La Tubercolosi : nuove prospettive terapeutiche

Roberto Parrella

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.
"AZIENDA OSPEDALIERA SPECIALISTICA DEI COLLI"
Monaldi - Cotugno - C.T.O.

UOC MALATTIE INFETTIVE RESPIRATORIE

Il sottoscritto Roberto Parrella
in qualità di relatore

ai sensi dell’art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

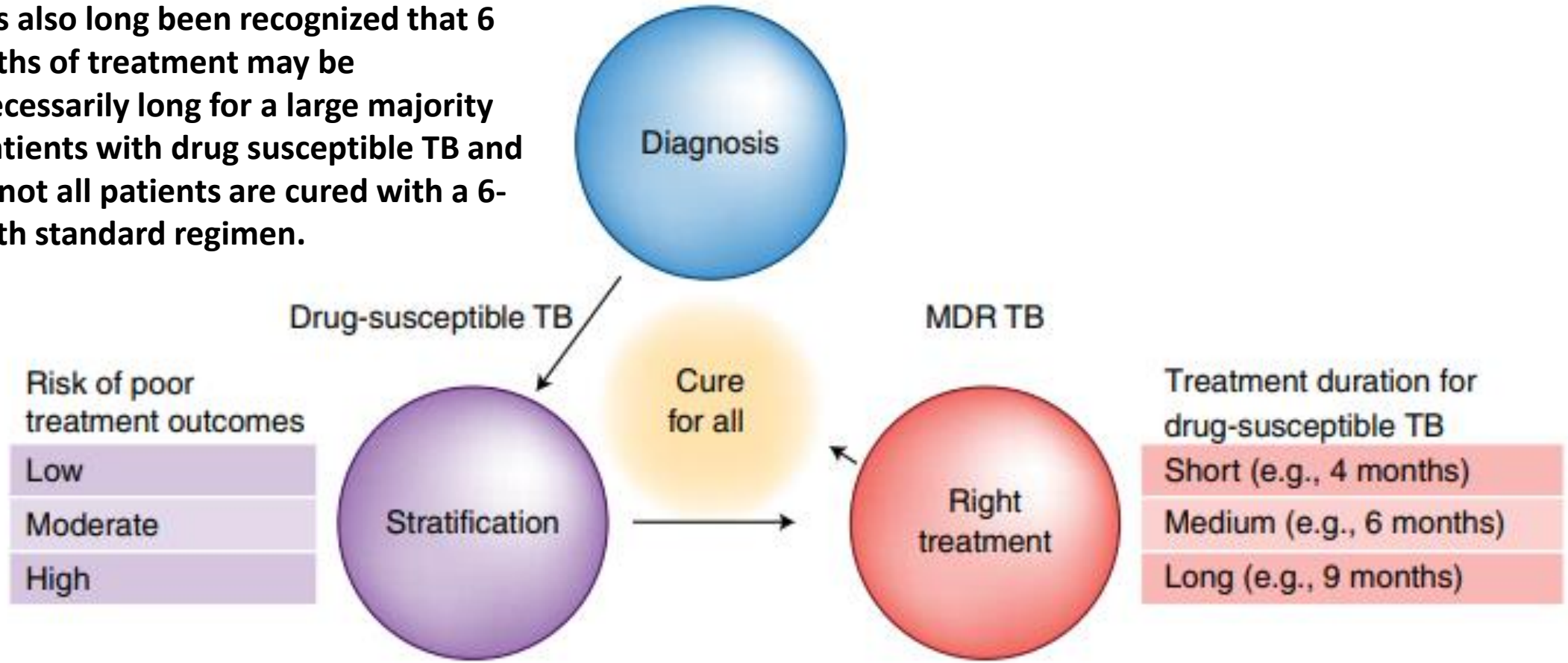
dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

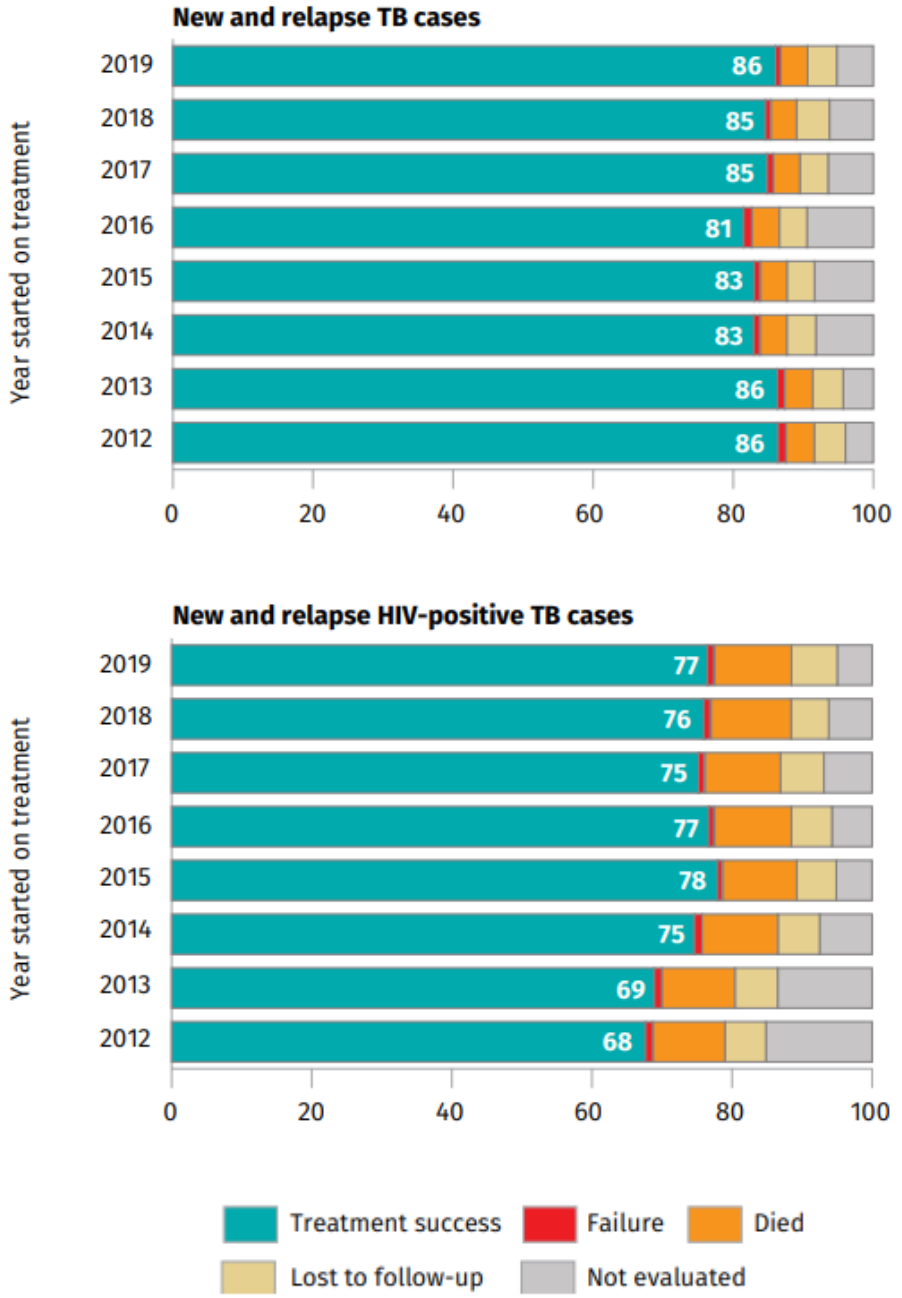
GILEAD, INSMED

A stratified approach to tuberculosis treatment

- **Pulmonary TB has a spectrum of disease, ranging from minimal to severe.**
- **It has also long been recognized that 6 months of treatment may be unnecessarily long for a large majority of patients with drug susceptible TB and that not all patients are cured with a 6-month standard regimen.**



- TB is a preventable and treatable infectious disease.
- According to the latest estimates from the WHO, more than 85% of patients affected by DS-TB achieve a successful outcome with anti-TB therapies.
- Presently there are 21 medicines from several drug classes available for the treatment of TB



- **Tuberculosis (TB) has remained a global health challenge despite the availability of effective anti-tubercular drugs and various treatment strategies.**

- **Apart from the complications related to TB disease per se, adverse effects of antitubercular therapy (ATT) also contribute to morbidity.**

- **In addition to the adverse effects, the long duration of the treatment regimen also reduces the patient's acceptability of ATT.**

- **The available "short-course treatment regimens" are still relatively long, thereby adversely affecting treatment compliance.**

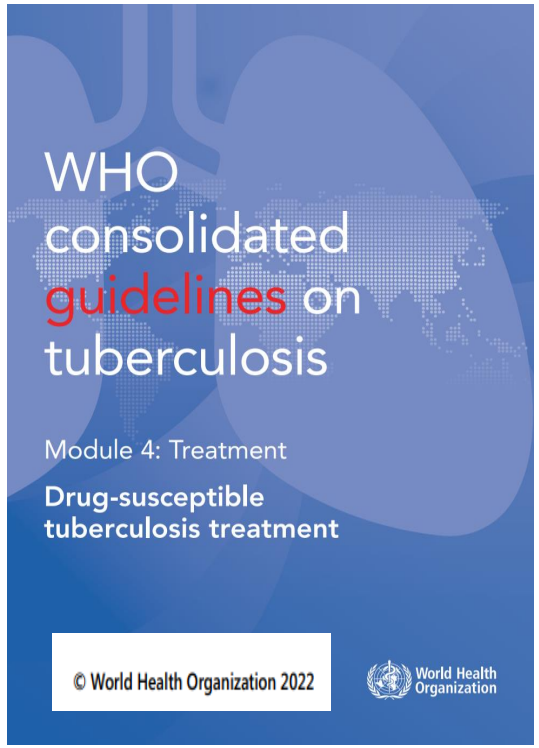
- **There is a need for effective, safe, short and intensive regimens for TB which can reduce the treatment cost and adverse effects, thereby improving its acceptance.**

https://doi.org/10.1183/2312508X.10024622

Current TB Therapy and Unmet Needs

Patient Population	Current Therapy	Unmet Needs
Drug-Susceptible TB	4 drugs; ≥6 month therapy	Shorter, simpler therapy
Drug-Resistant M(X)DR-TB	Few drugs (including injectables); ≥18 months therapy; toxicities	Totally oral, shorter, more efficacious, safer and lower cost therapy
TB/HIV Co-Infection	Drug-drug interactions with HIV medications	Ability to co-administer TB regimens with ARVs
Latent TB Infection	6-9 months of treatment	Shorter, safer therapy
Children	4 drugs; ≥6 month therapy	Shorter, simpler therapy with pediatric-friendly dosing

- Significant improvements in therapy are needed for all patient populations



Standard 6-month regimen

Treatment of drug-susceptible TB using 6-month regimen

Recommendation 1.

New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (strong recommendation, high certainty of evidence)

Remarks

A: The recommendation also applies to extrapulmonary TB – except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy.

B: WHO recommends that national TB control programmes provide supervision and support for all TB patients in order to ensure completion of the full course of therapy.

C: WHO recommends drug resistance surveys (or surveillance) for monitoring the impact of the treatment programme, as well as for designing standard regimens.

- This recommendation also applies to EPTB except **TB of the central nervous system, bone or joint** for which some expert groups suggest longer therapy.
- Pregnancy/children
- Daily
- Fixed dose combinations are preferrable
- If sputum smears are found positive at the end of intensive phase, extension of intensive phase is **not recommended**

The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Factors associated with *loss to follow-up* before and after treatment initiation among patients with tuberculosis: A 5-year observation in China

Youli Jiang[1†], Jingfang Chen[2†], Meng Ying[2], Linlin Liu[2], Min Li[1], Shuihua Lu[1], Zhihuan Li[3], Peize Zhang[1], Qingyao Xie[1], Xuhui Liu[2*] and Hongzhou Lu[2*]

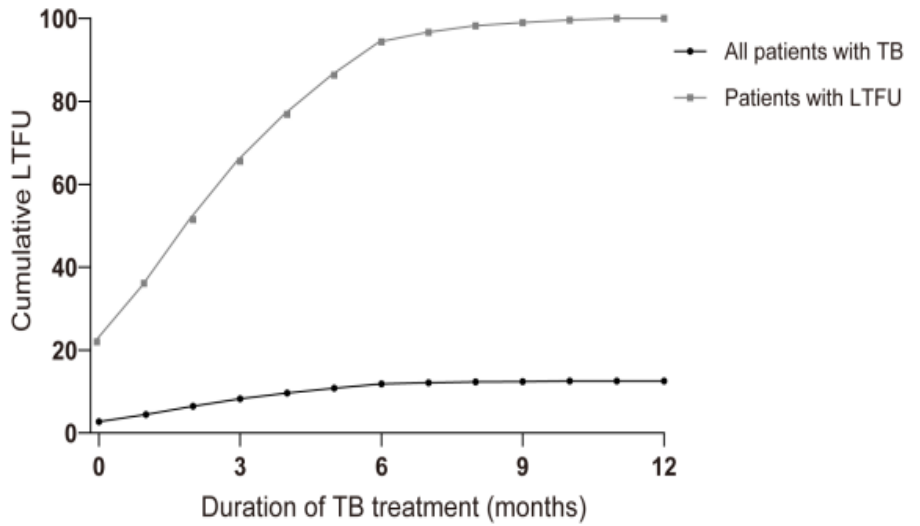


FIGURE 2
Comparison of cumulative percentage and event occurrence time of loss-to-follow-up (LTFU) cases in all patients with tuberculosis (TB) and patients with LTFU only over the treatment course (months). Nb. All patients with TB (*n*=24,265), patients with LTFU (*n*=3,046).

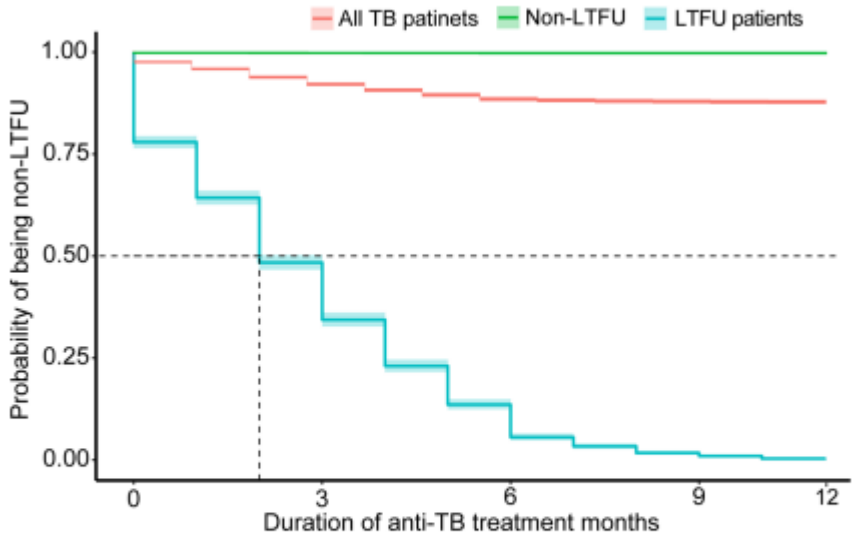


FIGURE 3
Time to loss to follow-up after diagnosing TB, using Kaplan–Meier analysis (*n*=24,265).

Factors of loss to follow-up during tuberculosis treatment in a low-incidence region☆

Facteurs prédictifs de perte de vue des patients traités pour tuberculose dans une région de faible incidence

M. Tetart [a], A. Meybeck [a,*], A. Assaf [a], M. Valette [a], P. Choisy [a], N. Blondiaux [b], E. Senneville [a]

Clinical and microbiological data, according to outcome.
Données cliniques et microbiologiques, selon le devenir.

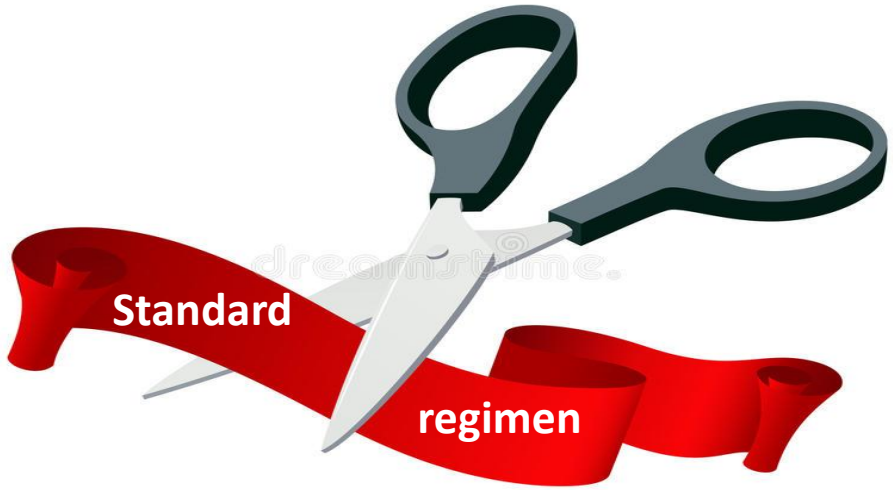
Characteristics	Total *n* = 190	Lost to follow-up *n* = 28	Successfully treated *n* = 124
Comorbidities			
High blood pressure	31 (16%)	5 (18%)	16 (13%)
Respiratory insufficiency	16 (8%)	4 (14%)	9 (7%)
Diabetes	17 (9%)	3 (11%)	6 (5%)
Neurological disease	14 (7%)	3 (11%)	8 (6%)
Cardiac insufficiency	8 (4%)	2 (7%)	4 (3%)
Immunosuppression			
HIV infection	44 (23%)	1 (4%)	37 (30%)
Other	28 (15%)	6 (21%)	14 (11%)
Hepatitis B or C chronic infection	11 (6%)	1 (4%)	10 (8%)
Depressive syndrome	60 (32%)	12 (43%)	41 (33%)
Prior TB treatment	32 (17%)	10 (36%)	17 (14%)
Anatomical site			
Pulmonary TB alone	83 (454%)		52 (42%)
Extrapulmonary TB	107 (56%)	11 (39%)	72 (58%)
Adenitis	61	5	46
Pleural	17	3	12
Genitourinary	18	2	9
Digestive	17	2	10
Bone	15	0	8
Meningitis	14	0	8
Pericarditis	7	1	5
Other	9	0	5
Symptoms			
Fatigue	141 (74%)	22 (77%)	91 (74%)
Cough	112 (59%)	19 (68%)	73 (59%)
Fever	106 (56%)	16 (57%)	63 (51%)
Sweats	96 (51%)	13 (46%)	63 (51%)
Dyspnea	40 (21%)	5 (18%)	28 (23%)
Thoracic pain	34 (18%)	5 (18%)	22 (18%)
Microbiological data			
Positive sputum smear	99 (52%)	15 (54%)	66 (56%)
Radiological data			
Cavitation	62 (33%)	10 (36%)	40 (32%)
Miliary pattern	37 (19%)	4 (14%)	20 (16%)

Treatment and outcome.
Traitement et évolution.

Characteristics	Total *n* = 190	Lost to follow-up *n* = 28	Successfully treated *n* = 124
Initial therapy			
Quadritherapy	156 (82%)	22 (82%)	106 (86%)
Triple therapy	20 (10%)	3 (11%)	11 (9%)
Fixed-dose formulation	129 (68%)	19 (70%)	88 (72%)
Anti-TB drug adverse events	88 (46%)	15 (56%)	58 (48%)
Grade 3-4	55 (29%)	10 (37%)	33 (27%)
Adjunctive therapy			
Corticosteroids	36 (19%)	3 (11%)	24 (20%)
Surgery	12 (6%)	1 (4%)	10 (8%)
Assistance to compliance			
DOT	8 (4%)	2 (8%)	5 (4%)
Therapeutic education	6 (3%)	0	5 (4%)
Sanatorium	4 (2%)	0	4 (3%)
Duration of hospitalization (days)			
< 15	61 (32%)	8 (30%)	43 (35%)
15–29	59 (30%)	11 (41%)	39 (32%)
30–59	46 (24%)	6 (22%)	28 (23%)
> 60	19 (10%)	2 (7%)	19 (10%)
Unknown	5 (3%)	0	0
Hospitalization in the intensive care unit	21 (11%)	2 (7%)	10 (8%)

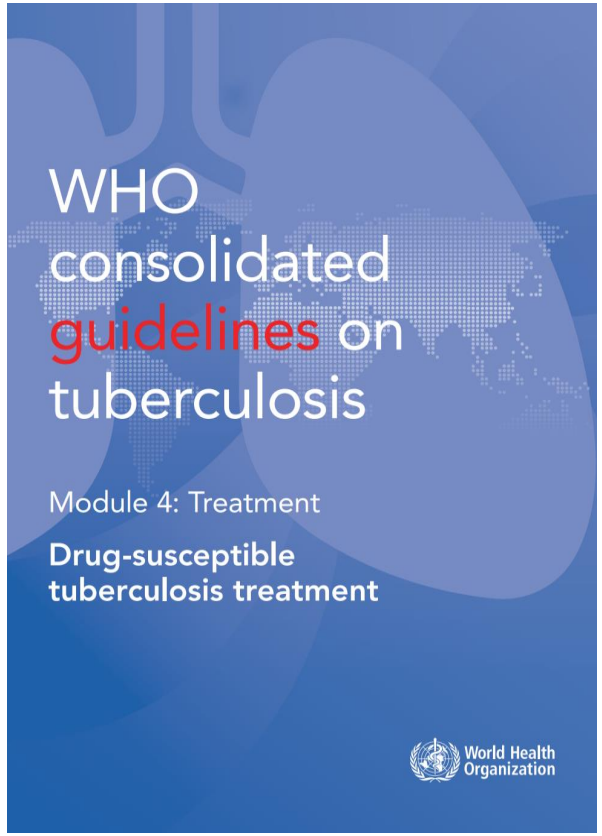
Médecine et maladies infectieuses 50 (2020) 28–35

Regime breve



- Shorter treatment regimens for TB disease can be more convenient and help patients finish treatment **faster**.

Treatment of drug-susceptible TB using 4-month regimens



- **Since the discovery of first-line anti-TB medicines and treatment regimens, there has been a search for shorter and more effective treatments for TB disease. This has resulted in various trials and other studies designed to assess whether treatment can be shortened, while remaining highly effective.**
- **Three phase III trials (i.e. REMoxTB, OFLOTUB, RIFAQUIN) failed to demonstrate non-inferiority of shorter regimens to treat DS-TB .**
- **A recent phase III trial (TBTC study 31/ACTG A5349, or S31/A5349, referred to below as "Study 31") assessed the safety and efficacy of two 4-month regimens for the treatment of DS-TB .**
- **Study 31 was the first and only phase III trial to demonstrate the non inferiority of the 4-month regimen for treatment of DS-TB when compared to the standard of care.**
- **This was the only trial to Study 31 was an international, multicentre, randomized, open-label, controlled, three-arm non inferiority trial among adolescents and adults (aged 12 years and above) with smear-positive10 and culture-positive pulmonary DS-TB.**

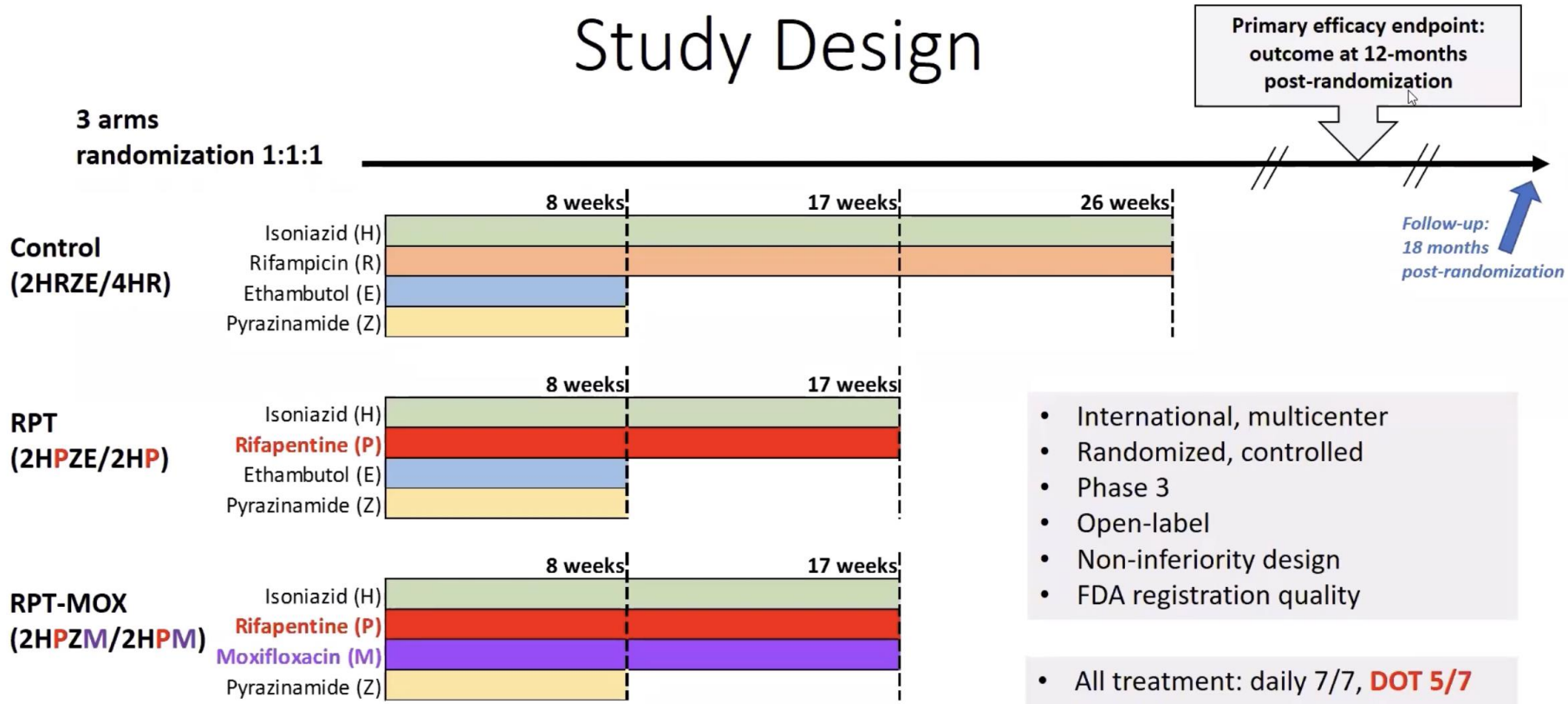
Study 31/ACTG A5349 was an international, multicentre, randomized, open-label, controlled, three-arm non inferiority trial among adolescents and adults (aged 12 years and above) with smear-positive and culture-positive pulmonary DS-TB . Study participants were recruited from 13 countries.

The **study objectives** were to evaluate the **efficacy** of:

1) a **rifapentine-containing regimen** to determine whether the single substitution of rifapentine for rifampicin makes it possible to **reduce** the duration of treatment for drug-susceptible pulmonary TB **to four months**; and

2) **a rifapentine-containing regimen that additionally substitutes moxifloxacin for ethambutol** and continues moxifloxacin throughout treatment, to determine whether the duration of treatment can be reduced, compared with the currently recommended 6-month regimen using a non-inferiority margin of 6.6 percentage points

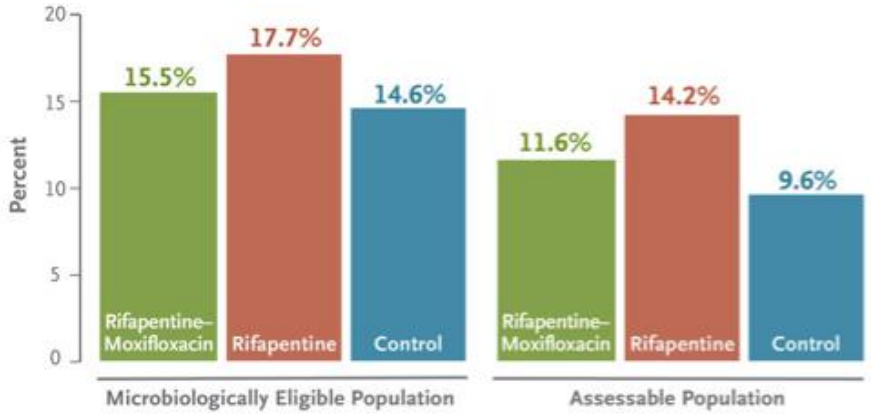
Study Design



- International, multicenter
- Randomized, controlled
- Phase 3
- Open-label
- Non-inferiority design
- FDA registration quality

- All treatment: daily 7/7, **DOT 5/7**
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT, no food with RIF

Safety labs & adverse events check: Weeks 2, 4, 8, 12, 17, 22, 26
Sputum at above plus Months 9, 12, 15, 18

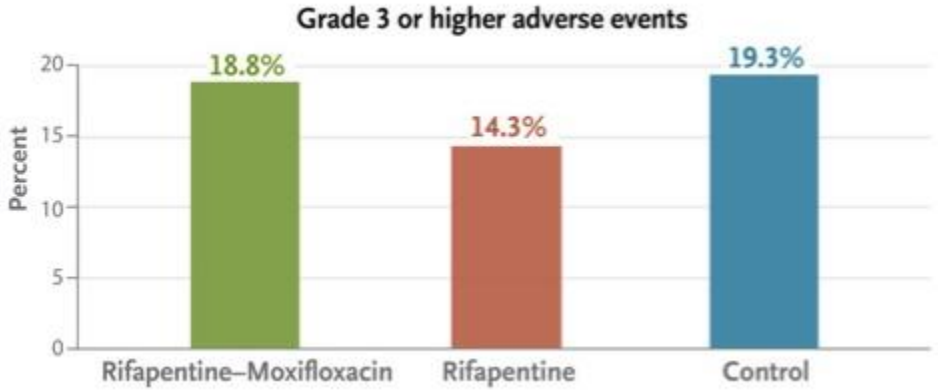


Outcome status: Favorable (Cure)

Primary efficacy analysis

Assessable analysis population

Outcome	Control (2HRZE/4HR)	RPT (2HPZE/2HP)	RPT-MOX (2HPZM/2HPM)	Total
Total in analysis population	**726**	**752**	**756**	**2234**
Total Favorable	**656 (90.4%)**	**645 (85.8%)**	**668 (88.4%)**	**1969 (88.1%)**
Culture negative at Month 12	643 (88.6%)	636 (84.6%)	656 (86.8%)	1935 (86.6%)
Seen at Month 12, but no sputum produced, or culture contaminated or unevaluable	13 (1.8%)	9 (1.2%)	12 (1.6%)	34 (1.5%)



CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.

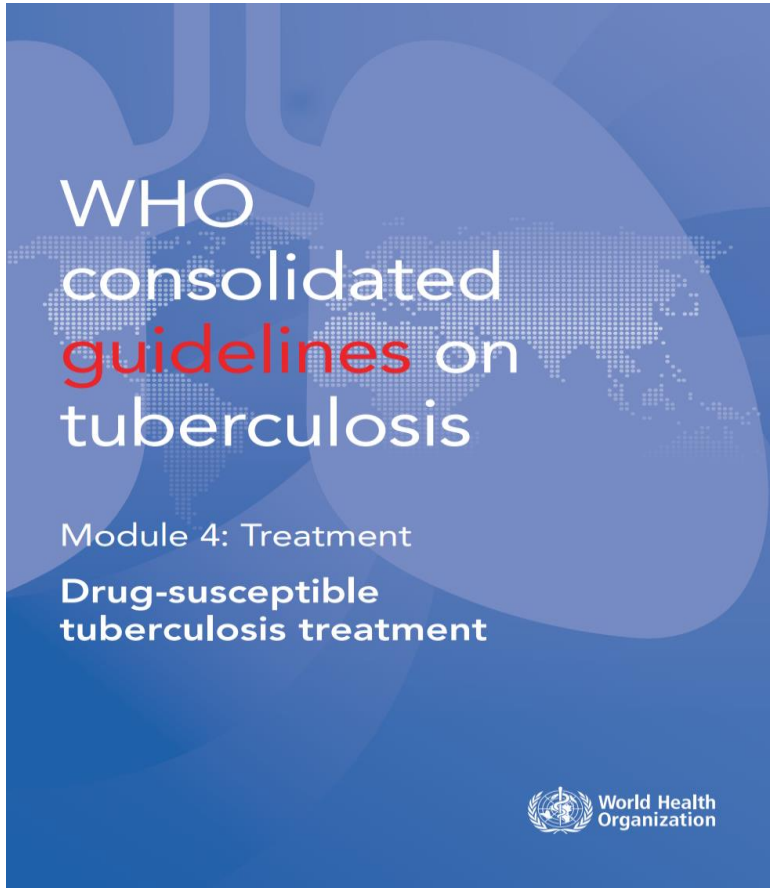
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- How the trial regimens perform in HIV-coinfected patients
- Whether the shorter treatment duration offsets the likely higher cost of the rifapentine–moxifloxacin regimen

N Engl J Med 2021; 384:1705-1718 DOI: 10.1056/NEJMoa2033400

Treatment of drug-susceptible TB using 4-month regimens



Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[8] (conditional recommendation, moderate certainty of evidence) – new recommendation.

2 months H + P + M + Z

and

2 months H + P + M

Two months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide,
followed by two months of isoniazid, rifapentine, and moxifloxacin

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.
- **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).

La rifapentina:

- ❖ non c’è ancora in Europa
- ❖ costa di più della rifampicina
- ❖ Si accumula nell’organismo con rischi di effetti collaterali non facilmente controllabili nemmeno con la sospensione

La moxifloxacina:

- ❖ costa di più dell’ etambutolo
- ❖ può dare problemi neurologici, gastrici, QTc lungo e tendinei

Treatment of drug-susceptible and drug-resistant tuberculosis

Christoph Lange, Thomas Theo Brehm, Dumitru Chesov ,Yousra Kherabi and Lorenzo Guglielmetti

This shorter treatment regimen has the potential to reduce the burden on healthcare systems, increase treatment adherence and allow faster cure.

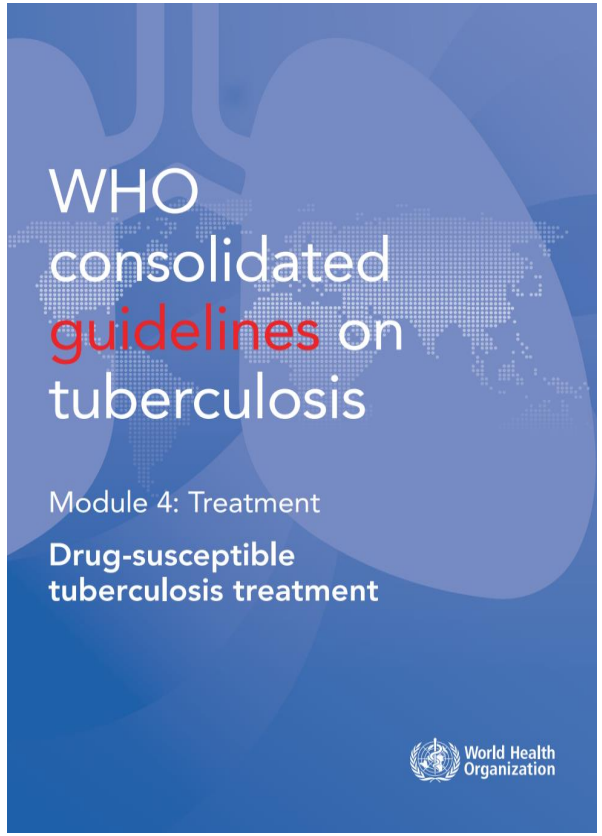
However, implementation and uptake are hampered by the limited availability of rifapentine.

As of March 2020, rifapentine has been registered only in 13 countries worldwide

A recent survey within the TB Network European Trials group (TBnet) showed that by October 2021, rifapentine was available in only 6 (14%) out of 43 participating countries of the WHO European region

https://doi.org/10.1183/2312508X.10024622

Treatment of drug-susceptible TB using 4-month regimens



Recommendation 7.

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used (strong recommendation, moderate certainty of evidence) – new recommendation.

Remarks:

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern;
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.
- The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV[16], or of isoniazid resistance[17].

SHINE trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

ABSTRACT

BACKGROUND
Two thirds of children with tuberculosis have nonsevere disease, which may be treatable with a shorter regimen than the current 6-month regimen.

METHODS
We conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 months (16 weeks) or 6 months (24 weeks) of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the World Health Organization. The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified intention-to-treat population). A noninferiority margin of 6 percentage points was used. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment.

RESULTS
From July 2016 through July 2018, a total of 1204 children underwent randomization (602 in each group). The median age of the participants was 3.5 years (range, 2 months to 15 years), 52% were male, 11% had human immunodeficiency virus infection, and 14% had bacteriologically confirmed tuberculosis. Retention by 72 weeks was 95%, and adherence to the assigned treatment was 94%. A total of 16 participants (3%) in the 4-month group had a primary-outcome event, as compared with 18 (3%) in the 6-month group (adjusted difference, −0.4 percentage points; 95% confidence interval, −2.2 to 1.5). The noninferiority of 4 months of treatment was consistent across the intention-to-treat, per-protocol, and key secondary analyses, including when the analysis was restricted to the 958 participants (80%) independently adjudicated to have tuberculosis at baseline. A total of 95 participants (8%) had an adverse event of grade 3 or higher, including 15 adverse drug reactions (11 hepatic events, all but 2 of which occurred within the first 8 weeks, when the treatments were the same in the two groups).

CONCLUSIONS
Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, nonsevere, smear-negative tuberculosis. (Funded by the U.K. Medical Research Council and others; SHINE ISRCTN number, ISRCTN63579542.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Turkova can be contacted at a.turkova@ucl.ac.uk or at the Medical Research Council Clinical Trials Unit, University College London, 90 High Holborn, London WC1V 6LJ, United Kingdom.

*The members of the SHINE Trial Team are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Gibb and Crook contributed equally to this article.

This article was updated on March 18, 2022, at NEJM.org.

N Engl J Med 2022;386:911-22.
DOI: 10.1056/NEJMoa2104535

CME at NEJM.org

1. Control regimen: 8 weeks RHZ(E) + 16 weeks RH

2. Shorter regimen: 8 weeks RHZ(E) + 8 weeks RH

Inclusion criteria: symptomatic **nonsevere** TB: respiratory TB confined to one lobe (opacification of <1 lobe) with no cavities, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymphnode TB

Randomization 1:1

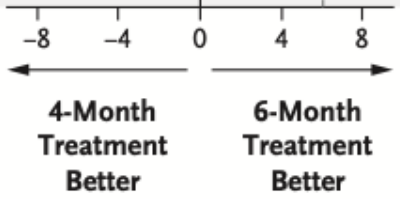
Primary outcome: unfavorable status by 72 weeks

Noninferiority margin: 6 percentage points

Courtesy of Marina Tadolini

SHINE trial

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)



Unfavorable status:

- treatment failure (treatment extension, change, or restart or tuberculosis recurrence),
- loss to follow-up during treatment,
- death,

with the exclusion of all the participants who had undergone randomization but did not complete 4 months of treatment (modified intention-to-treat population)

Courtesy of Marina Tadolini

1. Shorter regimens

2. Modified (increased) drugs dosage

- Standard rifampicin dosage (10 mg/Kg) may not be optimal
- Increased Rifampicin dosage might:
  - Daily dosage of 20 mg/Kg have bactericidal activity up to twice that of the 600-mg dose (reducing contagiousness duration)
  - Increase the sterilizing effect (reducing treatment duration) – [less certainty]
  - Prevent the emergence of rifampicin-resistant mutants (< risk of MDR-TB)
  - No costs issue

Safety of Rifampicin at High Dose for Difficult-to-Treat Tuberculosis: Protocol for RIAlta Phase 2b/c Trial

Juan Espinosa-Pereiro [1,2,†], Samiksha Ghimire [3,†], Marieke G. G. Sturkenboom [3], Jan-Willem C. Alffenaar [3,4,5,6], Margarida Tavares [7], Sarita Aguirre [8], Arturo Battaglia [9], Gladys Molinas [9], Teresa Tórtola [10], Onno W. Akkerman [11,12], Adrian Sanchez-Montalva [1,2,13,*] and Cecile Magis-Escurra [14]

- **A meta-analysis of 13 studies from 1979 to 2021, including adults with TB meningitis and pulmonary TB receiving doses up to 35 mg/kg, did not show an increase in the incidence of Severe Adverse Events (SAE), with a pooled Incidence Risk Ratio of 1.00 (95% confidence interval 0.82–1.23)**

- **Therefore, increased doses might have the potential to shorten DS-TB treatment.**

- **Pharmacokinetic studies show that a low proportion of patients reach target exposures with the current standard doses of rifampicin. For example, in a clinical trial in Indonesia, only 48% of the participants receiving standard dose rifampicin reached the 8 mg/L threshold for maximum plasma concentrations (Cmax) deemed to be effective**

- **In addition, adults with TB and other comorbidities such as HIV and diabetes may have lower exposure to rifampicin.**

Safety of Rifampicin at High Dose for Difficult-to-Treat Tuberculosis: Protocol for RIAlta Phase 2b/c Trial

Juan Espinosa-Pereiro [1,2,†], Samiksha Ghimire [3,†], Marieke G. G. Sturkenboom [3], Jan-Willem C. Alffenaar [3,4,5,6], Margarida Tavares [7], Sarita Aguirre [8], Arturo Battaglia [9], Gladys Molinas [9], Teresa Tórtola [10], Onno W. Akkerman [11,12], Adrian Sanchez-Montalva [1,2,13,*] and Cecile Magis-Escurra [14]

Table 1. Comparison of recent phase 2 trials using high-dose rifampicin for tuberculosis.

Study	Trial ID	Design	Population	Key Exclusion Criteria	Arms	Max. Rifampicin (mg/kg/day)	Follow-Up (Weeks)
Ruslami 2013	NCT01158755	Phase 2b, open label, randomized	≥15 years old with clinically suspected TB meningitis	Body weight < 30 kg, liver disease	2	13	26
HR1	NCT01392911	Phase 2a, open label, sequential allocation	18–65 years old with confirmed pulmonary DS-TB	High alcohol consumption, diabetes	7	50	2
RIFATOX	ISRCTN55670677	Phase 2b, open label, randomized	18–65 years old with confirmed pulmonary DS-TB	High alcohol consumption, diabetes, HIV	3	20	16
HIGH RIF-2	NCT00760149	Phase 2b, double blind, randomized	18–65 years old with confirmed pulmonary DS-TB	Body weight < 50 kg, clinical hepatitis/cholestasis	3	20	12
MAMS-TB	NCT01785186	Phase 2b,c, open-label, randomized	≥18 years old with confirmed pulmonary DS-TB	High alcohol consumption, HIV infection with <200 CD4	5	35	48
HIRIF	NCT01408914	Phase 2b, double blind, randomized	18–60 years old with confirmed pulmonary DS-TB	Body weight < 30 kg, viral hepatitis	2	20	26
RifT	ISRCTN42218549	Phase 2, open label, randomized	≥18 years old with clinically suspected TB meningitis	Cirrhosis or clinical jaundice	3	35	24
RIFAVIRENZ	NCT01986543	Phase 2, open label, randomized	≥15 years old with confirmed pulmonary DS-TB	AIDS-defining infection, pharmacological immunosuppression	2	20	28
RIAlta	NCT04768231	phase 2b,c, open label, historical controls	≥60 or ≥18 years old (with HIV, HBV, HCV, DM), pulmonary and extrapulmonary TB	Decompensated chronic liver disease, oral anticoagulation	1	35	72

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D., Christine Sekaggya-Wiltshire, Ph.D., Anchalee Avihingsanon, M.D., Rohit Sarin, M.D., Padmasayee Papineni, F.R.C.P., Andrew J. Nunn, M.Sc., and Angela M. Crook, Ph.D., for the TRUNCATE-TB Trial Team*

METHODS

- In this adaptive, open-label, noninferiority trial, we randomly assigned participants with rifampin-susceptible pulmonary tuberculosis to undergo either standard treatment (rifampin and isoniazid for 24 weeks with pyrazinamide and ethambutol for the first 8 weeks) or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse.
- There were four strategy groups with different initial regimens;
- noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–linezolid and bedaquiline–linezolid (each with isoniazid, pyrazinamide, and ethambutol).
- The primary outcome was a composite of death, ongoing treatment, or active disease at week 96.
- The noninferiority margin was 12 percentage points.

TRUNCATE-TB Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 9, 2023 VOL. 388 NO. 10

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D., Christine Sekaggya-Wiltshire, Ph.D., Anchalee Avihingsanon, M.D., Rohit Sarin, M.D., Padmasayee Papineni, F.R.C.P., Andrew J. Nunn, M.Sc., and Angela M. Crook, Ph.D., for the TRUNCATE-TB Trial Team*

ABSTRACT

BACKGROUND

Tuberculosis is usually treated with a 6-month rifampin-based regimen. Whether a strategy involving shorter initial treatment may lead to similar outcomes is unclear.

METHODS

In this adaptive, open-label, noninferiority trial, we randomly assigned participants with rifampin-susceptible pulmonary tuberculosis to undergo either standard treatment (rifampin and isoniazid for 24 weeks with pyrazinamide and ethambutol for the first 8 weeks) or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–linezolid and bedaquiline–linezolid (each with isoniazid, pyrazinamide, and ethambutol). The primary outcome was a composite of death, ongoing treatment, or active disease at week 96. The noninferiority margin was 12 percentage points.

RESULTS

Of the 674 participants in the intention-to-treat population, 4 (0.6%) withdrew consent or were lost to follow-up. A primary-outcome event occurred in 7 of the 181 participants (3.9%) in the standard-treatment group, as compared with 21 of the 184 participants (11.4%) in the strategy group with an initial rifampin–linezolid regimen (adjusted difference, 7.4 percentage points; 97.5% confidence interval [CI], 1.7 to 13.2; noninferiority not met) and 11 of the 189 participants (5.8%) in the strategy group with an initial bedaquiline–linezolid regimen (adjusted difference, 0.8 percentage points; 97.5% CI, −3.4 to 5.1; noninferiority met). The mean total duration of treatment was 180 days in the standard-treatment group, 106 days in the rifampin–linezolid strategy group, and 85 days in the bedaquiline–linezolid strategy group. The incidences of grade 3 or 4 adverse events and serious adverse events were similar in the three groups.

CONCLUSIONS

A strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment for tuberculosis with respect to clinical outcomes. The strategy was associated with a shorter total duration of treatment and with no evident safety concerns. (Funded by the Singapore National Medical Research Council and others; TRUNCATE-TB ClinicalTrials.gov number, NCT03474198.)

The authors' affiliations are listed in the Appendix. Prof. Paton can be contacted at nick_paton@nus.edu.sg or at Yong Loo Lin School of Medicine, NUHS Tower Block Level 10, 1E Kent Ridge Rd., Singapore 119228.

*A complete list of members of the TRUNCATE-TB Trial Team is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 20, 2023, at NEJM.org.

N Engl J Med 2023;388:873-87.
DOI: 10.1056/NEJMoa2212537

CME at NEJM.org

Initial Treatment Regimens used in the fully-enrolled ***Strategy Groups*** *evaluated for* ***unsatisfactory outcome***

Standard Treatment	24 w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8 w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8 w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8 w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8 w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

TRUNCATE-TB Trial

Unsatisfactory outcome (primary outcome), MITT

Outcome	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	Adjusted difference (97.5% CI)
Unsatisfactory outcome – no. (%)	7 (3.9)	21 (11.4)	7.4 (1.7 –13.2)

Outcome	Standard treatment (N= 181)	TRUNCATE strategy (BDQ/LZD) (N=189)	Adjusted difference (97.5% CI)
Unsatisfactory outcome – no. (%)	7 (3.9)	11 (5.8)	0.8 (-3.4 to 5.1)

Non inferiority margin: 12 percentage points

Treatment regimens for drug-susceptible PTB

Regimen	Intensive phase		Continuation phase		Comment
	Drugs	Duration, months	Drugs	Duration, months	
Regimen 1	H R Z E	2	H R	4	Traditional regimen
Regimen 2	H Rpt Z Mfx	4			Endorsed for nonpregnant patients aged ⩾12 years with body weight ⩾40 kg with drug-susceptible PTB by the WHO
Regimen 3	H R Z (E)	2	H R	2	Endorsed for children and adolescents between 3 months and 16 years of age with presumed drug-susceptible non-severe disease by the WHO

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; Rpt: rifapentine; Mfx: moxifloxacin.

https://doi.org/10.1183/2312508X.10024622

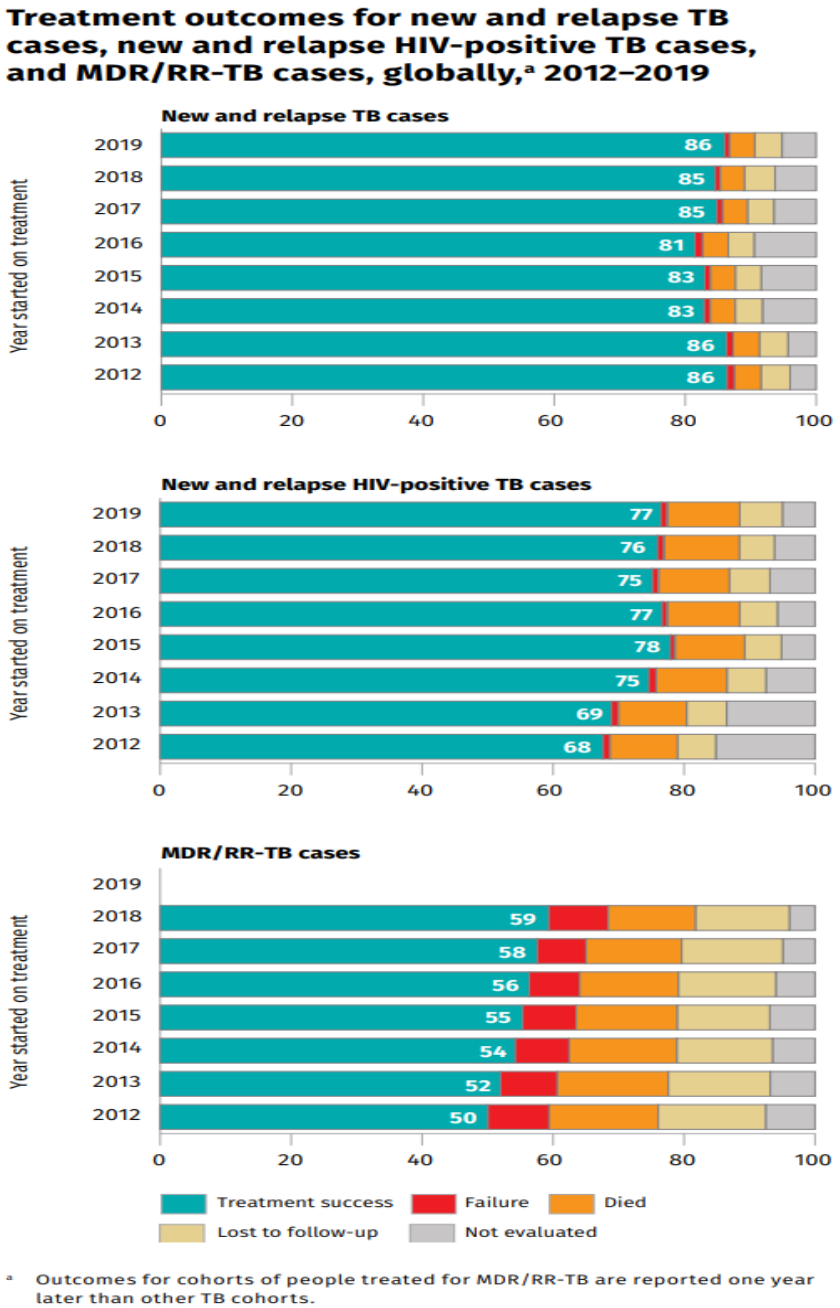
TB & antimicrobial resistance (#AMR)

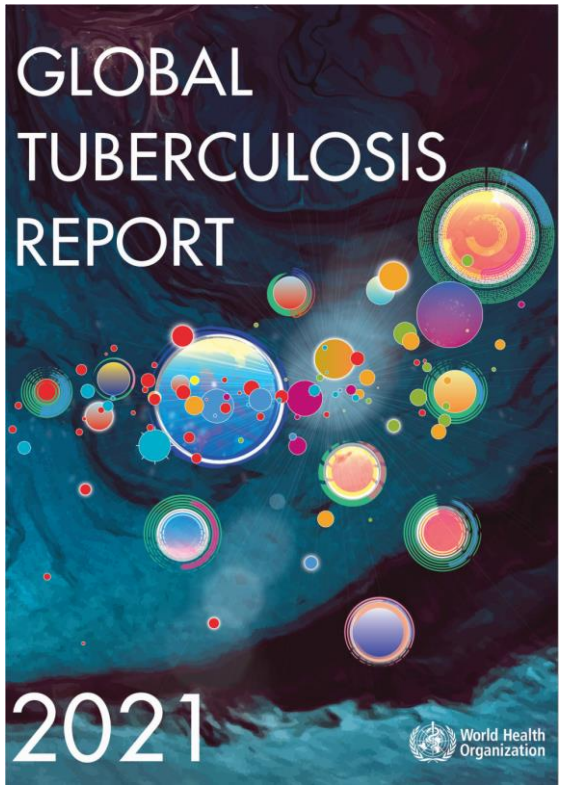
TB VAX ARM

For the past decades, treatment against DR-TB was recommended for a duration of at least 18 months with a combination of at least four active compounds was associated with a high rate of adverse drug events and high costs and resulted in not more than 60% treatment success overall .

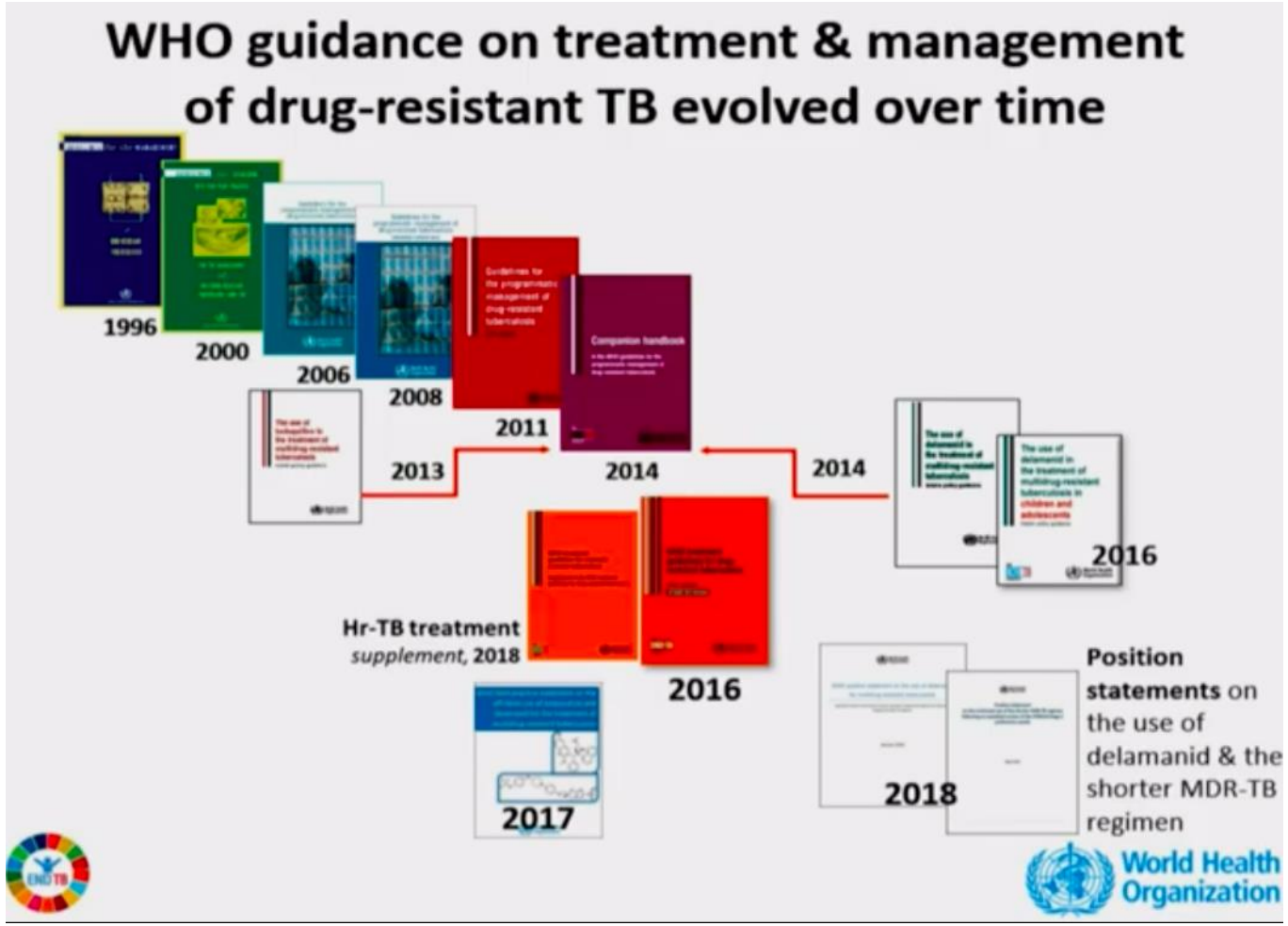
C. LANGE ET AL.

THE CHALLENGE OF TB IN THE 21ST CENTURY





MDR/XDR TB

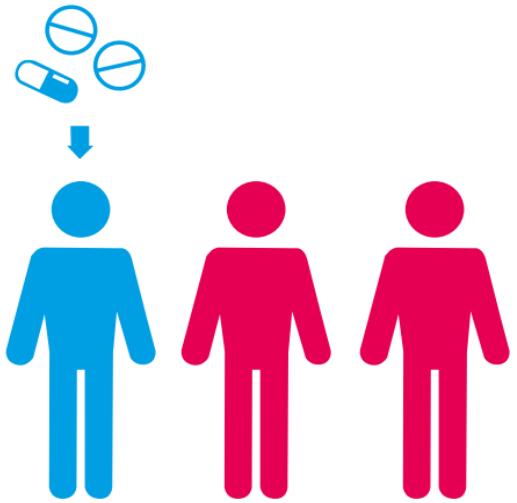


- In its 2016 guidelines, the WHO recommended that all cases of rifampicin-resistant TB, regardless of isoniazid susceptibility (*i.e.* RMR-TB), should be managed as MDR-TB.

- **In 2018, WHO revised its guidelines recommending the use of shorter and all-oral regimens:**
  - **SCALE UP OF DR-TB TREATMENT THROUGH DECENTRALIZED CARE**
  - **OUTPATIENT TREATMENTS**
  - **REDUCED PATIENTS DISCONFORT**
  - **LESS SIDE EFFECTS**
  - **REDUCED MONITORING**

Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis,

27-29 October 2020



World Health Organization

Box 2. Definition of pre-XDR-TB and updated definition of XDR-TB[a]

Pre-XDR-TB: TB caused by ***Mycobacterium tuberculosis*** **(*M. tuberculosis*)** strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone[a]

XDR-TB: TB caused by ***Mycobacterium tuberculosis*** **(*M. tuberculosis*)** strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone[a] and at least one additional Group A drug[b]

	Steps	Medicine	Abbreviation
Group A	Include all three medicines	Levofloxacin OR moxifloxacin	Lfx Mfx
		Bedaquiline[#,¶]	Bdq
		Linezolid[+]	Lzd
Group B	Add one or both medicines	Clofazimine	Cfz
		Cycloserine OR terizidone	Cs Trd
Group C	Add to complete the regimen and when medicines from groups A and B cannot be used	Ethambutol	E
		Delamanid[¶,§]	Dlm
		Pyrazinamide[f]	Z
		Imipenem–cilastatin OR meropenem[##]	Ipm–Cln Mpm
		Amikacin (OR streptomycin)[¶¶]	Am (S)
		Ethionamide OR prothionamide[++]	Eto Pto
		p-Aminosalicylic acid[++]	PAS

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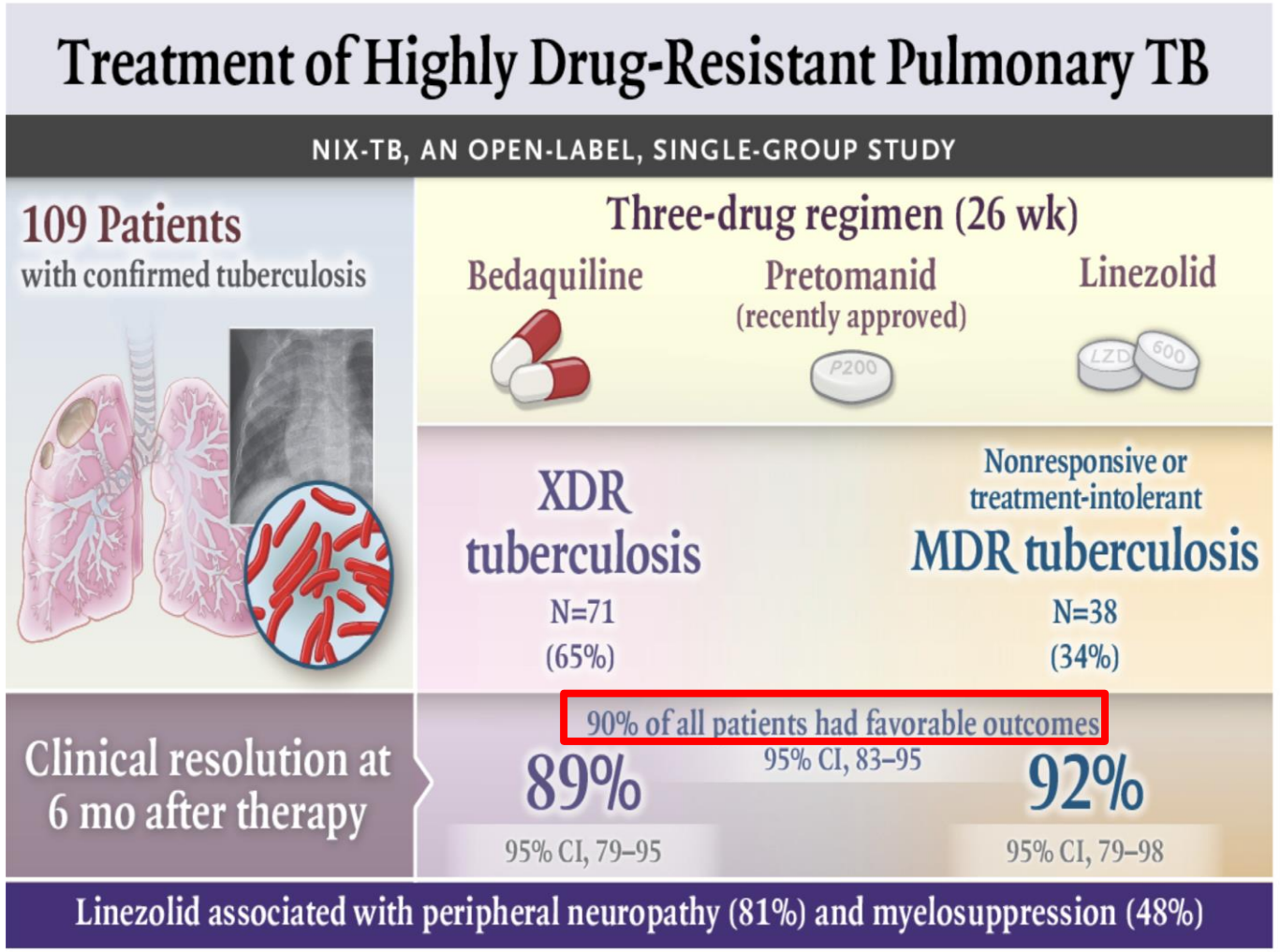
Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Pretomanid, a nitroimidazooxazine that inhibits mycolic acid biosynthesis and thereby blocks mycobacterial cell-wall production, also acts as a respiratory poison against non-replicating bacteria after nitric oxide release under anaerobic conditions

STUDY DESIGN

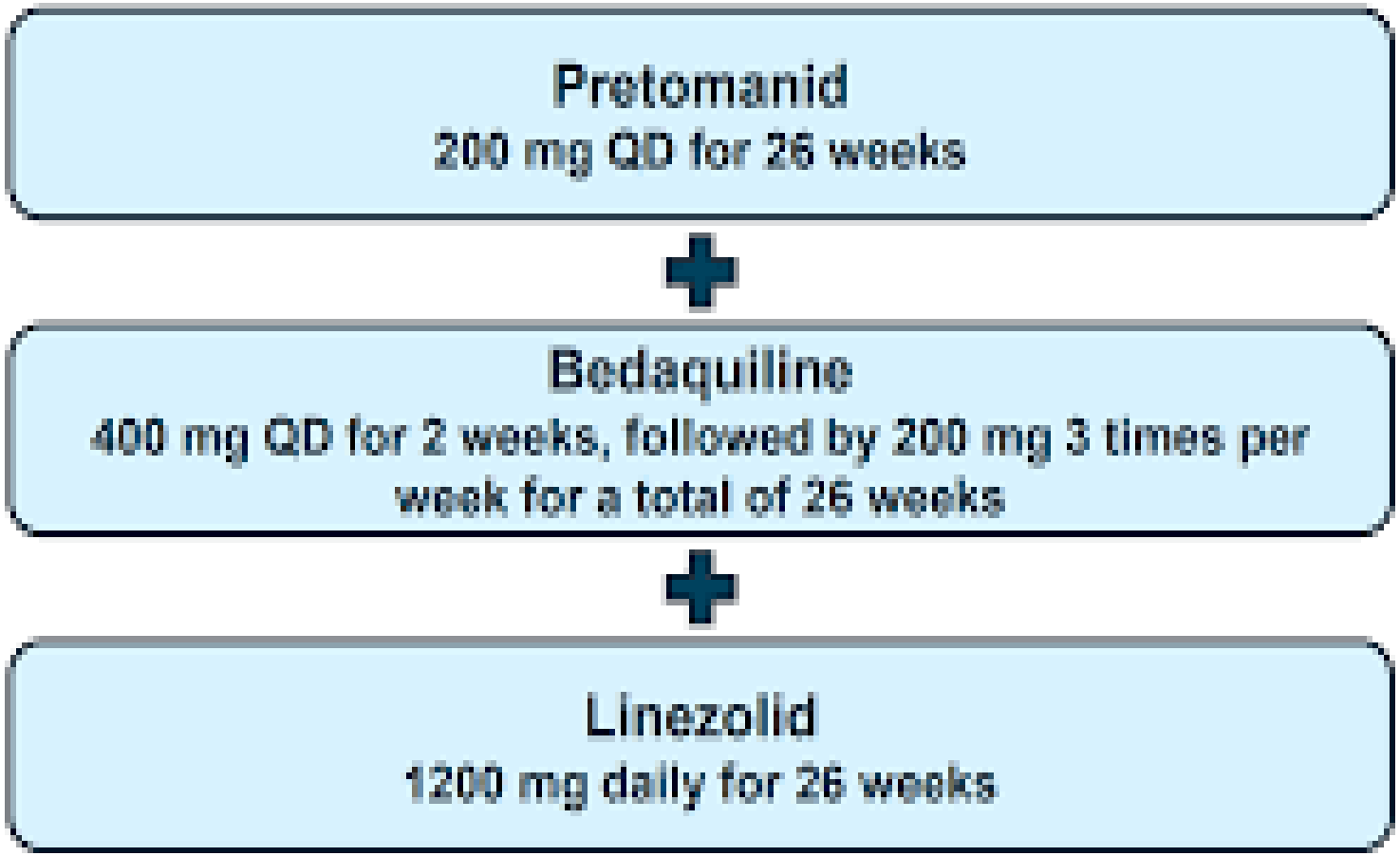
Nix-TB is an open-label, single-group study involving patients with XDR tuberculosis and patients with MDR tuberculosis that is not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. All patients received 26 weeks of daily oral treatment, with an option to extend treatment to 39 weeks if they were culture-positive at week 16. An interim analysis for safety was conducted after every 15 enrollments.



The outcome of the Nix-TB trial changed the prospect for the treatment of patients with DR-TB substantially in 2020

The combination of bedaquiline, pretomanid, and linezolid led to a favorable outcome at 6 months after the end of therapy in a high percentage of patients with highly drug-resistant forms of tuberculosis; some associated toxic effects were observed. (Funded by the TB Alliance and others; ClinicalTrials.gov number, NCT02333799.)

Nix-TB Dosing of BPaL Regimen



Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

N Engl J Med 2022;387:810-23.
DOI: 10.1056/NEJMoa2119430

ZeNix Trial

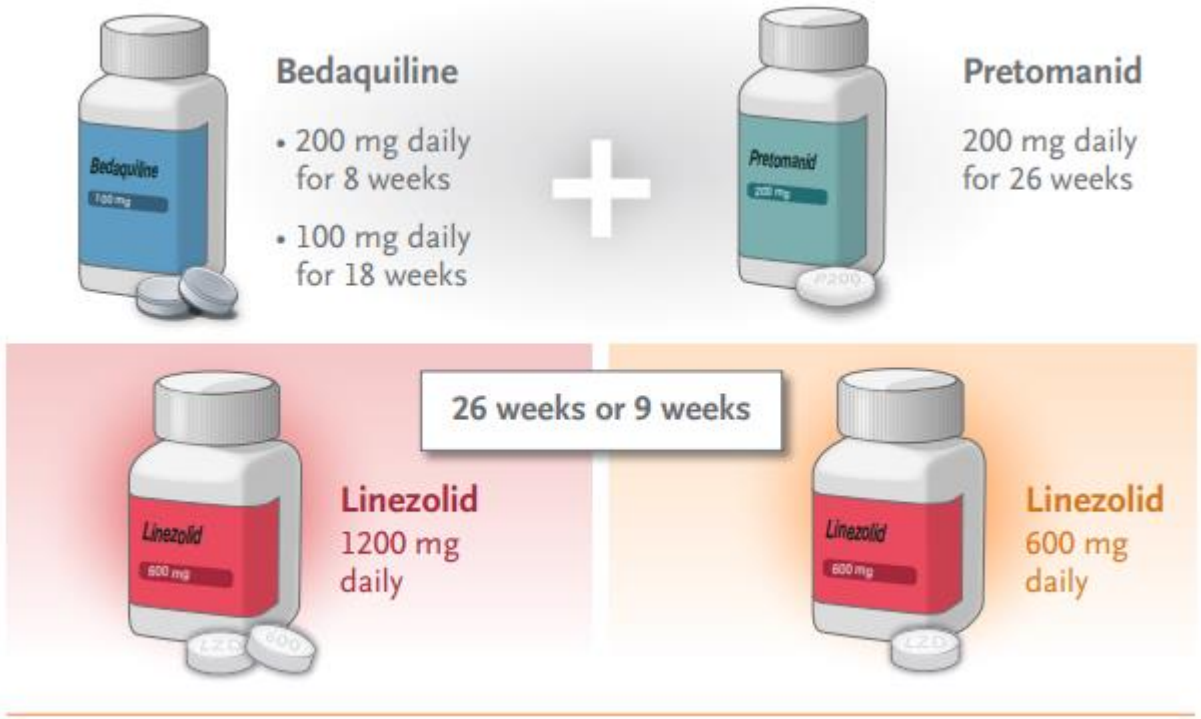
CLINICAL PROBLEM

Bedaquiline–pretomanid–linezolid has had efficacy against highly drug-resistant tuberculosis, but the incidence of adverse events with the 1200-mg daily dose of linezolid has been high. Whether a different dose and duration of linezolid treatment might reduce adverse events while maintaining efficacy is unclear.

CLINICAL TRIAL

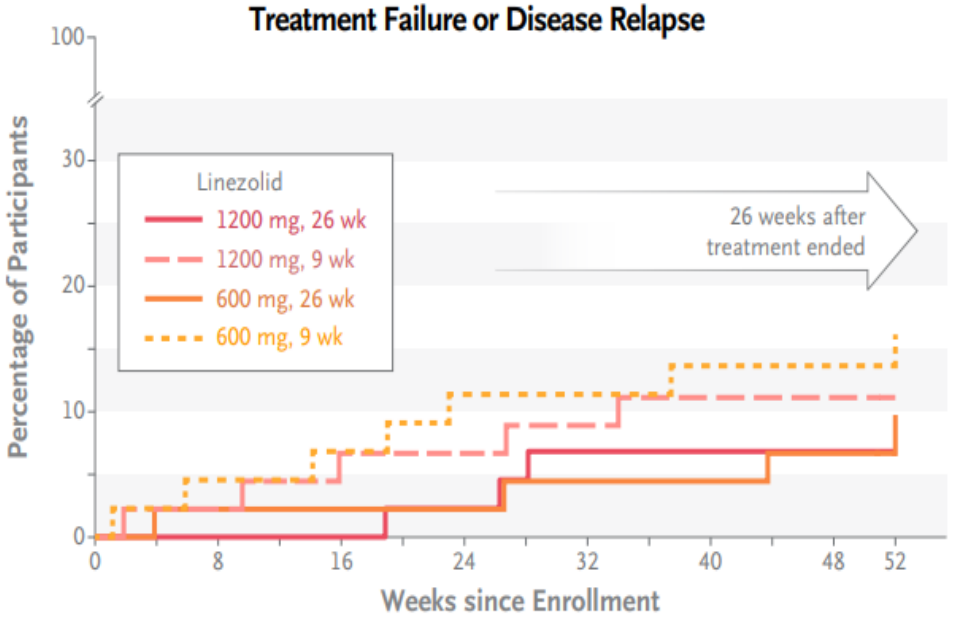
Design: A dose-blind, randomized trial assessed the efficacy and safety of four regimens of linezolid as part of bedaquiline–pretomanid–linezolid treatment for highly drug-resistant tuberculosis.

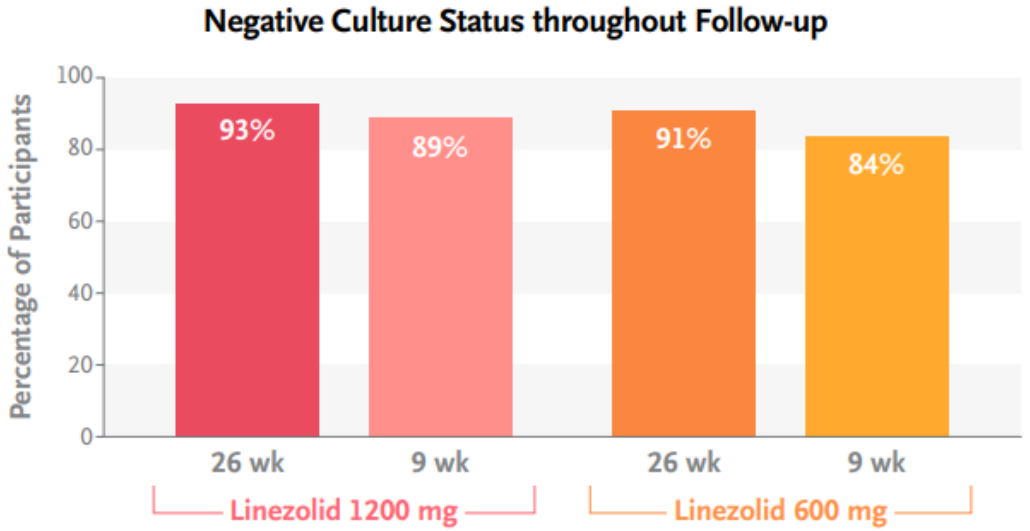
Intervention: 181 participants (≥14 years of age in South Africa and the country of Georgia and ≥18 years of age in Russia and Moldova) with extensively drug-resistant (XDR) tuberculosis, pre-XDR tuberculosis, or rifampin-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued owing to side effects were assigned to receive bedaquiline and pretomanid for 26 weeks, along with linezolid at one of two doses for either 26 weeks or 9 weeks.



The primary end point was treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment.
A favorable outcome was maintenance of negative culture status throughout follow-up in participants who had not had an unfavorable outcome previously.

ZeNix Trial





Peripheral neuropathy occurred in 38%, 24%, 24%, and 13%, respectively and **myelosuppression** occurred in 22%, 15%, 2%, and 7%,respectively.

Efficacy: In the four treatment groups, the incidence of treatment failure or disease relapse (the primary end point) ranged from 7 to 16%; the incidence of a favorable outcome ranged from 84 to 93%.

LIMITATIONS AND REMAINING QUESTIONS

- The small sample size limits the precision of estimates of efficacy.
- The trial was not powered for formal comparisons of efficacy among the treatment groups.

CONCLUSIONS

In patients with highly drug-resistant tuberculosis, 600 mg of linezolid for 26 weeks resulted in a more favorable risk–benefit profile than other dose–duration regimens tested.

Berry et al. Trials (2022) 23:484
https://doi.org/10.1186/s13063-022-06331-8

Trials

STUDY PROTOCOL Open Access

TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II–III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis

Catherine Berry[1*], Philipp du Cros[1,2], Katherine Fielding[3], Suzanne Gajewski[4], Emil Kazounis[1], Timothy D. McHugh[5], Corinne Merle[6], Ilaria Motta[1], David A. J. Moore[7] and Bern-Thomas Nyang'wa[8]

Intervention description {11a}

Investigational regimens in stage 1:

Regimen 1: bedaquiline + pretomanid + linezolid + moxifloxacin for 24 weeks

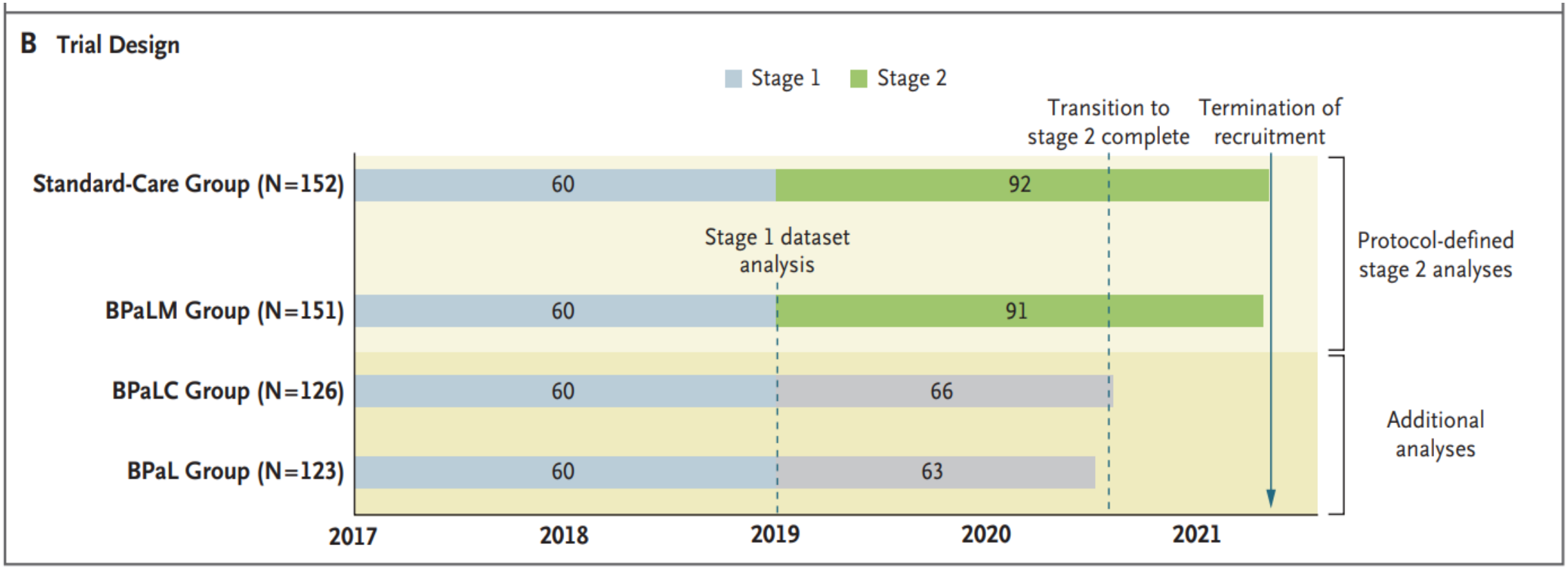
Regimen 2: bedaquiline + pretomanid + linezolid + clofazimine for 24 weeks

Regimen 3: bedaquiline + pretomanid + linezolid for 24 weeks

Investigational regimen in stage 2 (Table 2):

Regimen 1: bedaquiline (B) + pretomanid (Pa) + linezolid (Lzd) + moxifloxacin (Mfx) for 24 weeks

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis



N Engl J Med 2022;387:2331-43.
DOI: 10.1056/NEJMoa2117166

TB Practecal
Innovating MDR-TB Treatment

STAGE 1 - EFFICACY (MITT)

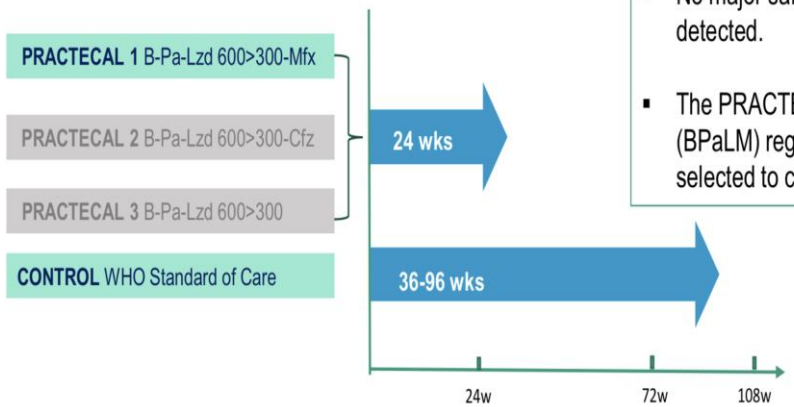
Stage 1 primary outcome: by arm (among those who have attended the week 12 visit and have a culture result available, not including late exclusions)

	Control	PRACTECAL Arm 1 (BPaLM)	PRACTECAL Arm 2 (BPaLC)	PRACTECAL Arm 3 (BPaL)
Number with culture conversion in liquid media at 8 weeks post randomisation, n/N (%) [85 % CI]		37/48 (77.1%) [66.4, 85.6]	33/49 (67.3%) [56.2, 77.2]	21/46 (45.7%) [34.4, 57.3]

TB Practecal
Innovating MDR-TB Treatment

STAGE 1 >> STAGE 2

- All 3 investigational arms met criteria for stage 2 eligibility.
- No major safety signals were detected.
- The PRACTECAL arm1 (BPaLM) regimen was selected to continue to stage 2.



MEDECINS SANS FRONTIERES

Courtesy of Ilaria Motta

CONCLUSIONS

>>

TB Practecal
Innovating MDR-TB Treatment

- **24 week all oral regimens containing a backbone of bedaquiline, pretomanid and tapered dose linezolid are both safe and efficacious in the treatment of rifampicin resistant tuberculosis**
- Treatment effects were consistent across all subgroups for BPaLM
- Efficacy appears to be BPaLM > BPaLC > BPaL >>SOC
- Patients taking investigational arms had fewer grade 3 and above AEs and SAEs as compared to SoC at week 72 (BPaLM> BPaL > BPaLC >> SOC)

The phase II/III clinical trial found that the new shorter BPaLM treatment regimen was very effective against rifampicin-resistant TB. 89 per cent of patients in the BPaLM group were cured, compared to 52 per cent in the standard of care group.

Courtesy of Ilaria Motta

A revolution in the management of multidrug-resistant tuberculosis

Keertan Dheda ✉ • Christoph Lange

THE LANCET

VOLUME 400, ISSUE 10366, P1823-1825, NOVEMBER 26, 2022

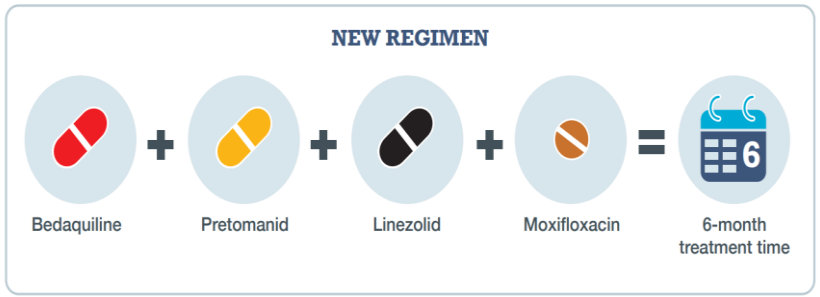
World Health Organization

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

May 2022

The New Regimen

In May 2022 WHO recommended this regimen to treat DR-TB:



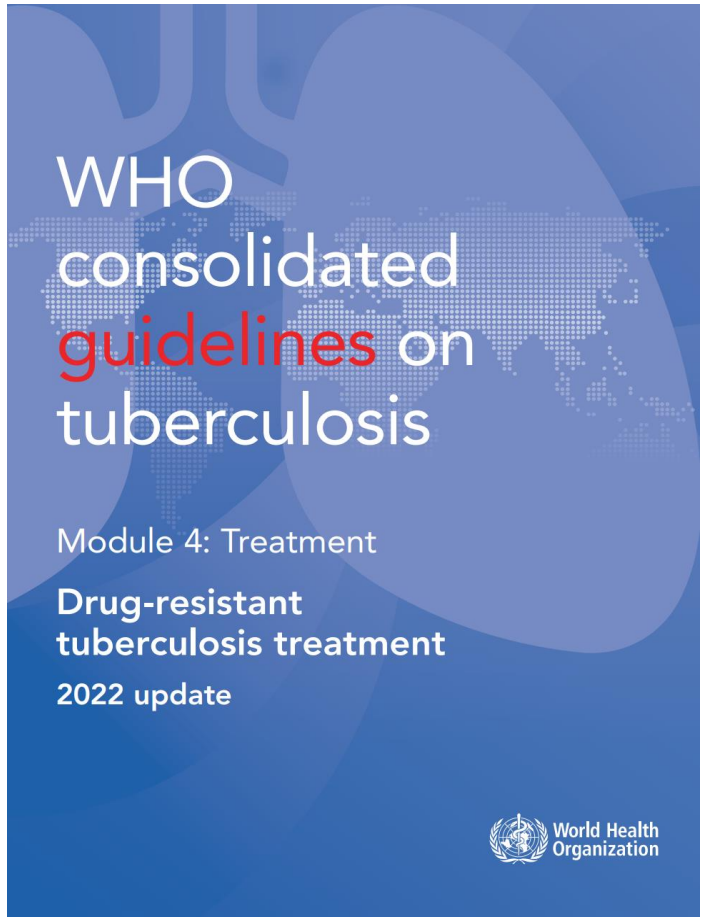
WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Drug-resistant tuberculosis treatment

2022 update

World Health Organization



1)

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

1.1 Recommendation

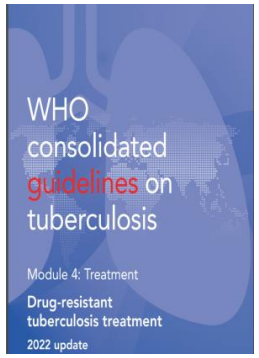
NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

- Bedaquiline (4 tablets 100 mg die for the first 14 days, 2 tablets 100 mg 3 times per week from the day 15)
- Pretomanid (1 tablet 200 mg die) full stomach
- Linezolid (1 tablet 600 mg die)
- Moxifloxacin (1 tablet 400 mg die)

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.



BPaLM regimen

6 months (26 weeks) all-oral treatment regimen of bedaquiline, pretomanid, linezolid and moxifloxacin)

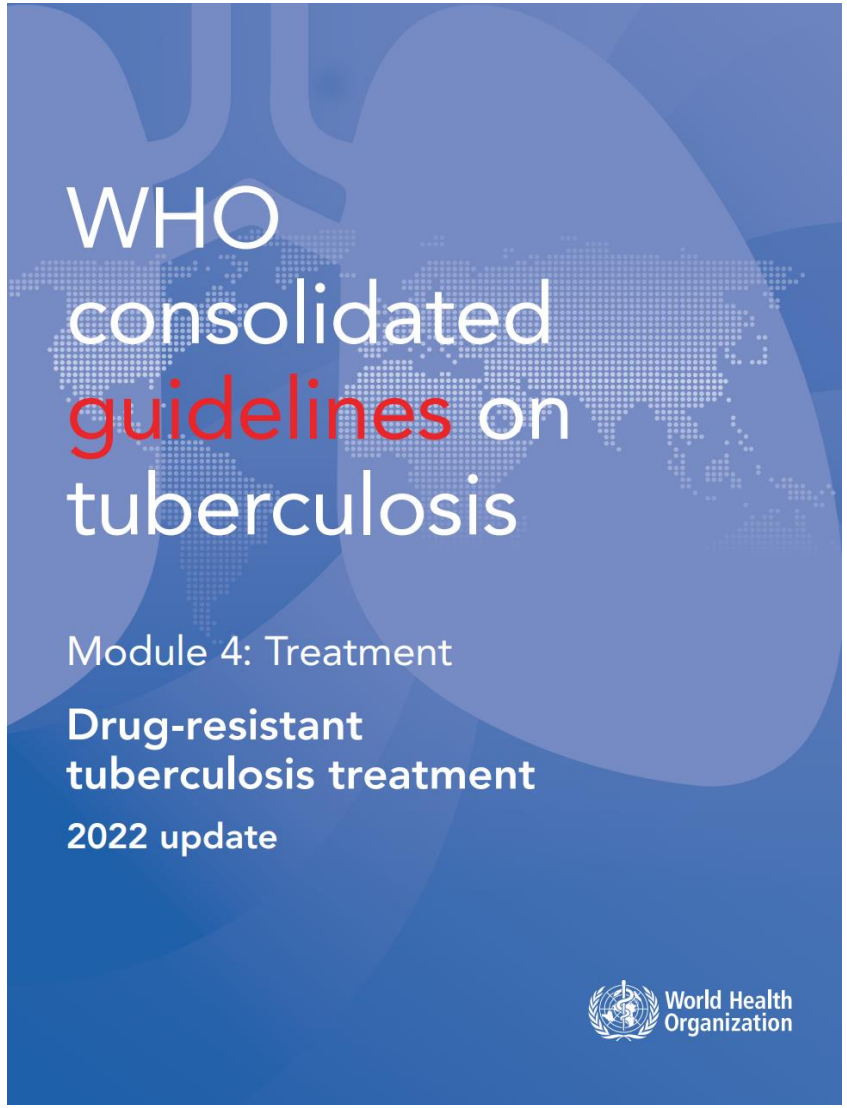
- **In patients with MDR-/RR-TB where fluoroquinolone susceptibility is presumed or documented this regimen should be the treatment of choice**.

- It is possible to omit moxifloxacin and continue with the BPaL regimen for MDR-/RR-TB patients with confirmed fluoroquinolone resistance (based on the results of the ZeNiX-TB and TB PRACTECAL trials).

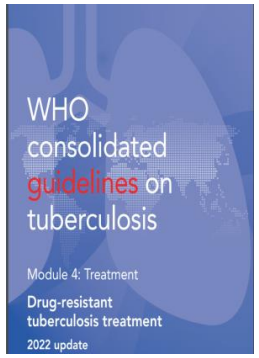
- **When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 39 weeks** (counting from the start of the therapy with BPaLM/BPaL). **This extension is justified in cases of failure to convert culture between months 4 and 6 while on treatment**; alternatively, it can be based on the clinical judgement of the treating physician.

- Ideally, missing doses of all three or four drugs in the regimen should be avoided; however if doses are missed, any interruption of longer than 7 days should be made up by extending the treatment duration (for the number of missed doseses). Up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses

- Therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.



2. This recommendation applies to the following:
   a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
   b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.[11]
   c. Adults and adolescents aged 14 years and older.
   d. All people regardless of HIV status.
   e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.[12]
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[13]



Short-regimen 9-12 months all-oral

- **For those who are not eligible for the shorter BPaLM/BPaL regiments :**

9-month all-oral treatment regimen consisting of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if acid-fast bacilli are still detectable in the patient's sputum at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months).

2)

The regimen can be summarized as: **4–6 $Bdq_{(6\,m)}$ -Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E**

Initial phase: **4–6 $Bdq_{(6\,m)}$-Lfx-Cfz-Z-E-Hh-Eto**

Continuation phase: **5 Lfx-Cfz-Z-E**

- **Ethionamide can be replaced by 2 months of linezolid (600 mg daily**).

- Patients with MDR-/RR-TB **are eligible for this regimen if resistance to fluoroquinolones has been excluded** (based on operational data from South Africa)

Section 2. Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis

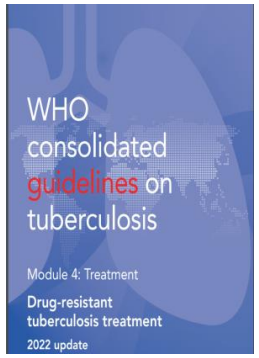
2.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
2.1	**A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.** *(Conditional recommendation, very low certainty in the evidence)*

results available. Based on the available evidence, this regimen can be a preferred option for patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin), for whom resistance to fluoroquinolones has been ruled out, in the following situations;

- without resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance[34]);
- without exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed);
- with no extensive TB disease and with no severe extrapulmonary TB;
- not pregnant; and
- if a child, aged 6 years or more.



Longer individualised 18-month regimens

3)

- For patients with MDR-/RR-TB who are not eligible for
- Or had no favourable treatment outcome using the above 6-month or 9-month regimens,
- Have TB disease caused by M. tuberculosis strains with extensive drug resistance (e.g. XDR-TB)
- or have intolerance to key components of the above-mentioned regiments
- These regimens have a duration of at least 18 months and are individually designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history (based on the results of an individual patient data analysis

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

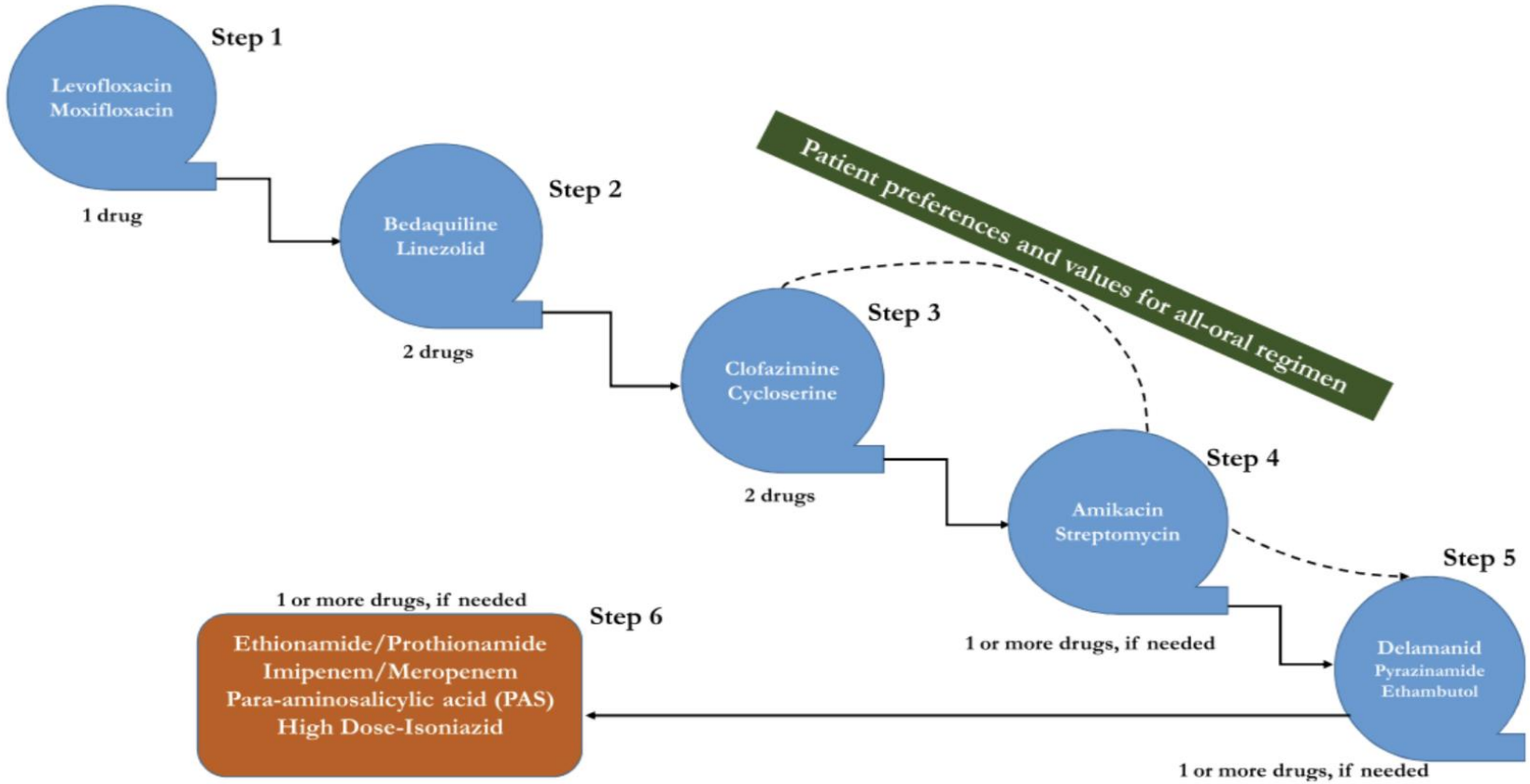


Figure 1. How to design the regimen for multidrug-resistant tuberculosis.
In the text and figure we focus mainly on the ATS/CDC/ERS/IDSA guideline, as - although largely consistent with the 2019 WHO ones - they provide additional clinical elements with main focus on low-TB incidence countries. Additional minor differences include less focus on injectables and the WHO shorter regimen, more focus on tailoring the regimen to drug-resistances identified, a larger number of drugs and a slightly different prioritization of the drugs.
The 2019 WHO MDR-TB guidelines recommend that all 3 Group A drugs (bedaquiline, linezolid, levofloxacin/moxifloxacin) and 1 Group B drug (clofazimine, cycloserine/terizidone) are prescribed (4 versus 5 drugs recommended by ATS/CDC/ERS/IDSA guidelines). If only 1 or 2 Group A drugs are prescribed, both Group B drugs should be prescribed. If needed, Group C drugs (ethambutol, delamanid, pyrazinamide, imipenem, meropenem, amikacin/streptomycin, para-aminosalycilic acid, ethionamide/prothionamide) should be administered.

TABLE 5 Factors to be considered for selection of treatment regimens for patients with MDR-/RR-TB

Regimen	MDR-/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive PTB	EPTB	Age <14 years
6-month BPaLM/ BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualised 18-month	Yes[#]/No	Yes[#]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness Patient or family preference Access to and cost of regimen component drugs					

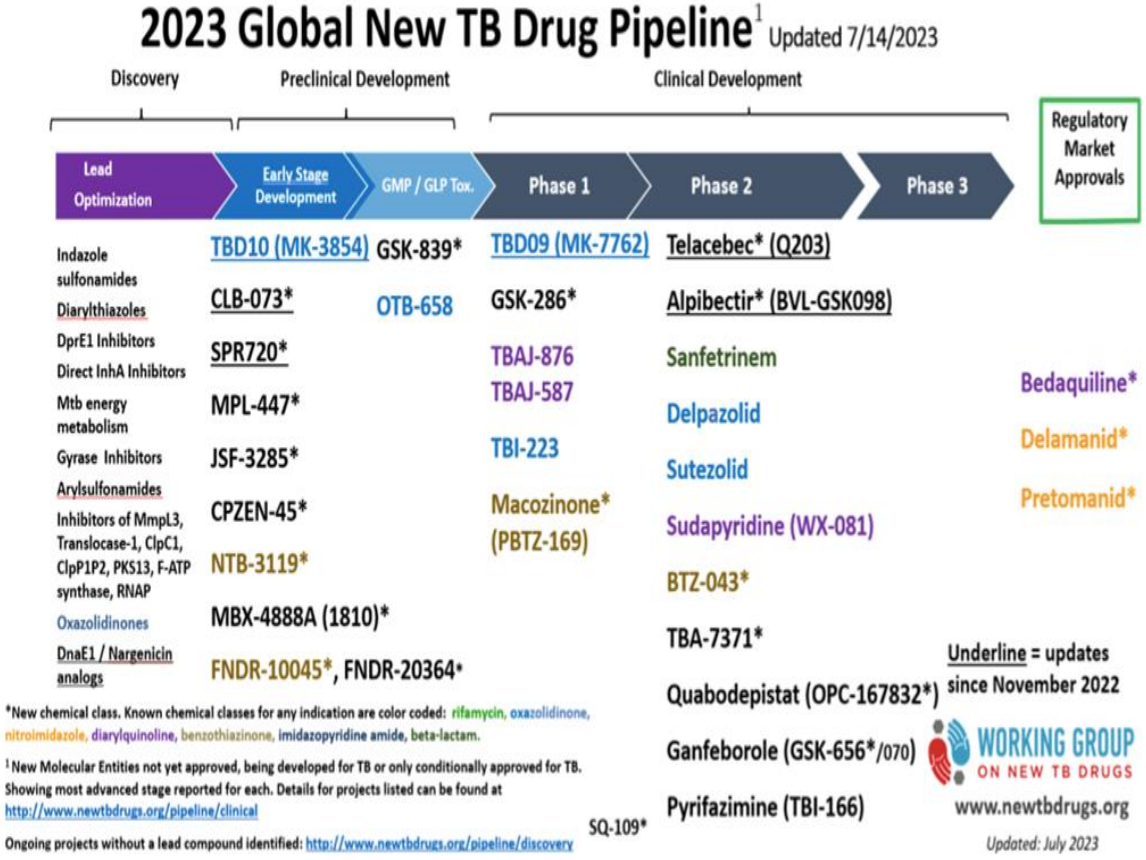
BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system. [#]: when 6-month BPaLM/BPaL and 9-month regimens cannot be used. Reproduced and modified from [75] with permission.

- **Patients with XDR-TB or those who have failed treatments with MDR-/RR-TB therapies should be managed in referral centres.**
- **The management of difficult-to-treat patients should be discussed in interdisciplinary boards**

European Respiratory Society, 2023; pp. 117–138 [https://doi.org/10.1183/2312508X.10024622


ONE-SIZE FITSALL
STORE
SALE


One size
does NOT
fit all.



- **Currently the pipeline of new TB drugs candidate is flourishing like never before.**
- **Thus, 19 new or repurposed compounds for treatment of DS-TB and DR-TB are at present in phase 1 or 2 clinical trials**
- **Of these new drugs, 10 are of new classes or with a new mechanism of action.**

TABLE 6 Novel anti-TB medicines in phase 1 and 2 clinical development

Class	Mechanism of action	Trial phase			
		Phase 1A	Phase 1B	Phase 2A	Phase 2B/C
Diarylquinolines	Inhibits ATP synthase and bacterial respiration	TBAJ-587 TBAJ-876			
				Sudapyridine (WX-081)	
Riminophenazine	Inhibits ion transport and bacterial respiration			Pyrifazimine (TBI-166)	
Oxozalidone	Inhibits protein synthesis (23S ribosome)				Delpazolid (LCB01-0371) Sutezolid (PNU-100480)
				Tedizolid	
			TBI-223		
Carbapenem	Inhibits cell wall synthesis			Sanfetrinem	
Amido-piperidine	Inhibits cell wall synthesis *via* boosting ethionamide			BVL-GSK098	
DprE1 inhibitors	Inhibits cell wall synthesis			BTZ-043 Macozinone (PBTZ169)	
					OPC-167832
				TBA-7371	
QcrB inhibitor	Inhibits ATP synthesis			Telacebec (Q203)	
MmpL3 inhibitor	Inhibits cell wall synthesis				SQ109
GyrB inhibitor	Inhibits bacterial DNA synthesis	SPR720			
Cholesterol catabolism inhibitor		GSK-286			
LeuRS inhibitor	Inhibits protein synthesis			GSK-656	

ATP: adenosine 5'-triphosphate.

https://doi.org/10.1183/2312508X.10024622

Ongoing clinical trials

- The global pipeline of clinical research on TB treatment is evolving
- The majority of trials aim to show non-inferiority of an experimental regimen with a shorter treatment duration compared to a control, which is usually standardised for DS-TB and individualised for RR-TB.

Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Experimental treatment duration, months	Notes	ClinicalTrials.gov identifier
Rifampicin-susceptible TB							
Beijing Chest Hospital	4	Yes	China	Isoniazid, rifampicin, pyrazinamide, ethambutol, and levofloxacin for the full course; or isoniazid, rifampicin, pyrazinamide, and ethambutol for the full course	4.5		NCT02901288
CLO-Fast (ACTG 5362)	2	Yes	Multicountry	Clofazimine, ethambutol, isoniazid, pyrazinamide, and rifapentine for 8 weeks, followed by clofazimine, isoniazid, pyrazinamide, and rifapentine for 8 weeks	3		NCT04311502
Hi-DoRi-3	3	Yes	South Korea	Isoniazid, rifampicin 30 $mg \cdot kg^{-1}$, and pyrazinamide	3 months after culture conversion	Treatment duration based on sputum culture conversion	NCT04485156
OptiRiMoxTB	3	Yes	Multicountry	Ethambutol, isoniazid, pyrazinamide, and rifampicin 35 $mg \cdot kg^{-1}$, or isoniazid, moxifloxacin, pyrazinamide, and rifampicin 35 $mg \cdot kg^{-1}$	4		NCT05575518
ORIENT	3	Yes	China	Isoniazid, moxifloxacin, and pyrazinamide, plus: rifapentine 600 $mg \cdot day^{-1}$, or rifapentine 1200 $mg \cdot day^{-1}$, or rifapentine 1800$mg \cdot day^{-1}$	4–6	Multi-arm, multi-stage clinical trial	NCT05401071
PredictTB	2	Yes	Multicountry	2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 2 months of isoniazid and rifampicin	4	Strategy trial; only participants with moderate disease are randomised	NCT02821832
PRESCIENT	2	Yes	Multicountry	Bedaquiline, clofazimine, delamanid, and pyrazinamide	2		NCT05556746

Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Experimental treatment duration, months	Notes	ClinicalTrials.gov identifier
RIAlta	2	No	Multicountry	Rifampicin (35 $mg \cdot kg^{-1}$ per day), isoniazid, pyrazinamide and ethambutol	6	Comparison to historical controls	NCT04768231
RIFASHORT	3	Yes	Multicountry	Standard regimen with rifampicin at 1200 $mg \cdot day^{-1}$; or standard regimen with rifampicin at 1800 $mg \cdot day^{-1}$	4		NCT02581527
SimpliciTB	2/3	Yes	Multicountry	Bedaquiline, pretomanid, moxifloxacin, and pyrazinamide	4	Includes a non-randomised arm with RR-TB patients	NCT03338621
TRUNCATE-TB	2/3	Yes	Multicountry	Isoniazid, high-dose rifampicin, pyrazinamide, ethambutol, and linezolid; isoniazid, high-dose rifampicin, pyrazinamide, ethambutol, and clofazimine; isoniazid, rifapentine, pyrazinamide, levofloxaxin, and linezolid; bedaquiline, isoniazid, pyrazinamide, ethambutol, and linezolid	2	Multi-arm, multi-stage clinical trial	NCT03474198

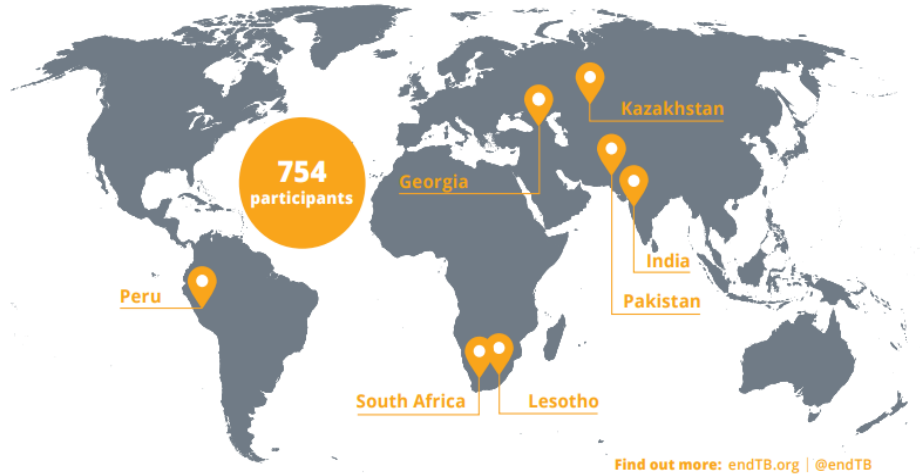
Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Experimental treatment duration, months	Notes	ClinicalTrials.gov identifier
RR-TB							
ACTG A5356	2	No	Multicountry	Bedaquiline, clofazimine, delamanid, plus linezolid at different dosages	6		NCT05007821
BEAT Tuberculosis	3	Yes	South Africa	Bedaquiline, delamanid, and linezolid, plus levofloxacin or clofazimine	6	Strategy trial; experimental regimen adapted according to rapid molecular testing	NCT04062201
DRAMATIC	2	No	Multicountry	Levofloxacin, bedaquiline, linezolid, delamanid, and clofazimine	4–9	Duration-randomised clinical trial	NCT03828201
endTB	3	Yes	Multicountry	Bedaquiline, moxifloxacin, linezolid, and pyrazinamide; or bedaquiline, clofazimine, levofloxacin, linezolid, and pyrazinamide; or bedaquiline, delamanid, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, moxifloxacin, and pyrazinamide	9	Trial implementing Bayesian adaptive randomisation	NCT02754765
GRACE-TB	NS	Yes	China	Individualised regimens	NS	Individualised regimen guided by rapid molecular tests	NCT03604848
InDEX	4	Yes	South Africa	Individualised regimens	NS	Gene-derived individualised regimen	NCT03237182
PROSPECT	4	No	China	Clofazimine, cycloserine, levofloxacin, linezolid, and prothionamide; or bedaquiline, clofazimine, cycloserine, levofloxacin, and linezolid	6 (first regimen), 9 (second regimen)		NCT05306223
TB-TRUST	3	Yes	China	Levofloxacin, linezolid, cycloserine, and pyrazinamide (or clofazimine if resistant to pyrazinamide)	6–9		NCT03867136
Rifampicin-resistant, fluoroquinolone-resistant tuberculosis							
endTB-Q	3	Yes	Multicountry	Bedaquiline, clofazimine, delamanid, and linezolid	6–9	Strategy trial; duration adapted to extent of disease and treatment response.	NCT03896685
mBPaL	3	No	India	Bedaquiline, pretomanid, and linezolid at different dosages	6		NCT05040126

endTB Clinical trial results

High-quality evidence on new, all-oral, shortened MDR-TB regimens

Trial registration number: ClinicalTrials.gov ID: NCT02754765

endTB trial site



Study treatment regimens

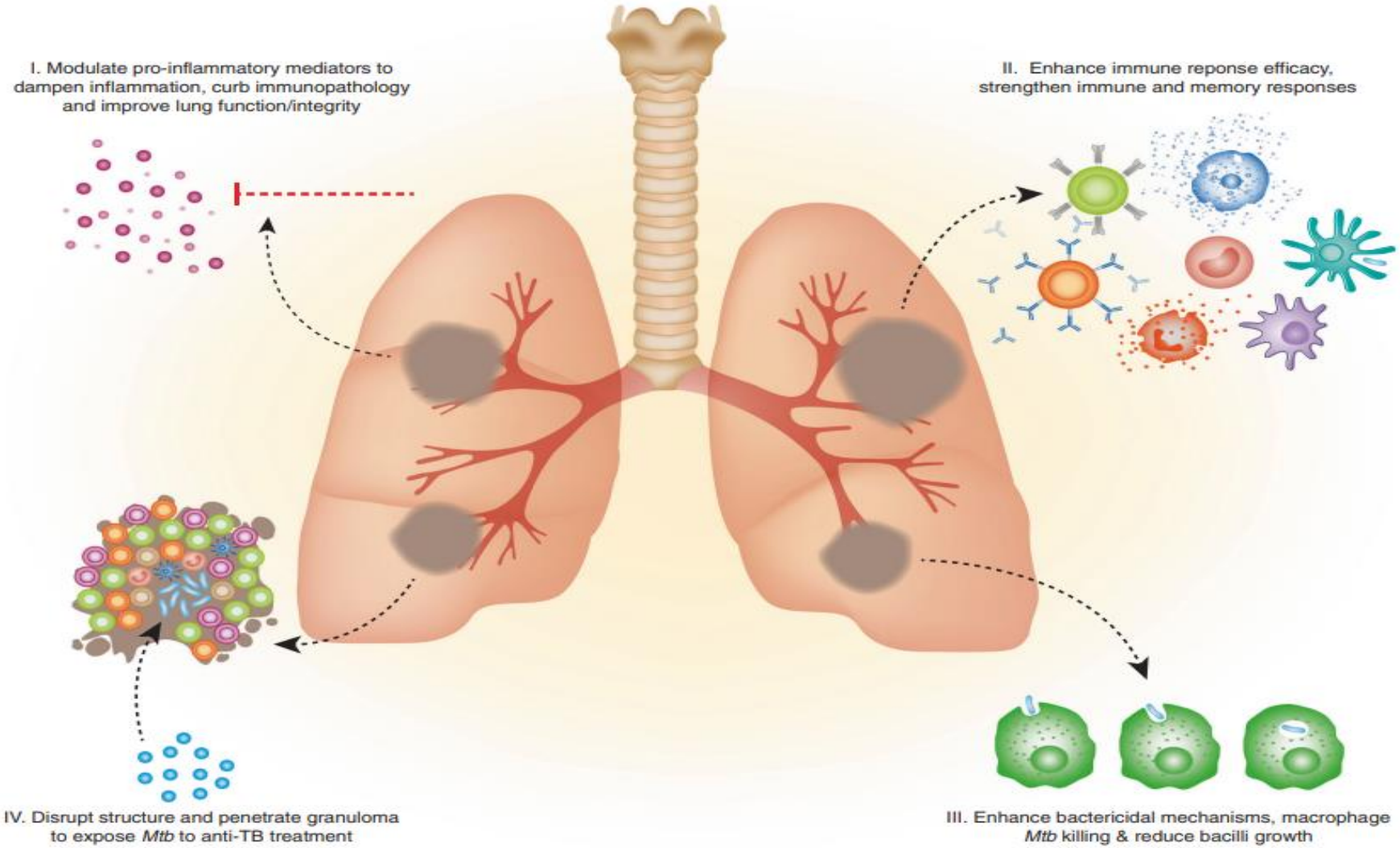
Trial Regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Quinolone	Pyrazinamide	Non-inferiority established
endTB 1 - BLMZ	Bdq			Lzd	Mfx	Z	Yes
endTB 2 - BLLCZ	Bdq		Cfz	Lzd	Lfx	Z	Yes*
endTB 3 - BDLLZ	Bdq	Dlm		Lzd	Lfx	Z	Yes
endTB 4 - DLLCZ		Dlm	Cfz	Lzd	Lfx	Z	No
endTB 5 - DMCZ		Dlm	Cfz		Mfx	Z	Inconclusive**
Control Arm	Standard of care, composed according to WHO Guidelines						

endTB 1 to 5 = 9 months - Control Arm = 18-24 months.
Mfx = moxifloxacin; Lfx = levofloxacin.
*superiority was also established; **non-inferiority was established in mITT (modified intent to treat) population but not in PP (per protocol) population.

Therapeutic host-directed strategies to improve outcome in tuberculosis

C. Young[1], G. Walzl[1] and N. Du Plessis[1]

Mucosal Immunology (2020) 13:190 – 204



Monocyte and Macrophage miRNA: Potent Biomarker and Target for Host-Directed Therapy for Tuberculosis

Pavithra Sampath, Krisna Moorthi Periyasamy, Uma Devi Ranganathan and Ramalingam Bethunaickan *

Front. Immunol. 12:667206.
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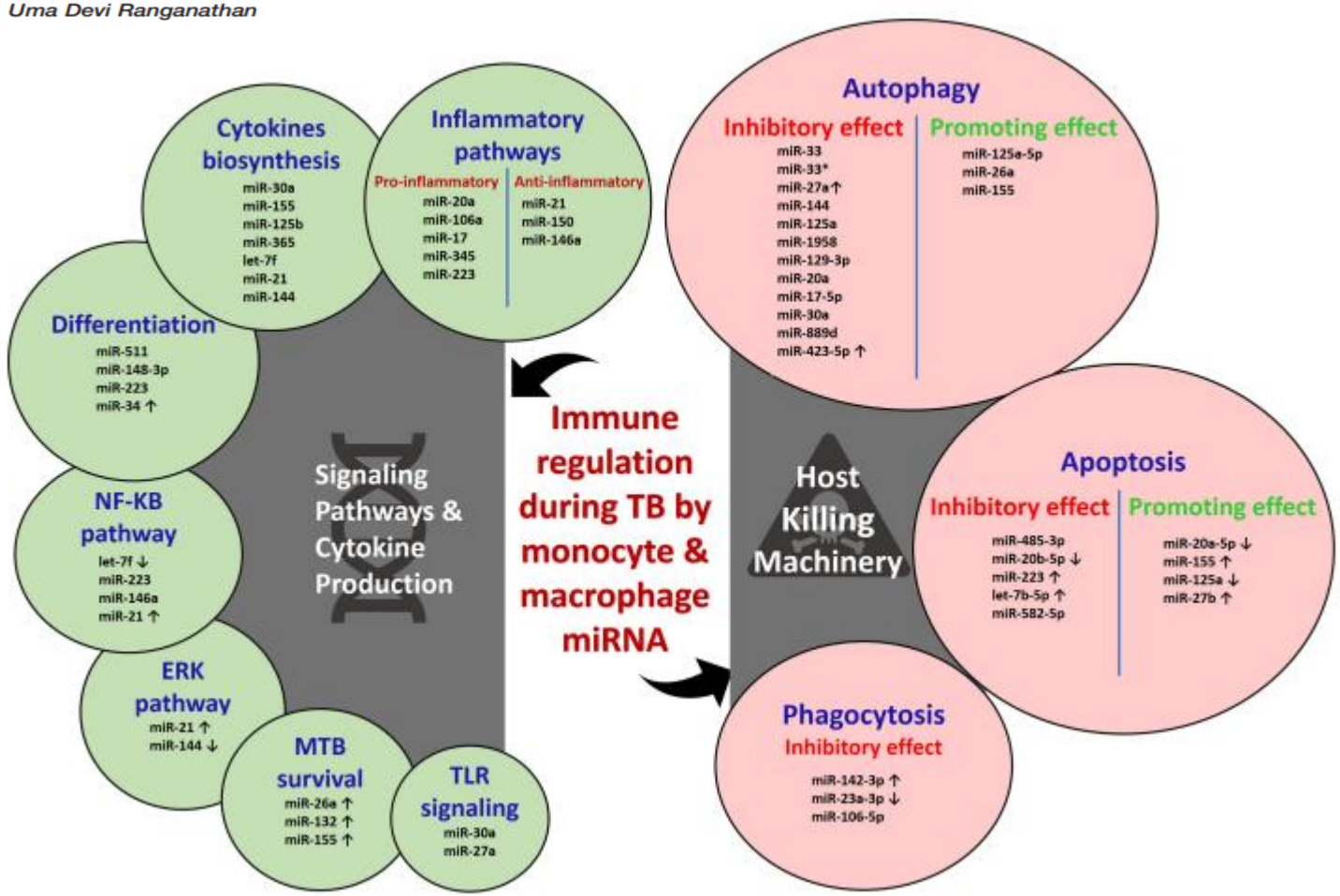
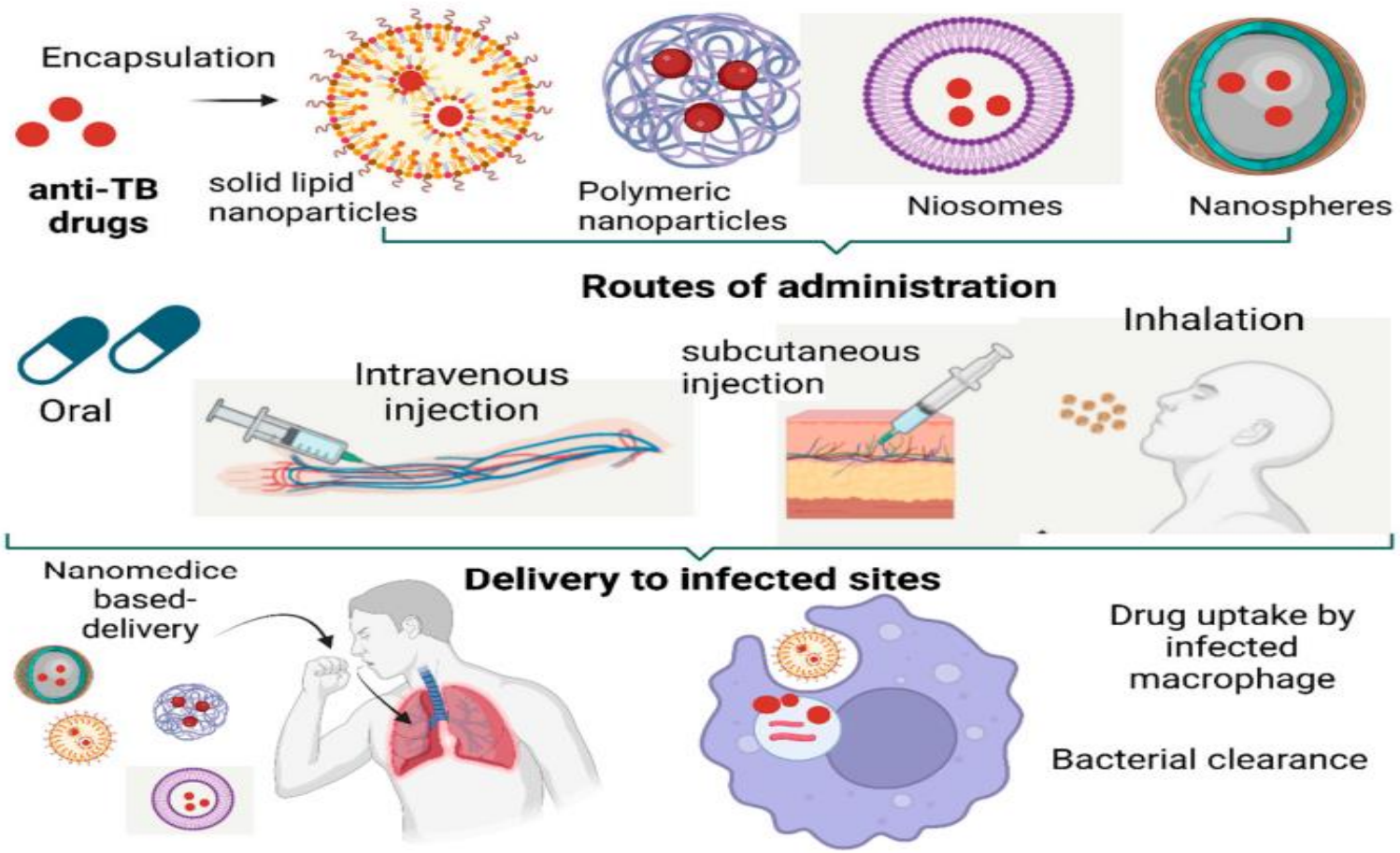


Host immune regulation by monocyte and macrophage miRNAs during tuberculosis

A Current Perspective on the Potential of Nanomedicine for Anti-Tuberculosis Therapy

Khushboo Borah Slater [1,*], Daniel Kim [1], Pooja Chand [1], Ye Xu [1], Hanif Shaikh [2,3] and Vaishali Undale [2]



Trop. Med. Infect. Dis. **2023**, *8*, 100

Conclusion

- Recent years have seen much-awaited improvements in TB treatment.
- The historical paradigm of the 6-month “short course” treatment for DS-TB has fallen
- In addition, recent reports suggest that further treatment shortening may be possible
- History has shown how quickly new TB drugs can be followed by the emergence of drug resistance
- By introducing new regimens with scarce global capacity for DST, past mistakes are being repeated
- **Finally, access to new drugs and regimens is a global emergency that requires commitment and adequate investments**.
- Future efforts should be directed to protect these recent advances


"We combined all your medications into ONE convenient dose."
NICKEL