Kortere behandlingsregimer ved MDR-TB

TB og Einar Heldal-dagen, FHI
7.sept 2023

Synne Jenum

Ph.D, overlege

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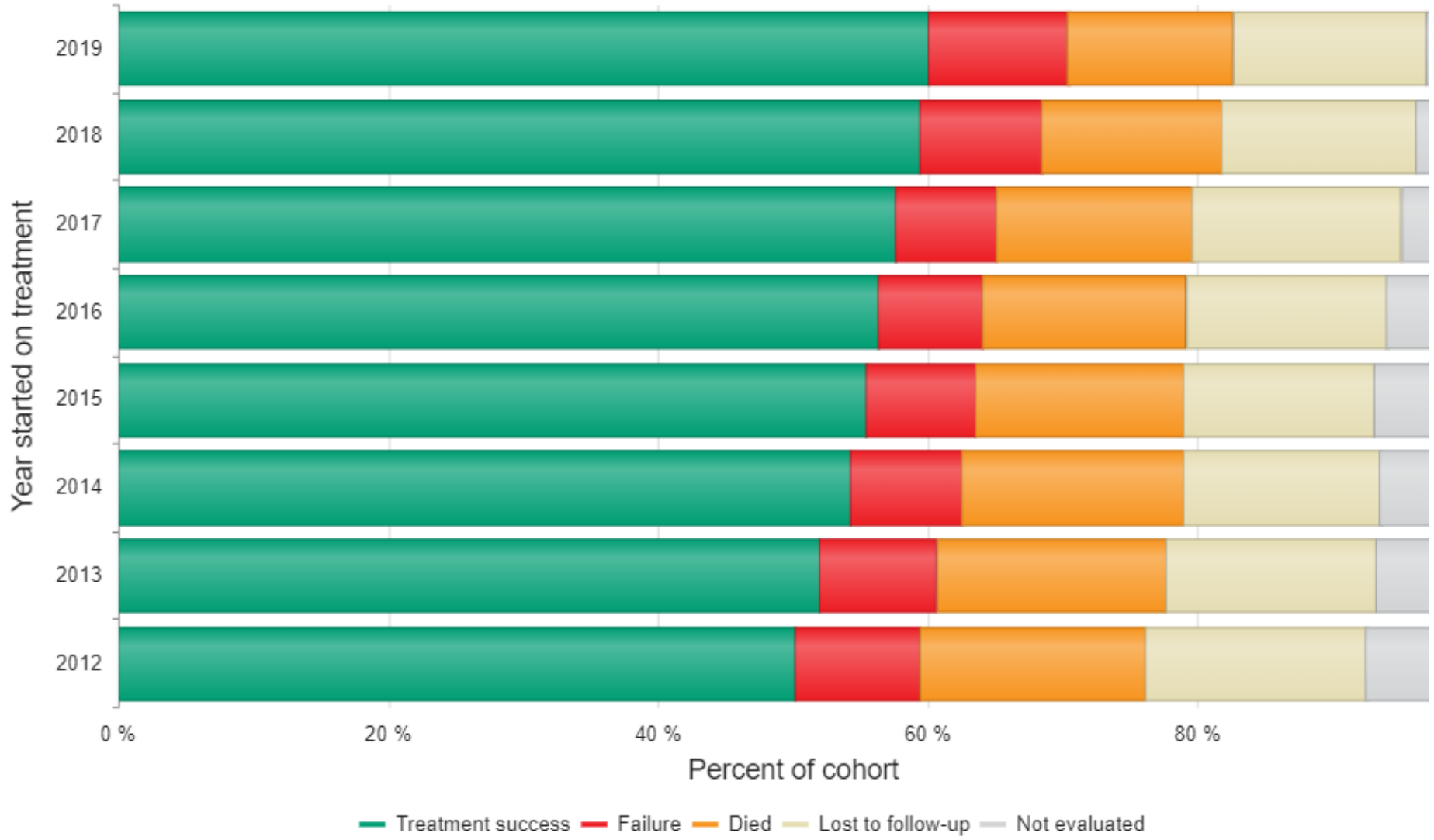
Oslo Universitetssykehus.

WHO 2019

Groups & steps	Medicine		
Group A: Include all three medicines **3 medikamenter**	levofloxacin *OR*	Lfx	Artralgi, QTc, GI, hodepine.
	moxifloxacin	Mfx	
	bedaquiline[2,3]	Bdq	QTc, GI, hodepine.
	linezolid[4]	Lzd	Benmarg, nevropathi.
Group B: Add one or both medicines **1-2 medikamenter**	clofazimine	Cfz	QTc, hud.
	cycloserine *OR*	Cs	Nevropsykiatriske, hodepine, nevropathi
	terizidone	Trd	
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E	
	delamanid[3,5]	Dlm	
	pyrazinamide[6]	Z	
	imipenem–cilastatin *OR*	Ipm–Cln	
	meropenem[7]	Mpm	
	amikacin	Am	Hørsel, nyrer
	(*OR* streptomycin)[8]	(S)	
+ pyridoxin høydose	ethionamide *OR*	Eto	Kvalme, nevropathi.
	prothionamide[9]	Pto	
	p-aminosalicylic acid[9]	PAS	

Behandle tom 12 mndr fra 1. dyrkningsneg luftveisprøve

Fig. 3.4.7 Treatment outcomes for people diagnosed with MDR/RR-TB globally, 2012–2019

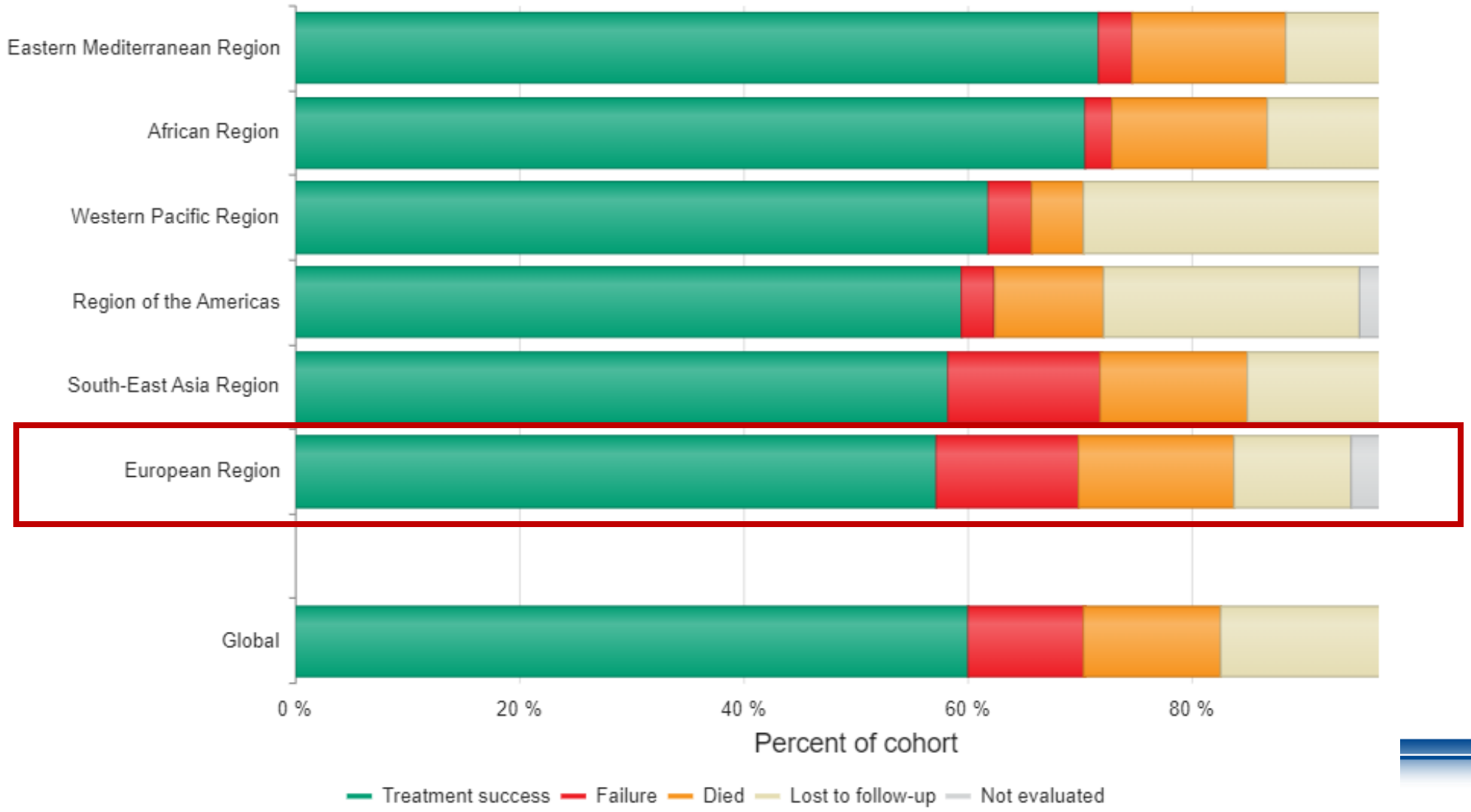


WHO. Global TB Report 2022

Treatment failure include toxicity-related drug replacement (≥2 drugs).

WHO 2013 Definitions and reporting framwork for TB ISBN 978 92 4 150534 5

Fig. 3.4.8 Treatment outcomes for people diagnosed with MDR/RR-TB who were started on treatment in 2019, WHO regions and globally



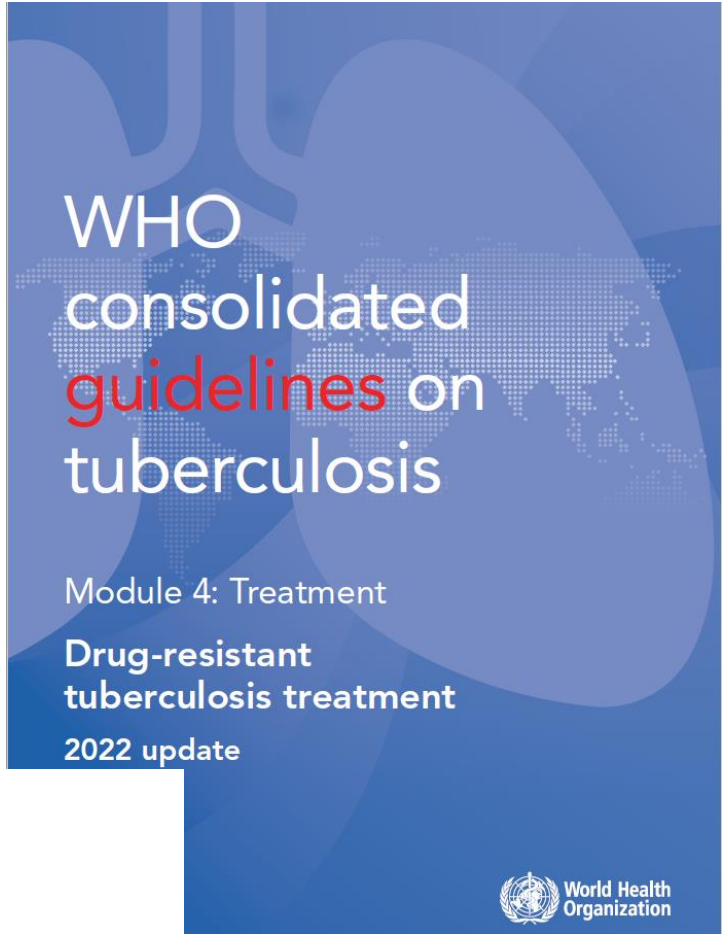
WHO. Global TB Report 2022

Kurativ behandling ved MDR-TB

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)

1.1 WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients.

(Conditional recommendation, very low certainty of evidence)



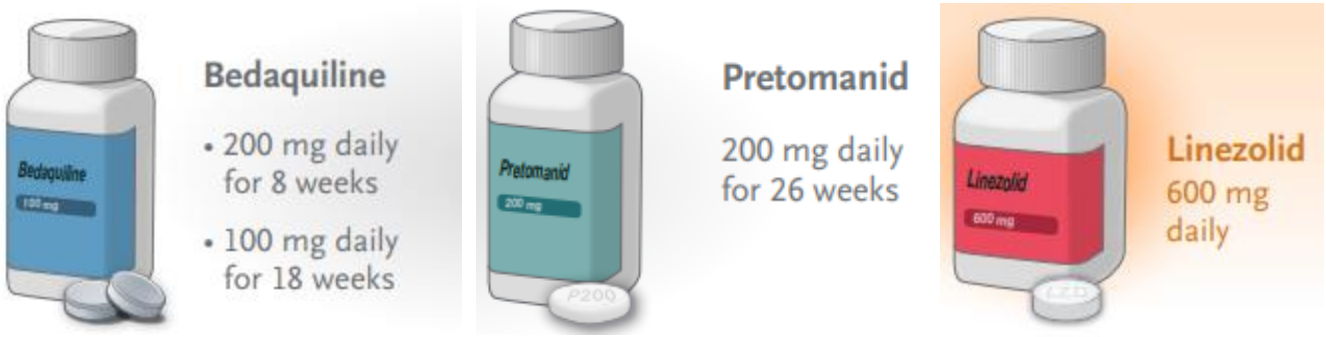
World Health Organization

Rapid communication:
Key changes to the treatment of drug-resistant tuberculosis

May 2022

Hva er nytt?

BPaL(M) -regimet



Evt + moxifloxacin/levofloxacin

Kortere behandling

The NExT Study. Esmail A et al. AJRCCM 2022 May 15;205(10):1214-1227

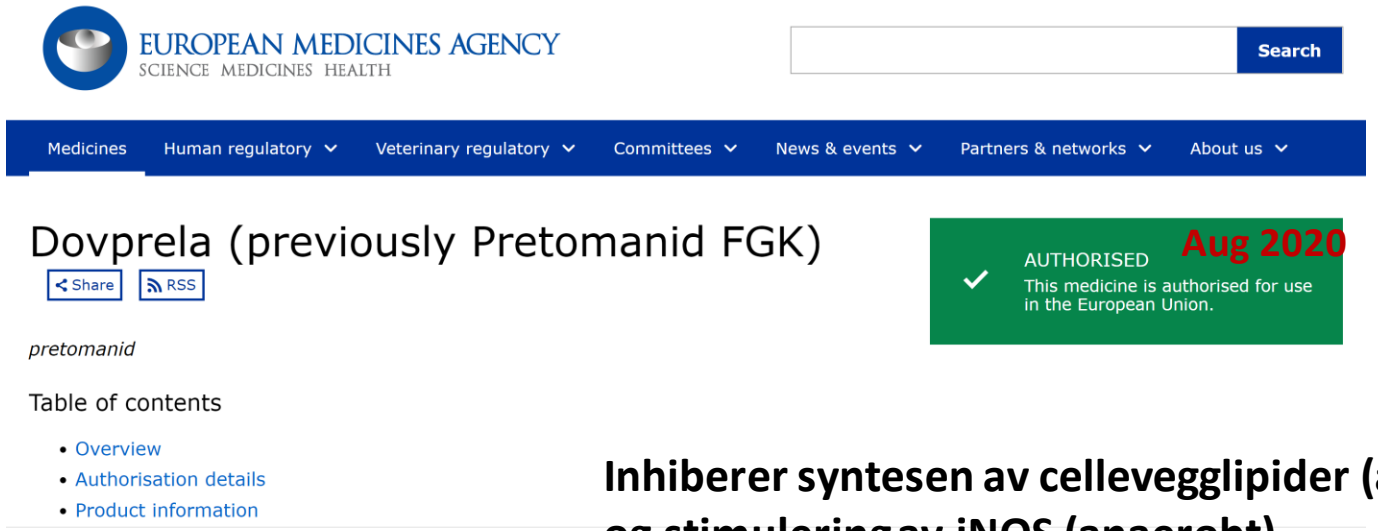
TB-PRACTECAL. Nyang'wa. CROI 2022. Abstr 79

The ZeNix Trial. Conradie F et al. NEJM 2022 Sept 1;387(9):810-823

The STREAM stage 1. Goodall RL et al. Lancet 2022;400:1858-68

SimpliTB. Preliminary ECCMID 2023

Pretomanid – nytt medikament



Inhiberer syntesen av cellevegglipider (aerobt) og stimulering av iNOS (anaerobt)

Pretomanid 28 tbl a 200 mg 44 000 NOK.
Blå resept §4
Leveringstid ca 3 uker

Inneholder laktose.
BPaL: GI-sympt, transaminaser, nevropathi, benmargsdepr
Obs interaksjoner:

- Metaboliseres via CYP3A4
- Inhibierer BCRP, OATP1B3 og P-gp

6-month all-oral regimen for MDR-TB. (NexT)

Esmail A et al., AJRCCM 2022 May 15;205(10):1214-1227.

Injectable

Dec 2014 – Sept 2016

WHO Pre-2016. 18-20 months
Kanamycin (inj)
Moxifloxacin
Clofazimin
Pyrazimamid
Terizidone/Ethionamid/INH high-dose

Dec 2016 – Sept 2018

WHO Post-2016. 9-11 months
Kanamycin (inj)
Moxifloxacin/Levofloxacin
Clofazimin
Pyrazimamid
Ethambutol
Terizidone/Ethio

Open-label RCT
South Africa

111 randomized
mITT (44:49)
per-protocol (43:44)

VS

Outcome at 24 m from inclusion

All-oral

NexT
Gr A - Bedaquilin
Gr A - Linezolid (600 mg)
Gr A - Levofloxacin
Gr C – Pyrazimamid
Terizidone (B)/Ethionamid (C)/ INH high-dose (C)

Termination Nov 2018

According to WHO 2019 (STREAM I), BDQ included in SOC in South-Africa

Oslo universitetssykehus

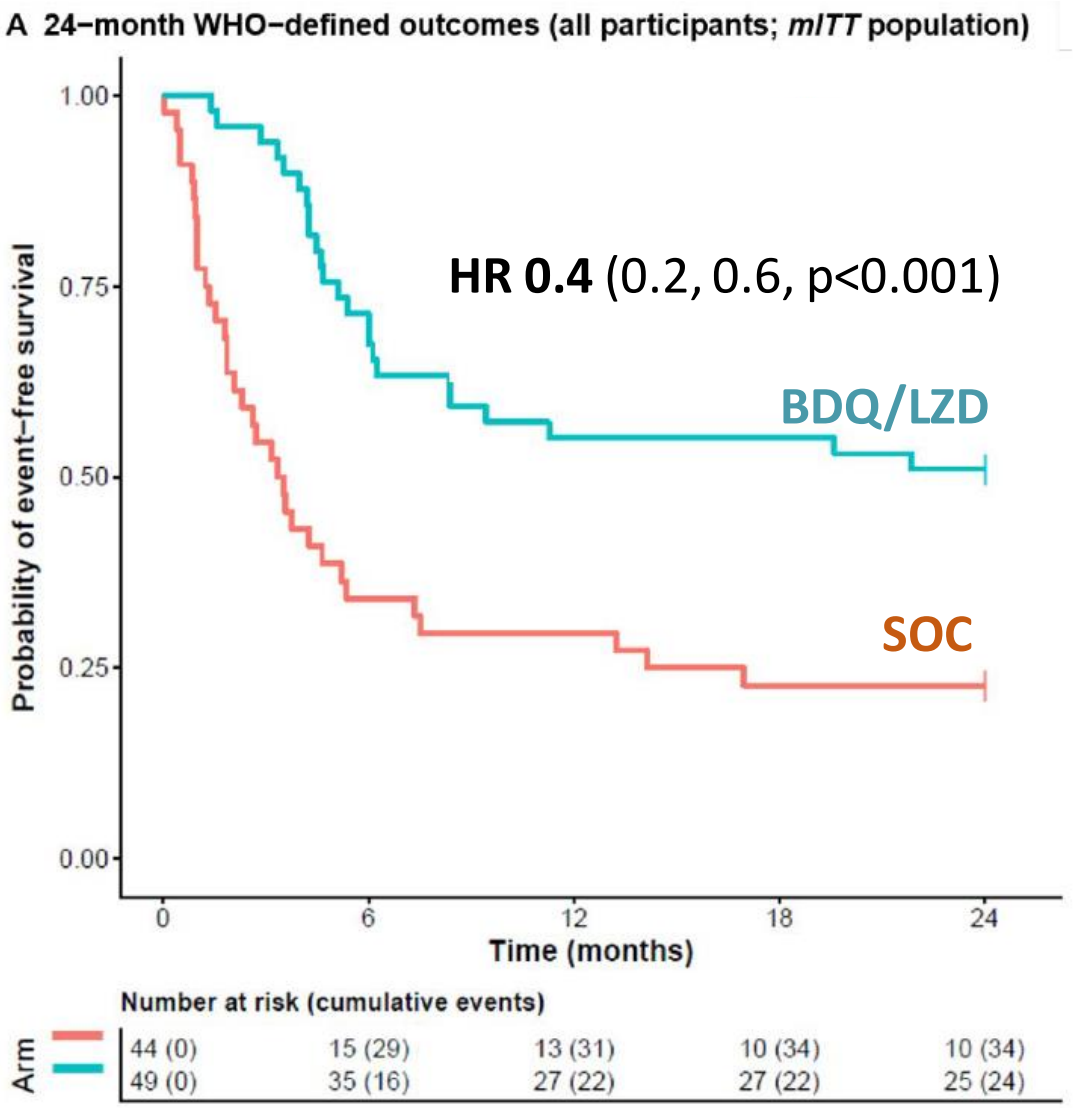
Slide: Synne Jenum 07.09.23

6-month all-oral regimen for MDR-TB. (NexT)

Esmail A et al., AJRCCM 2022 May 15;205(10):1214-1227

67% male
50% smokers
55% HIV co-infection
52% cavitary disease

Modified Intention-To-Treat, 24 months	SOC	BDQ/LZD	RR ratio (95% CI)
WHO Favourable outcome Cured+Treatment completion AND no unfavorable outcome	**10/44 (22.7%)**	**25/49 (51.0%)**	**2.2 (1.2, 4.1)**
Patient-centered outcome ≥12 m relapse-free cure AND no unfavorable outcome	30/44 (68.2%)	33/49 (67.4%)	1.0 (0.8, 1.3)



Slide: Synne Jenum 07.09.23

6-month all oral (TB-PRACTECAL)

Nyang'wa. CROI 2022. Abstr 79

BPaL= Bedaquiline
Pretomanid
Linezolid

Open-label RCT

Belarus, Uzbekistan, South Africa

23% HIV-infection
30% cavitary disease
28% FQ-resistance

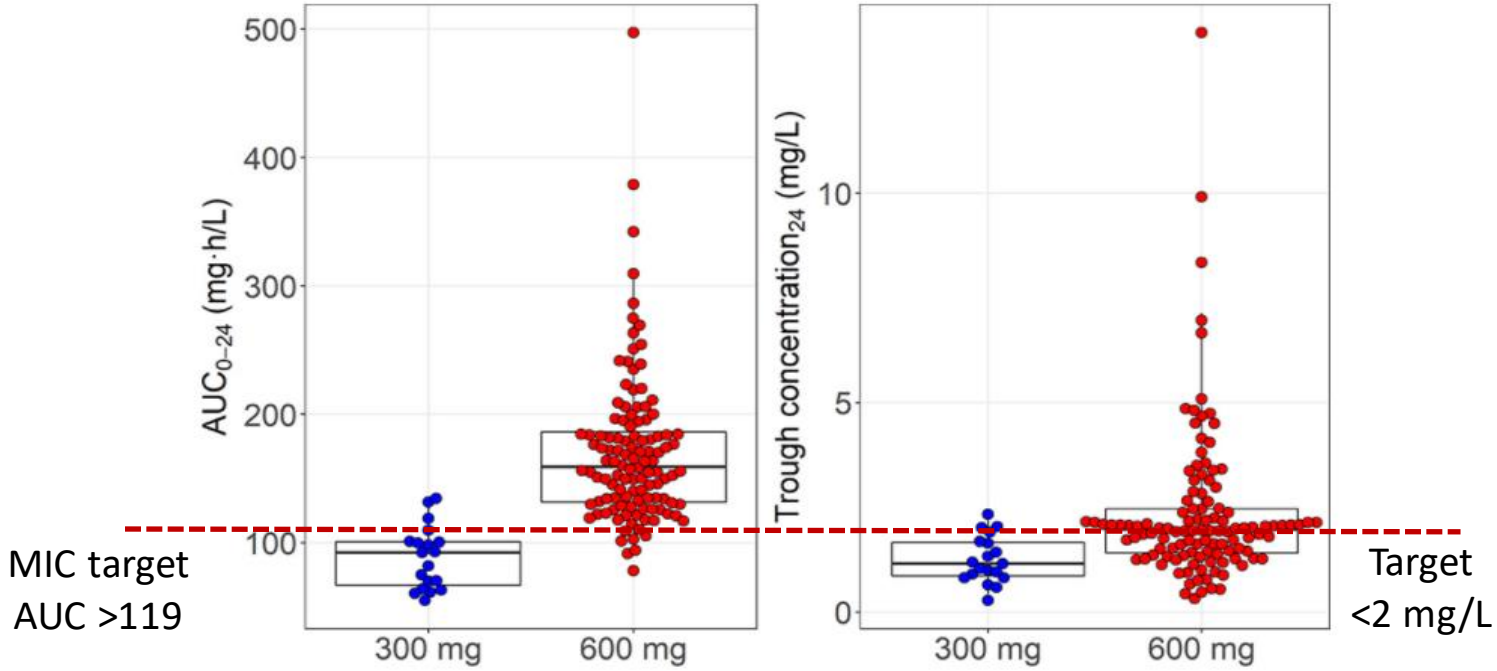
Primary Outcomes mITT n (%)	BPaL (n = 60)	BPaL + Clofazimine (n = 64)	BPaL + Moxifloxacin (n = 62)	WHO SoC 36-96 wk (n = 66)
Unfavorable outcomes	**14 (23.3)**	**12 (18.8)**	**7 (11.3)**	**32 (48.5)**
Death	0	1 (1.6)	0	2 (3.0)
▪ Early discontinuation	8 (13.3)	6 (9.4)	5 (8.1)	28 (42.4)
▪ Treatment failure	0	1 (1.6)	0	0
▪ Lost to follow-up	3 (5.0)	3 (4.7)	2 (3.2)	2 (3.0)
▪ Recurrence	3 (5.0)	1 (1.6)	0	0
P value for noninferiority	<.0001	<.0001	<.0001	
***P* value for superiority**	**.001**	**<.0001**	**<.0001**	
Risk ratio (98.3% CI)	0.48 (-∞ to 0.85)	0.39 (-∞ to 0.71)	0.23 (-∞ to 0.52)	
SAE or new grade 3 AE	**15 (21.7)**	**23 (31.9)**	**14 (19.4)**	**43 (58.9)**

Adapted from: Slide credit: clinicaloptions.com

«BPaL» 6 months Nix-TB
Trial XDR/MDR (65%/17%)
Single-arm
Bedaquiline
Pretomanid
Linezolid (1200mg)

90% Cure
81% polynevropathi
48% myelosuppression
Condradie F et al., NEJM 2020;382:893-902

Linezolid works but at a cost!



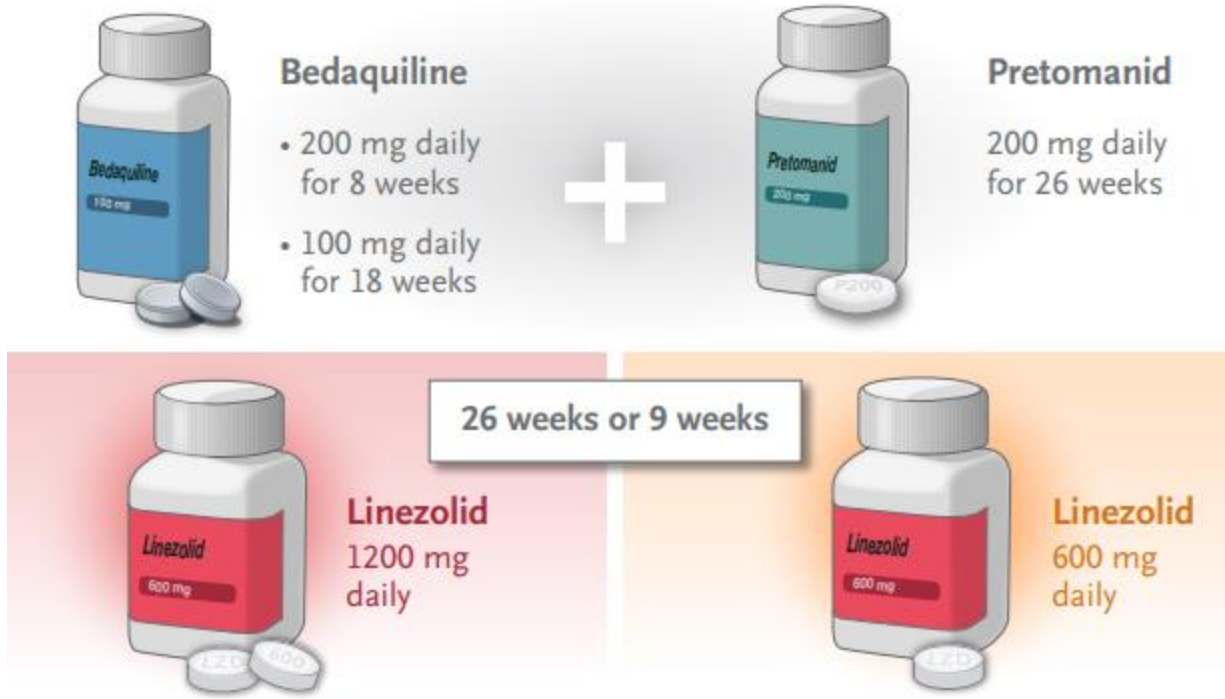
Abdelwahab MT et al Antimicrob Agents Chemother. 2021;17:65(12):e0138121) 124

BPaL regimens for Drug-Resistant TB

Conradie et al., NEJM 2022 Sept 1;387(9):810-823

67% male
36% smokers
20% HIV co-infection
62% cavitary disease
41% XDR-TB
47% pre-XDR

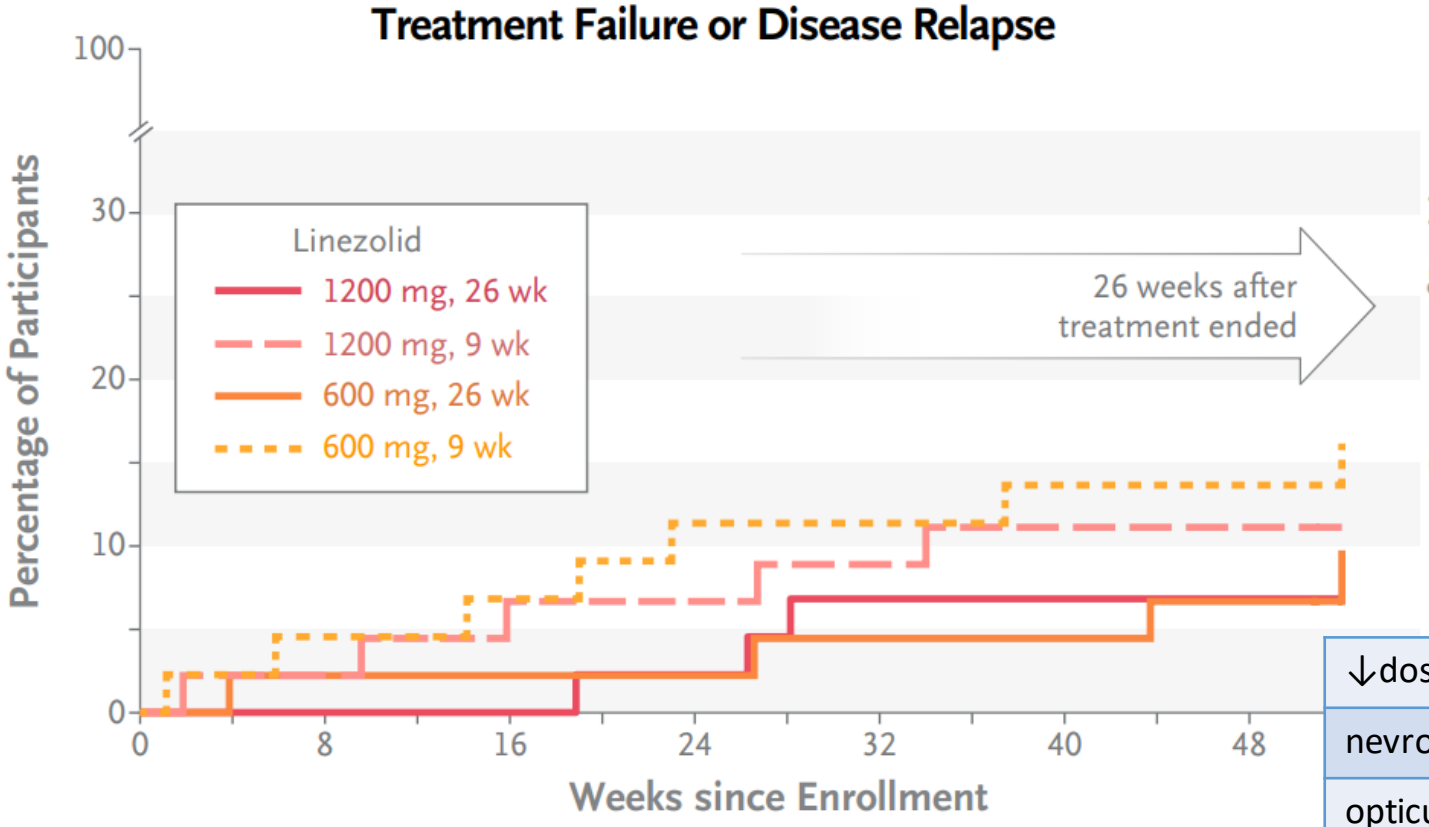
36% South Africa
64% Georgia, Moldova, Russia

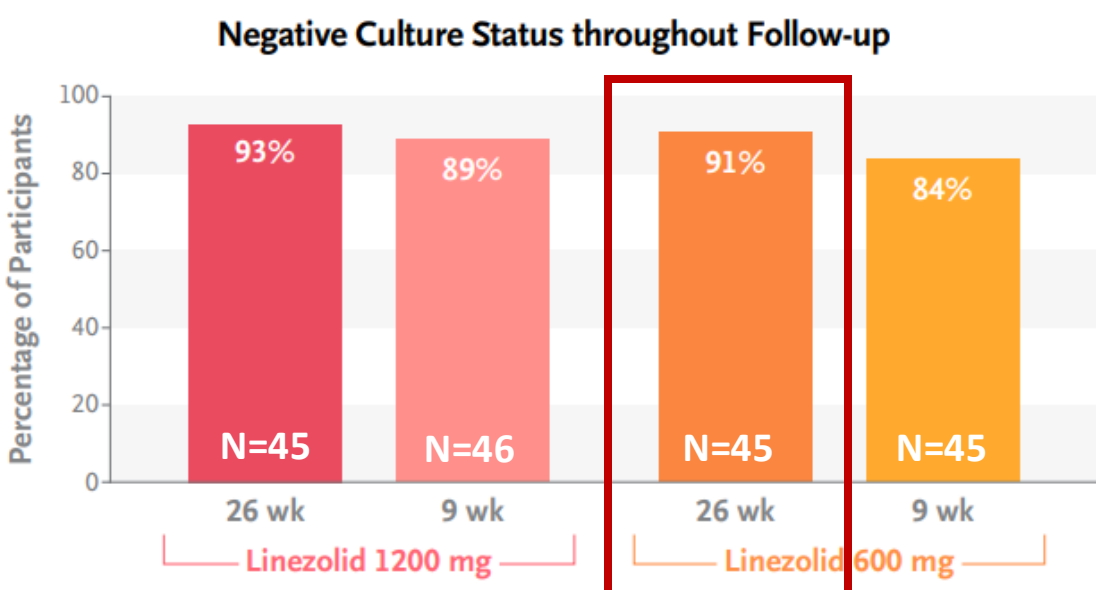


BPaL	BPaL	BPaL	BPaL
Lz 1200 mg, 26 wk	Lz 1200 mg, 9 wk	Lz 600 mg, 26 wk	Lz 600 mg, 9 wk
(n = 45)	(n = 46)	(n = 45)	(n = 45)

BPaL regimens for Drug-Resistant TB (ZeNix Trial)

Conradie et al., NEJM 2022 Sept 1;387(9):810-823

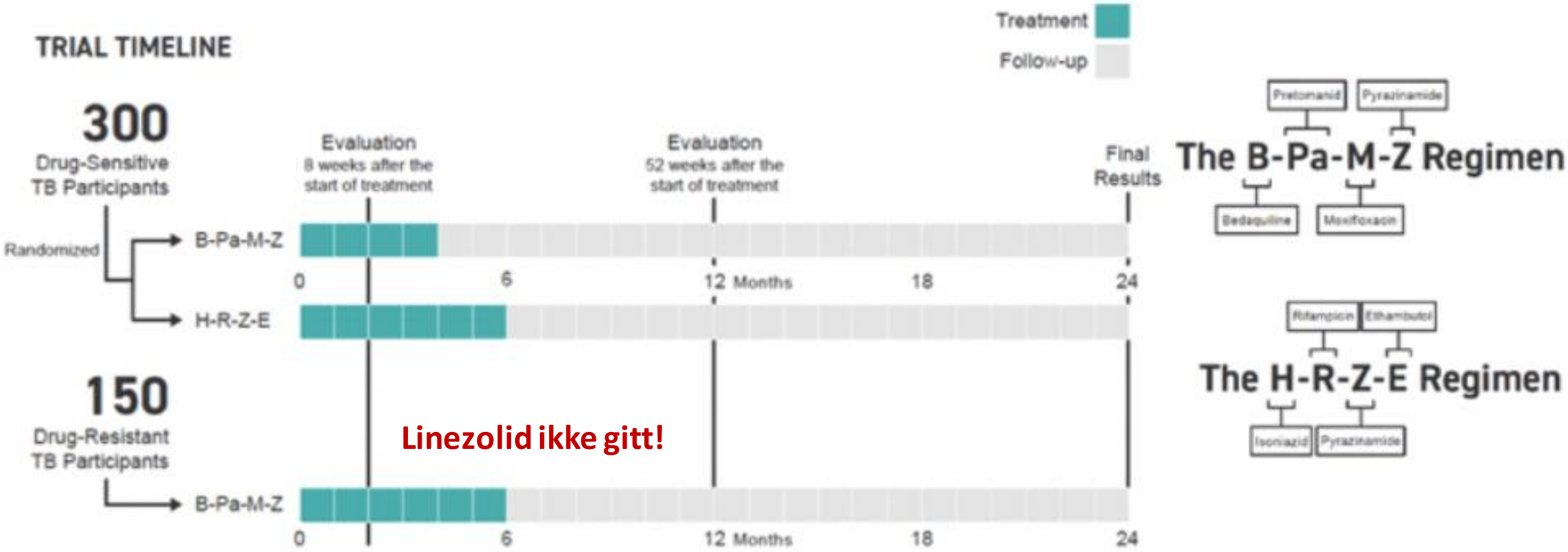




↓dose/stop	50%	30%	13%	13%
nevropathy ≤3	38%	24%	24%	-
opticusnevritis	9%	-	-	-
↓bonemarrow	22%	15%	2%	13%

SimpliciTB Study Design

SIMPLICITB



BPaMZ Dosing: Bedaquiline (B) at a dose of 200 mg daily for eight weeks followed by 100 mg daily to end of treatment, together with daily pretomanid (Pa) 200mg, moxifloxacin (M) 400mg and pyrazinamide (Z) 1500mg

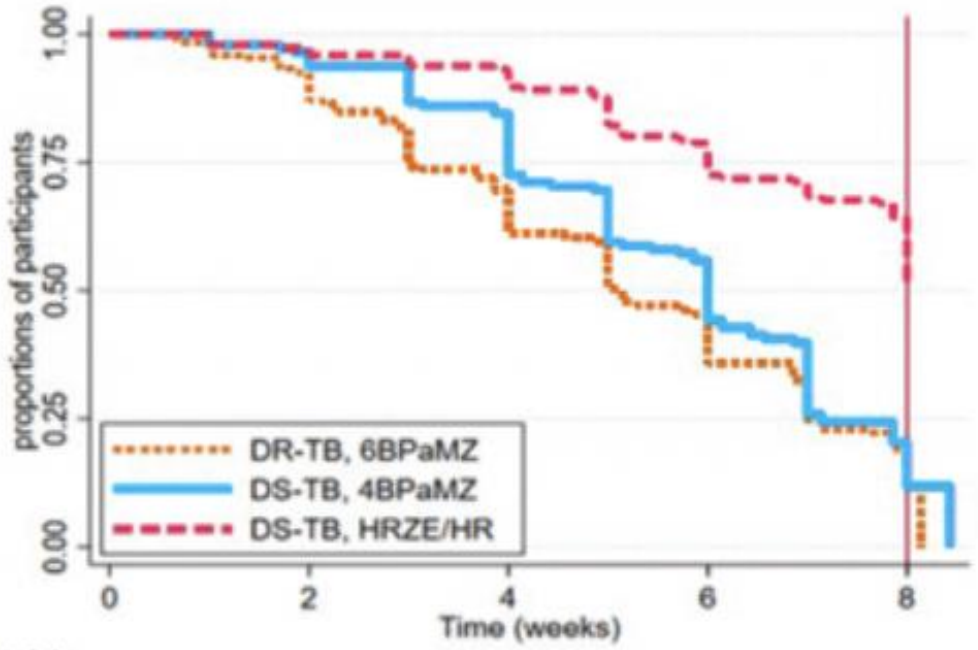
SimpliciTB Participant Baseline Characteristics

MDR-TB

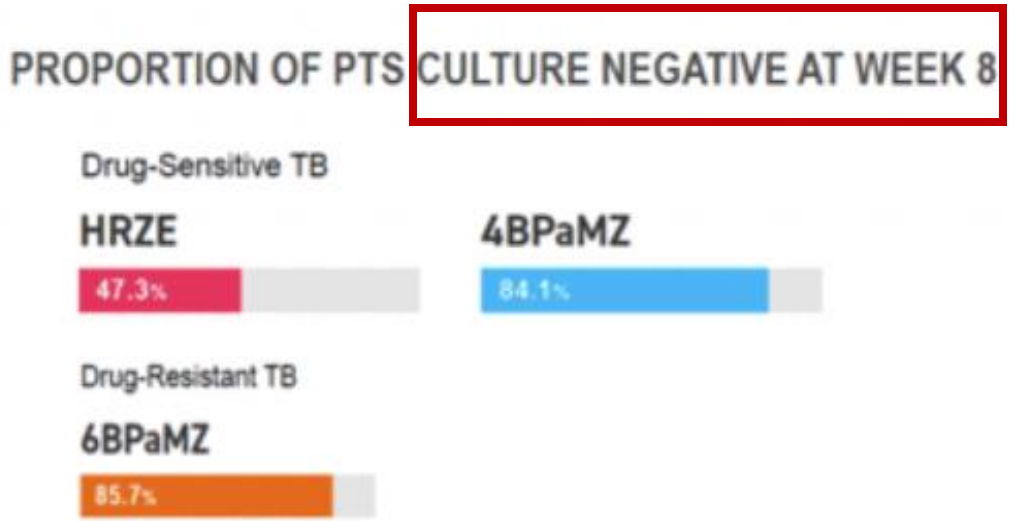
Parameter		2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=152) n (%)
Median Age (years) - IQR		34.0 (26.0, 46.0)	35.0 (25.0, 45.0)	35.0 (26.0, 47.0)
Male sex – n (%)		118 (77.1%)	112 (74.7%)	94 (61.8%)
Race	White	25 (16.3%)	29 (19.3%)	31 (20.4%)
	Black	119 (77.8%)	108 (72.0%)	82 (54.0%)
	Mixed	6 (3.9%)	5 (3.3%)	26 (17.1%)
	Asian	3 (2.0%)	8 (5.3%)	13 (8.6%)
HIV positive – n (%)		27 (17.6%)	25 (16.7%)	35 (23.0%)
Median BMI - (kg/m²)		18.7 (17.2, 20.4)	19.3 (17.6, 21.4)	19.3 (17.1, 22.2)
WHO Smear grade				
	1+	28 (18.3%)	20 (13.3%)	37 (24.3%)
	2+	53 (34.6%)	49 (32.7%)	47 (30.9%)
	3+	72 (47.1%)	81 (54.0%)	67 (44.1%)
Median time to positive sputum culture at baseline (IQR)		5.0 (4.2, 6.5)	4.6 (3.9, 6.2)	6.2 (4.7, 8.9)
Cavities in chest XR				
	Absent	37 (24.2%)	31 (20.7%)	31 (20.4%)
	Unilateral	76 (49.7%)	75 (50.0%)	70 (46.0%)
	Bilateral	40 (26.1%)	44 (29.3%)	50 (32.9%)

Primary Efficacy Endpoint
Time To Culture Negative Status By 8 Weeks (MITT)

SIMPLICITB

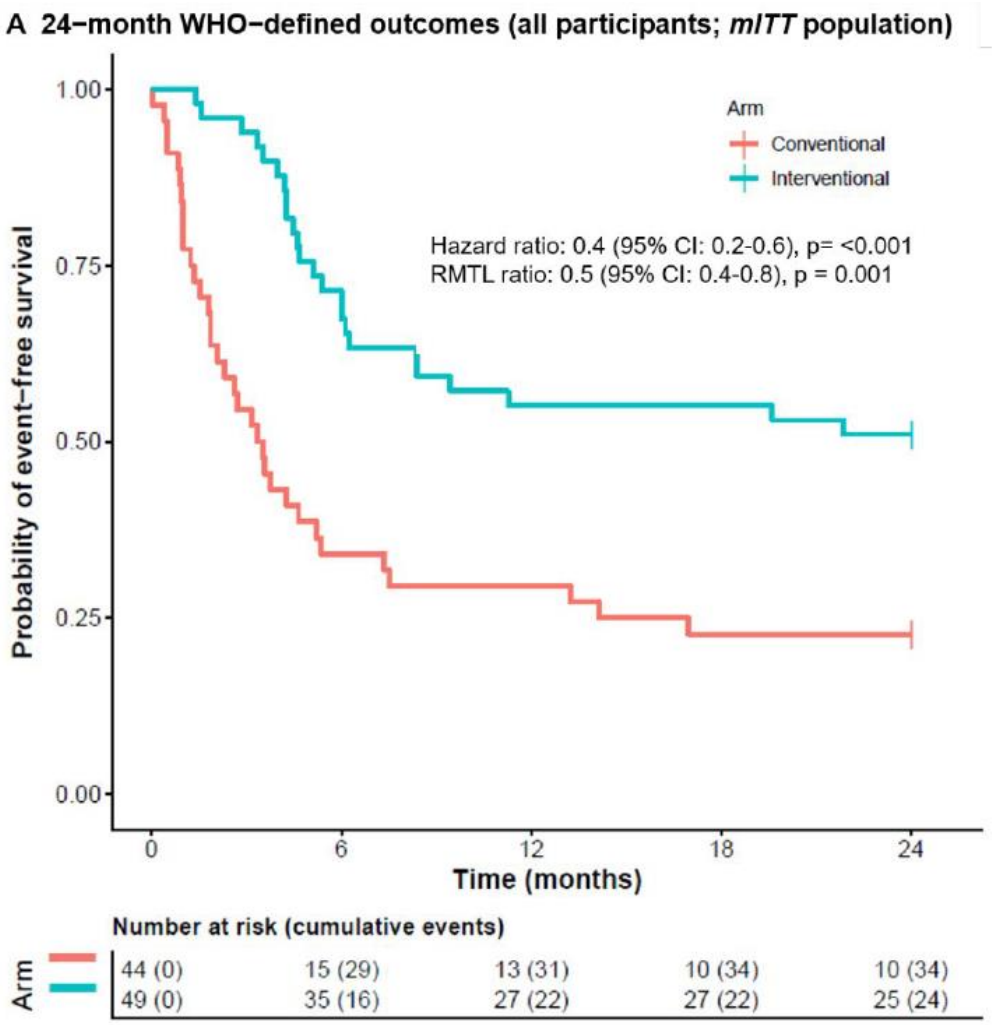


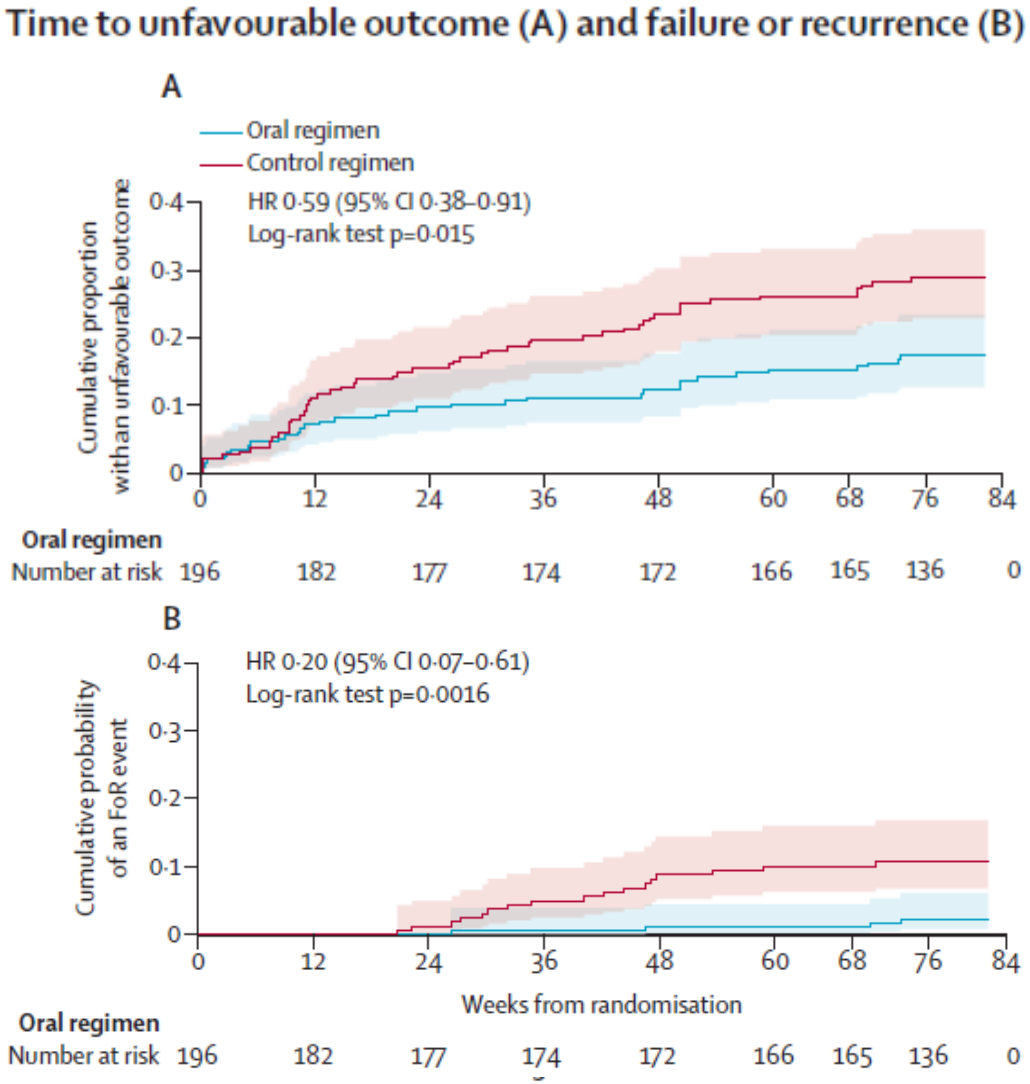
Number at risk					
DR-TB, 6BPaMZ	133	122	90	67	24
DS-TB, 4BPaMZ	145	139	119	77	26
DS-TB, HRZE/HR	148	143	136	114	93



Dersom BPaL(M) IKKE kan brukes

Kortere behandlingstid er OK uansett!





The NExT Study
Esmail A et al. AJRCCM 2022 May 15;205(10):1214-1227

STREAM stage 2
Goodall RL et al. Lancet 2022;400:1858-68

Smittsomhet og isolasjon ved MDR-TB

Argument for lenger isolasjonstid av MDR-TB 2 ting:

1) Medisinene vi har tilgjengelige er **mindre effektive**

2) Smitte har **større konsekvens**.

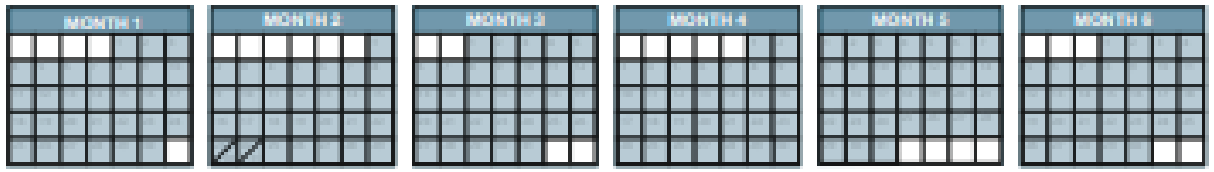
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Paton NI et al. DOI: 10.1056/NEJMoa2212537

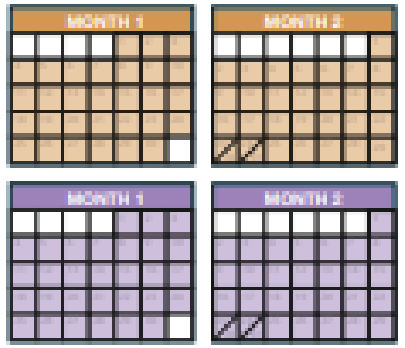
Standard Treatment (24 Wk)



Pyrazinamide and ethambutol

Rifampin and isoniazid

Strategy Groups Included in the Noninferiority Analysis



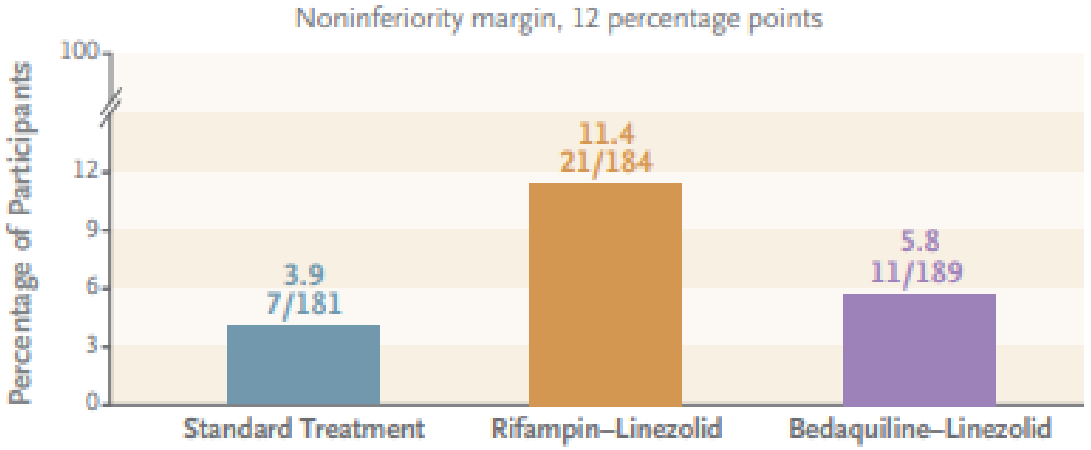
Rifampin and linezolid

Bedaquiline and linezolid

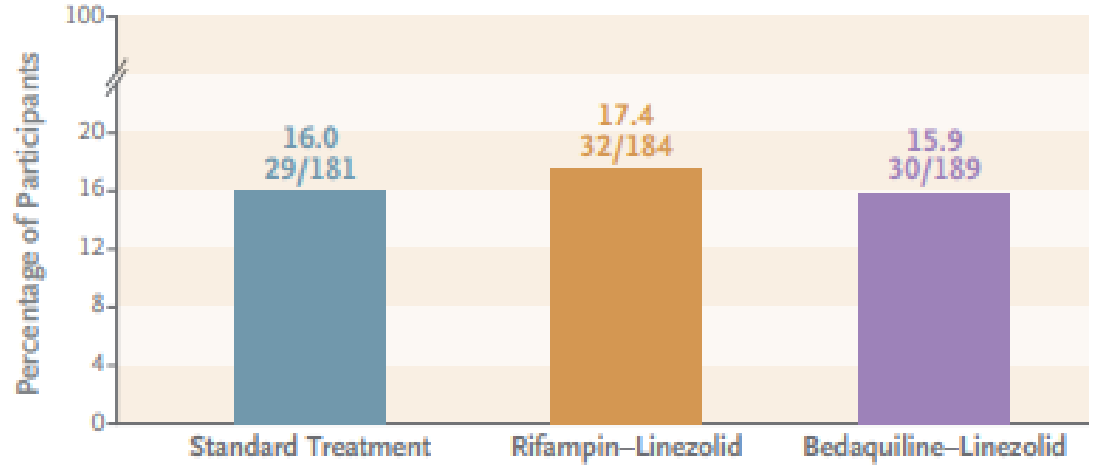
Extended treatment for persistent disease, post-treatment monitoring, and retreatment for relapse

Isoniazid, pyrazinamide, and ethambutol

Death, Ongoing Treatment, or Active Disease



Grade 3 or 4 Adverse Events



Takk for innsatsen

Einar Heldal