

- Preclinical data ? / EBA ? / Time to SCC ? / 2M culture conversion ?

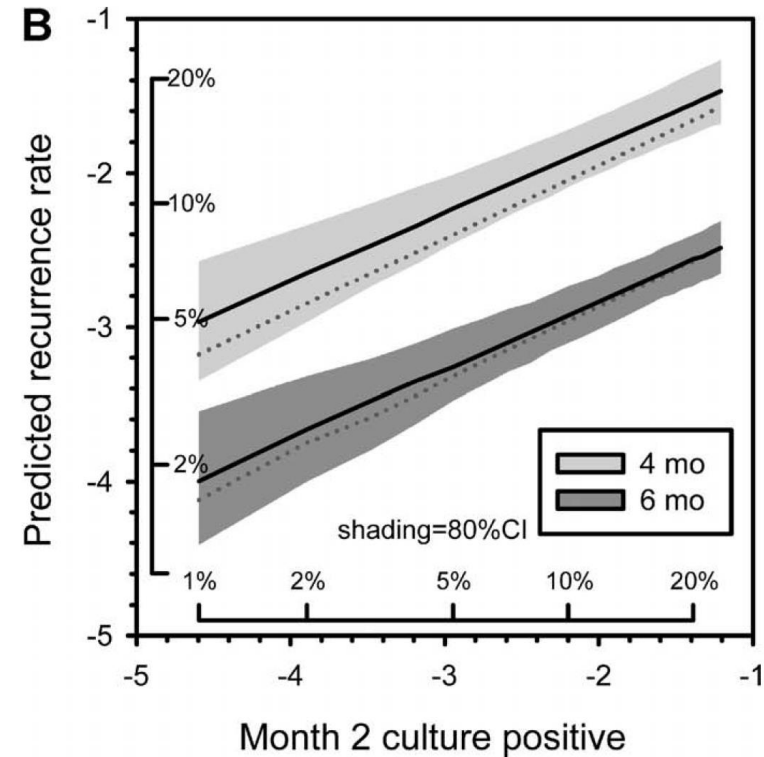
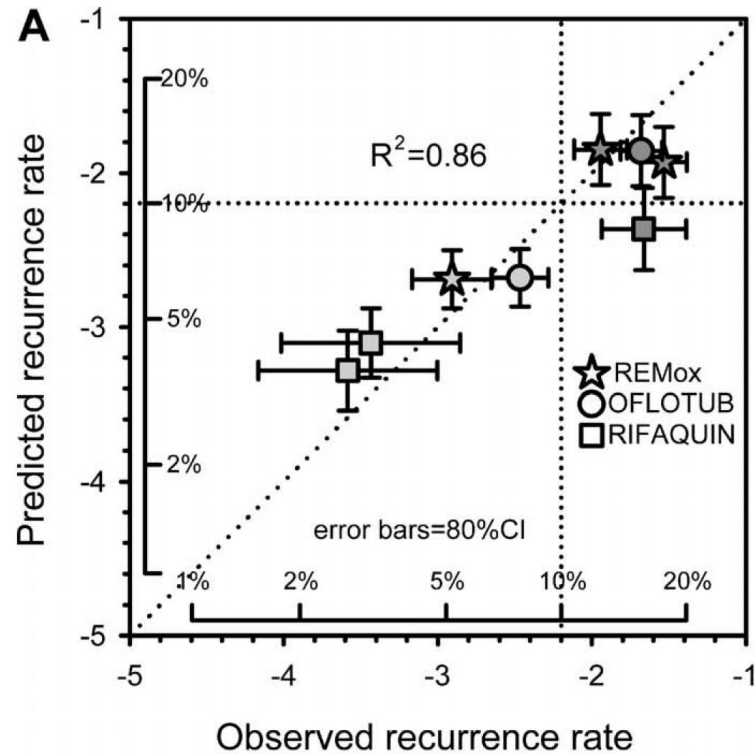
→ Insufficient for predicting “relapse-free cure” in phase 3 trials of shorter regimens

2. Inter-individual variation in PK/PD

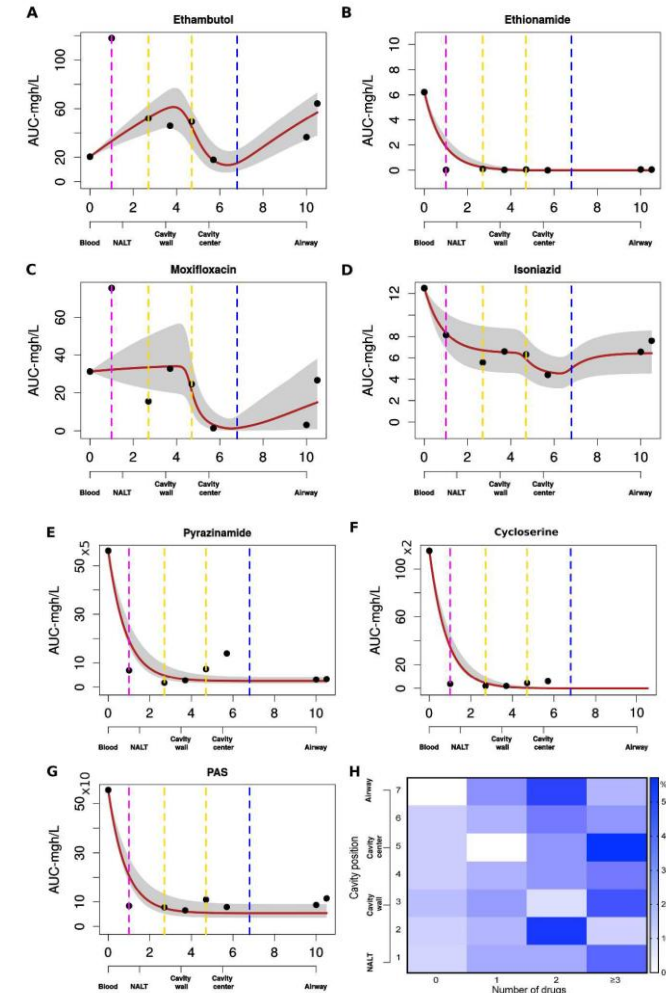
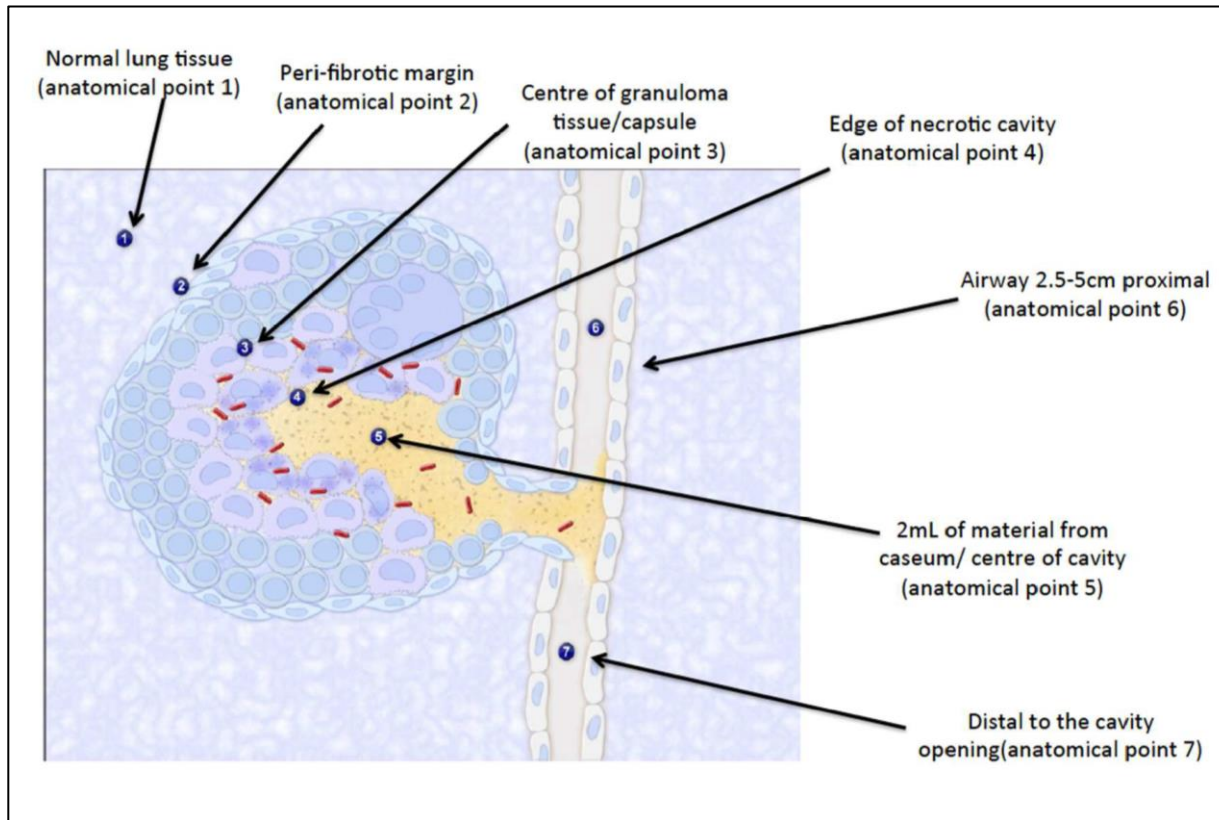
3. Drug absorption and metabolism in diverse microenvironmental conditions

4. Lack of accurate biomarkers to predict treatment response and optimal duration

Considerations for clinical trials



Considerations for clinical trials



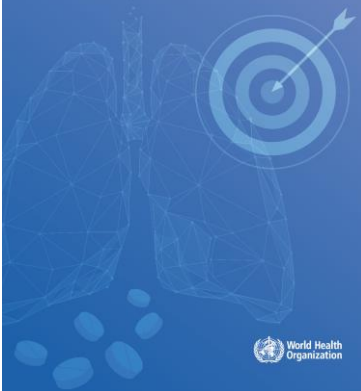


Table 3.3. Requirements for regimen characteristics for TRP for RS-TB

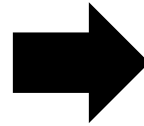
Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Indication and need for DST	The regimen is indicated for patients with active TB disease caused by <i>RS M. tuberculosis</i> strains.	The regimen is indicated for patients with active TB disease caused by <i>RS M. tuberculosis</i> strains, including the forms with monoresistance to any other medicine in the current HRZE combination – except rifampicin.	All TRPs are placed within the context of recommended susceptibility testing for rifampicin at time of TB diagnosis, using WHO-recommended rapid molecular tests (2).
Efficacy	The regimen has efficacy <i>as good as</i> the SOC of RS-TB.	The regimen has efficacy <i>better than</i> the SOC of RS-TB.	The current 6-month standard regimen has an efficacy for the treatment of DS-TB of about 95% under trial conditions (47)
Duration	3–4 months	≤2 months	The <i>minimum target</i> is selected as an improvement on the current shorter treatment being recommended by WHO (i.e. the 2HPMZ/2HPM regimen), and the <i>optimal target</i> is aspirational, as suggested in a recent publication on the potential use of a 2-month regimen strategy (48).
Safety, monitoring and tolerability	The incidence and severity of adverse events should be <i>equal to or lower than</i> with the SOC. No more than monthly clinical and laboratory monitoring for drug toxicity needed, except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes).	The incidence and severity of adverse events should be <i>lower than</i> with the SOC. No active clinical monitoring and no laboratory monitoring for drug toxicity needed, except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes).	The current standard 6-month regimen for TB has known safety issues with the component drugs, most notably hepatotoxicity (49). The proportion of patients experiencing Grade 3 or 4 TEAEs when treated with HRZE was 19–25% in the 6-month HRZE control arms of the REMox trial (50), the Study 31 (2HPMZ/2HPM) (51), and the PaMZ Phase 2B trial (52). Among participants receiving the 4-month isoniazid, rifapentine, moxifloxacin and pyrazinamide regimen in the 2HPMZ/2HPM trial, 19% experienced Grade 3 or higher adverse events (51).

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
	<i>Tolerability</i> should be <i>equal to or better than</i> with the SOC.	<i>Tolerability</i> should be <i>better than</i> with the SOC.	Lastly, data from the recently conducted SimpliciTb trial showed similar proportions of Grade ≥3 TEAEs in the 6-month HRZE arm and in the 4-month BPamZ arm (40% and 32%, respectively) but the proportion of TEAEs leading to treatment discontinuation was higher in the 4BPamZ arm than in the 6HRZE arm (11% vs 2%), mainly due to hepatotoxicity that was probably caused by the pretomanid/ pyrazinamide association.
Propensity to develop resistance	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is <i>equal to or lower than</i> with the SOC.	Potential for the acquisition or amplification of resistance during or after treatment to one or more drugs in the regimen is <i>lower than</i> with the SOC.	Drug resistance observed during regimen development should be studied intensively and expertise should be made available by developers for DST development and population-based surveillance of genomic mutations. In particular, regimen developers should transfer high-quality data and technology on active pharmaceutical ingredients (e.g. MIC distribution or mutation sites of resistant strains) to facilitate the development of suitable DST to the novel regimen components. Where possible, this should take place early in the clinical development pathway (see also Section 5.1). One study found that among patients receiving HRZE with strong patient support, 2.1% acquired resistance during or after treatment to one or more drugs in the regimen (53), whereas another study found no acquisition of drug resistance (0/768) (51).
Pill burden	Not greater than SOC (6-months HRZE) individual drugs.	1 pill per day for adult dose.	A high pill burden affects tolerability and treatment adherence, so an FDC formulation is highly desirable. Additional considerations include–, for example, the size of pills and the availability of scored, water-dispersible forms for paediatric use. Initial formulations studied in explanatory trials may not meet these requirements; however, developers should have a viable pathway to reduce pill burden for successful regimens. Standalone drugs should also be available in case of adverse effects due to one of the component drugs leading to treatment discontinuation.

We hope...



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