New Drugs, New Regimens, Drug Trials

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17 October 2018

Overview

- TB treatment clinical trials: treatment shortening
  - Historical trials (1970s-1980s)
  - Recent and ongoing drug sensitive TB (DS-TB) trials
  - Recent and ongoing multidrug-resistant TB (MDR-TB) trials
- Future trials: new paradigm for evaluating novel drugs and drug combinations – NexGen EBA

Historical TB Treatment Shortening Trials

- Shortening TB treatment duration has been a major goal of TB since effective antibiotic therapy was identified
  - From 1950s to 1980s, British Medical Research Council (BMRC) successfully conducted multiple trials to reduce treatment duration from 24 to 6 months, maintaining relapse rates 1-2%
  - In 1970s-1980s, attempts to reduce duration further to 4 or 3 months failed, with relapse rate increasing to about 12% for 4-mo treatment
  - 6 months became the standard treatment duration for DS-TB

Historical TB Treatment Shortening Trials

Table III. Bacteriological relapse rates in smear- and culture positive disease: highly effective six-month regimens with isoniazid and rifampicin (HR) throughout

Study	*Regimen**	*Follow-up* (months)	*Patients assessed*	*Bacterio-logical relapses*	*95% confidence limits*
East African/BMRC (current)	2SHRZ/HRZ	24	40	0	0.3–2.4
	2SHRZ/HR	24	40	1 (2%)	
		6	115	1 (1%)	
Singapore/BMRC (1981)	2SHRZ/HRZ	24	78	0	
	2SHRZ/HR		80	2 (2%)	
Second British Thoracic Association Study (1981) (unpublished data)	2SHRZ/HR	9	69	0	
Second British Thoracic Association Study (1981) (unpublished data)	2EHRZ/HR	12	79	1 (1%)	0.03–7
Zierski (1981)†	2SHRZ/H_2R_2	18	84	0	0–4
Hong Kong/BMRC (1981)	$SHRZE_3$	12	150	1 (1%)	0.06–2
	$SHRZ_3$		150	2 (1%)	
	$EHRZ_3$		164	4 (2%)	
	EHRZ		161	1 (1%)	
Eule (1981)†	$SHRZ_2$	6	61	0	0–6

* For definitions of regimens see Tables I and II. For intermittent regimens the number of doses a week is shown by the suffix number.

† Personal communication.

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
S = streptomycin

Fox W. Br J Dis Chest 1981; 75:331.

Historical TB Treatment Shortening Trials

Table IV. Bacteriological relapse rates in smear- and culture-positive disease: regimens of less than six months' duration (all except one having streptomycin, isoniazid, rifampicin and pyrazinamide (SHRZ) daily for two or three months)

Duration	*Study*	*Regimen**	*Follow-up* (months)	*Patients assessed*	*Bacteriological relapses*	*95% confidence limits*
4½–5 months (18–22 weeks)	Second French Study Pretet (1981) (unpublished data)	2SHRZ/HRZ (18w)	12	64	2 (3%)	
	Mehrotra et al. (1981)	3SHRZ/RH (19w)	12	46	1 (2%)	
		3SHRZ/SHZ_2 (19w)	12	43	1 (2%)	
	Tuberculosis Research Centre, Madras (1981)†	2SHRZ/SHZ_2 (21½–22w)	43	129	8 (6%)	
	Tuberculosis Research Centre, Centre, Madras (1981)†	3SHRZ/SHZ_2 (21½–22w)	7	183	5 (3%)‡	
	All patients			465	17 (3%)	2–6
4 months (17 weeks)	Singapore/BMRC (1981)	2SHRZ/RHZ	26	79	9 (11%)	
	East African/BMRC (1981)			104	17 (16%)	
	Singapore/BMRC (1981)	2SHRZ/RH	26	77	6 (8%)	
	East African/BMRC (1981)			104	11 (11%)	
	All patients			364	43 (12%)	9–16
3 months	Second French Study (Pretet 1981) (unpublished data)	SHR	12	64	11 (17%)	9–29
		SH_3R_3				
	Eule (1981)‖	SHRZ	9	61¶	12 (20%)	11–32
	Tuberculosis Research Centre, Madras (1981)†	SHRZ	9	192	26 (14%)	9–19
	Mehrotra et al. (1981)	SHRZ	12	54	3 (6%)	1–15
	All SHRZ		9–12	307	41 (13%)	10–18

* For definitions of regimens see Tables I, II and III.
† Tripathy, personal communication.
‡ One more patient received chemotherapy for radiographic deterioration.
‖ Personal communication.
¶ A further patient was still bacteriologically positive at three months and classified as a failure of chemotherapy.

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
S = streptomycin

Fox W. Br J Dis Chest 1981; 75:331.

Historical TB Treatment Shortening Trials

Table V. Level of success of regimens of different duration in smear- and culture-positive disease

Duration of chemotherapy (months)	*Patients assessed**	*Bacteriological relapses*	*95% confidence limits*
9	298	3 (1%)	0.2–2.9
6	422	4 (1%)	0.3–2.4
4½–5	465	16 (3%)	2–6
4	364	43 (12%)	9–16
3	307	41 (13%)	10–18

* The regimens and duration of follow-up are given in Tables II, III and IV. (The six-month and shorter durations all contain streptomycin, isoniazid, rifampicin and pyrazinamide.)

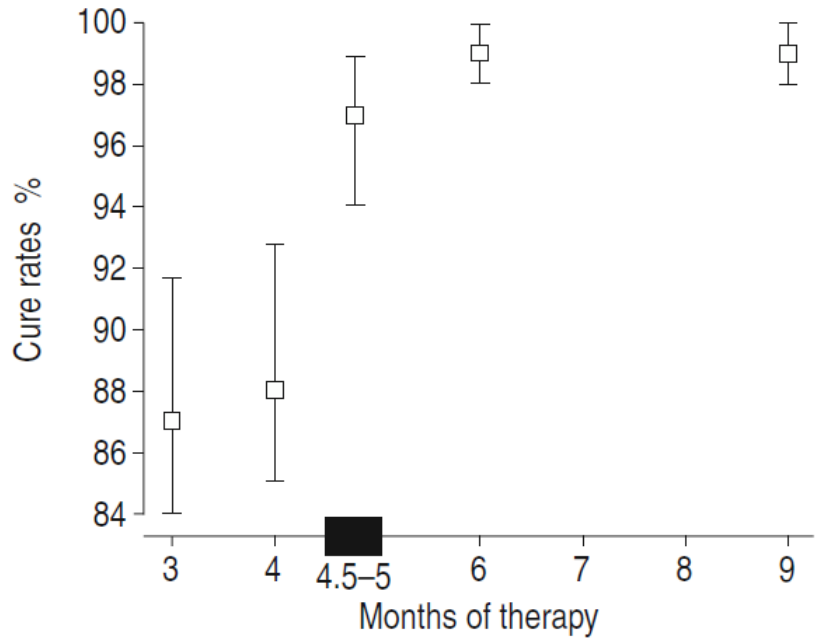

Fig. 2.–A meta-analytical representation of cure rates for tuberculosis regimens (reported in trials from around the world) of varying duration and constituents (American College of Chest Physicians, 1995). The 9-month regimens consisted of isonicotinic acid hydrazide (INH) and rifampicin (RIF), usually with streptomycin (SM) and/or ethambutol (EMB) but not pyrazinamide (PZA). All of the shorter regimens included INH, RIF, PZA, and SM or EMB. The trials were all done under "study conditions" including directly-observed therapy. Thus, they reflect the regimens' capabilities, not the predictably less successful outcomes under "programme conditions". Data are presented as mean±95% confidence limits.

Fox W. Br J Dis Chest 1981; 75:331.

Iseman MD. Eur Resp J 2002;20 suppl 36:87s-94s.

Recent and Ongoing Treatment Shortening DS-TB Trials

REMoxTB

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

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ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

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OFLOTUB

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

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RIFAQUIN

Results: Primary Endpoint

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
M = moxifloxacin
P = rifapentine
G = gatifloxacin

	Months 1-2	Months 3-4	Months 5-6	Unfavorable Outcome (per protocol) (adjusted difference from control)
RIFAQUIN				
Control	HRZE	HR	HR	4.9% (18 mo post randomization)
Arm 1	**M**RZE	**MP** (1x/wk)	**MP** (1x/wk)	3.2% (-1.8%, 95% CI -6.9 to 3.3)
Arm 2	**M**RZE	**MP** (2x/wk)	--	18.2% (13.6%, 95% CI 7.0-20.2)
OFLOTUB				
Control	HRZE	HR	HR	11.3% (24 mo post randomization)
Intervention	HRZ**G**	HR**G**	--	17.7% (5.5%, 95% CI 1.6-9.4)
REMoxTB				
Control	HRZE	HR	HR	8% (18 mo post randomization)
INH arm	HRZ**M**	HR**M**	--	15% (6.1%, 97.5% CI 1.7-10.5)
ETH arm	**M**RZE	**M**R	--	20% (11.4%, 97.5% CI 6.7-16.1)

Beijing Chest Hospital Shortened Regimens for DS-TB

	Months 1-2	Months 3-4	Months 5-6
Control	HRZE	HR	HR
Arm 1	HRZEL (4.5 mo)		
Arm 2	HRZE (4.5 mo)		

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
L = levofloxacin

- Randomized, controlled, non-inferiority study; sample size: 3900 with noninferiority margin 5%
- Inclusion criteria: adults, AFB smear positive; exclusions: HIV+, uncontrolled diabetes
- Locations: multiple sites across China
- Study started August 2016; estimated completion December 2020

High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial (PanACEA)

Lancet Infect Dis 2017; 17: 39–49

Martin J Boeree, Norbert Heinrich*, Rob Aarnoutse, Andreas H Diacon, Rodney Dawson, Sunita Rehal, Gibson S Kibiki, Gavin Churchyard, Ian Sanne, Nyanda E Ntinginya, Lilian T Minja, Robert D Hunt, Salome Charalambous, Madeleine Hanekom, Hadija H Semvua, Stellah G Mpagama, Christina Manyama, Bariki Mtafya, Klaus Reither, Robert S Wallis, Amour Venter, Kim Narunsky, Anka Mekota, Sonja Henne, Angela Colbers, Georgette Plemper van Balen, Stephen H Gillespie, Patrick P J Phillips, Michael Hoelscher, on behalf of the PanACEA consortium†*

	Months 1-2	Months 3-4	Months 5-6
Control	$HR_{10}ZE$	HR	HR
Arm 1	$HR_{35}ZE$	HR	
Arm 2	$HR_{10}ZQ$	HR	
Arm 3	$HR_{20}ZQ$	HR	
Arm 4	$HR_{20}ZM$	HR	

	Control	$RIF_{35}HZE$	RIFQHZ	$RIF_{20}QHZ$	$RIF_{20}MHZ$	Total
Total in analysis (mITT)	123	63	58	56	63	363
Number of culture conversions during 26-week follow-up (MGIT culture)	101 (82%)	51 (81%)	44 (76%)	48 (86%)	52 (83%)	296 (82%)
Number of culture conversions during 26-week follow-up (solid culture)	117 (95%)	59 (94%)	59 (97%)	54 (96%)	59 (94%)	345 (95%)
Primary analysis to 12 weeks (MGIT culture)						
Cumulative probability of culture conversion by 12 weeks	70·1%	79·9%	65·2%	58·6%	78·7%	..
Median time to culture conversion (IQR)	62 (41–83)	48 (34–69)	63 (48–83)	66 (41–83)	55 (41–69)	..
Adjusted hazard ratio (95%)*	..	1·78 (1·22–2·58) p=0·003	0·85 (0·57–1·27) p=0·42	0·76 (0·50–1·17) p=0·21	1·42 (0·98–2·05) p=0·07	..
Hazard ratio (95%), unadjusted	..	1·46 (1·02–2·11) p=0·04	0·90 (0·60–1·34) p=0·60	0·76 (0·50–1·16) p=0·21	1·34 (0·93–1·93) p=0·12	..
Solid LJ culture to 12 weeks (secondary)						
Cumulative probability of culture conversion by 12 weeks	97·3%	100·0%	94·4%	94·2%	98·0%	..
Median time to culture conversion (IQR)	27 (13–48)	20 (7–41)	20 (7–48)	20 (11–44)	29 (20–48)	..
Adjusted hazard ratio (95% CI)*	..	1·23 (0·89–1·69) p=0·21	0·91 (0·66–1·27) p=0·58	0·98 (0·70–1·38) p=0·93	0·77 (0·56–1·06) p=0·11	..
Unadjusted hazard ratio (95% CI)	..	1·28 (0·93–1·75) p=0·13	1·02 (0·73–1·41) p=0·92	1·06 (0·76–1·47) p=0·74	0·90 (0·65–1·23) p=0·50	..

LJ=Löwenstein-Jensen. MGIT=mycobacteria growth indicator tube. mITT=modified intention to treat. $RIF_{35}HZE$=rifampicin 35 mg/kg, isoniazid, pyrazinamide, ethambutol. RIFQHZ=rifampicin 10 mg/kg, isoniazid, pyrazinamide, SQ109 300 mg. $RIF_{20}QHZ$=rifampicin 20 mg/kg, isoniazid, pyrazinamide, SQ109 300 mg. $RIF_{20}MHZ$=rifampicin 20 mg/kg, isoniazid, pyrazinamide, moxifloxacin 400 mg. Doses of concomitant drugs are detailed in Procedures. *Analysis adjusted for HIV status, GeneXpert cycle threshold (<16, ≥16), and site. MGIT analyses also adjusted for baseline time to positivity.

***Table 2*: Summary of analyses of time to culture conversion in MGIT culture (primary) and on solid LJ culture (secondary) to 12 weeks**

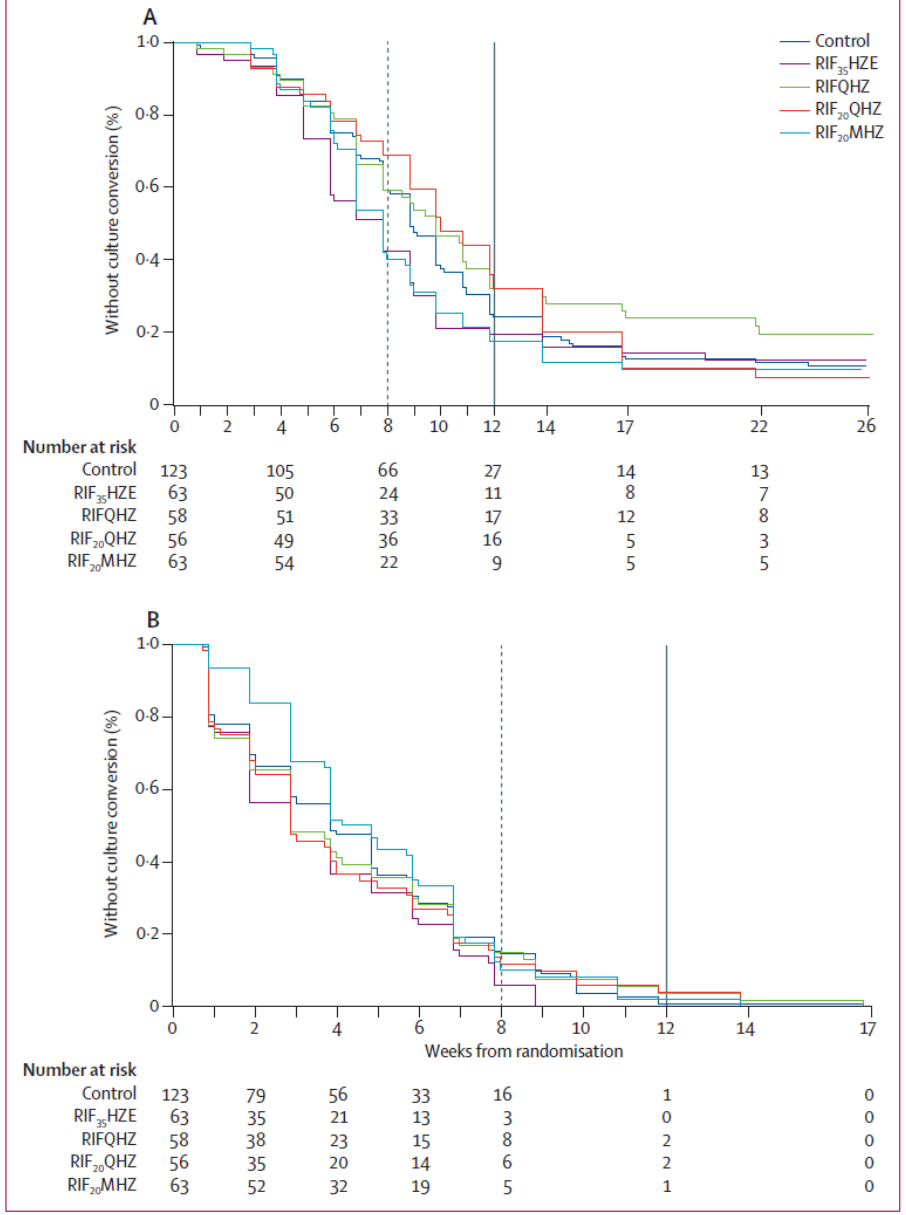

***Figure 2*: Kaplan-Meier curve for time to culture conversion**
(A) Time to culture conversion in liquid MGIT media. (B) Time to culture conversion on solid Löwenstein-Jensen media. MGIT=mycobacteria growth indicator tube. $RIF_{35}HZE$=rifampicin 35 mg/kg, isoniazid, pyrazinamide, ethambutol. RIFQHZ=rifampicin 10 mg/kg, isoniazid, pyrazinamide, SQ109 300 mg. $RIF_{20}QHZ$=rifampicin 20 mg/kg, isoniazid, pyrazinamide, SQ109 300 mg. $RIF_{20}MHZ$=rifampicin 20 mg/kg, isoniazid, pyrazinamide, moxifloxacin 400 mg. Doses of concomitant drugs are detailed in Procedures. Dashed vertical line refers to the week 8 time-point (cutoff in post-hoc analysis). Solid vertical line refers to the week 12 time-point (cutoff in primary analysis).

RIFASHORT

Randomized Trial to Evaluate Toxicity and Efficacy of 1200mg and 1800mg Rifampicin for Pulmonary Tuberculosis

	Months 1-2	Months 3-4	Months 5-6
Control	$HR_{600}ZE$	HR_{600}	HR_{600}
Arm 1	$HR_{1200}ZE$	HR_{1200}	
Arm 2	$HR_{1800}ZE$	HR_{1800}	

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol

- Randomized, phase 3 study; sample size: 654
- Inclusion criteria: adults; exclusion: HIV, diabetes
- Locations: Botswana, Uganda, Peru
- Study started February 2017; estimated completion January 2020

Daily Rifapentine for Treatment of Pulmonary Tuberculosis

A Randomized, Dose-Ranging Trial

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Am J Respir Crit Care Med Vol 191, Iss 3, pp 333–343, Feb 1, 2015

Primary endpoint: week 8 culture conversion

Table 3. Percentages of Participants with Negative Cultures at Completion of Intensive Phase Treatment, by Treatment Assignment, for the Modified Intention-to-Treat Analysis Group

	Rifampin	Rifapentine 10 mg/kg	Rifapentine 15 mg/kg	Rifapentine 20 mg/kg
Solid culture medium				
% (n/n) with negative cultures	81.3 (52/64)	92.5 (62/67)	89.4 (59/66)	94.7 (54/57)
% difference vs. rifampin (95% CI)		11.3 (−1.7 to 24.3)	8.1 (−5.5 to 21.8)	13.5 (0.6 to 26.3)
P value		0.097	0.29	0.049
Liquid culture medium				
% (n/n) with negative cultures	56.3 (36/64)	74.6 (50/67)	69.7 (46/66)	82.5 (47/57)
% difference vs. rifampin (95% CI)		18.4 (0.8 to 35.9)	13.4 (−4.5 to 31.4)	26.2 (8.9 to 43.5)
P value		0.042	0.16	0.004

Table 1. Baseline Characteristics of Participants in the Intention-to-Treat Analysis Population

Characteristic	Overall (*n* = 334)	Rifampin (*n* = 85)	Rifapentine 10 mg/kg (*n* = 87)	Rifapentine 15 mg/kg (*n* = 81)	Rifapentine 20 mg/kg (*n* = 81)
Enrolled at African site, n (%)	190 (56.9)	45 (52.9)	49 (56.3)	48 (59.3)	48 (59.3)
Cavitation on chest radiograph at enrollment, n (%)	257 (77.0)	69 (81.2)	67 (77.0)	61 (75.3)	60 (74.1)
Median (range) age, yr	31 (18–78)	33 (19–78)	29 (19–66)	31 (18–69)	31 (19–70)
Male, n (%)	230 (68.9)	55 (64.7)	63 (72.4)	58 (71.6)	54 (66.7)
History of smoking cigarettes, n (%)	142 (42.5)	45 (52.9)	32 (36.8)	30 (37.0)	35 (43.2)
HIV-positive, n (%)	26 (7.8)	5 (5.9)	6 (6.9)	4 (4.9)	11 (13.6)
Median (IQR) CD4 count for HIV-positive participants, cells/μl	321 (196–429)	277 (257–400)	428 (415–434)	353 (134–474)	283 (156–414)
Median (IQR) # days of prestudy TB treatment	2 (0–3)	2 (0–4)	2 (0–4)	2 (0–3)	1 (0–3)
Median (IQR) body mass index, kg/m^2	19.4 (17.8–21.4)	19.2 (17.5–21.2)	19.1 (17.6–21.1)	19.5 (17.9–21.5)	19.7 (18.1–22.0)
Serum or plasma ALT > ULN, n (%)	35 (10.5)	9 (10.6)	7 (8.1)	11 (13.6)	8 (9.9)
High sputum smear grade, n (%)	186 (56.0)	50 (59.5)	47 (54.0)	39 (48.2)	50 (62.5)
Median (IQR) days to detection in MGIT culture	6.6 (5.0–9.0)	6.9 (5.5–8.5)	7.0 (5.1–10.5)	7.0 (4.8–9.3)	6.4 (4.7–8.6)
Rifapentine dose in mg, n (%)					
450 mg	—	—	49 (56.3)	0 (0)	0 (0)
600 mg	—	—	37 (42.5)	38 (46.9)	0 (0)
900 mg	—	—	1 (1.2)	39 (48.2)	44 (54.3)
1,200 mg	—	—	0 (0)	4 (4.9)	33 (40.7)
1,500 mg	—	—	0 (0)	0 (0)	4 (4.9)

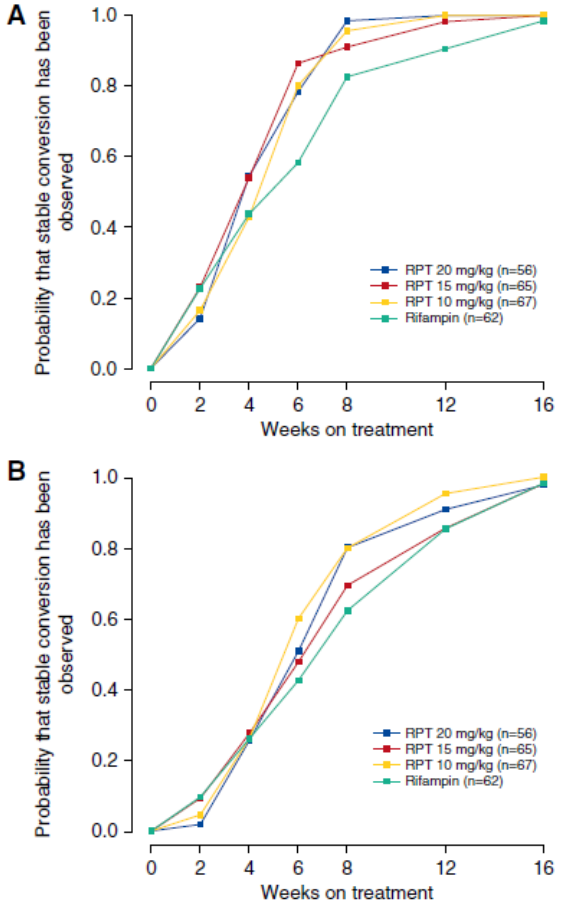


Figure 2. Time to stable culture conversion for the modified intention-to-treat analysis group: by assigned treatment group, and as assessed using solid culture medium (*P* = 0.010) (*A*) and liquid culture medium (*P* = 0.32) (*B*);

TBTC Study 31/ACTG Study A5349

	Months 1-2	Months 3-4	Months 5-6
Control	HRZE	HR	HR
Arm 1	HPZE	HP	
Arm 2	HPZM	HPM	

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
P = rifapentine 1200 mg
M = moxifloxacin

- Randomized phase 3 study; sample size 2500
- Inclusion criteria: Adults; children ≥12; HIV-; HIV+ with CD4 ≥100
- Locations: multiple international sites in Asia, Africa, North America, South America
- Study started January 2016; estimated completion December 2019

Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis

Rodney Dawson, Andreas H Diacon, Daniel Everitt, Christo van Niekerk, Peter R Donald, Divan A Burger, Robert Schall, Melvin Spigelman, Almari Conradie, Kathleen Eisenach, Amour Venter, Prudence Ive, Liesl Page-Shipp, Ebrahim Variava, Klaus Reither, Nyanda E Ntinginya, Alexander Pym, Florian von Groote-Bidlingmaier, Carl M Mendel

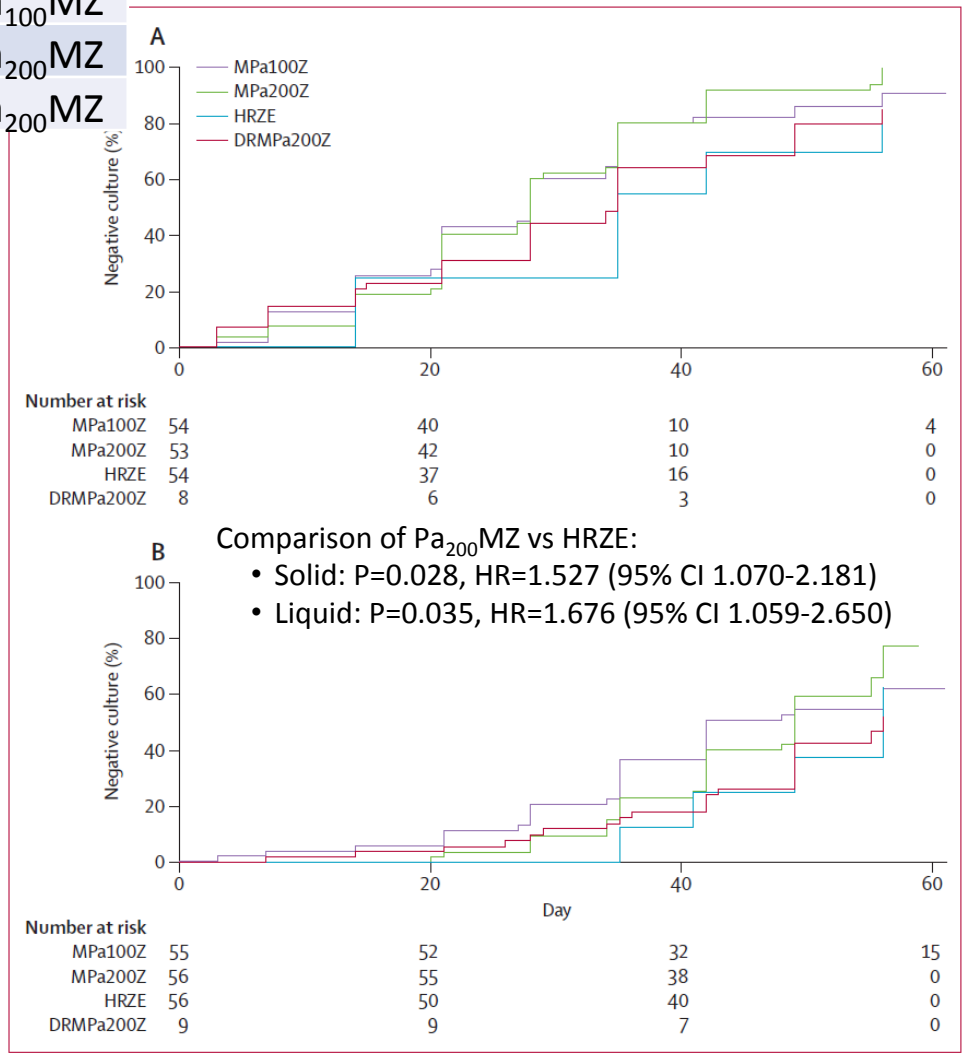
Lancet 2015; 385: 1738–47

	Months 1-2
Control	HRZE
DS-TB 1	$Pa_{100}MZ$
DS-TB 2	$Pa_{200}MZ$
MDR-TB	$Pa_{200}MZ$

	Patients with drug-susceptible tuberculosis			Patients with drug-resistant tuberculosis
	Moxifloxacin, 100 mg pretomanid, and pyrazinamide (n=56)	Moxifloxacin, 200 mg pretomanid, and pyrazinamide (n=54)	Isoniazid, rifampicin, pyrazinamide, and ethambutol (n=54)	Moxifloxacin, 200 mg pretomanid, and pyrazinamide (n=9)
Mean change in daily log_{10}CFU counts for days 0–56				
Posterior estimate (95% Bayesian credibility interval)	0·133 (0·109–0·155)	0·155 (0·133–0·178)	0·112 (0·093–0·131)	0·117 (0·070–0·174)
Mean change in daily log_{10}CFU counts for days 7–56				
Posterior estimate (95% Bayesian credibility interval)	0·115 (0·090–0·140)	0·145 (0·120–0·171)	0·103 (0·081–0·125)	0·104 (0·054–0·167)

Data are derived from the joint Bayesian non-linear mixed effects regression model. The differences between moxifloxacin, 200 mg pretomanid, and pyrazinamide versus isoniazid, rifampicin, pyrazinamide, and ethambutol with respect to bactericidal activity assessed by CFU for days 0–56 (0·043, 95% Bayesian credibility interval 0·013–0·073) and 7–56 (0·041, 0·008–0·076) were significant. No other comparisons were significant. Patients with tuberculosis resistant to pyrazinamide or moxifloxacin at baseline were excluded. CFU=colony forming units. NLME=non-linear mixed effects modelling.

Table 2: **Bactericidal activity characterised by joint Bayesian NLME modelling of the daily rate of change in mean count of log_{10}CFU of *Mycobacterium tuberculosis* per mL sputum (efficacy analysis population)**



Comparison of $Pa_{200}MZ$ vs HRZE:

- Solid: P=0.028, HR=1.527 (95% CI 1.070-2.181)
- Liquid: P=0.035, HR=1.676 (95% CI 1.059-2.650)

Figure 3: **Kaplan-Meier curves of time to sputum culture conversion**
(A) Solid media and (B) liquid media. The curves are applicable to valid non-missing weekly data only. MPa100Z=moxifloxacin, 100 mg pretomanid, and pyrazinamide. MPa200Z=moxifloxacin, 200 mg pretomanid, and pyrazinamide. HRZE=isoniazid, rifampicin, and pyrazinamide-ethambutol. DRMPa200Z=patients with drug-resistant tuberculosis treated with moxifloxacin, 200 mg pretomanid, and pyrazinamide.

NC-006 STAND (PaMZ)

	Months 1-2	Months 3-4	Months 5-6
Control	HRZE	HR	HR
DS-TB 1	$Pa_{200}MZ$	$Pa_{200}MZ$	$Pa_{200}MZ$
DS-TB 2	$Pa_{200}MZ$	$Pa_{200}MZ$	
DS-TB 3	$Pa_{100}MZ$	$Pa_{100}MZ$	
MDR-TB	$Pa_{200}MZ$	$Pa_{200}MZ$	$Pa_{200}MZ$

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
Pa = pretomanid (Pa-824)
M = moxifloxacin

- Partially randomized phase 3 study; sample size 1500
- Inclusion criteria: Adults; HIV-; HIV+ with CD4 ≥100; stable diabetes
- Locations: multiple international sites in Asia and Africa
- Study started February 2015; paused after 284 enrolled due to hepatoxicity
- Closed to new enrollment due to results of NC-005 study

NC-005 BPaMZ

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol

B = bedaquiline
Pa = pretomanid (Pa-824)
M = moxifloxacin

- From October 2014-May 2016, 180 DS-TB patients randomized to 3 arms, 60 MDR-TB patients enrolled in South Africa, Tanzania, and Uganda
- Participants treated on study for 2 months, then referred for continued treatment

	N	Months 1-2	Culture negative (Solid Culture)	HR (95% CI) (Solid Culture)	Culture negative (Liquid Culture)	HR (95% CI) (Liquid Culture)
Control	61	HRZE	86%	1.0	51%	1.0
DS-TB 1	59	$B_{loading}PaZ$	89%	1.3 (0.9-1.8)	66%	1.7 (1.1-2.8)
DS-TB 2	60	$B_{200}PaZ$	84%	1.1 (0.8-1.6)	75%*	2.0 (1.3-3.2)
MDR-TB	60	$B_{200}PaMZ$	100%* (Z-sens) 95%* (Z-res)	2.2 (1.5-3.2) 2.6 (1.5-4.6)	96%* (Z-sens) 78%* (Z-res)	3.5 (2.1-5.6) 2.0 (1.1-3.4)

* $P<0.05$ compared to control

CROI 2017 abstract 724LB.

NC-008 SimpliciTB

Trial to Evaluate the Efficacy, Safety and Tolerability of BPaMZ in Drug-Sensitive (DS-TB) Adult Patients and Drug-Resistant (DR-TB) Adult Patients

	Months 1-2	Months 3-4	Months 5-6
Control	HRZE	HR	HR
DS-TB	B_{200}PaMZ	B_{100}PaMZ	
DR-TB*	B_{200}PaMZ	B_{100}PaMZ	B_{100}PaMZ

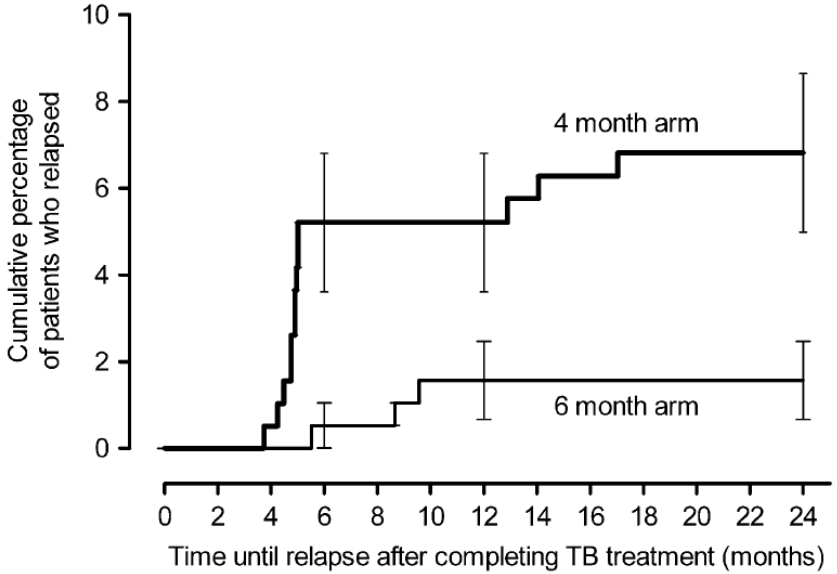
* Resistant to either INH or RIF

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
B = bedaquiline
Pa = pretomanid (Pa-824) 200mg
M = moxifloxacin

- Partially randomized phase 2c study; sample size 450
- Inclusion criteria: Adults; HIV-; HIV+ with CD4 ≥100; FQ sensitive; stable diabetes
- Locations: multiple international sites in Africa, Asia, Europe, and South America
- Study started August 2018; estimated to complete in 2022

DMID 01-009

- Trial only shortened treatment to 4 mo among those with less severe disease:
  - No cavity on baseline CXR
  - Sputum culture converted to negative by 2 months of treatment
- Trial stopped early due to higher relapse rate in 4-mo arm compared to 6-mo arm (7.0% vs 1.6%, p<0.01)
- Despite study failure, 4-mo arm treatment success rate increased from about 80-85% to 93%



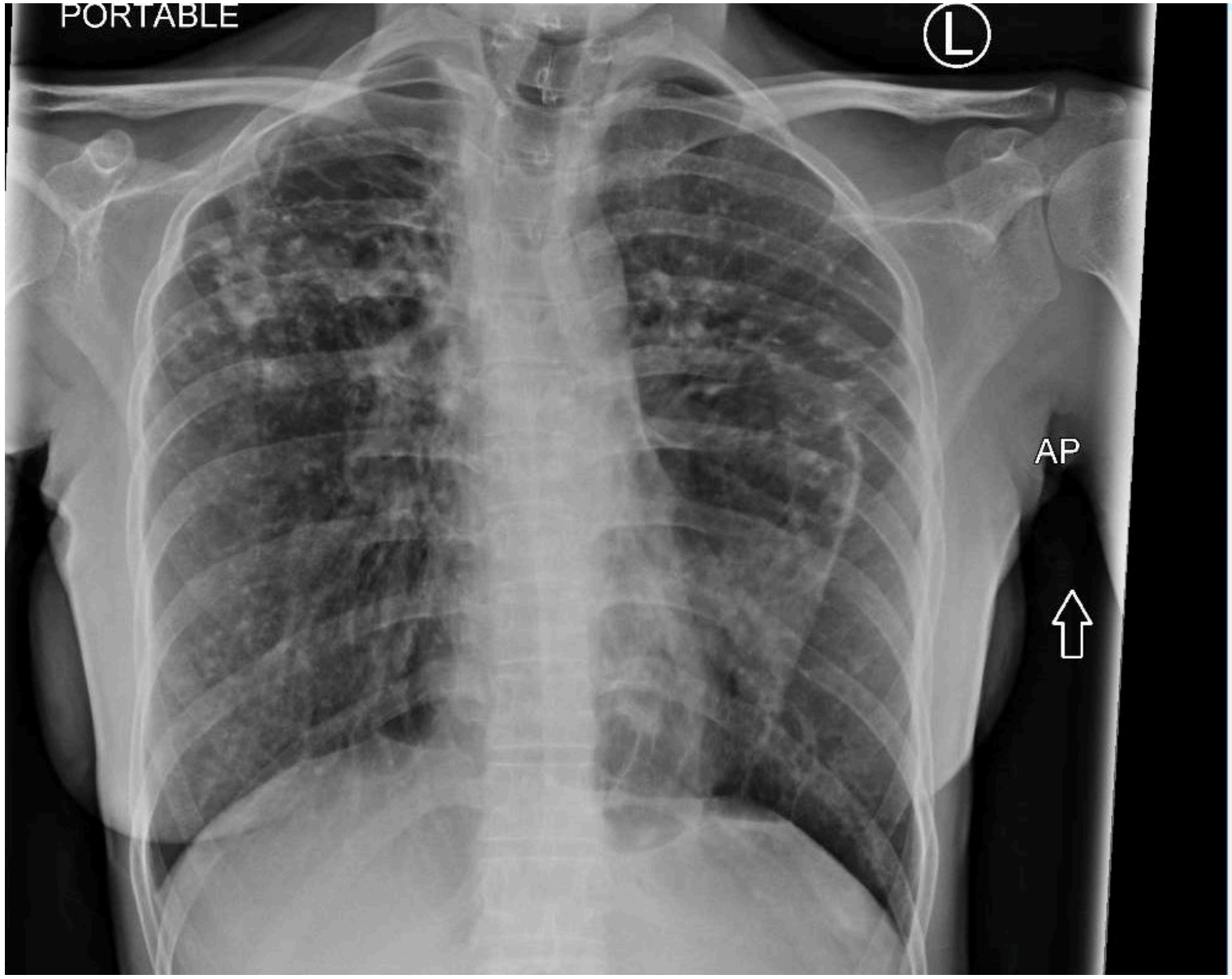
Number at Risk

6 Month Arm	193	193	191	190	187	184	182
4 Month Arm	193	193	192	181	178	174	173

Figure 2. Kaplan Meier curve showing the cumulative percentage of patients who relapsed after completing anti-tuberculosis (TB) treatment. The chi-square test for a difference in the percentage of patients who relapsed by treatment arm was significant ($P < 0.01$). *Error bars* represent the standard error of the mean percentage of patients who relapsed at 6, 12, and 24 months of follow-up after completing treatment.

Johnson JL. Am J Respir Crit Care Med, 2009. **180**(6): p. 558-63.

Sensitivity of CXR for Cavities



CLINICAL INDICATION: Active pulmonary tuberculosis infection causing shortness of breath. Clinical Evaluation. pulmonary TB ;

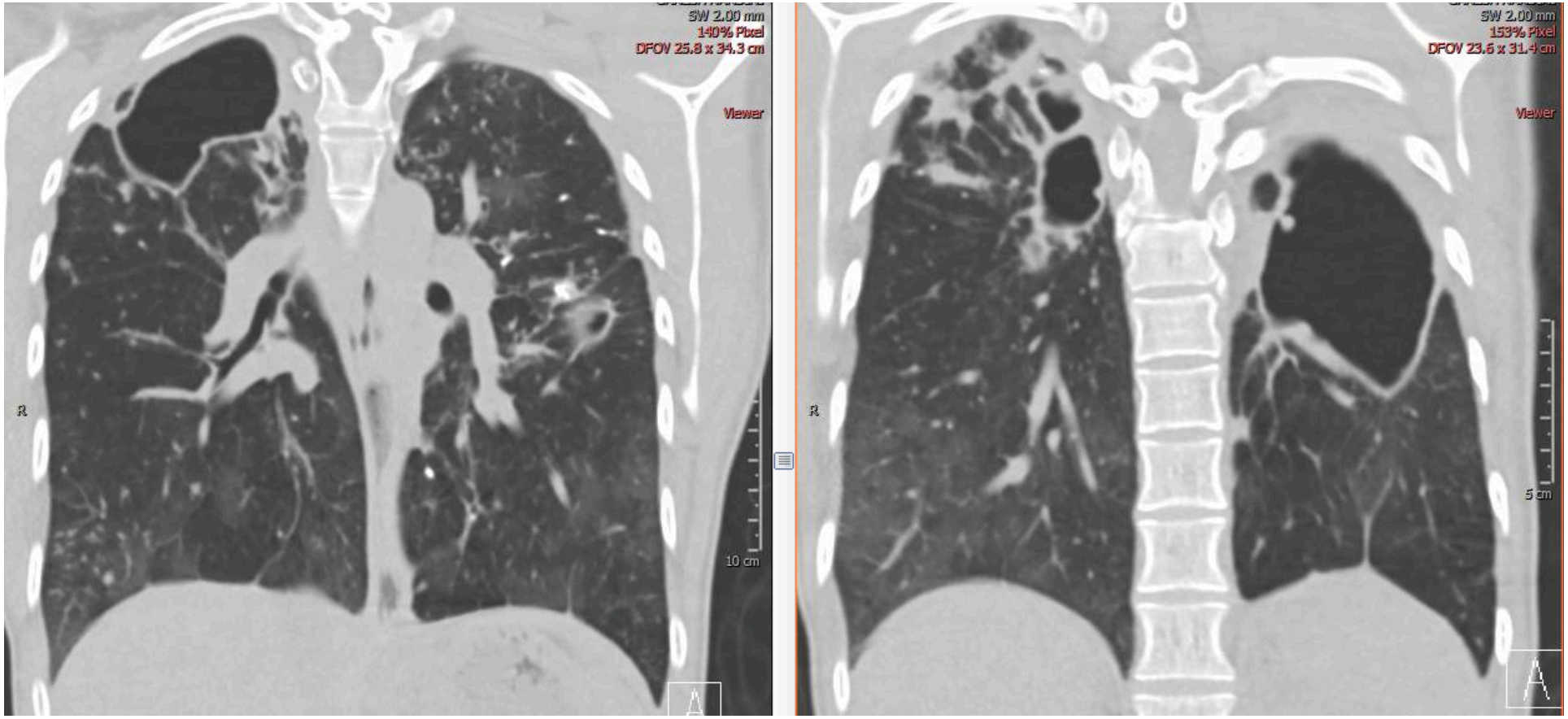
TECHNIQUE: Chest AP one view

COMPARISON: No prior chest radiograph available for comparison

FINDINGS::
Nodular opacities in the upper lungs consistent with history of tuberculosis.
Linear scarring ill-defined opacity in both mid and lower lungs, with architectural distortion in the right perihilar region, also due to tuberculosis infection.
Nodularity in the left mid and lower lung.
Cardiac silhouette within normal radiographic limits.
Probable mediastinal paratracheal mediastinal soft tissue thickening.
Skeletal structures intact without focal destructive osseous disease.

IMPRESSION:
Nodular densities in the upper lungs and left perihilar region with extensive linear scarring and architectural distortion in the perihilar regions, consistent with history of tuberculosis.

CT Scan


SW 2.00 mm
140% Pixel
DFOV 25.8 x 34.3 cm
Viewer
R
10 cm
SW 2.00 mm
153% Pixel
DFOV 23.6 x 31.4 cm
Viewer
R
5 cm

Predicting Treatment Response: Radiology

- CXR resolution insufficient to clearly identify and follow disease pathology
- PET/CT scans well established in oncology to stage disease and predict outcomes
- Analysis of 35 MDR-TB patients with PET/CT scans at 0, 2, 6 mo of treatment
- Changes on PET and CT scans correlated with final treatment outcomes 6 mo after end of therapy

Table 1. Sensitivity and specificity of 2-month sputum culture conversion compared to CT and PET scan changes for predicting treatment outcomes.

Modality	Sensitivity	Specificity
PET (2 months)	0.96 (23/24)*	0.75 (3/4)*
Automated CT (6 months): HU −100 to 200	0.96 (23/24)*	0.75 (3/4)*
Automated CT (2 months): HU −100 to 200	0.79 (19/24)*	0.75 (3/4)*
Culture—solid (2 months)	0.79 (19/24)	0.5 (2/4)
Smear (2 months)	0.75 (18/24)	0.5 (2/4)
Culture—liquid (2 months)	0.58 (14/24)	0.5 (2/4)

*Estimates have been corrected for bias in selection of optimal threshold using cross-validation.

Chen RY. Sci Trans Med 2014;6;265ra166.

Predicting Treatment Response: Microbiology

- Traditionally measured by month 2 sputum culture conversion rate as surrogate marker of sputum bacterial load
- Month 2 sputum culture conversion rate associated with treatment relapse in multiple studies
- Association on an individual patient level is poor

	Studies (n)	Sample size (N)	Hierarchical regression model		Odds ratio (95% CI)	PPV* (95% CI)	NPV* (95% CI)
			Sensitivity (95% CI)	Specificity (95% CI)			
Relapse							
Culture	4	1298	40% (25–56%)	85% (77–91%)	3·8 (2·2–6·8)	18% (14–21%)	95% (95–96%)
Smear	6	9848	24% (12–42%)	83% (72–90%)	1·5 (1·1–2·2)	10% (8–12%)	93% (93–94%)
Failure							
Smear	7	20 062	57% (41–73%)	81% (72–87%)	5·8 (4·3–7·8)	9% (9–10%)	98% (98–98%)

*Ability of smear to predict poor outcomes, assuming 7% risk of relapse and 3% risk of failure. NPV=negative predictive value; PPV=positive predictive value.

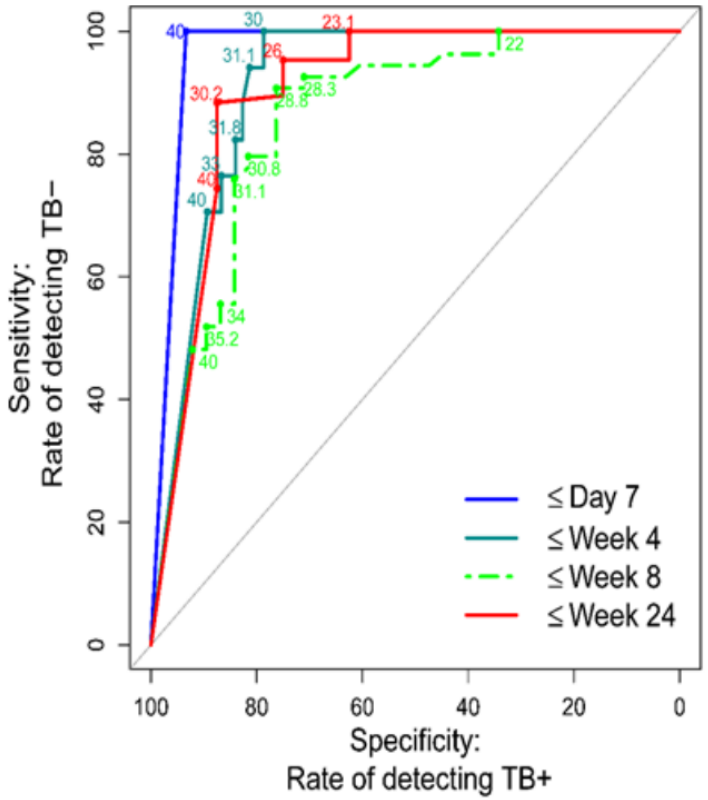
Table 5: **Pooled summary estimates for relapse or failure for patients with a positive sputum culture or smear at 2 months**

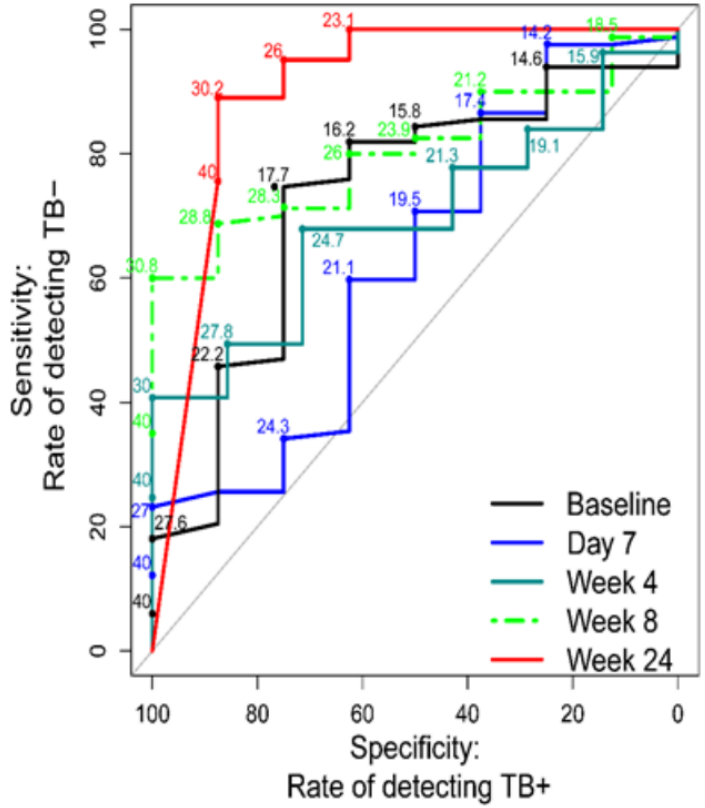
Horne DJ. Lancet Infect Dis 2010;10:387-94.

Predicting Treatment Response: Bacterial Load

ROC curve for direct Xpert Ct relative to culture negativity at the same time point; AUC values:

- Day 7 = 96.7
- Week 4 = 91.2
- Week 8 = 86.0
- Week 24 = 90.2





ROC curve for direct Xpert Ct to predict treatment failure at the end of treatment; AUC values:

- Week 8 = 80.2
- Week 24 = 90.2

Shenai S. PLoS ONE 2016;11(8):e0160062.

Predict TB

Using Biomarkers to Predict TB Treatment Duration

DMID 01-009 study

- Baseline: no cavity on CXR
- Treatment response:
  - Month 2 sputum culture negative

Predict TB

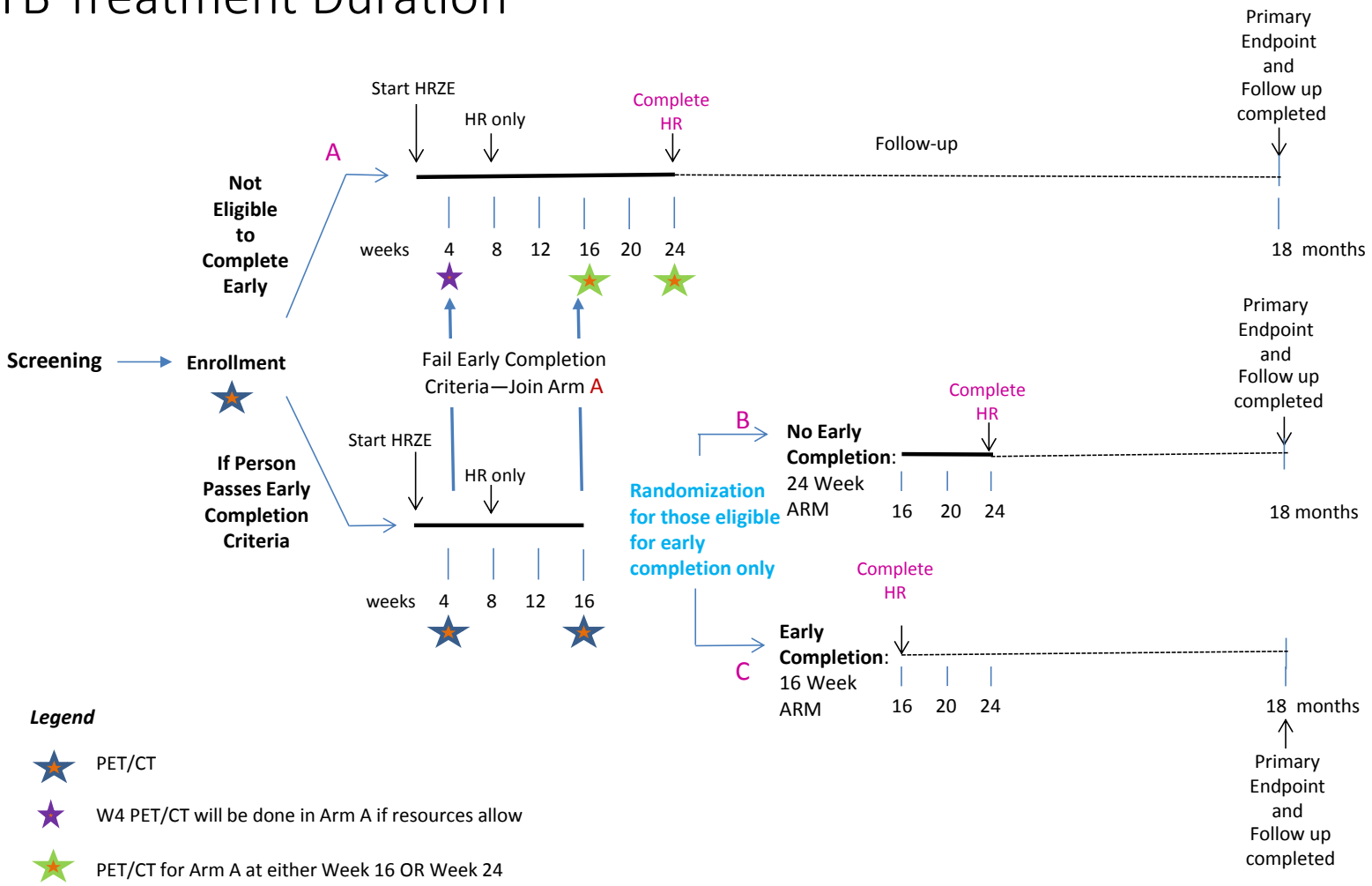
- Baseline: PET/CT burden of disease
- Treatment response:
  - Month 1 PET/CT burden of disease
  - Month 4 Xpert MTB/RIF cycle

Study	4-month Treatment Success Rate
Prior studies (no stratification)	80-85%
DMID 01-009	93%
Predict TB	?

Predict TB

Using Biomarkers to Predict TB Treatment Duration

- Partially randomized phase 2 study;
- Sample size: 310 in Arms B and C combined
- Inclusion criteria: adults; HIV-; diabetes negative
- Locations:
  - Cape Town, South Africa;
  - Henan, China
- Study started June 2017; estimated to complete in 2022



TRUNCATE-TB

Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-sensitive Tuberculosis

	Months 1-2	Months 3-4	Months 5-6
Control	$HR_{10}ZE$	HR	HR
DS-TB 1	$HR_{35}ZE$**Li**	*	
DS-TB 2	$HR_{35}ZE$**C**	*	
DS-TB 3	H**P**Z**LiLe**	*	
DS-TB 4	HZE**LiB**	*	

* If persistent symptoms and smear+ at wk 8, extend treatment to wk 12; if persistent symptoms and smear+ at wk 12, switch to standard treatment and extend to 24 wks

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
Li = linezolid 600 mg
C = clofazimine 200 mg
P = rifapentine 1200 mg
Le = levofloxacin 1000 mg
B = bedaquiline

- Randomized, adaptive study with treatment x2 mo (may be extended), those who relapse (predicted to always be drug sensitive and to occur early) will be retreated with standard 6 mo regimen; sample size 900 (180/arm)
- Hypothesis: TRUNCATE-TB management strategy non-inferior to standard treatment at 96 wks (2 yrs)
- Exclusion criteria: children, severe clinical TB, baseline smear 3+, CXR cavity >4cm, HIV+, poorly controlled diabetes
- Locations: Philippines, Singapore, Thailand
- Study started March 2018: estimated to complete March 2022

Recent and Ongoing Treatment Shortening MDR-TB Trials

Bangladesh Regimen

- Observational study; patients assigned sequentially to one of six standardized regimens
- "A new regimen cohort was started once the outcomes of the previous one(s) seemed sufficiently clear, without striving for statistical significance."

TABLE 1. REGIMENS SEQUENTIALLY USED IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS, BANGLADESH DAMIEN FOUNDATION PROJECTS

Regimen (sequence)	Intensive Phase	Continuation Phase 1	Continuation Phase 2	Patients Enrolled	
				Number	Col %
1	3* KCOEHZP	12 OEHZP	6 EP	59	13.8
2	3(+) KCOEHZP	12 OHEZP		44	10.3
3	3(4) KCOEZP	12 OEZP		35	8.2
4	3(+) KCOEHZP	12 OHEZ		45	10.5
5	3(+) KCOEHZP	12 OHEZC		38	8.9
6	4(+) KCGEHZP	5 GEZC		206	48.2
Total number of patients enrolled				427	100.0

Definition of abbreviations: C = clofazimine; Col % = column percent; E = ethambutol; G = gatifloxacin; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; Z = pyrazinamide.

* Numbers in front of phase indicate months. 3(4) indicates minimum of 3 mo, prolonged to 4 mo if no conversion by end of 3 mo. 3(+) indicates minimum of 3 mo, prolonged until conversion is achieved, if no conversion by the end of 3 mo. 4(+) indicates minimum of 4 mo, prolonged until conversion is achieved, if no conversion by the end of 4 mo. All drugs were given daily throughout under direct observation.

Mo 1-4: kanamycin, clofazimine, gatifloxacin, ethambutol, INH, PZA, prothionamide

Mo 5-9: gatifloxacin, ethambutol, PZA, clofazimine

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

[1]International Union Against Tuberculosis and Lung Disease, Paris, France; [2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Damien Foundation Bangladesh, Dhaka, Bangladesh; and [4]Institute of Social and Preventive Medicine, University of Zurich, Switzerland

Am J Respir Crit Care Med Vol 182. pp 684–692, 2010

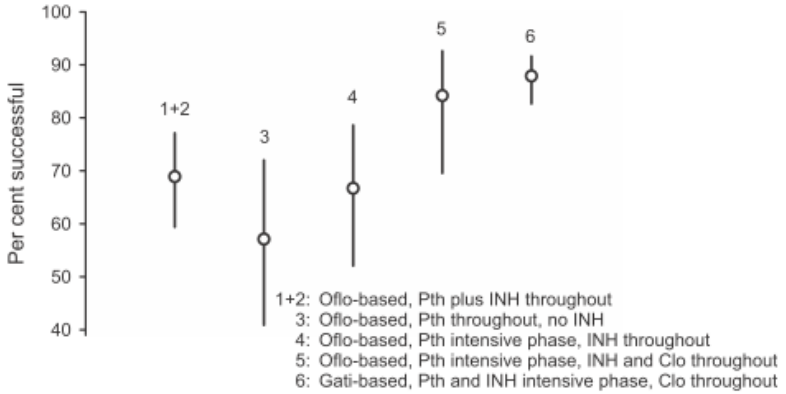


Figure 2. Proportion of patients with a successful outcome in the treatment of multidrug-resistant tuberculosis. Successful outcome was defined as treatment completion or a relapse-free cure. Death, default, failure (including one clinical failure without bacteriological evidence), and relapse were considered unsuccessful outcomes. Numbers denote regimen number. Clo = clofazimine; Gati = gatifloxacin; INH = isoniazid; Oflo = ofloxacin; Pth = prothionamide.

TABLE 5. OUTCOME OF TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS GROUPED BY REGIMEN CATEGORY, BANGLADESH DAMIEN FOUNDATION PROJECTS

Outcome	Regimens 1+2		Regimen 3		Regimen 4		Regimen 5		Regimen 6		Total	
	n	Col %	n	Col %	n	Col %	n	Col %	n	Col %	n	Col %
Completion*	0	0.0	0	0.0	0	0.0	0	0.0	11	5.3	11	2.6
Cure	71	68.9	20	57.1	30	66.7	32	84.2	170	82.5	323	75.7
Death	11	10.7	5	14.3	4	8.9	2	5.3	11	5.3	33	7.7
Default	15	14.6	7	20.0	4	8.9	3	7.9	12	5.8	41	9.6
Failure	6	5.8	3	8.6	6	13.3	1	2.6	1	0.5	17	4.0
Relapse	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.2
Not fitting any of the above†	0	0.0	0	0.0	1	2.2	0	0.0	0	0.0	1	0.2
Total	103	100.0	35	100.0	45	100.0	38	100.0	206	100.0	427	

Definition of abbreviation: Col % = column percent.

* Treatment completion is reported only for the gatifloxacin-treated cohort because cure criteria could not always be met due to the short regimen and incomplete post-treatment follow-up. However, all had converted, one patient with two and one with three negative cultures during treatment (and before moving away), and the others all had at least four negative cultures.

† One patient failed clinically but not according to the bacteriological criteria, and the treatment was changed to a salvage regimen. Although all cultures preceding the event were negative, this patient would not fit the analysis criteria. In the final analysis on effectiveness and survival, this patient was counted as an adverse outcome.

STREAM Stage 1

Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB

H = isoniazid 10 mg/kg
Z = pyrazinamide
E = ethambutol

C = clofazimine
K = kanamycin
Pr = prothionamide
M = moxifloxacin hi-dose

- Randomized phase 3 study with 10% non-inferiority margin; primary outcome at 2.5 yrs after randomization
- Inclusion criteria: Adults; HIV-; HIV+ with CD4 ≥50; pre-XDR or XDR-TB excluded
- Locations: Ethiopia, Mongolia, Vietnam, South Africa
- Study started July 2012; accrual completed June 2015 with 424 enrolled
- Preliminary results presented at 2017 Union World Conference on Lung Health; final results in 2018

	Months 1-4	Months 5-9	Months 10-24	Success Rate	Adjusted Difference (95% CI)
Control	Local WHO	Local WHO	Local WHO	80.6%	2.1% (-6.9 to 11.2)
MDR-TB	MCEZKHPr	MCEZ		78.1%	

STREAM Stage 2

Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB

H = isoniazid 10 mg/kg
Z = pyrazinamide
E = ethambutol
M = moxifloxacin high dose

C = clofazimine
K = kanamycin
Pr = prothionamide
L = levofloxacin
B = bedaquiline

	Months 1-2	Months 3-4	Months 5-6	Months 7-9	Months 10-24
Regimen A	Local WHO		Local WHO		Local WHO
Regimen B	MCEZHKPr		MCEZ		
Regimen C	**L**CEZH**B**Pr		**L**CEZ**B**		
Regimen D	**L**CZHK**B**	**L**CZ**B** (28 wks)			

STREAM Stage 1

L for M; B for K

6mo; 2mo K; no E

- Goals: fully oral 9-month regimen; 6-month regimen
- Randomized phase 3 study; sample size 1155 with 10% non-inferiority margin; primary outcome at 18 months after randomization (Regimen B is control)
- Inclusion criteria: adults; HIV-; HIV+ with CD4 ≥50; pre-XDR or XDR-TB excluded
- Locations: multiple sites in Asia, Africa, Europe
- Study started April 2016; estimated completion December 2021

MDR-END

Treatment Shortening of MDR-TB using Existing and New Drugs

	Months 1-8	Months 9-12	Months 13-24
Control	Local WHO	Local WHO	Local WHO
Experimental	DLiLeZ	DLiLeZ	

D = delamanid
Li = linezolid 600
Le = levofloxacin
Z = pyrazinamide

- Randomized controlled trial; sample size 238; treated for 9-12 months depending on time of sputum culture conversion to negative
- Inclusion criteria: adults; FQ-resistance excluded
- Location: South Korea
- Study started Jan 2016; estimated completion Dec 2019

endTB

Evaluating Newly Approved Drugs for MDR-TB

	Months 1-9	Months 10-24
Control	WHO	WHO
Arm 1	BLiMZ	
Arm 2	BLiLeCZ	
Arm 3	BDLiLeZ	
Arm 4	DLiLeCZ	

B = bedaquiline
Li = linezolid
M = moxifloxacin
Z = pyrazinamide
Le = levofloxacin
C = clofazimine
D = delamanid

- Phase 3 randomized clinical non-inferiority trial; sample size 750
- Inclusion criteria: Adults, children ≥15; FQ-resistance is excluded
- Locations: multiple clinics in Asia, Africa, South America
- Study started Dec 2016; estimated to complete in April 2021

Li = linezolid 600
B = bedaquiline
Le = levofloxacin
Eth = ethionamide
H = isoniazid 12.5 mg/kg
T = terizidone
Z = pyrazinamide

NEXT

Evaluating a New Treatment Regimen for MDR-TB

	Months 1-2	Months 3-4	Months 5-6	Months 7-9	Months 10-24
Control	Local WHO		Local WHO		Local WHO
Experimental	BLiLeZ(EthHT)*			BLiLeZ(EthHT)	

* Ethionamide vs. high-dose isoniazid vs terizidone therapy determined based on individualized, gene-directed testing

- Randomized controlled trial with completely oral regimen; sample size 300; treated for 6-9 months, stopping when 3 consecutive negative sputum cultures achieved
- Inclusion criteria: adults with simple MDR-TB; pre-XDR or XDR-TB excluded
- Location: South Africa
- Study started Oct 2015; estimated completion Jan 2019

NC-008 SimpliciTB

Trial to Evaluate the Efficacy, Safety and Tolerability of BPaMZ in Drug-Sensitive (DS-TB) and Drug-Resistant (DR-TB) Adult Patients

	Months 1-2	Months 3-4	Months 5-6
Control	HRZE	HR	HR
DS-TB	B_{200}PaMZ	B_{100}PaMZ	
DR-TB*	B_{200}PaMZ	B_{100}PaMZ	B_{100}PaMZ

* Resistant to either INH or RIF

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
B = bedaquiline
Pa = pretomanid (Pa-824) 200mg
M = moxifloxacin

- Partially randomized phase 2c study; sample size 450
- Inclusion criteria: Adults; HIV-; HIV+ with CD4 ≥100; FQ sensitive; stable diabetes
- Locations: multiple international sites in Africa, Asia, Europe, and South America
- Study started August 2018; estimated to complete in 2022

Nix-TB (XDR-TB or unresponsive MDR-TB)

Safety and Efficacy of Bedaquiline plus PA-824 plus Linezolid in Subjects with Drug Resistant Pulmonary Tuberculosis

	Months 1-2	Months 3-4*	Months 5-6
XDR-TB	$BPaL_{1200}$		

* Treatment extended for additional 3 mo (9-mo total) if culture+ at month 4

B = bedaquiline
Pa = pretomanid (Pa-824)
L = linezolid 1200 mg

- Single arm phase 3 clinical trial; 109 participants enrolled (accrual closed early due to opening of ZeNiX study)
- Inclusion criteria: Adults, children ≥14; HIV-; HIV+ with CD4 >50
- Locations: South Africa
- Study started March 2015; estimated to complete in October 2021
- Preliminary results (CROI 2017): at 6-mo after completion of therapy, 29/35 (83%) successful outcome, 2 relapses/reinfections, 4 deaths (all during initial 8 wks)

ZeNix (XDR-TB or unresponsive MDR-TB)

Safety and Efficacy of Various Doses and Durations of Linezolid plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB

	Months 1-2	Months 3-4*	Months 5-6
Arm 1	$B_{200}PaL_{1200}$	$B_{100}PaL_{1200}$	
Arm 2	$B_{200}PaL_{1200}$	$B_{100}Pa$	
Arm 3	$B_{200}PaL_{600}$	$B_{100}PaL_{600}$	
Arm 4	$B_{200}PaL_{600}$	$B_{100}Pa$	

B = bedaquiline
Pa = pretomanid (Pa-824)
L = linezolid

* Treatment extended for additional 3 mo (9-mo total) if culture+ at month 4

- Phase 3 randomized clinical trial; LZD treatment dose/duration blinded (placebo-controlled); sample size 180
- Inclusion criteria: Adults, children ≥14; HIV-; HIV+
- Locations: South Africa, Georgia
- Study started Nov 2017; estimated to complete in Jan 2022

TB-PRACTECAL (XDR-TB or unresponsive MDR-TB)

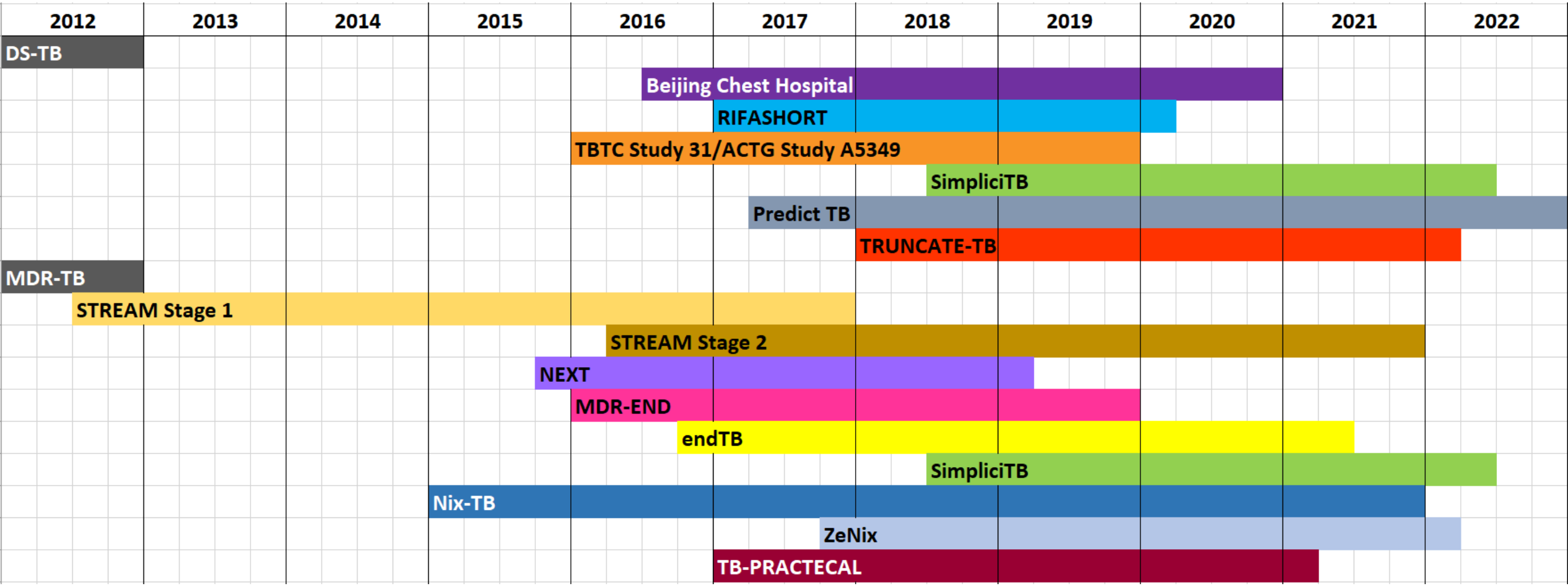
Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s)

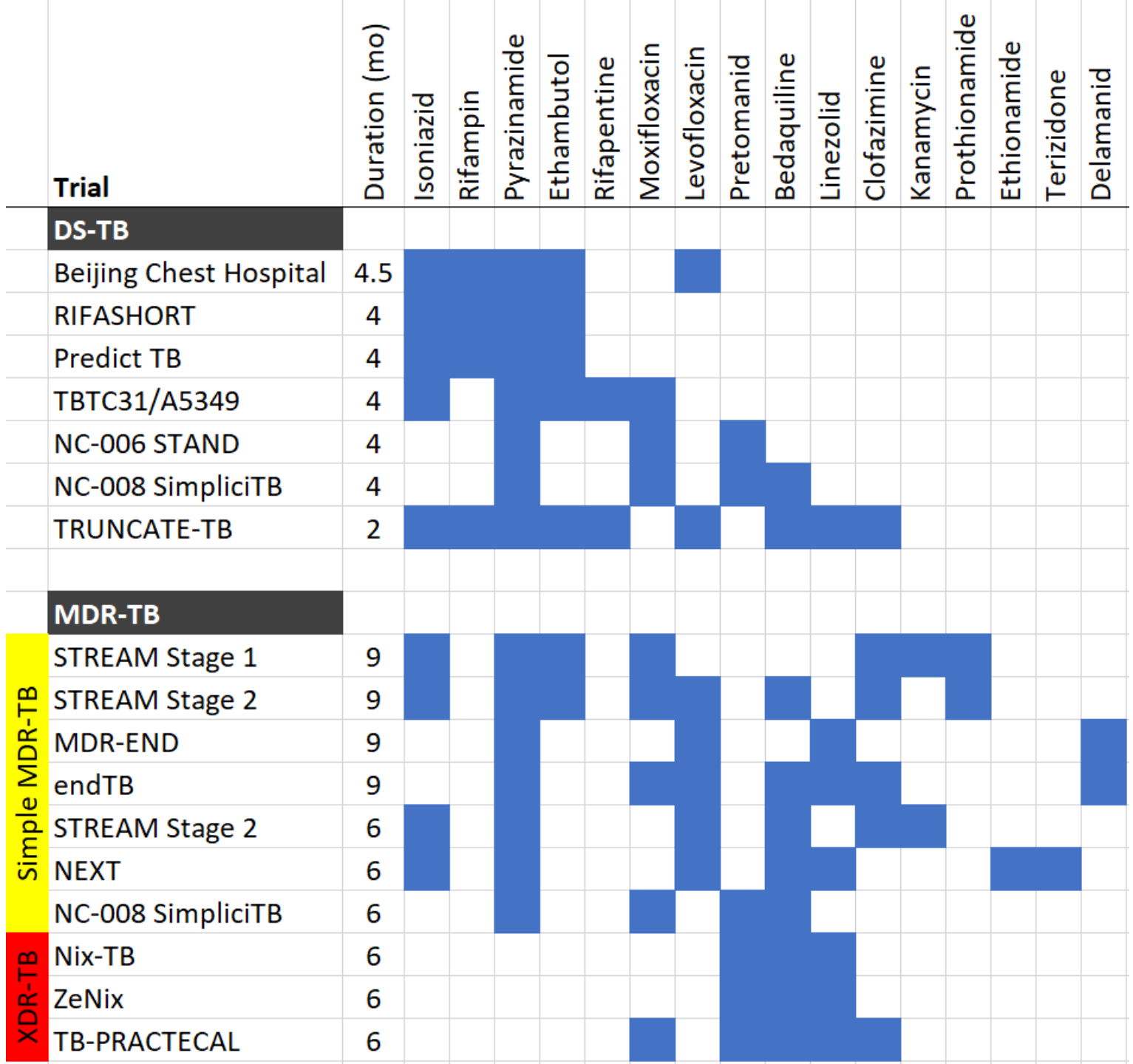
	Months 1-6	Months 7-24
Control	WHO	WHO
Arm 1	BPaLM	
Arm 2	BPaLC	
Arm 3	BPaL	

B = bedaquiline
Pa = pretomanid (Pa-824)
L = linezolid
M = moxifloxacin
C = clofazimine

- Phase 2-3 randomized clinical trial; sample size 630
- Inclusion criteria: adults, HIV+ or –
- Locations: multiple clinics in Belarus, South Africa, Uzbekistan
- Study started Jan 2017; estimated to complete in Mar 2021

Timeline of Current Clinical Trials




Trial
Duration (mo)
Isoniazid
Rifampin
Pyrazinamide
Ethambutol
Rifapentine
Moxifloxacin
Levofloxacin
Pretomanid
Bedaquiline
Linezolid
Clofazimine
Kanamycin
Prothionamide
Ethionamide
Terizidone
Delamanid
DS-TB
Beijing Chest Hospital 4.5
RIFASHORT 4
Predict TB 4
TBTC31/A5349 4
NC-006 STAND 4
NC-008 SimpliciTB 4
TRUNCATE-TB 2
MDR-TB
Simple MDR-TB
STREAM Stage 1 9
STREAM Stage 2 9
MDR-END 9
endTB 9
STREAM Stage 2 6
NEXT 6
NC-008 SimpliciTB 6
XDR-TB
Nix-TB 6
ZeNix 6
TB-PRACTECAL 6

2018 Global New TB Drug Pipeline [1]

Early Stage

Caprazene nucleoside CPZEN-45*

Spectinamide 1810*

Gyrase inhibitor SPR-720 (pVXc-486)*

Pyrazolopyridine carboxamide TB-47*

Fluoroquinolone DC-159a

GMP/ GLP Tox.

BTZ-043*

TBAJ-587

TBI-223

GSK-286*

Phase 1

TBI-166

Macozinone* (PBTZ-169)

OPC-167832*

Q203*

GSK-656* (070)

TBA-7371*

Contezolid (MRX-4/MRX-1)

Phase 2

Delpazolid (LCB01-0371)

Sutezolid (PNU100480)

SQ-109*

Macozinone* (PBTZ-169)

Phase 3

Bedaquiline* (TMC-207)

Delamanid* (OPC-67683)

Pretomanid* (PA-824)

Underline = new to Phase since October 2017

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: Energy / QcrB / ATP Synthase

Early Stage

- Caprazene nucleoside CPZEN-45*
- Spectinamide 1810*
- Fluoroquinolone DC-159a
- Gyrase inhibitor SPR-720 (pVXc-486)*
- Pyrazolopyridine carboxamide TB-47*

GMP / GLP Tox.

- BTZ-043*
- TBAJ-587
- TBI-223
- GSK-286*

Phase 1

- TBI-166
- Macozinone* (PBTZ-169)
- OPC-167832*
- Q203*
- GSK-656*
- Contezolid (MRX-4/MRX-1)
- TBA-7371*

Phase 2

- Delpazolid (LCB01-0371)
- Sutezolid (PNU-100480)
- SQ-109*
- Macozinone* (PBTZ-169)

Phase 3

- Bedaquiline (TMC-207)
- Delamanid (OPC-67683)
- Pretomanid (PA-824)

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WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: Protein Synthesis

Preclinical Development | **Clinical Development**

Early Stage	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazene nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU-100480)	Delamanid (OPC-67683)
Fluoroquinolone DC-159a	TBI-223	OPC-167832*	SQ-109*	Pretomanid (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	GSK-286*	Q203*	Macozinone* (PBTZ-169)	
Pyrazolopyridine carboxamide TB-47*		GSK-656*		
		Contezolid MRX-4/MRX-1		
		TBA-7371*		

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

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Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: Cell Wall DprE1

Preclinical Development | **Clinical Development**

Early Stage	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazene nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU-100480)	Delamanid (OPC-67683)
Fluoroquinolone DC-159a	TBI-223	OPC-167832*	SQ-109*	Pretomanid (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	GSK-286*	Q203*	Macozinone* (PBTZ-169)	
Pyrazolopyridine carboxamide TB-47*		GSK-656*		
		Contezolid MRX-4/MRX-1		
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WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: MmpL3

Preclinical Development | **Clinical Development**

Early Stage	GMP/ GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazen nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU100480)	Delamanid (OPC-67683)
Fluoroquinolone DC-159a	TBI-166	OPC-167832*	SQ-109*	Pretomanid (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	TBI-223	Q203*	Macozinone* (PBTZ-169)	
Pyrazolopyridine carboxamide TB-47*	GSK-286*	GSK-656*		
		Contezolid (MRX-4/MRX-1)		
		TBA-7371*		

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

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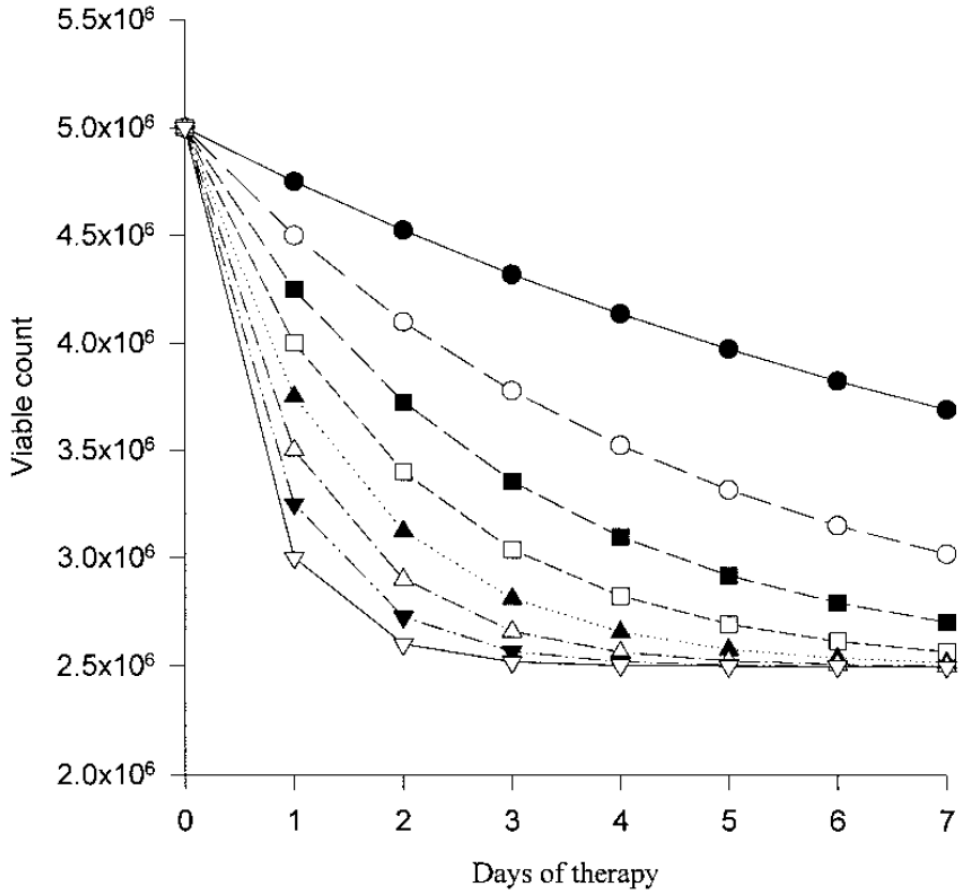
WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2018

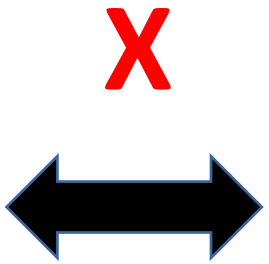
Early Bactericidal Activity (EBA) Studies

- EBA: Mean daily $\log_{10}$ decline of CFU/mL sputum/day on treatment (single drug or combination regimen) for up to 14 days
  - Small sample size
  - Short duration
  - Safe
  - Dosing/toxicity information
  - **Endorsed by U.S. FDA and TB Global Alliance**



*Early Bactericidal Activity (EBA):

1. **Fluoroquinolones** $_{2\text{-}7}$: 0.24-0.27
   SM+ INH+RIF+PZA+EMB (HRZE): 0.27
2. **INH** 300 $_{0\text{-}14}$: 0.192
3. **EMB** (25mg/kg) $_{0\text{-}14}$: 0.177
4. **RIF 10** $_{2\text{-}14}$: 0.113
5. **PZA** $_{\mathbf{0}\text{-}14}$: 0.096



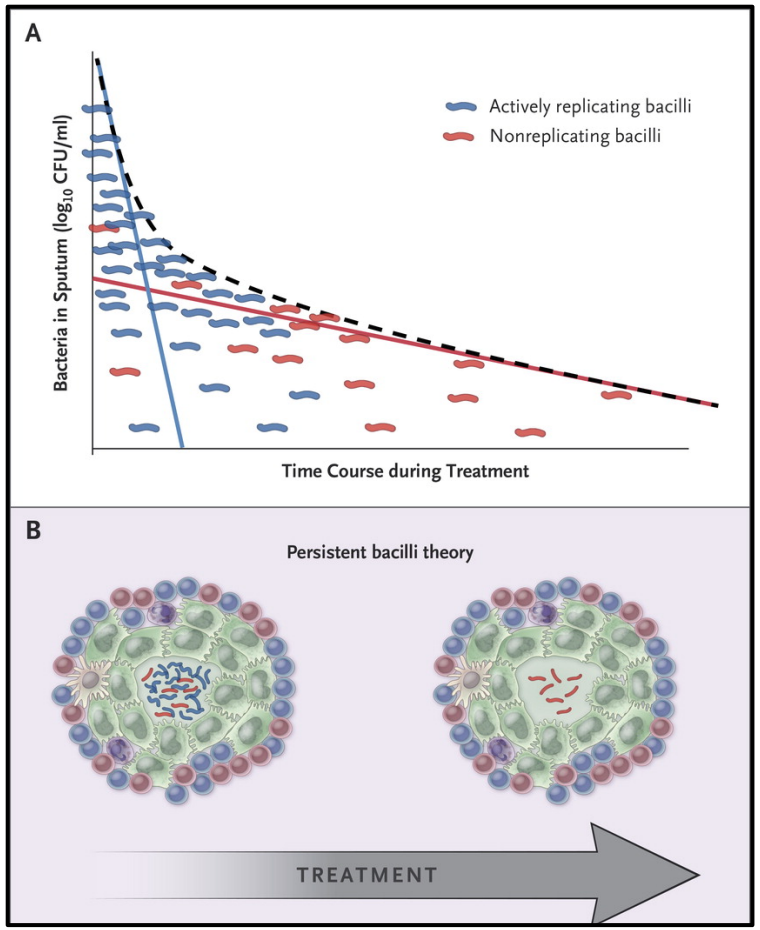
Clinical experience in achieving **durable cure**

1. **INH+RIF+PZA+EMB (HRZE)** [1]
2. **Rifampin (RIF; R)**
3. **Pyrazinamide (PZA; Z)**[1] **or Isoniazid (INH; H)**[1]
4. **Fluoroquinolones**[1]
5. **Ethambutol (EMB; E)**[1] (even at 25 mg/kg dose)

***Early Bactericidal Activity (EBA):** Mean daily $\log_{10}$ decline of CFU/mL sputum/day on drug(s) of interest for up to **14 days**

Jindani et al 2003. Am J Respir Crit Care Medicine
Jindani A et al. American Review of Respiratory Disease, Vol 121, 1980

[1]Original BMRC Phase III trials 1952-1986

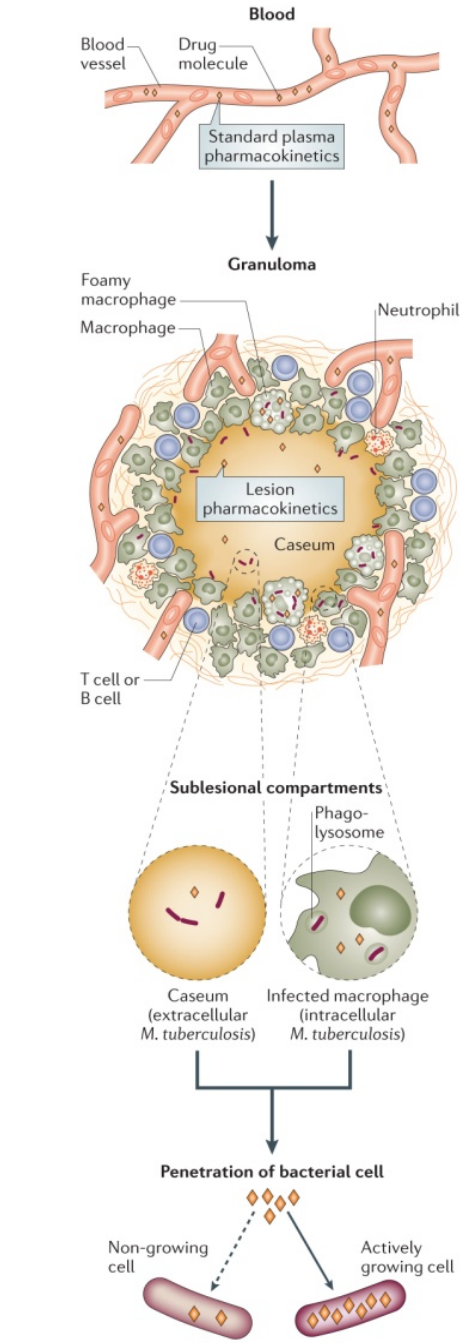


Why do EBA studies predict clinical treatment response so poorly?

Persistent Mtb populations sequestered in poorly vascularized compartments
(ex. caseum, inside granulomas)
= major culprit for relapse

Drug penetration and activity in these compartments is important for <u>durable cure</u>

Sputum measurements of Phase 2 methods may not capture treatment effects in these sequestered compartments

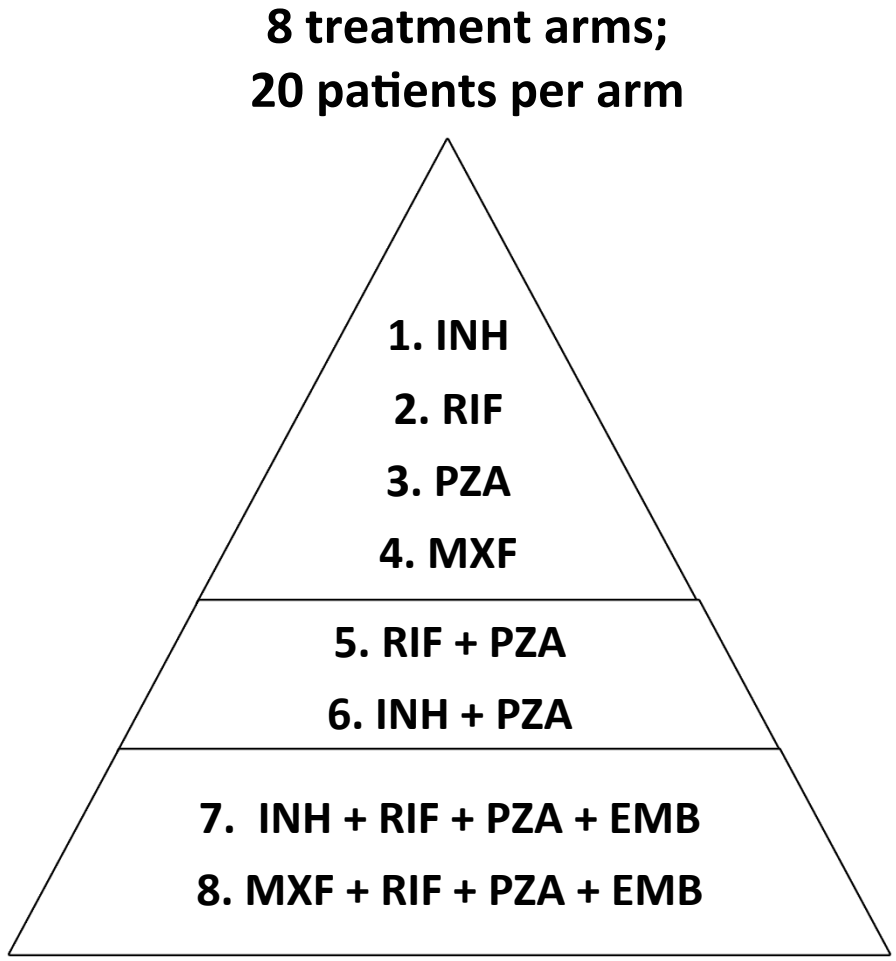


NEJM 2015; 373:2149-2160

Nat Rev Microbiology. 2014 Mar;12(3):159-67

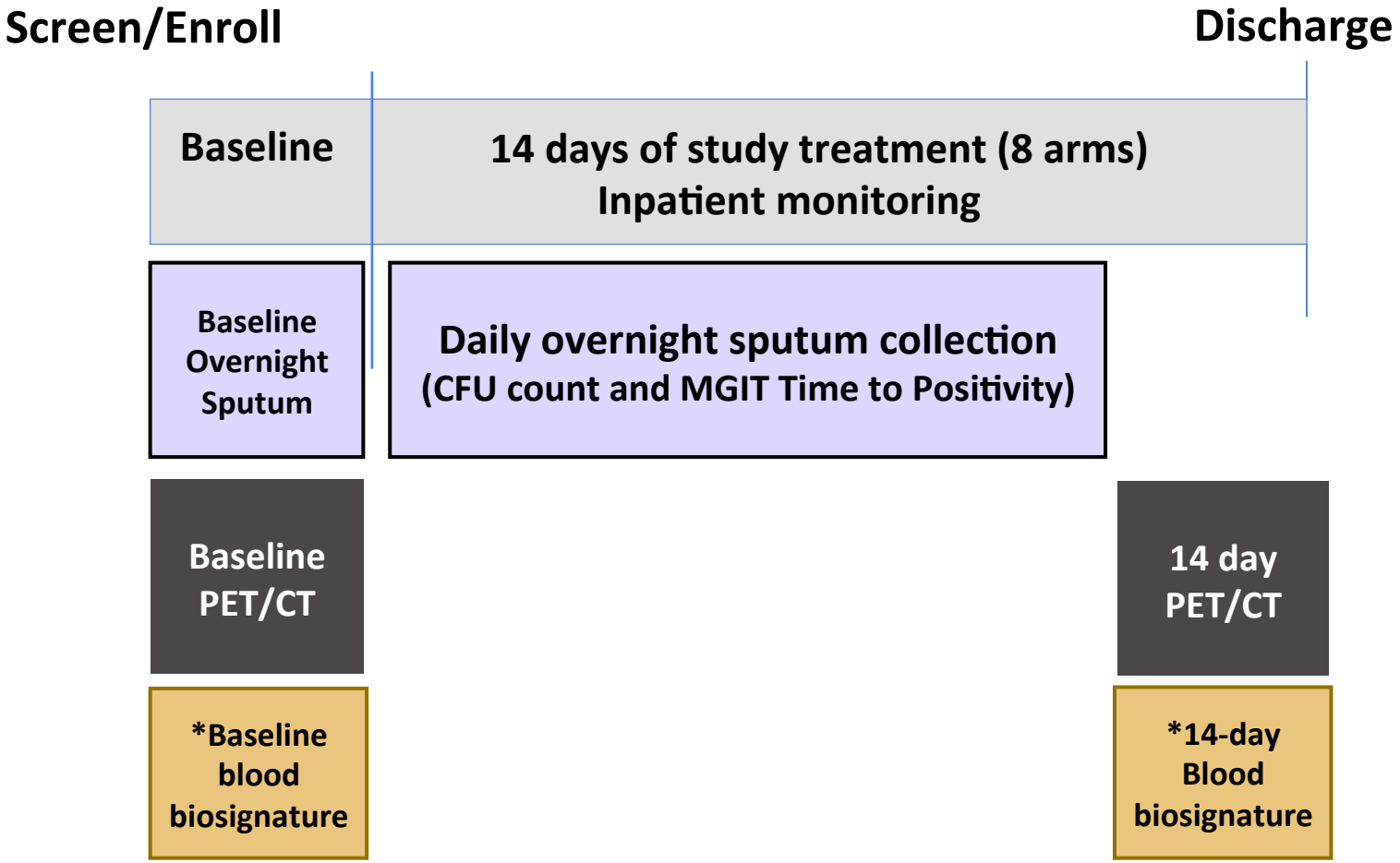
NexGen EBA

- Hypothesis: the ability of EBA studies to approximate the sterilizing potency of specific drugs or drug regimens will be improved by the addition of functional and anatomic radiologic markers ([^{18}F]-FDG-PET/CT) and dynamic immunologic markers.
- Prospective, randomized trial of pulmonary DS-TB patients in Cape Town, South Africa
- Patients randomized to 8 arms and treated for 14 days



INH = isoniazid; RIF = rifampin; PZA = pyrazinamide; EMB = ethambutol; MXF = moxifloxacin

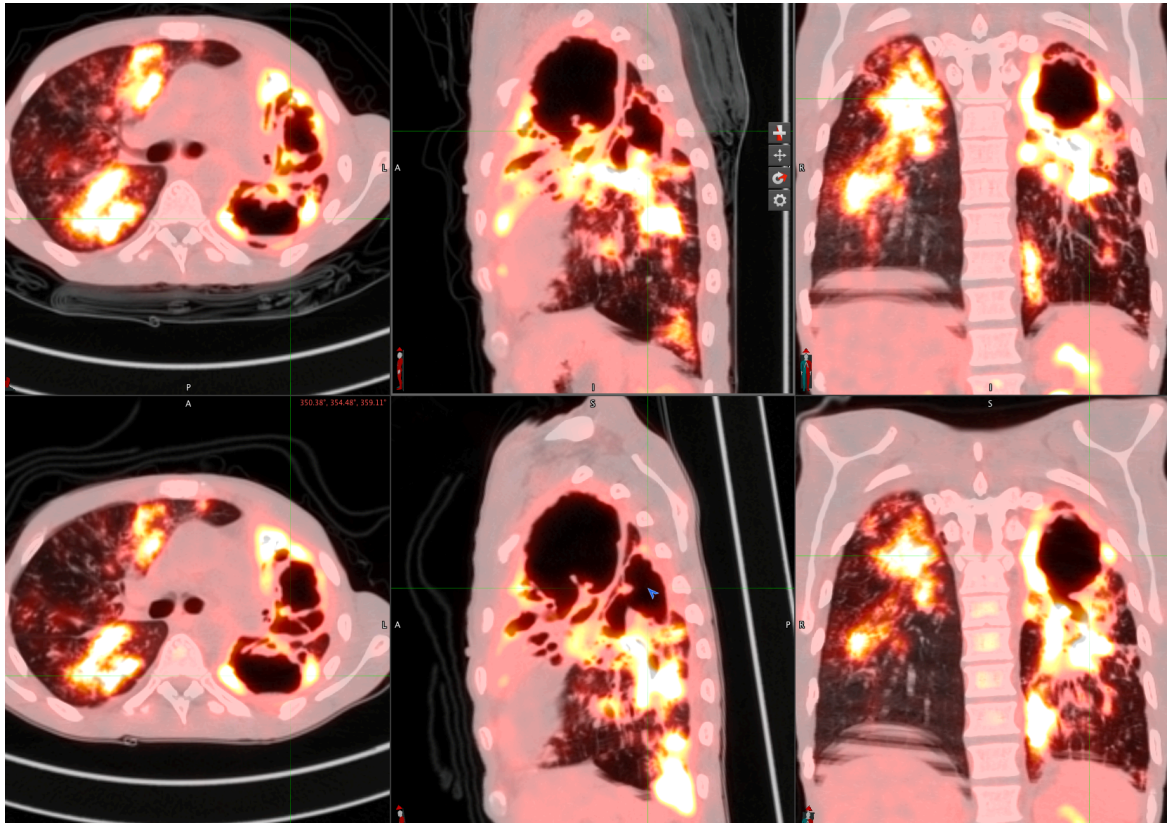
NexGen EBA



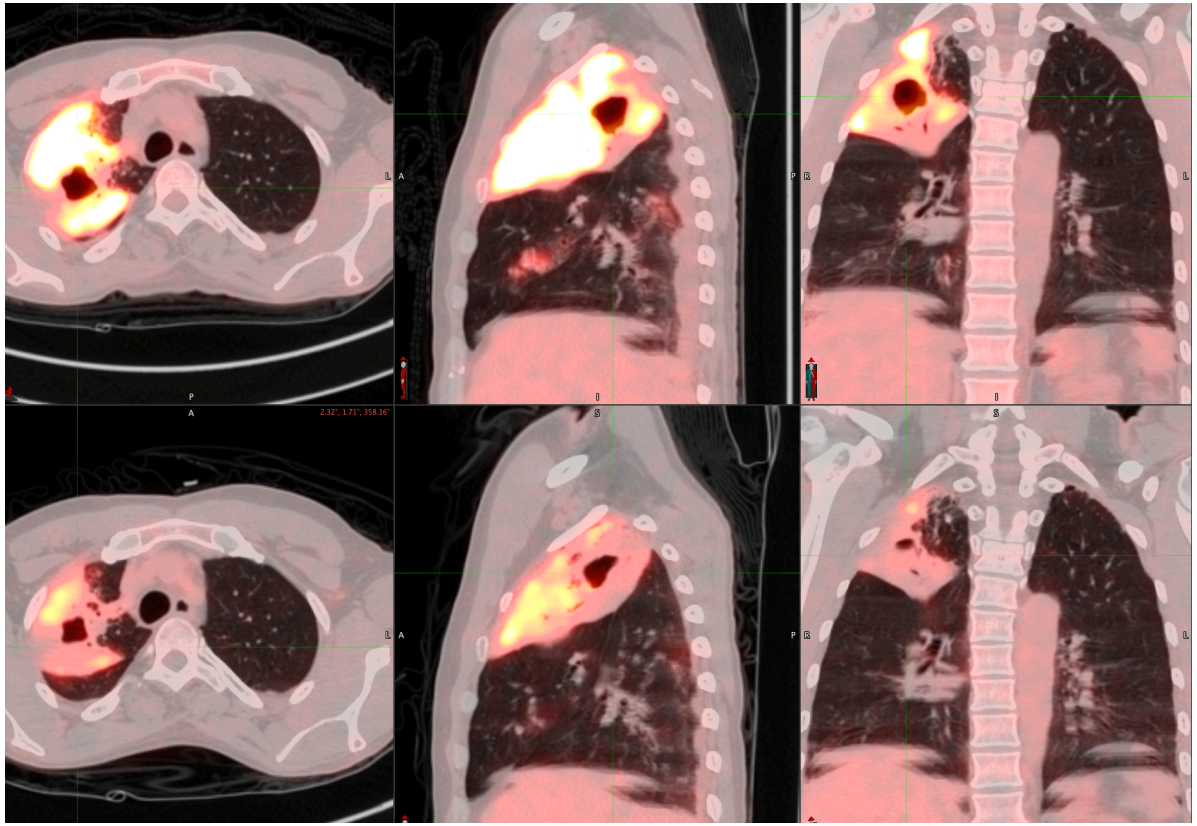
* Whole blood RNA signature [Thompson et al. Tuberculosis 2017; 107:48-58; Zak et al. Lancet 2016; 387: 2312–22.]

Can you see changes on PET/CT scan at 2 weeks?

1st participant to complete study



2nd participant to complete study



Conclusions

- Shortening TB treatment duration has been a research goal since effective TB therapy was established
  - With limited treatment options, all possible combinations and durations can be tested
  - With increasing numbers of novel drugs and drug classes becoming available, testing all possible combinations and durations is no longer practical or feasible
- Current methods to select best drugs/combinations and treatment durations are based on mice studies, EBA studies, and 2-month culture conversion rates
  - Recently completed treatment shortening clinical trials all failed
  - Currently ongoing trials generally also based on these same methods
- Better methodologies based on more than just sputum are needed to understand how to select the best drug combinations and durations in early phase trials to bring forward to later phase trials
- Future clinical trials based on better methodologies may have a better chance of success and thus consume fewer resources