Tubercolosi : aggiornamento in tema di terapia

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UOC MALATTIE INFETTIVE RESPIRATORIE

- No conflict of interest to declare.

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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OBJECTIVES OF ANTITUBERCULOSIS THERAPY

Treatment of tuberculosis is focused on both curing the individual patient and minimizing the transmission of *Mycobacterium tuberculosis* to other persons, thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides.

Box 5.1 Vision, Goal, and Key Global Indicators of the End TB strategy

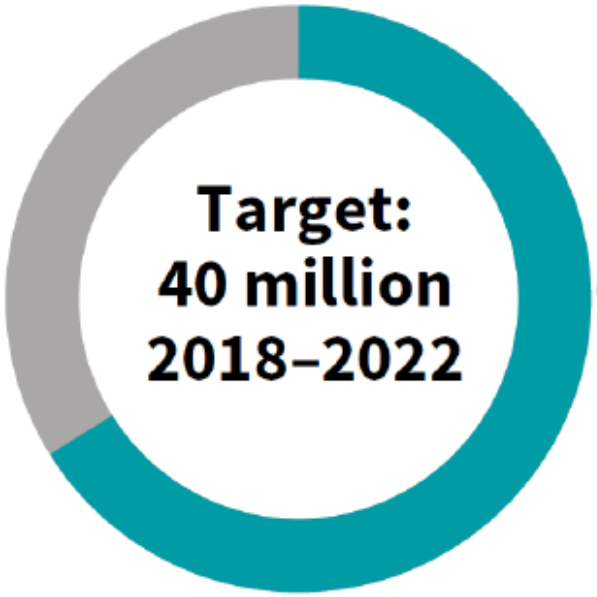
VISION	A WORLD FREE OF TB - zero deaths, disease and suffering due to TB			
GOAL	END THE GLOBAL TB PANDEMIC			
INDICATORS (compared with 2015 baseline)	**MILESTONES**		**TARGETS**	
	2020	**2025**	**SDG[a] 2030**	**END TB 2035**
Percentage reduction in tuberculosis deaths	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (less than 55 TB cases per 100,000 population)	20% < 85/100.000	50% < 55/100.000	80% < 20/100.000	90% < 10/100.000
Percentage of TB-affected households experiencing catastrophic costs due to TB	0%	0%	0%	0%

[a]Sustainable Development Goals' targets for TB by 2030

Principles
1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organization and communities
3. Protection and promotion of human rights, ethics, and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

UN high-level meeting on TB, 2018

Global TB treatment target off-track



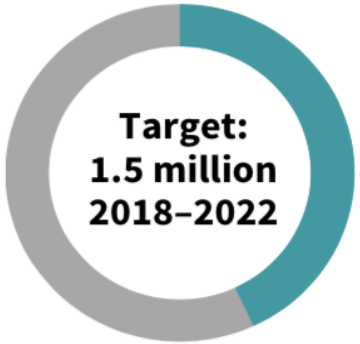
26.3 million (66%)

treated in 2018–2021

World Health Organization

GLOBAL TUBERCULOSIS REPORT 2022

MDR/RR-TB TREATMENT (ALL AGES)



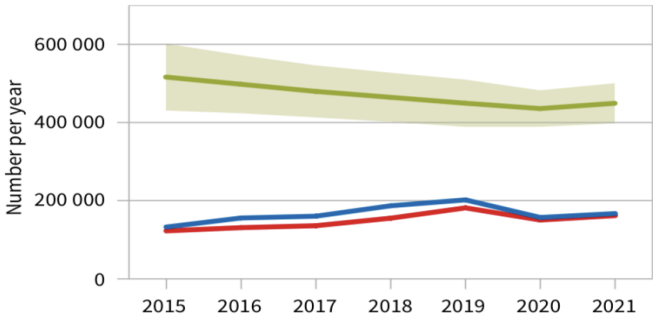
649 000
(43%)
treated in 2018–2021

MDR/RR-TB TREATMENT (CHILDREN)

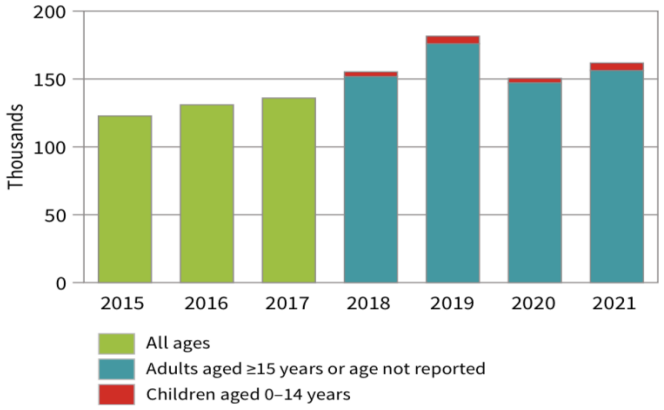
17 700
(15%)
treated in 2018–2021

Global number of people diagnosed with MDR/RR-TB (blue) and number enrolled on an MDR/RR-TB treatment regimen (red), compared with estimates of the global number of incident cases of MDR/RR-TB (green), 2015–2021

The shaded area represents the 95% uncertainty interval.

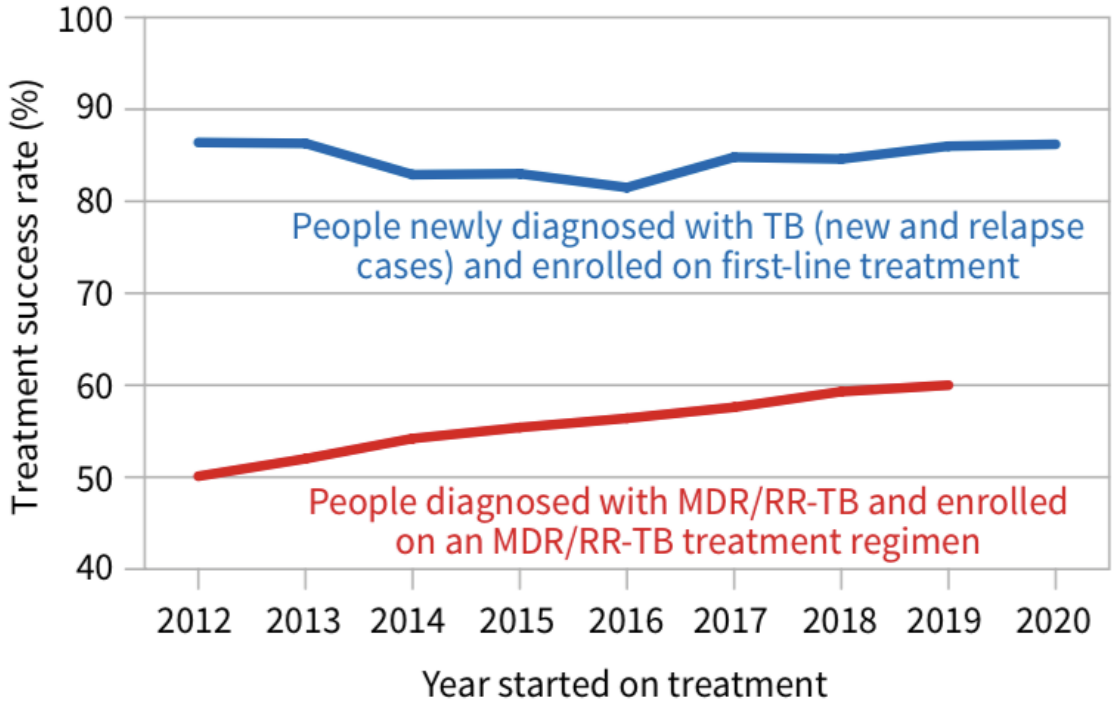


The global number of people reported to have been enrolled on treatment for MDR/RR-TB, 2015–2021[a]

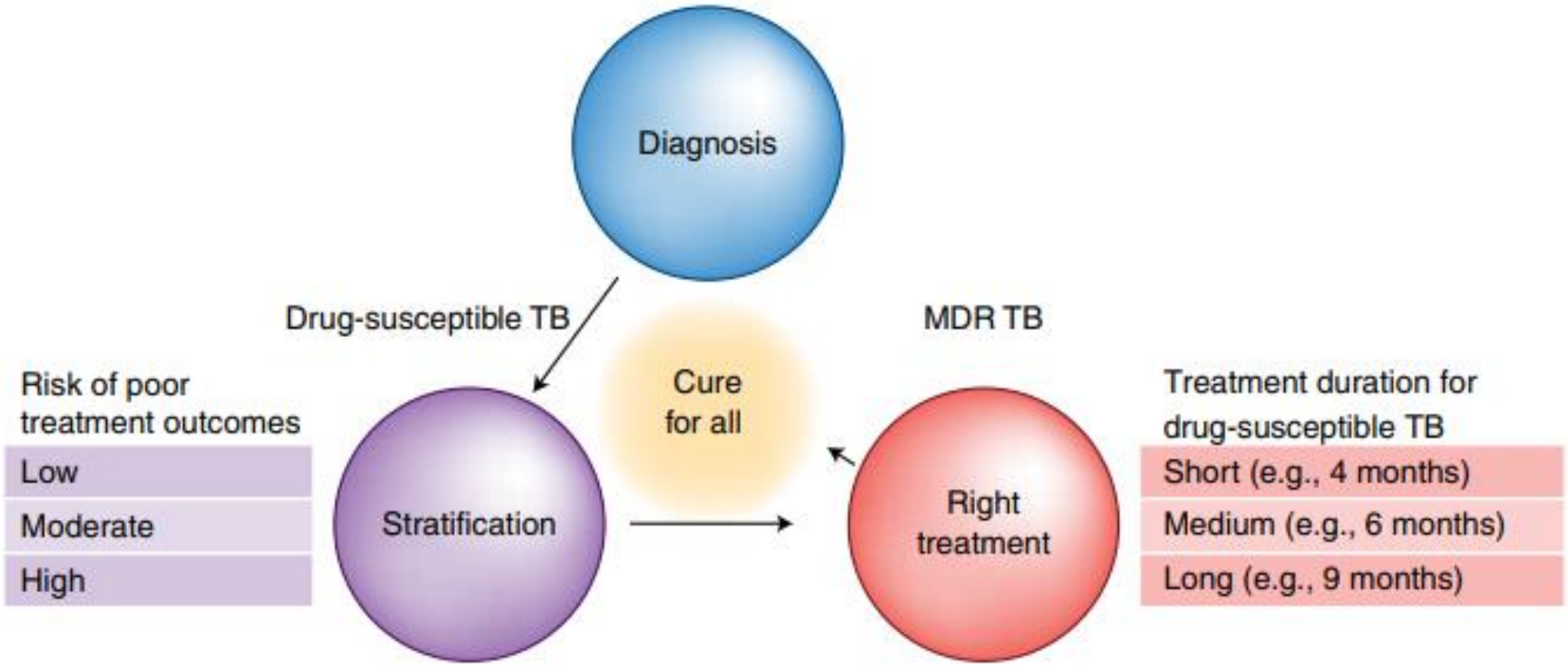


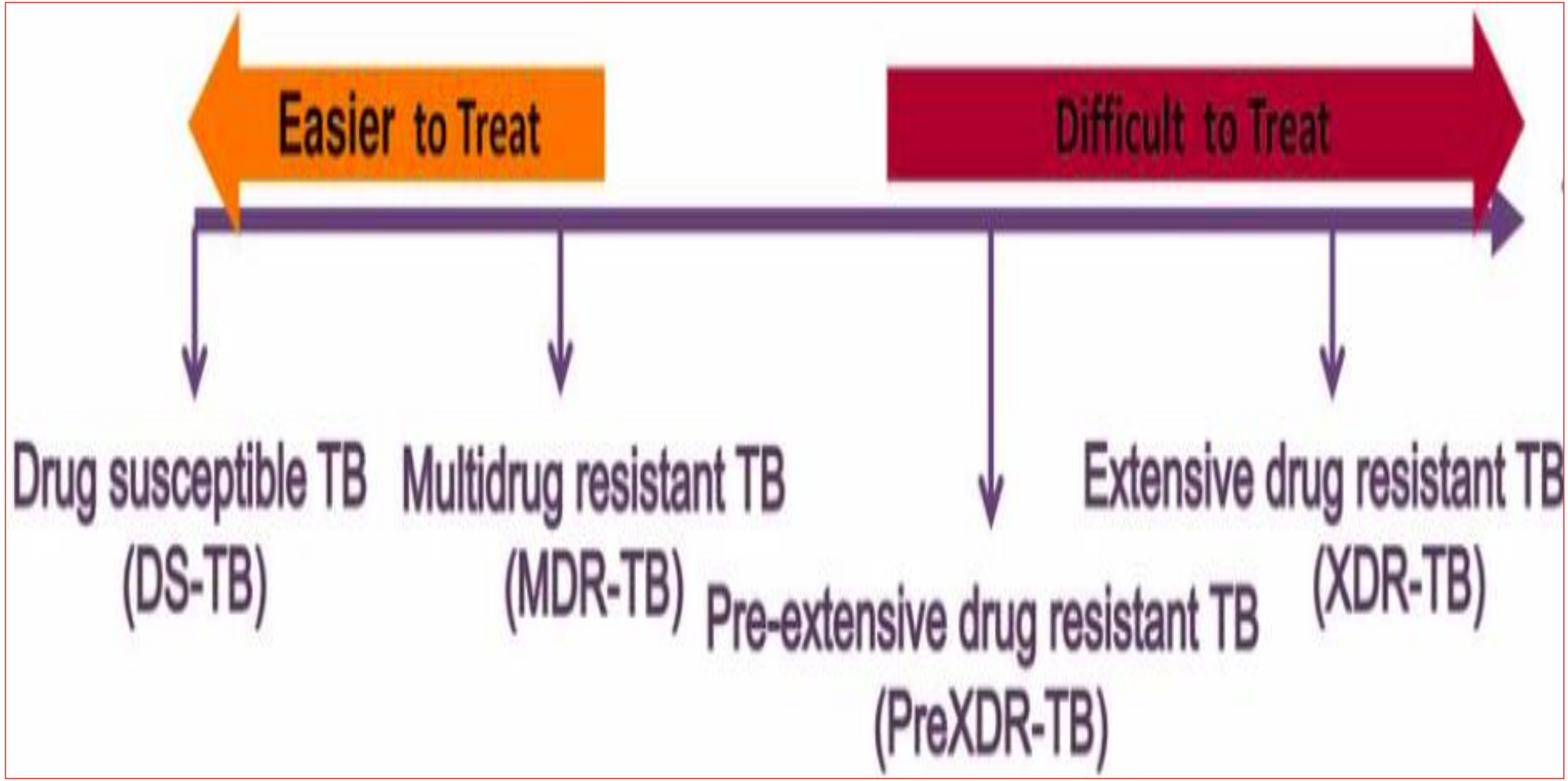
[a] Global data disaggregated by age are not available for the years before 2018.

Global success rates for people treated for TB, 2012–2020[a]



A stratified approach to tuberculosis treatment




Easier to Treat
Difficult to Treat
Drug susceptible TB
(DS-TB)
Multidrug resistant TB
(MDR-TB)
Pre-extensive drug resistant TB
(PreXDR-TB)
Extensive drug resistant TB
(XDR-TB)

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

An Urgent Need

Faster-acting and simplified TB drug regimens are required more urgently than ever in the fight against TB.

Today's drug regimens, which take between 6 and 24 months to complete, are lengthy and complicated to administer, and can be highly toxic.

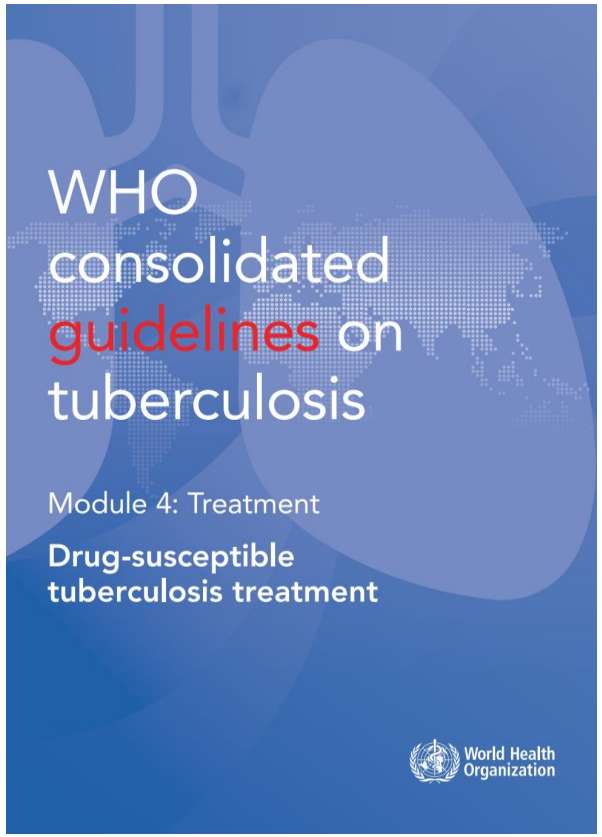
WORKING GROUP ON NEW TB DRUGS

Stop TB Partnership

DS - TB

- **Standard TB polmonare New diagnosis : RHZE(2) poi RH (4-7)**
- **Standard extra TB : RHZE (2) poi RH (7-10)**
- **Recidive polmonari : RHZE (2-3) poi RH (7-10)**

- **Elevata % di successi (>95%)**
- **rare recidive (2- 3%)**
- **buona tollerabilità**
- **bassi costi**



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

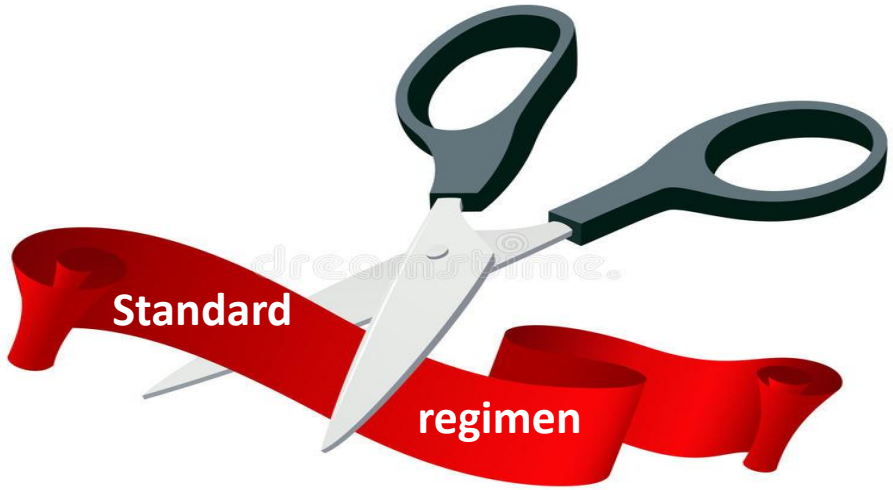
A: The recommendation also applies to extrapulmonary TB – except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy.

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.

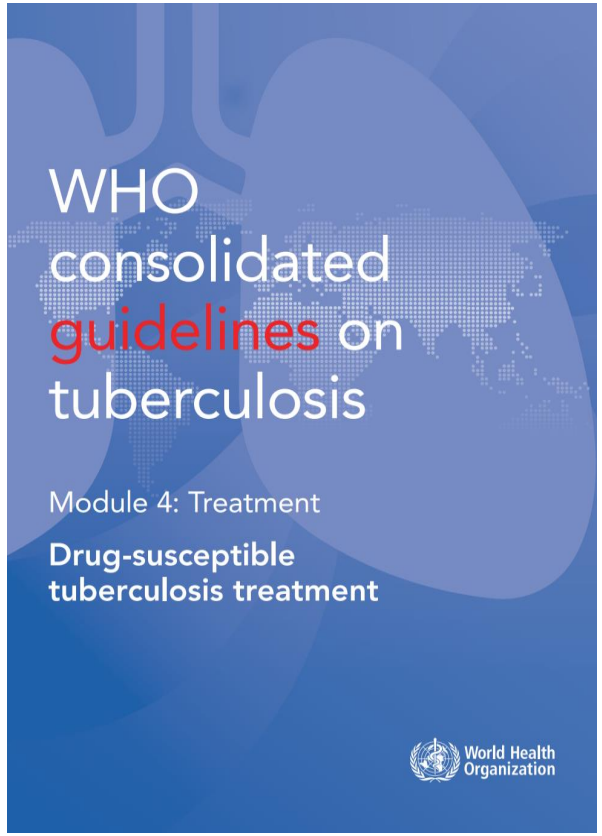
The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

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.**

DS-TB

- 8 weeks of once-daily rifapentine (1200 mg, within 1h of food ingestion), isoniazid, pyrazinamide, and moxifloxacin (400 mg)

followed by

- 9 weeks of once-daily rifapentine (1200 mg, within 1h of food ingestion), isoniazid, and moxifloxacin (400 mg).

total of 17 weeks for treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries

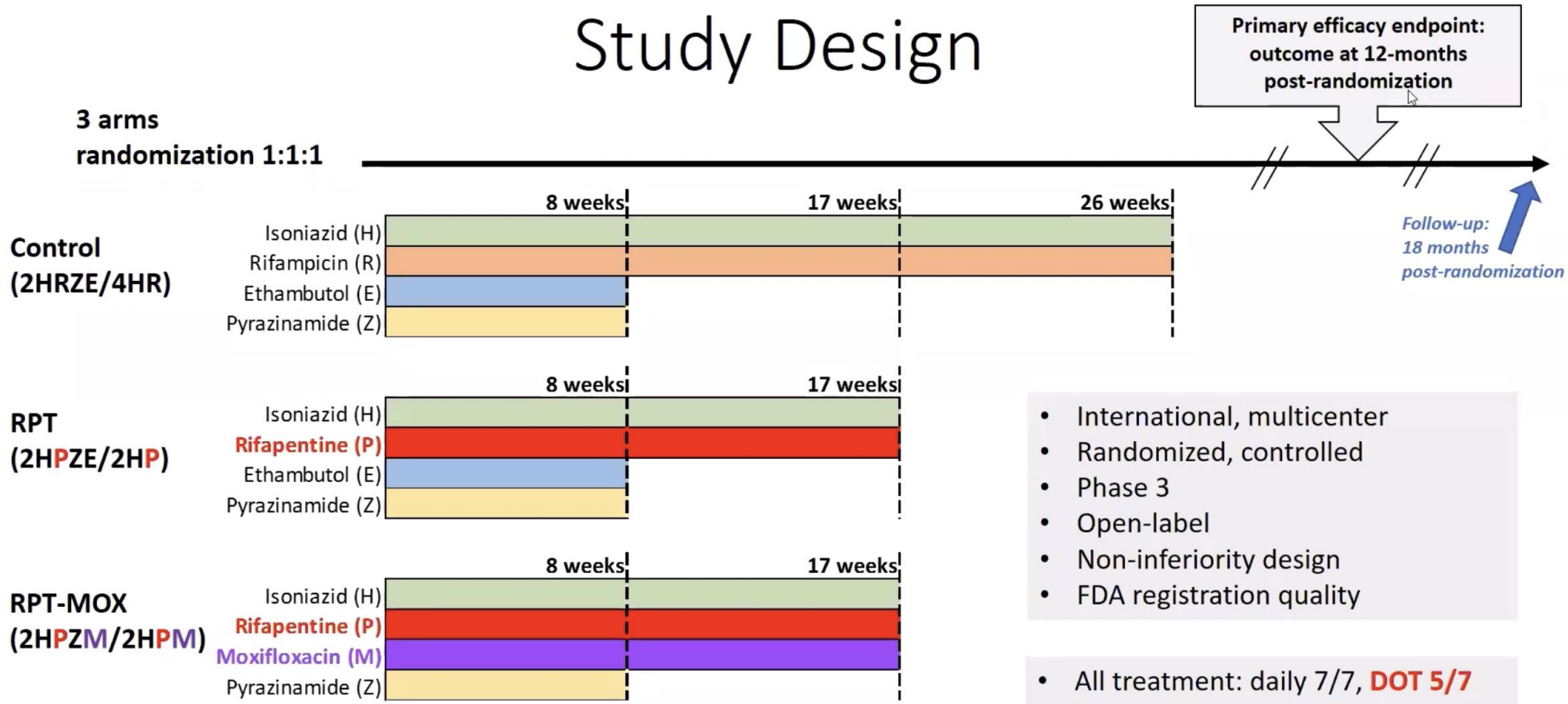
Study 31 was an international, multicentre, randomized, open-label, controlled, three-arm non inferiority trial among adolescents and adults (aged 12 years and above) with smear-positive and culture-positive pulmonary DS-TB . Study participants were recruited from 13 countries.

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**

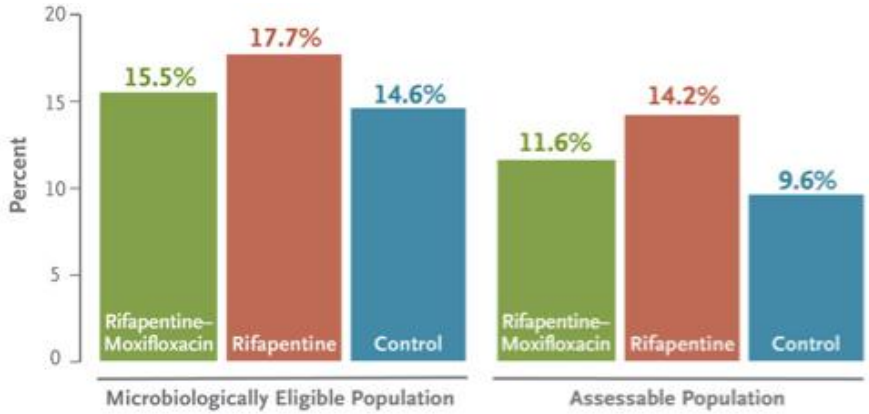
Study Design



- 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

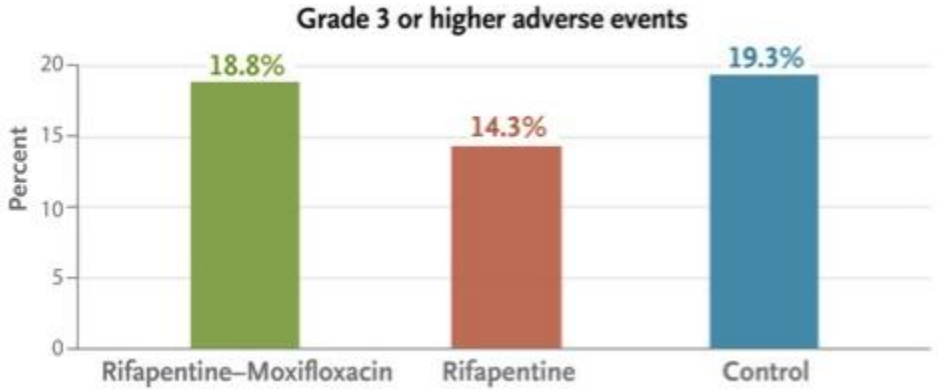


Outcome status: Favorable (Cure)

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.

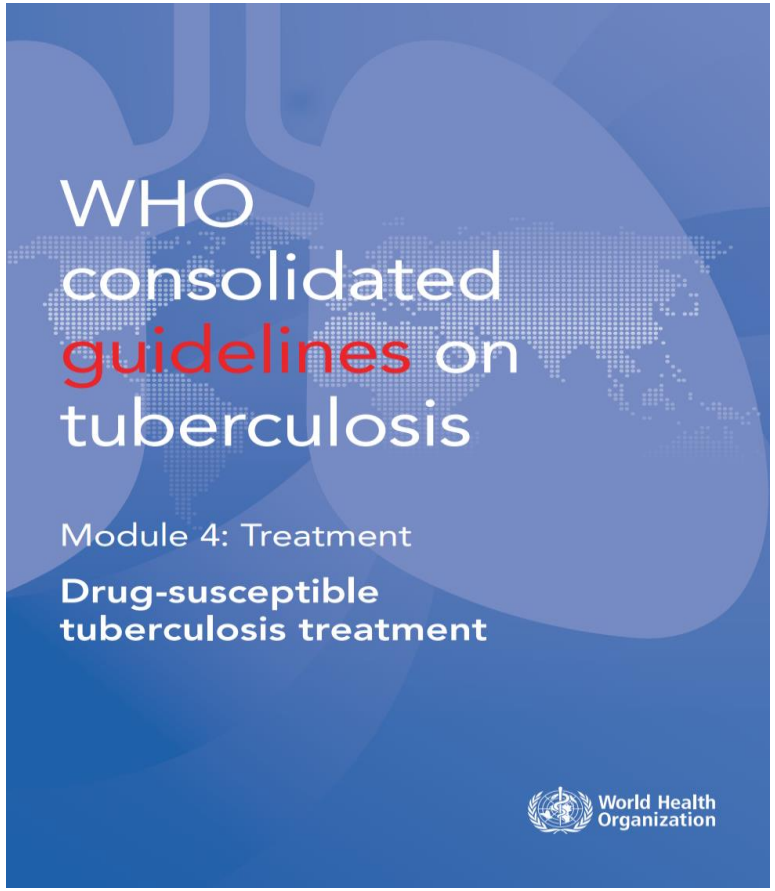
LIMITATIONS AND REMAINING QUESTIONS

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 contrallabili nemmeno con la sospensione

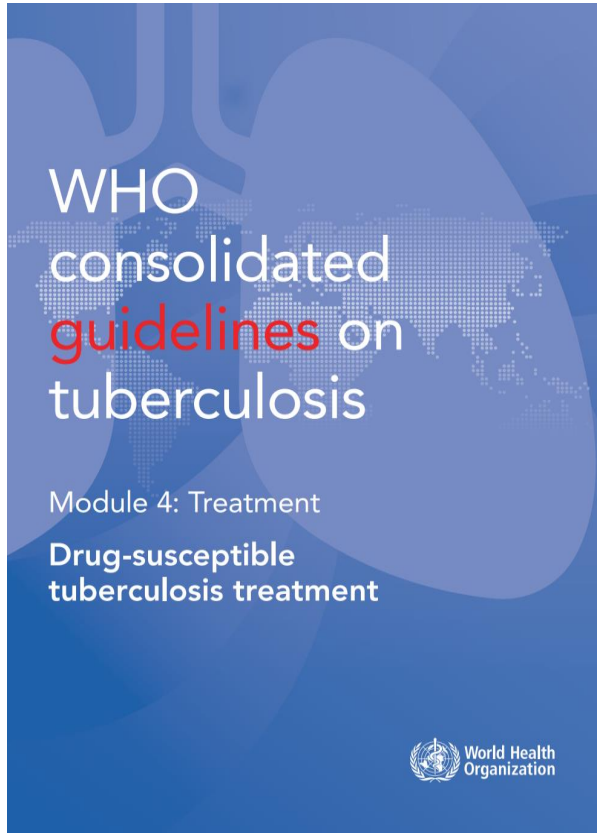
La moxifloxacina:

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

- ✓ Efficacia uguale…….più rapida negativizzazione ?

- ✓ Quindi ??????..... per solo 2 mesi in meno.

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].

- Drug resistance to the key first-line drugs rifampicin and isoniazid is increasing.
- The aim of the WHO “End TB Strategy” is to end the global TB pandemic by 2035. This ambitious goal depends needs before the year 2025:
  - vaccines,
  - new drugs
  - **optimization of standard drugs**
  - point-of-care diagnostic tests.
- Rifampicin, a drug with a well-known safety profile and efficacy data **is currently dosed sub-optimal**.
- The dose was selected when introduced in the 1970s because of financial reasons, fear for toxicity and because serum concentrations were well above the MIC.

Regime standard TB pansensibile

- **Rifampicina 10-12mg/kg/die max 600**
- **Isoniazide 5 (10 nei bambini)/kg/die max 300**
- **Pirazinamide 25-30 mg/kg/die**
- **Etambutolo 15-20 mg/kg/die**

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]

- Current standard treatment for drug susceptible tuberculosis (DS-TB) was designed 40 years ago and has remained unchanged except for a 4-month regimen using high-dose rifapentine and moxifloxacin following the results of a recent clinical trial
- The currently used once daily 10 mg/kg dosing of rifampicin was selected in the 1970s and was based on pharmacokinetics, toxicity, and cost concerns
- Some groups of people are more vulnerable to TB because of risk factors (e.g., advanced age, immunosuppression, diabetes, or liver disease) that increase their risk of active disease and poor treatment outcomes
- For example, treatment success rate was 86% globally, but only 77% for this people
- Optimal drug regimen, dose, and treatment duration are still not well established, as these vulnerable groups were underrepresented in previous clinical trials as these were conducted in mid-to-high TB burden countries.
- A rifampicin dose ranging trial in DS-TB patients by Boeree and colleagues reported that doses (up to 50 mg/kg) were safe and tolerated, and further improved the extended early bactericidal activity in TB patients .
- The optimized doses achieved up to 10-fold higher exposure in plasma (AUC0-24) and a higher early bactericidal activity measured by a decline in the colony-forming units count in sputum culture

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- **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.**

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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

- **In a study with doses up to 50 mg/kg a significant effect was observed in decrease of bacterial load suggesting that treatment duration can be shortened.**

- **There was poor tolerability of the highest dose, a dose of 40 mg/kg was well tolerated.**

- **In Indonesian patients with TB meningitis, intravenous high dose rifampicin was associated with better survival in patients with severe illness, but in another study 15 mg/kg rifampicin daily did not lead to higher survival compared to standard treatment in TB meningitis.**

- **In a Dutch TB expert center high dose rifampicin, in specific cases (low plasma concentrations and severe illness) was well tolerated for the whole 6-months treatment duration**

Courtesy of Dott. L. R. Codecasa

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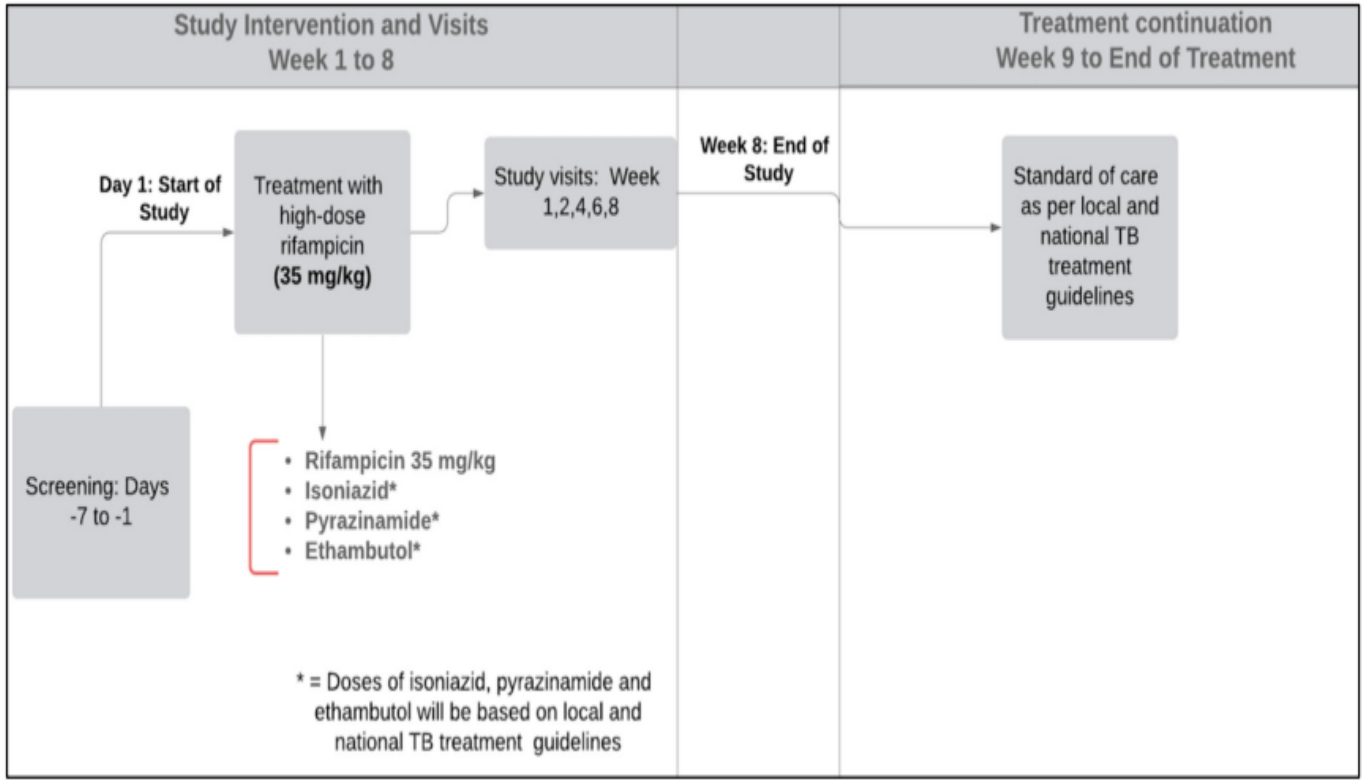


Table 3. Weight-band dosing of rifampicin.

High Dose Rifampicin (35 mg/kg)	Weight-Band Dosing					
	35–40 kg	41–50 kg	51–60 kg	61–70 kg	71–80 kg	≥80 kg
Rifampicin tablets (300 mg)	900 mg 3 tablets	900 mg 3 tablets	1500 mg 5 tablets	1500 mg 5 tablets	1800 mg 6 tablets	2400 mg 8 tablets
Rifampicin tablets (150 mg)	-	150 mg 1 tablet	-	150 mg 1 tablet	150 mg 1 tablet	-
Fixed dose combination (*150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol*)	450 mg 3 tablets	450 mg 3 tablets	450 mg 3 tablets	600 mg 4 tablets	750 mg 5 tablets	750 mg 5 tablets
Total rifampicin dose	1350 mg	1500 mg	1950 mg	2250 mg	2700 mg	3150 mg

TB & antimicrobial resistance (#AMR)

TB VAX ARM

MEDECINS SANS FRONTIERES

IT CAN TAKE

14,600 PILLS TO TREAT

ONE PERSON WITH DRUG-RESISTANT TB

IF YOU STACK UP THE # OF PILLS END-TO-END

THAT'S EQUIVALENT TO THE HEIGHT OF THE GOLDEN GATE BRIDGE

WE NEED BETTER TREATMENT NOW

MEDECINS SANS FRONTIERES

ACCESS TO EFFECTIVE DR-TB TREATMENT

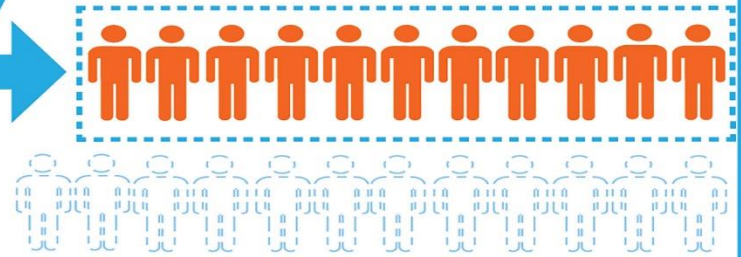
75% of people with DR-TB don't get effective treatment

Data: WHO Global TB Report 2018

of the **25%** that do,

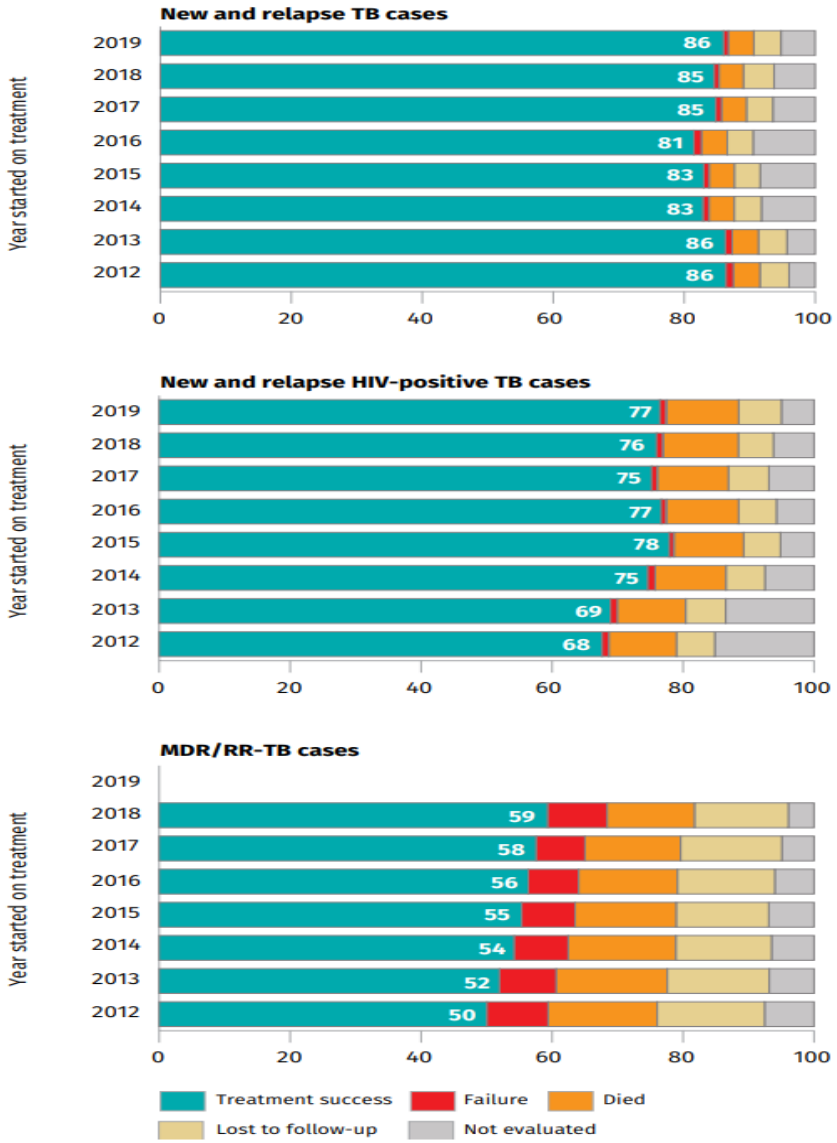
ONLY

HALF are cured.

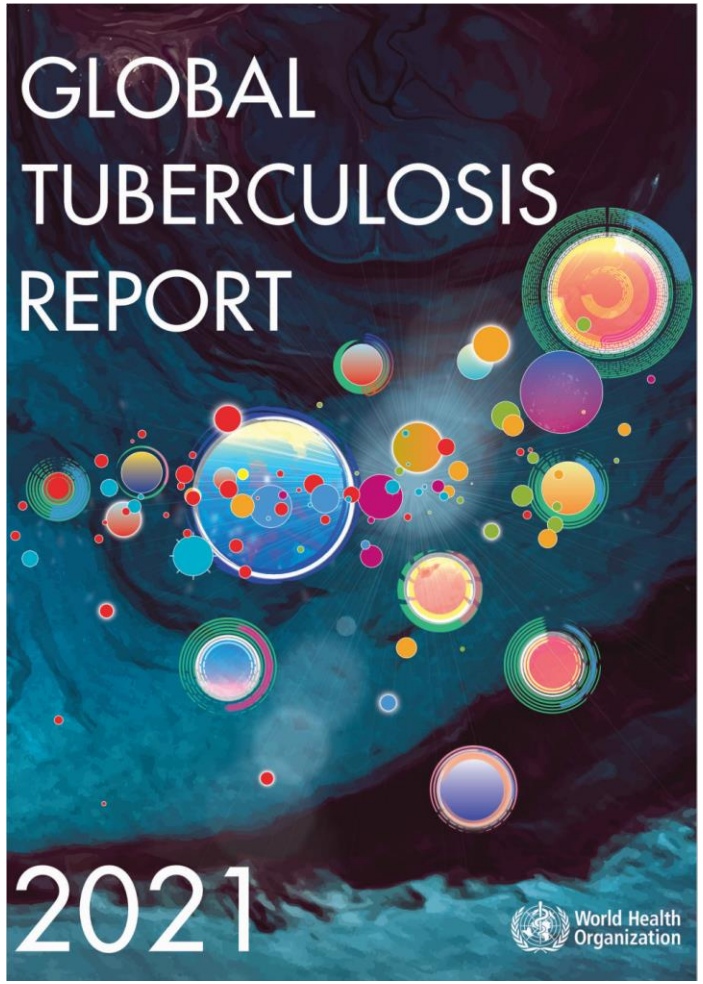


WE NEED BETTER TREATMENT NOW

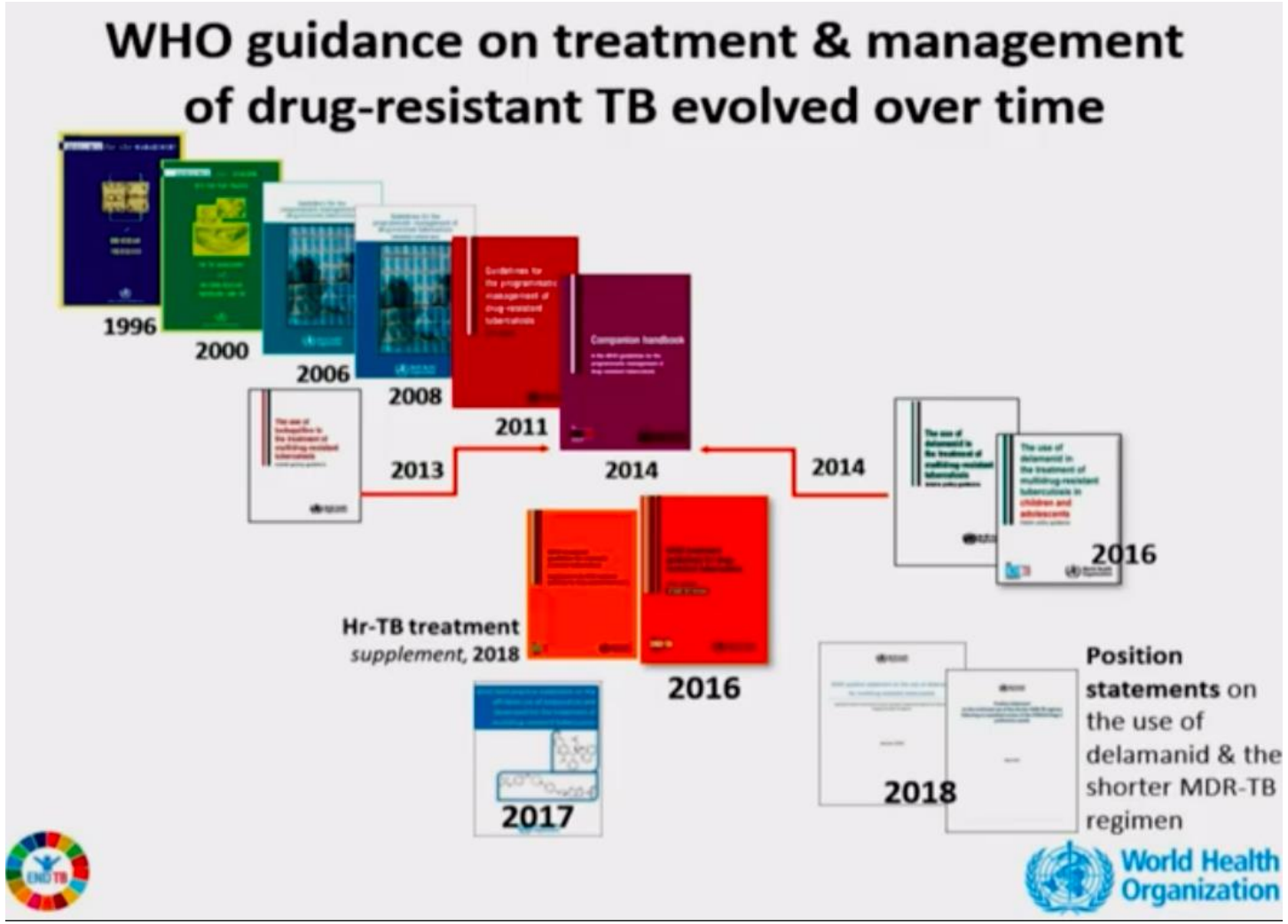
Treatment outcomes for new and relapse TB cases, new and relapse HIV-positive TB cases, and MDR/RR-TB cases, globally,[a] 2012–2019



[a] Outcomes for cohorts of people treated for MDR/RR-TB are reported one year later than other TB cohorts.



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.

Outcome of rifampicin mono-resistant and multidrug-resistant tuberculosis: a retrospective multicentre study from 1990 to 2016

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

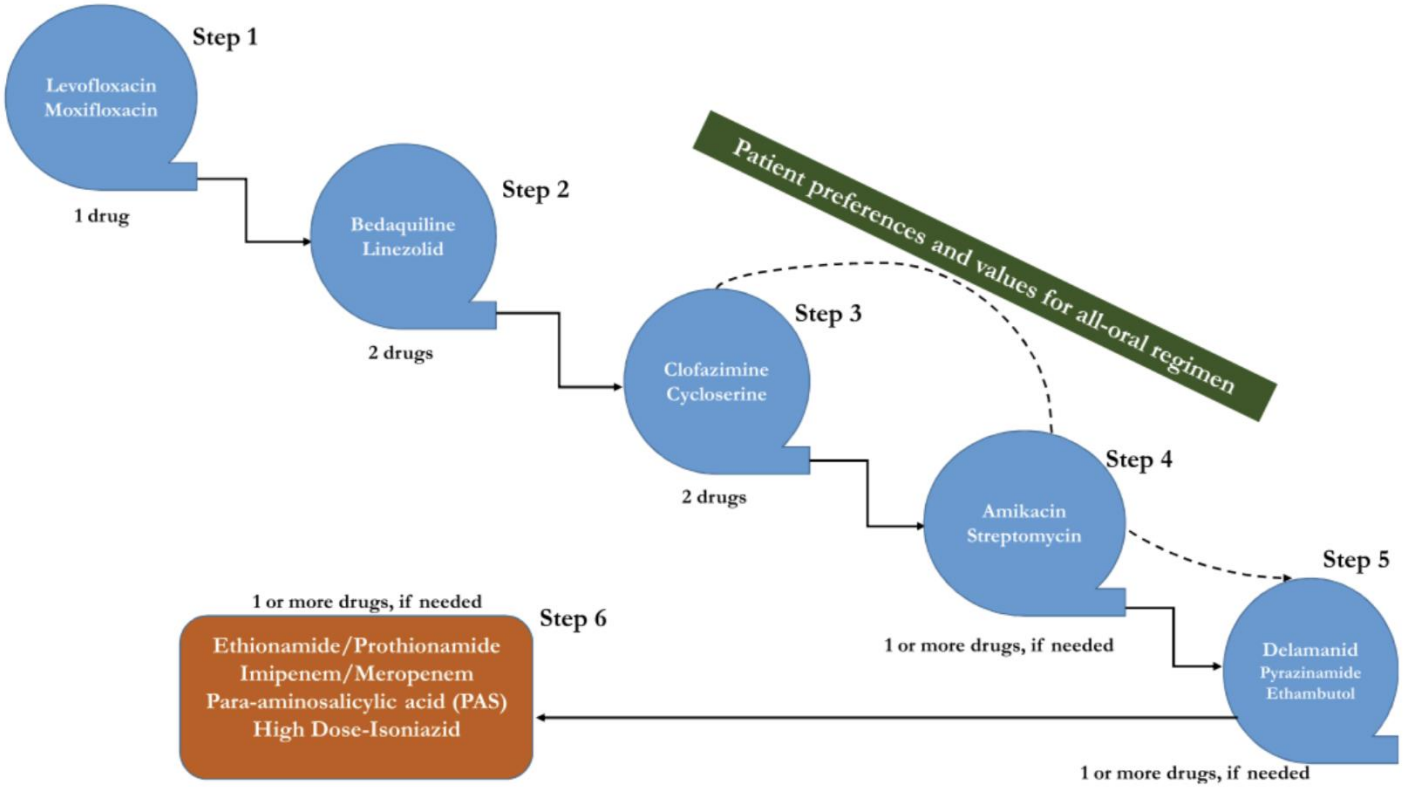


Figure 1. How to design the regimen for multidrug-resistant tuberculosis.
In the text and figure we focus mainly on the ATS/CDC/ERS/IDSA guideline, as - although largely consistent with the 2019 WHO ones - they provide additional clinical elements with main focus on low-TB incidence countries. Additional 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.

MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The

Section 3. Longer regimens for multidrug- or rifampicin-resistant tuberculosis

3.1 Recommendations

No.	Recommendation
3.1	**In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.** *(Conditional recommendation, very low certainty in the estimates of effect)*
3.2	**Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Conditional recommendation, very low certainty in the estimates of effect)*
3.3	**Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Strong recommendation, moderate certainty in the estimates of effect)*
3.4	**Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more.** **(***Strong recommendation, moderate certainty in the estimates of effect***)** **Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.** *(Conditional recommendation, very low certainty in the estimates of effect)*
3.5	**Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Strong recommendation, moderate certainty in the estimates of effect)*

3.6	**Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Conditional recommendation, very low certainty in the estimates of effect)*	
3.7	**Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Conditional recommendation, very low certainty in the estimates of effect)*	
3.8	**Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.** *(Conditional recommendation, moderate certainty in the estimates of effect)*	
3.9	**Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Conditional recommendation, very low certainty in the estimates of effect)*	
3.10	**Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Conditional recommendation, very low certainty in the estimates of effect)*[37]	
3.11	**Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.** *(Conditional recommendation, very low certainty in the estimates of effect)*	
3.12	**Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.** *(Conditional recommendation against use, very low certainty in the estimates of effect)*	
3.13	***P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.** *(Conditional recommendation against use, very low certainty in the estimates of effect)*	
3.14	**Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.** *(Strong recommendation against use, low certainty in the estimates of effect)*	

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.

The shorter all-oral bedaquiline-containing regimen for MDR/RR-TB

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**

- **The shorter all-oral bedaquiline-containing MDR/RR-TB regimen recommended by WHO in 2020 contains: *bedaquiline, levofloxacin/moxifloxacin, clofazimine, ethionamide, ethambutol, isoniazid (high dose) and pyrazinamide for 4 months***

  with the possibility of extending to 6 months if the patient remains sputum smear positive or culture positive at the end of the fourth month)

- **followed by 5 months of treatment with: *levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide.***
- ***Bedaquiline use in this regimen is for 6 months.***

Pretomanid for tuberculosis treatment: an update for clinical purposes

Sara Occhineri [a,b], Tommaso Matucci [a,b], Laura Rindi [c], Giusy Tiseo [a], Marco Falcone [a], Niccolò Riccardi [a,d,*], Giorgio Besozzi [d]

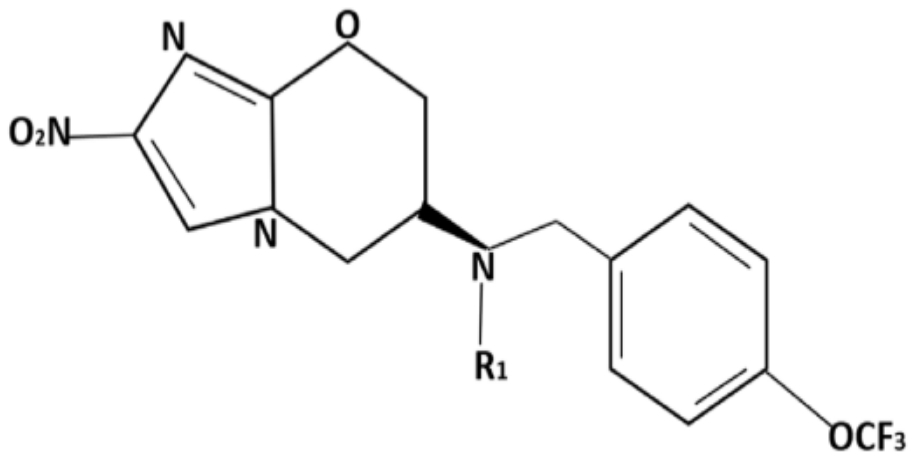


Fig. 2. Pretomanid chemical structure.

PA is an oral bicyclic nitroimidazooxazine anti-mycobacterial drug which includes the nitroimidazole pyran A/B ring, an ether link and an hydrophobic side chain. The chemical name is (6S)-2-Nitro-6- {[4-(trifluoromethoxy)phenyl]methoxy} −6,7-dihydro- 5H-imidazo[2,1-b] [1,3]oxazine (Fig. 2). The molecular formula is C14H12F3N3O5, and the molecular weight is 359.26 uma. (FDA Drug Approval Package, 2019; Cherian et al., 2011; Pstragowski et al., 2017).

3.3. Pharmacodynamics

PA is a prodrug and needs activation by *Mycobacterium tuberculosis* (Mtb) deazaflavin dependent-nitroreductase (ddn) which transforms PA into three primary active metabolites. The drug is clinically active against replicating and non-replicating bacilli through two main mechanisms of action (Pstragowski et al., 2017; Singh et al., 2008; Malo et al., 2021): 1) in aerobic conditions PA inhibits protein and lipid synthesis, which are essential components of the MTb cell, by a dose-dependent ability to decrease the availability of keto mycolic acids by an inadequate oxidative transformation of precursor hydroxymycolates; 2) in anaerobic state, PA generates des-nitro metabolites and the release of nitric oxide (NO). NO inhibits cytochrome *c* oxidase that leads to a significant reduction of the ATP concentration in cells (Li et al., 2021; Stancil et al., 2021; Villemagne et al., 2012; D'Ambrosio et al., 2015). This activity under anaerobic condition explains PA efficacy on non-replicating mycobacteria (Stancil et al., 2021; Singh et al., 2008; Manjunatha et al., 2009) comparable to R and LZD efficacy on inhibiting the growth of dormant phenotype Mtb (Diacon et al., 2012a,b; Ahmad et al., 2011; Wong et al., 2013; Fu and Tai, 2009). In vitro, the compound minimum inhibitory concentration (MIC) was estimated in between 0.015 and 0.25 μg/ml for drug-susceptible Mtb and among 0.03 and 0.53 μg/ml for drug-resistant strains (Pstragowski et al., 2017; Ginsberg et al., 2009a,b). In animal

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

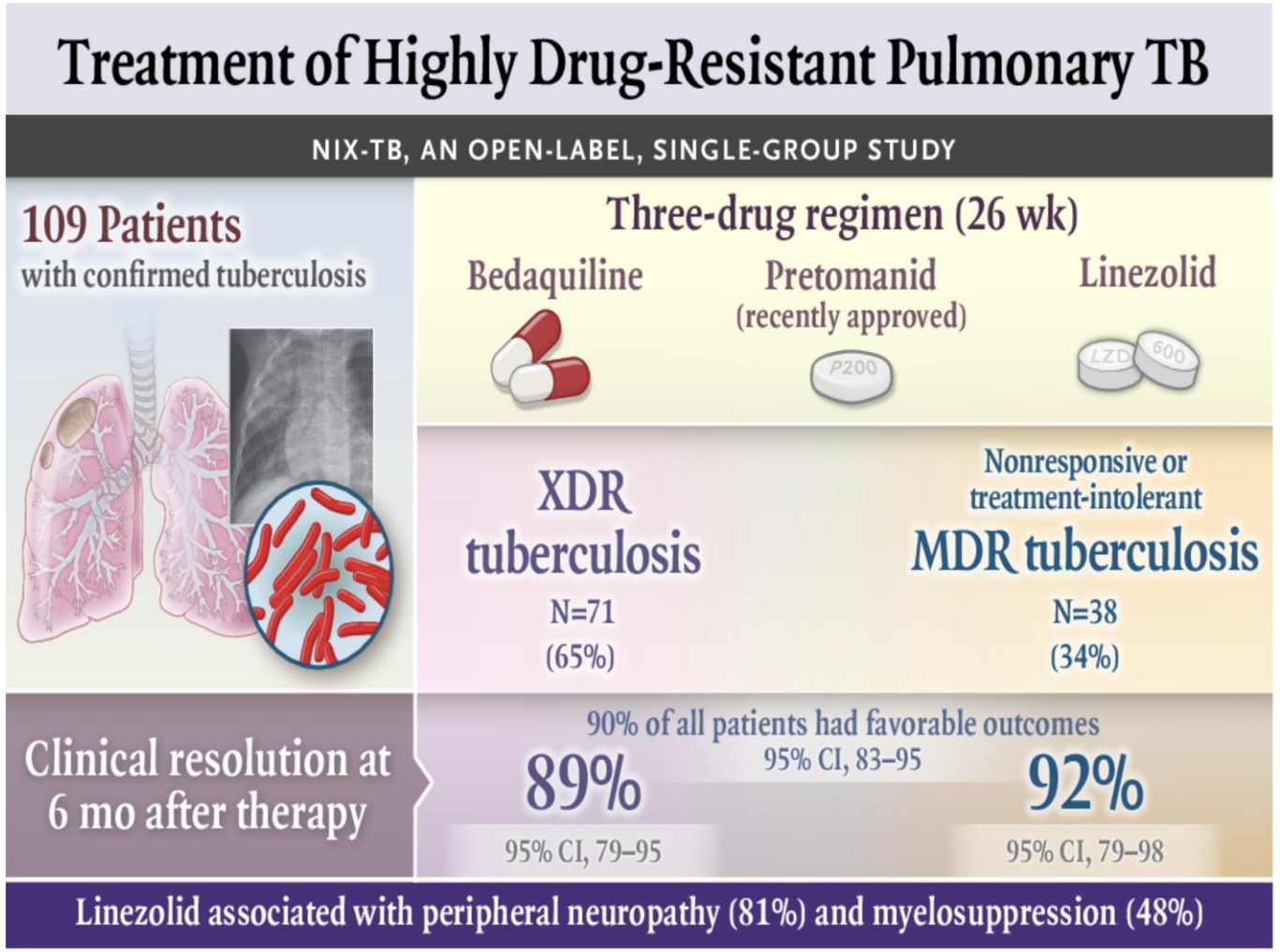
Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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

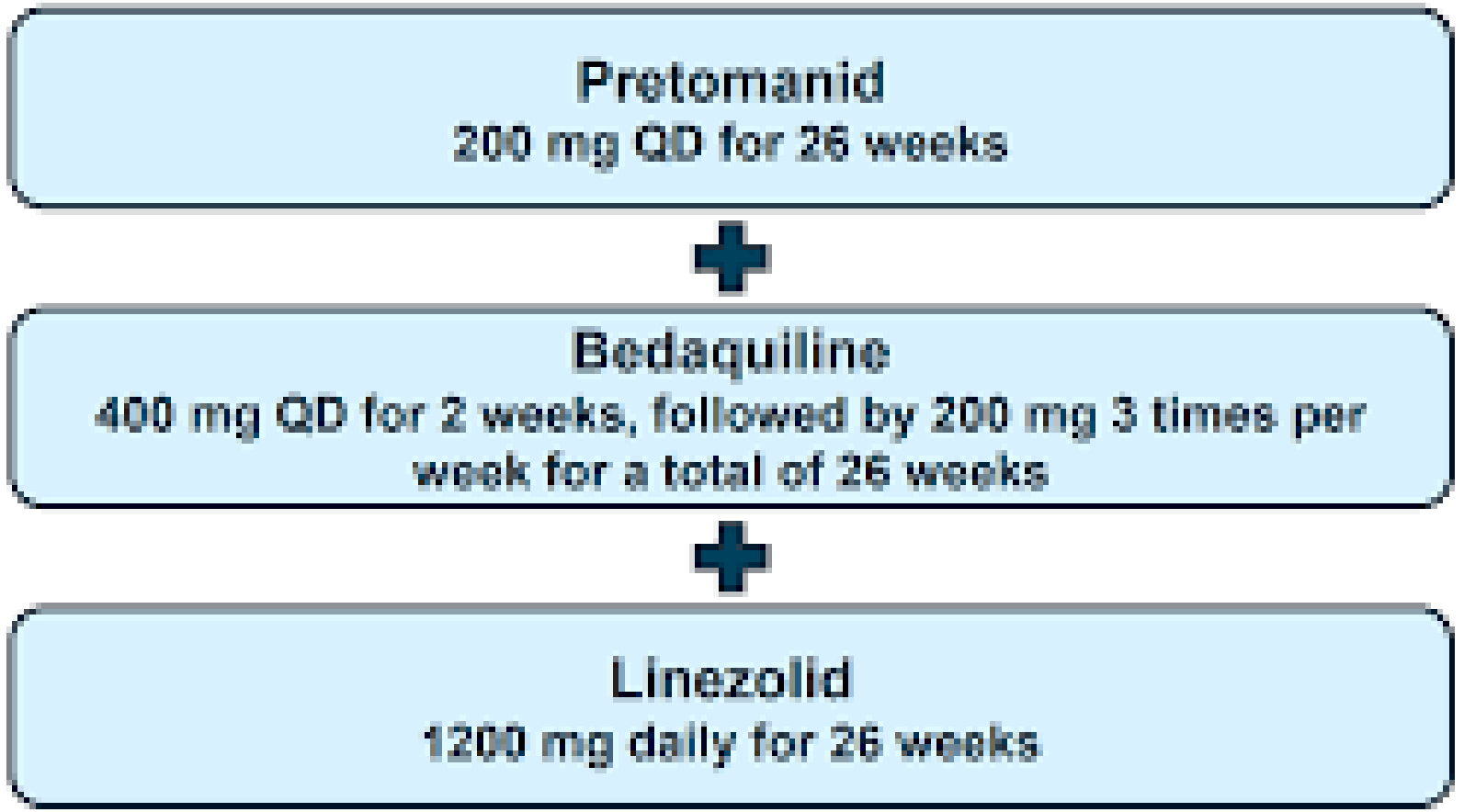
STUDY DESIGN

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 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



The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance

BPaL regimen: 6–9 Bdq- Pa-Lzd

Eligibility

- Pt. is diagnosed with bacteriologically confirmed pulmonary TB and has **laboratory-confirmed resistance to rifampicin and fluoroquinolones** with or without resistance to injectable agents.
- Pt. is aged at least 14 years at the time of enrolment; weighs 35 kg or more.
- Pt. is willing and able to provide informed consent to be enrolled in the operational research project and to adhere to the follow-up schedule.
- Pt. if the patient is not pregnant or breastfeeding and is willing to use effective contraception.
- Pt. **has no evidence in DST results of resistance to any of the component drugs**, or has not been previously exposed to any of the component drugs for 2 weeks or longer.
- Pt. has **no extrapulmonary TB** (including meningitis, other CNS TB, or TB osteomyelitis).

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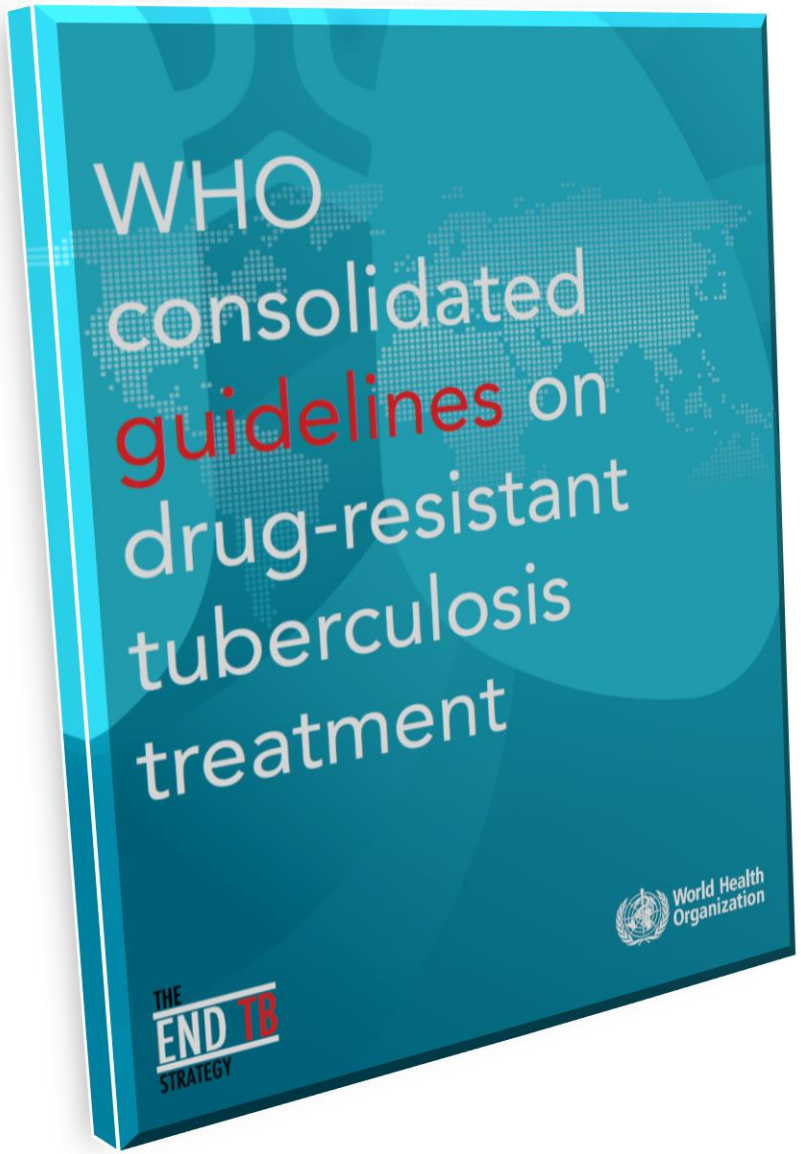
Table 3. Adverse Events That Occurred or Worsened during Treatment.

Event*	HIV Status		Linezolid Regimen		Overall (N=109)
	Negative (N=53)	Positive (N=56)	600 mg Twice Daily (N=44)	1200 mg Daily (N=65)	
			number (percent)		
Adverse event	53 (100)	56 (100)	44 (100)	65 (100)	109 (100)
Adverse event leading to death	3 (6)	3 (5)	4 (9)	2 (3)	6 (6)
Serious adverse event	10 (19)	9 (16)	13 (30)	6 (9)	19 (17)
Grade 3 or 4 adverse event	27 (51)	35 (62)	27 (61)	35 (54)	62 (57)

* A patient could have had more than one type of event.



Section 4. The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance

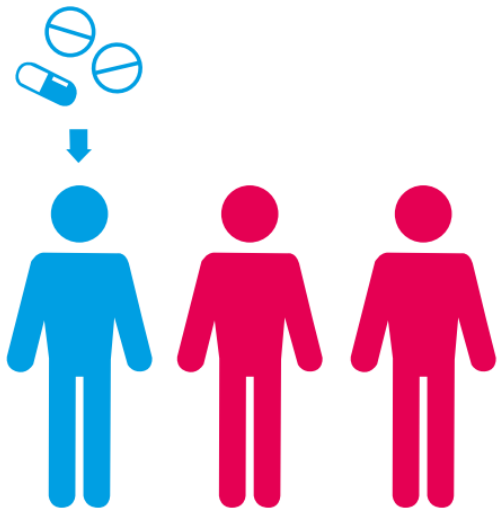
4.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
4.1	A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks. *(Conditional recommendation, very low certainty in the estimates of effect)*

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

27-29 October 2020

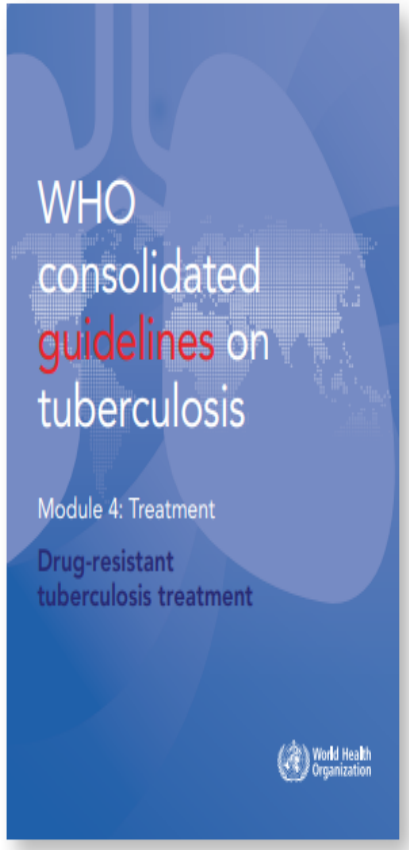


World Health Organization

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, may benefit from effective **all-oral treatment regimens**, shorter or longer.

1. For MDR/RR-TB patients without previous exposure to second-line treatment and bedaquiline, without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a **shorter, all-oral, bedaquiline-containing regimen**. In this group of patients, national programmes can phase out use of the injectable-containing shorter regimen.

2. For MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs will benefit from an **individualized longer regimen** designed using the priority grouping of medicines.



3. Novel **BPaL regimen** for MDR-TB with additional quinolone resistance under operational research conditions.

BPaL: bedaquiline, pretomanid and linezolid; DR-TB: drug-resistant tuberculosis; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

Aifa. Approvato pretomanid, farmaco per la tubercolosi polmonare a estesa farmacoresistenza

19 GENNAIO 2022 . AIFA, NEWS

L'**Agenzia italiana del farmaco** ha dato il via libera alla **rimborsabilità** di **pretomanid**, farmaco approvato esclusivamente per la **tubercolosi polmonare a estesa farmacoresistenza**.

La decisione di Aifa segue l'approvazione da parte della Agenzia Europea per i Medicinali dell'uso di pretomanid in associazione a bedaquilina e linezolid, come parte del regime con "BPaL" per il trattamento di adulti con TB polmonare a estesa farmacoresistenza (XDR) o intollerante al trattamento o multifarmacoresistente non reattiva (TI/NR MDR).

BPaL è un regime a 3 farmaci, tutti orali, della durata di 6 mesi che consente di ridurre il peso del trattamento e i problemi di aderenza, considerando in particolare il problema della insorgenza della resistenza antibiotica.

Gli attuali trattamenti per forme di tubercolosi a estesa farmacoresistenza consistono in combinazioni di molti farmaci diversi, che possono venire assunti per 18-20 mesi. I pazienti sono costretti a dover prendere fino a 20 pillole al giorno, con la conseguenza di numerosi effetti collaterali e spesso un considerevole impatto economico.

In Europa, ci sono circa 250 pazienti che soffrono di TB a estesa resistenza, il che rende pretomanid un farmaco orfano, con il potenziale di fornire un valore aggiunto e un migliore rapporto costo-efficacia per i pazienti e i sistemi sanitari, rispetto alla terapia standard.

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

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SITE IMPLEMENTATION

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TB-PRACTECAL IS:

- a regulatory-level,
- open-label,
- phase II/III,
- non-inferiority,
- randomised-controlled trial

Current standard care

PRACTECAL Arm-1 (BPaLM)

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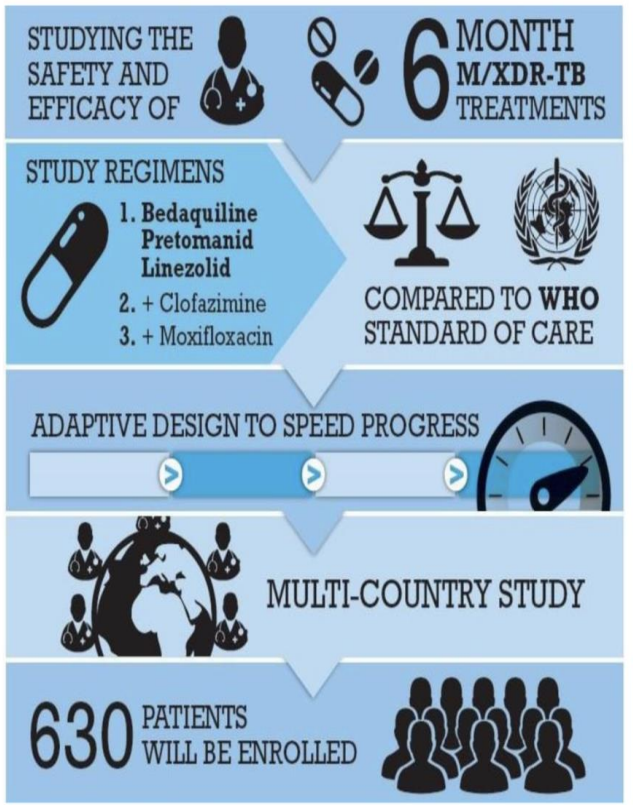
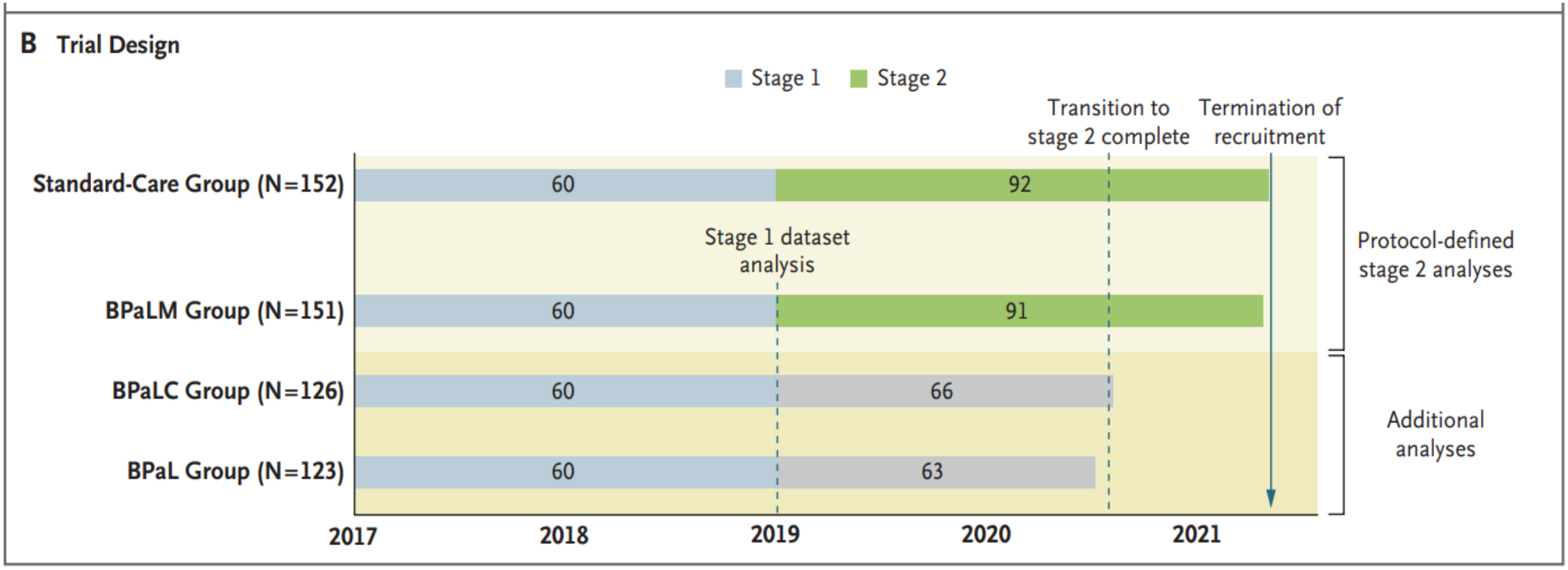


Courtesy of Ilaria Motta

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



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

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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]

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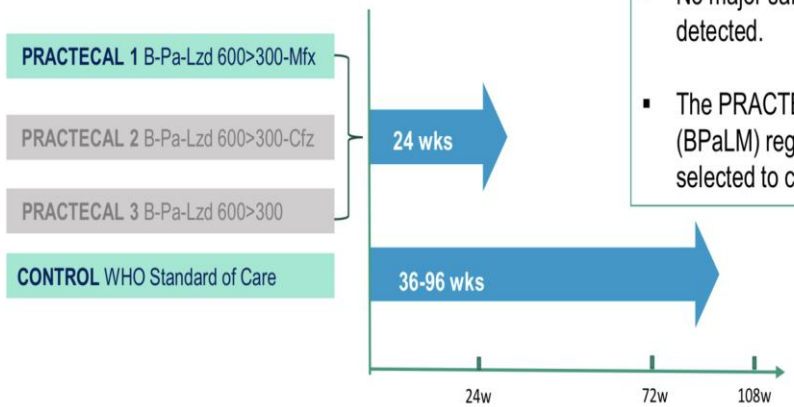
STAGE 1 >> STAGE 2

- 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

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

Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population		Modified Intention-to-Treat Population		Per-Protocol Population*	
	Standard-Care Group (N=73)	BPaLM Group (N=72)	Standard-Care Group (N=66)	BPaLM Group (N=62)	Standard-Care Group (N=33)	BPaLM Group (N=57)
Favorable outcome — no. (%)	34 (47)	55 (76)	34 (52)	55 (89)	29 (88)	55 (96)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)	32 (48)	7 (11)	4 (12)	2 (4)
Death — no. (%)	2 (3)	0	2 (3)	0	2 (6)	0
Early discontinuation — no. (%)	35 (48)	15 (21)	28 (42)	5 (8)	—	—
Adherence issues — no./total no. (%)	3/35 (9)	0	3/28 (11)	0	—	—
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)	17/28 (61)	5/5 (100)	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)	0	0	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	6/28 (21)	0	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	2/28 (7)	0	—	—
Treatment failure — no.	0	0	0	0	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)	2 (3)	2 (3)	2 (6)	2 (4)
Recurrence — no.	0	0	0	0	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)	—	−37 (−53 to −22)	—	−9 (−22 to 4)

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

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

Table 3. Outcomes at 72 Weeks in the Standard-Care, BPaLC, and BPaL Groups.*

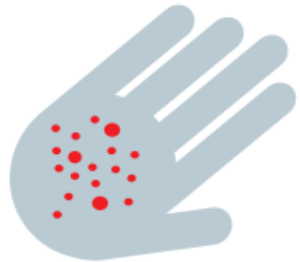
Variable	Intention-to-Treat Population			Modified Intention-to-Treat Population			Per-Protocol Population		
	Standard-Care Group (N=73)	BPaLC Group (N=72)	BPaL Group (N=70)	Standard-Care Group(N=66)	BPaLC Group (N=64)	BPaL Group (N=60)	Standard-Care Group(N=33)	BPaLC Group (N=58)	BPaL Group (N=52)
Favorable outcome — no. (%)	34 (47)	52 (72)	46 (66)	34 (52)	52 (81)	46 (77)	29 (88)	52 (90)	46 (88)
Primary outcome: unfavorable status — no. (%)	39 (53)	20 (28)	24 (34)	32 (48)	12 (19)	14 (23)	4 (12)	6 (10)	6 (12)
Death — no. (%)	2 (3)	1 (1)	0	2 (3)	1 (2)	0	2 (6)	1 (2)	0
Early discontinuation — no. (%)	35 (48)	14 (19)	18 (26)	28 (42)	6 (9)	8 (13)	—	—	—
Adherence issues — no./total no. (%)	3/35 (9)	2/14 (14)	2/18 (11)	3/28 (11)	2/6 (33)	2/8 (25)	—	—	—
Adverse event — no./total no. (%)	17/35 (49)	4/14 (29)	5/18 (28)	17/28 (25)	4/6 (67)	5/8 (62)	—	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	8/14 (57)	10/18 (6)	0	0	1/8 (12)	—	—	—
Did not receive at least one dose of trial medication — no./total no. (%)	0	0	1/18 (6)	—	—	—	—	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	0	6/28 (21)	0	0	—	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	0	2/28 (7)	0	0	—	—	—
Treatment failure — no. (%)	0	1 (1)	0	0	1 (2)	0	0	1 (2)	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	3 (4)	3 (4)	2 (3)	3 (5)	3 (5)	2 (6)	3 (5)	3 (6)
Recurrence — no. (%)	0	1 (1)	3 (4)	0	1 (2)	3 (5)	0	1 (2)	3 (6)
Risk difference for the primary outcome — percentage points (95% CI)	—	−26 (−41 to −10)	−19 (−36 to −2)	—	−30 (−45 to −14)	−25 (−41 to −9)	—	−2 (−15 to 12)	−1 (−15 to 14)

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

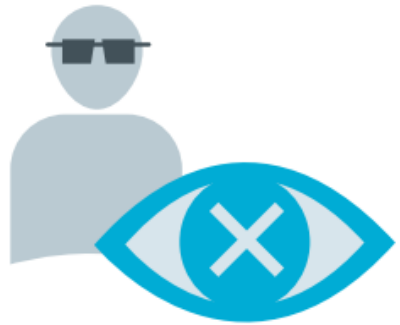
Side Effects

Headache

Nausea



Rash/itchiness of the skin

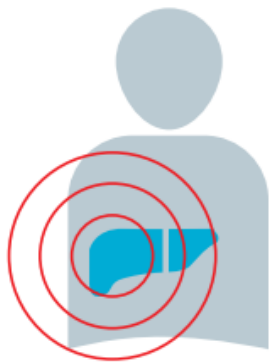


Vision loss / change in vision

Low blood count

Numbness / pain in hands and feet

Dizziness



Liver damage

CONCLUSIONS

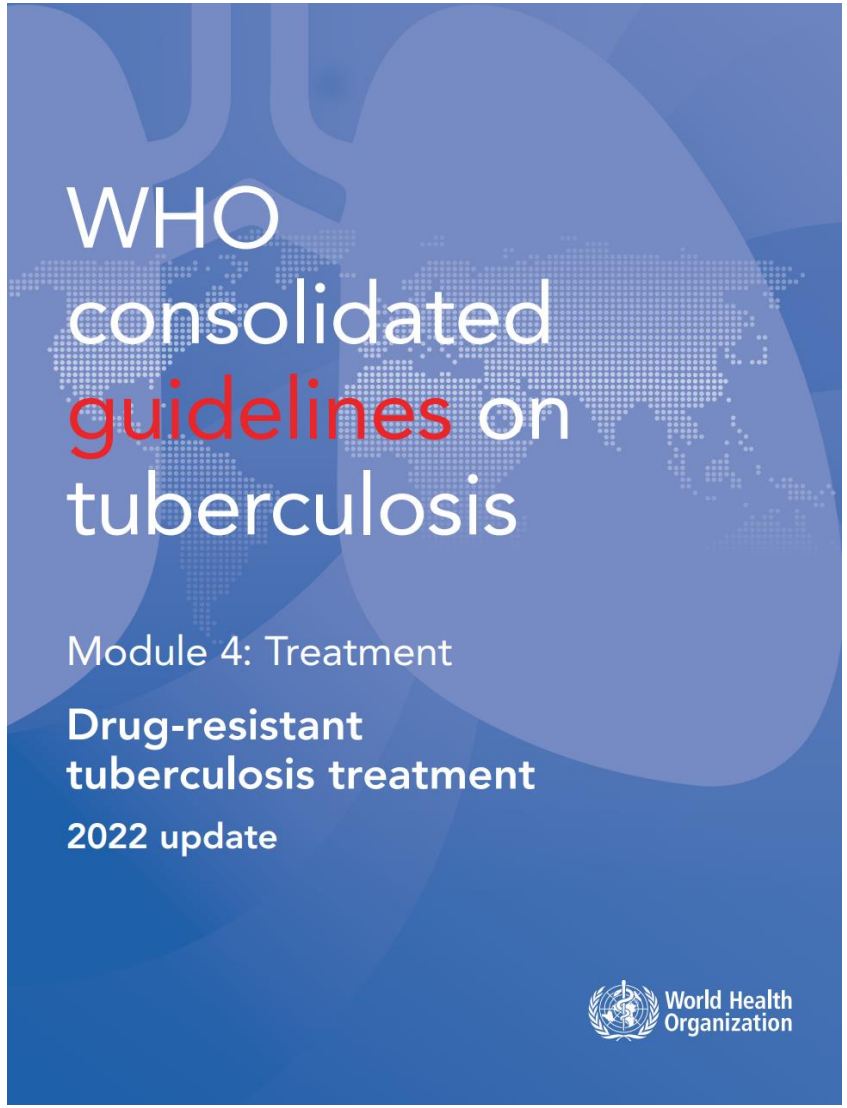
>>

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



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

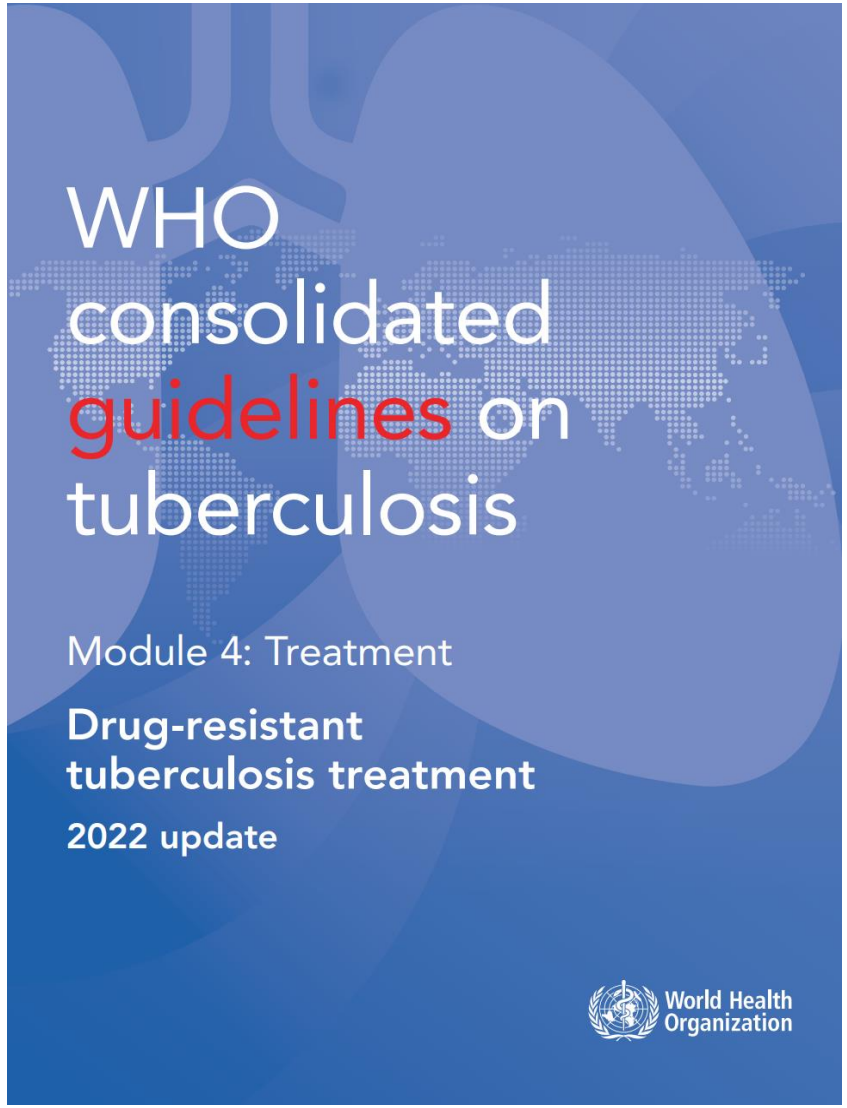
1.1 Recommendation

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)*

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.



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]

The New Regimen

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

NEW REGIMEN

Bedaquiline + Pretomanid + Linezolid + Moxifloxacin = 6-month treatment time

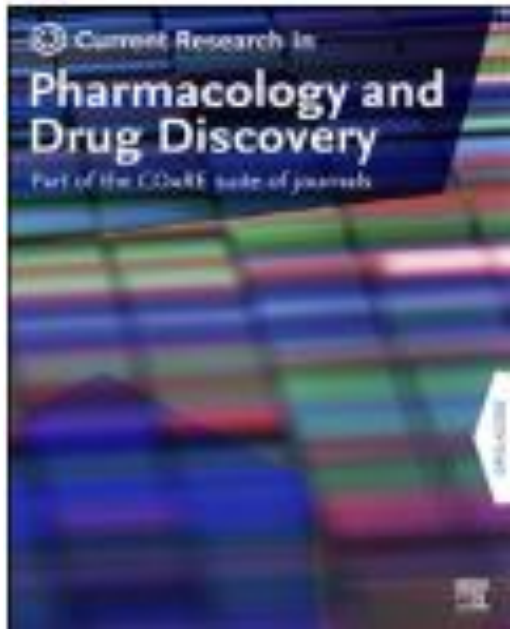
Table 2: Dosing of MDR-TB drugs for adults

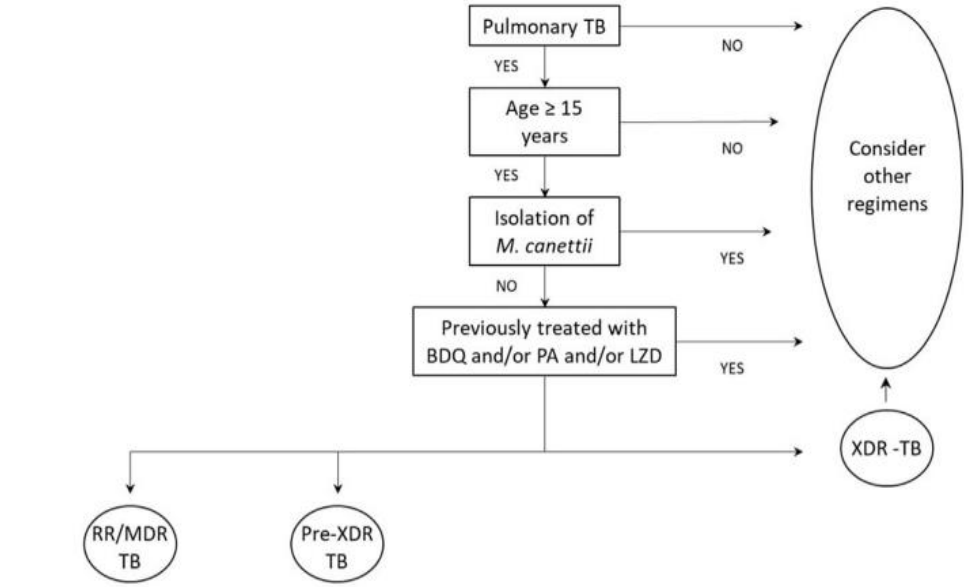
Drug	Weight group	
	30-50 kg	More than 50 kg
Bedaquiline (100 mg tablets)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards	
Delamanid (50 mg tablets)	100 mg twice daily (200 mg total daily dose) for 24 weeks	
Linezolid (600 mg tablets)	600 mg once daily + pyridoxine 50 mg daily*	
Levofloxacin (250 mg or 500 mg tablets)	750 mg	1000 mg
Moxifloxacin (400 mg tablets)	600 mg	800 mg
Clofazimine (100 mg gel capsules)	100 mg	100 mg
Ethambutol (400 mg tablets)	800 mg	1200 mg
Pyrazinamide (500 mg tablets)	1500 mg	2000 mg
Isoniazid, high dose (300 mg tablets)	400 mg	600 mg
Prothionamide (250 mg tablets)	500 mg	750 mg
Kanamycin (1000 mg vials)	15 mg per kilogram body weight (maximum 1 g)†	

* Linezolid dose is commonly reduced to 600 mg three times a week or 300 mg daily in patients with linezolid-induced peripheral neuropathy.

Pretomanid for tuberculosis treatment: an update for clinical purposes

Sara Occhineri [a,b], Tommaso Matucci [a,b], Laura Rindi [c], Giusy Tiseo [a], Marco Falcone [a], Niccolò Riccardi [a,d,*], Giorgio Besozzi [d]





BPaLM	BPaL	Adverse events	Avoid	Monitor
BDQ 400 mg once daily for 2 weeks then 200 mg 3 times per week for 24 weeks	**BDQ** 400 mg once daily for 2 weeks then 200 mg 3 times per week for 24 weeks;	QTcprolongation	Concomitant use of efavirenz; Torsades de Point; pre-existing QTc prolongation	ECG monitoring at initiation, on week 2 and then monthly
PA 200 mg once daily orally for 26 weeks;	**PA** 200 mg once daily orally for 26 weeks;	Livertoxicity	Concomitant use of alcool	ALT/AST monitoring at initiation, weekly the first month, every two weeks thesecond month then monthly
LZD 600 mg once daily orally for 16 weeks then 300 mg once daily for 8 weeks; *	**LZD** 600 mg once daily orally for 26 weeks.*	Peripheral neuropathy; bone marrow toxicity; diarrhoea; ocular toxicity	Concomitant use of carbamazepine/ amitriptyline; severe peripheral neuropathy; hypersenstivity to oxazolidinones	Neurological examination, blood test including neutrophil count at initiation, on week, then monthly; ophtalmic exam
MFX 400 mg once daily orally for 24 weeks.		Tendon damage; QTc prolongation	Pre-existing QTc prolongation	ECG monitoring at initiation, on week 2 and then monthly

TAKE HOME MESSAGES for DR-TB TREATMENT

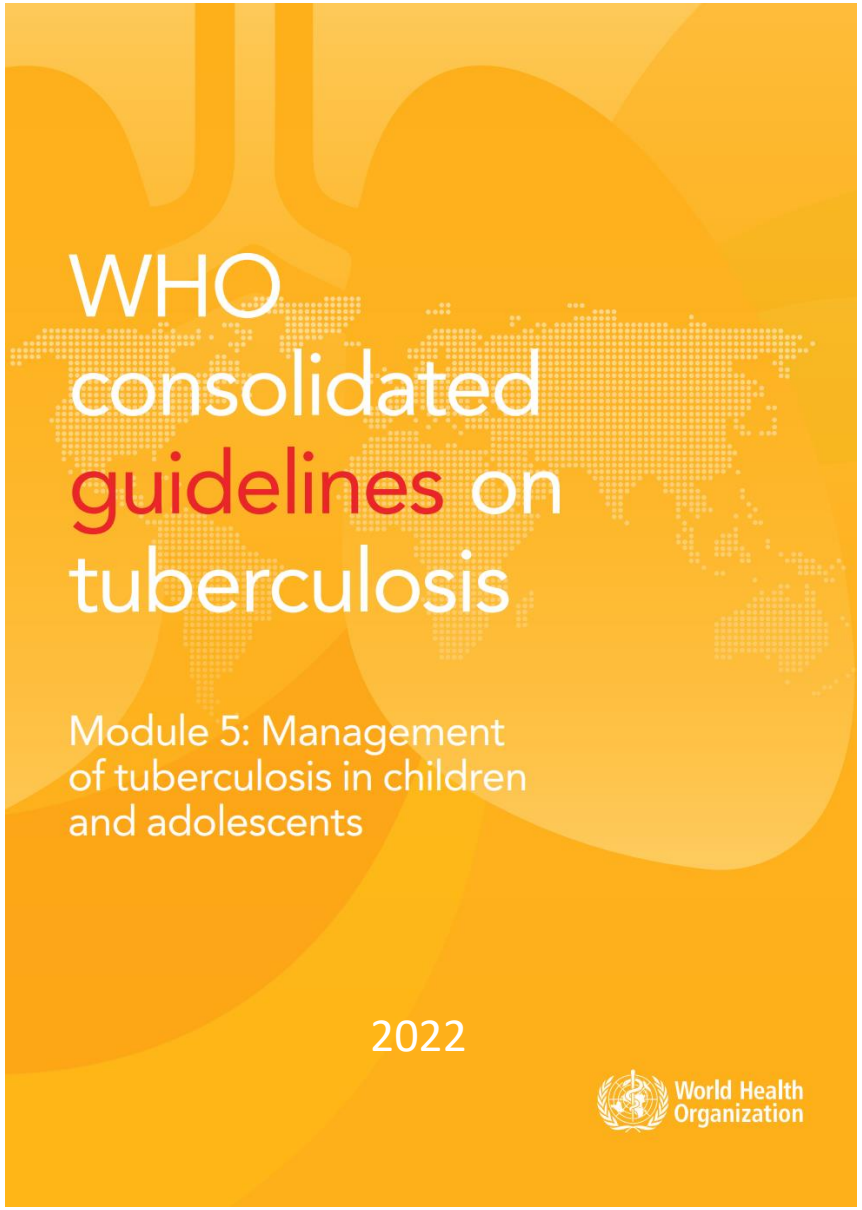
“There is more to TB than just the Mycobacteria”

“Each patient and Mycobacteria is a complex and unique mix of host and resistance”

“Better data will bring more tailored treatments (and hopefully a vaccine)”

“Each patient is worth fighting for, irrespectively of the DST”

R. Koch; Z. Udwadia; G. Sotgiu



•Diagnostic testing has expanded to include non-invasive specimens, such as stools.

•Rapid molecular diagnostics are recommended as the initial test for TB diagnosis for children and adolescents.

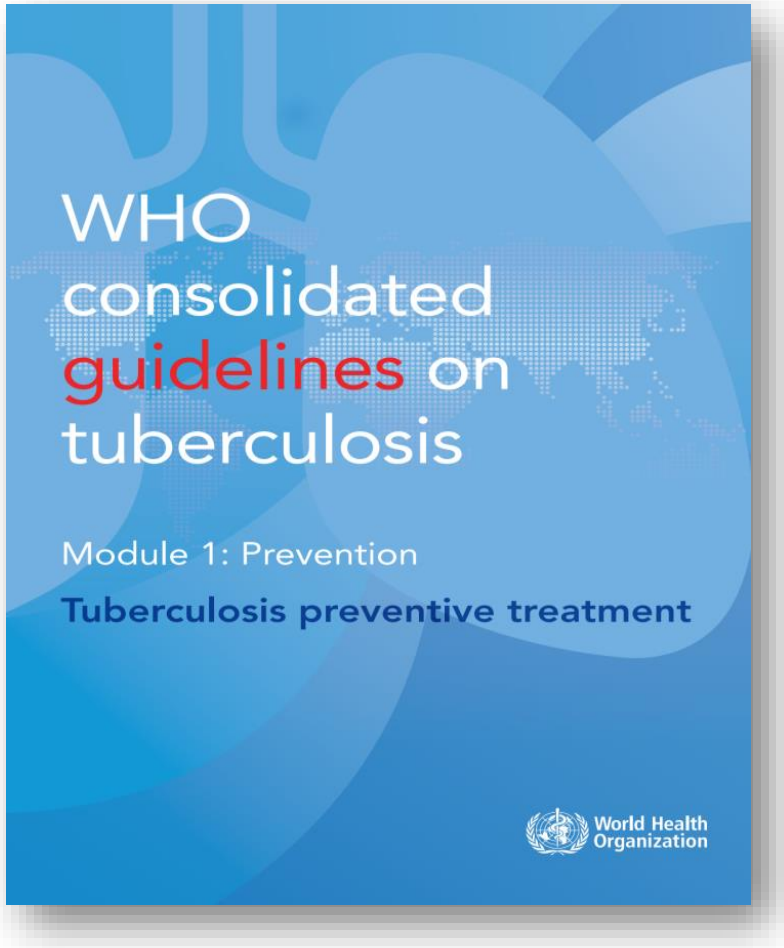
•Children and adolescents who have non-severe forms of drug-susceptible TB are now recommended to be treated for four months instead of six months, as well as TB meningitis, where a six-month regimen is now recommended instead of 12 months. This promotes a patient-centred approach that will reduce the costs of TB care for children, adolescents and their families.

•Two of the newest TB medicines to treat drug resistant TB (bedaquiline and delamanid) are now recommended for use in children of all ages, making it possible for children with drug-resistant TB to receive all-oral treatment regimens regardless of their age.

•New models of decentralized and integrated TB care are also recommended, which will allow more children and adolescents to access TB care or preventive treatment, closer to where they live.

2020 TPT guidelines – TPT options

- 6 or 9 months of daily isoniazid*
- 3 month regimen of weekly rifapentine plus isoniazid*
- 3 month regimen of daily isoniazid plus rifampicin*
- 4 months of daily rifampicin alone
- 1 month regimen of daily isoniazid plus rifapentine
- 36 months of daily isoniazid preventive treatment in PLHIV >10y in settings with high TB transmission
- 6 months regimen of levofloxacine for MDR-TB contacts



** Strong recommendation*

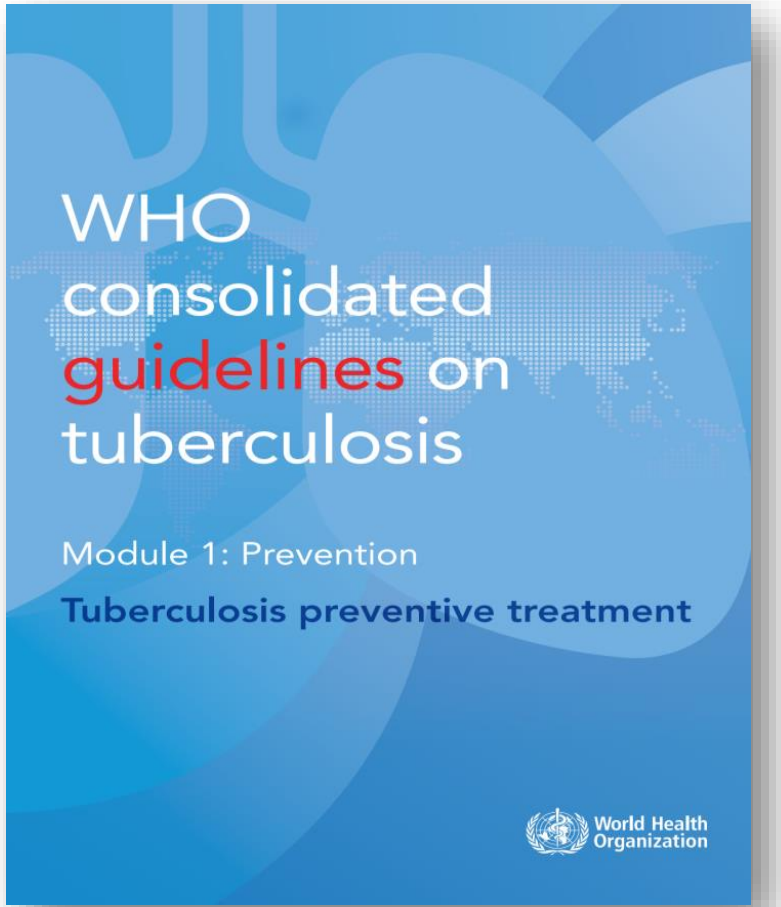


Table 3. Recommended dosages of medicines for TB preventive treatment

Regimen	Dose by weight band
6 or 9 months of daily isoniazid monotherapy (6H, 9H)	Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg)
Four months of daily rifampicin (4R)	Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)
Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)

Three months of rifapentine plus isoniazid weekly (12 doses) (3HP)

Age 2–14 years

Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
Isoniazid, 100 mg*	3	5	6	7	7
Rifapentine, 150 mg	2	3	4	5	5

Age >14 years

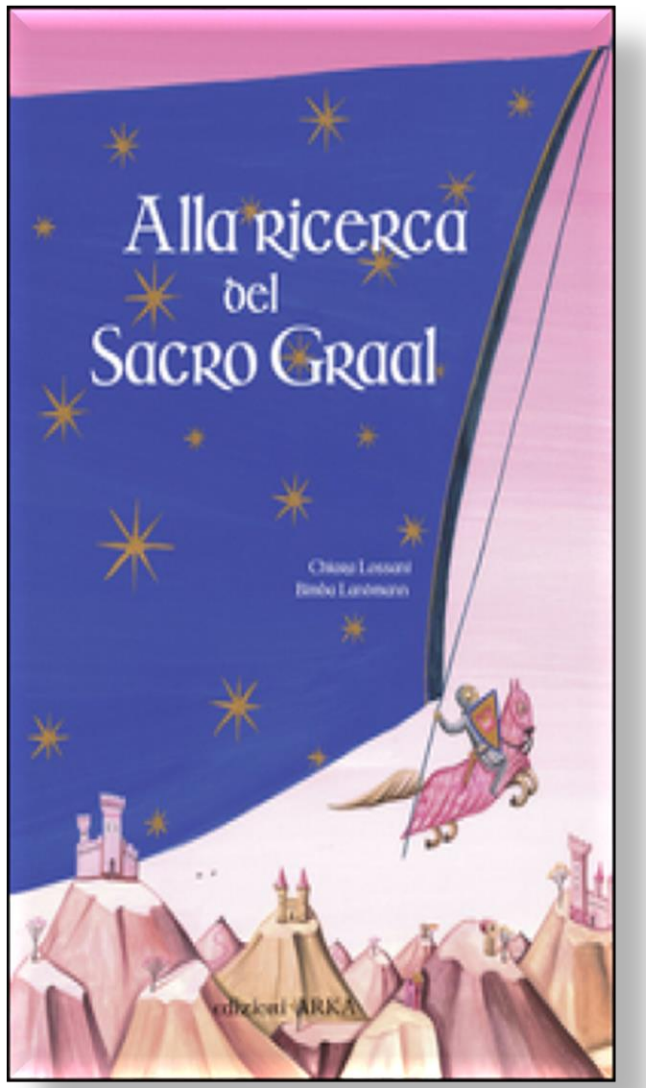
Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Isoniazid, 300 mg	3	3	3	3	3
Rifapentine, 150 mg	6	6	6	6	6

* 300mg formulation can be used to reduce pill burden

One month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Age >14 years, by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Age <15 years (range, approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day; 10–15 kg: 200–300mg/day; 16–23 kg: 300–400mg/day; 24–34 kg: 500–750mg/day


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

Pan-tuberculosis regimens: an argument against



The quest for a universal tuberculosis treatment regimen has become a Holy Grail for many working in the field of tuberculosis. It is argued that such a regimen, likely comprising three drugs (bedaquiline, an oxazolidinone-like sutezolid, and a nitroimidazole-like pretomanid or delamanid), would eliminate the need for drug-susceptibility testing, and have the biggest effect on reducing disease burden and mortality. It is certainly true that such a regimen could have real benefit for many people living with tuberculosis and the programmes that serve them. However, focusing on a universal regimen as the answer to the world's tuberculosis woes is a flawed approach for several reasons.

1. **Rapid resistance amplification will occur, with loss of effective drugs**
2. **Diagnostic and drug development will be impaired**
3. **Drug resistance and toxicity will become more difficult to manage**
4. **Unrealistic expectations about short-term effects will not be met (barriers)**
5. **Progress towards better ethical, health system and patient-centred care will be inhibited**

*Keertan Dheda, Tawanda Gumbo, Christoph Lange, C Robert Horsburgh Jr, Jennifer Furin

www.thelancet.com/respiratory Vol 6 April 2018


ONE-SIZE FITS ALL
STORE
SALE


One size
does NOT
fit all.

Better data, more tailored tuberculosis therapies

*Giovanni Sotgiu, *Giovanni Battista Migliori*
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giovannibattista.migliori@fsm.it

thelancet.com/infection **Vol 16 October 2016**

The new WHO-recommended regimen for multidrug-resistant tuberculosis (previously known as Bangladesh regimen), which is expected to increase patients' adherence and programmatic sustainability (being shorter and cheaper), includes pyrazinamide and fluoroquinolones among its core drugs.[12] The variability in drug resistance patterns calls for understanding of national and subnational epidemiology, and emphasises the need for rapid molecular methods and drug susceptibility testing to exclude drug resistance whenever there is suspicion that it might be present. Only with accurate and timely diagnosis will the spread of drug-resistant tuberculosis be contained.

2022 Global New TB Drug Pipeline[1] Updated 11/3/2022

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GMP / GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3** → **Regulatory Market Approvals**

Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13, F-ATP synthase
Oxazolidinones
DnaE1 / Nargenicin analogs

TBD-09, TBD-10 (MK-7762, -3854)
MPL-447*
JSF-3285*
CPZEN-45*
NTB-3119*
MBX-4888A (1810)*
FNDR-10045*, FNDR-20364*

GSK-839*
OTB-658

BVL-GSK098*
GSK-286*
TBAJ-876
TBAJ-587
TBI-223
Macozinone* (PBTZ-169)

Sanfetrinem
Delpazolid
Sutezolid
Sudapyridine (WX-081)
BTZ-043*
TBA-7371*
OPC-167832*
GSK-656* (070)
Telacebec*
Pyrifazimine (TBI-166)
SPR720*
SQ-109*

Results Reported / Expected in 2022/23

TB Practecal
ZeNix
Simplici TB (4-month regimen)
Truncate TB (2-month regimens)
STREAM 2
Bedaquiline*
Delamanid*
Pretomanid*

Underline = updates since May 2022

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

[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 identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

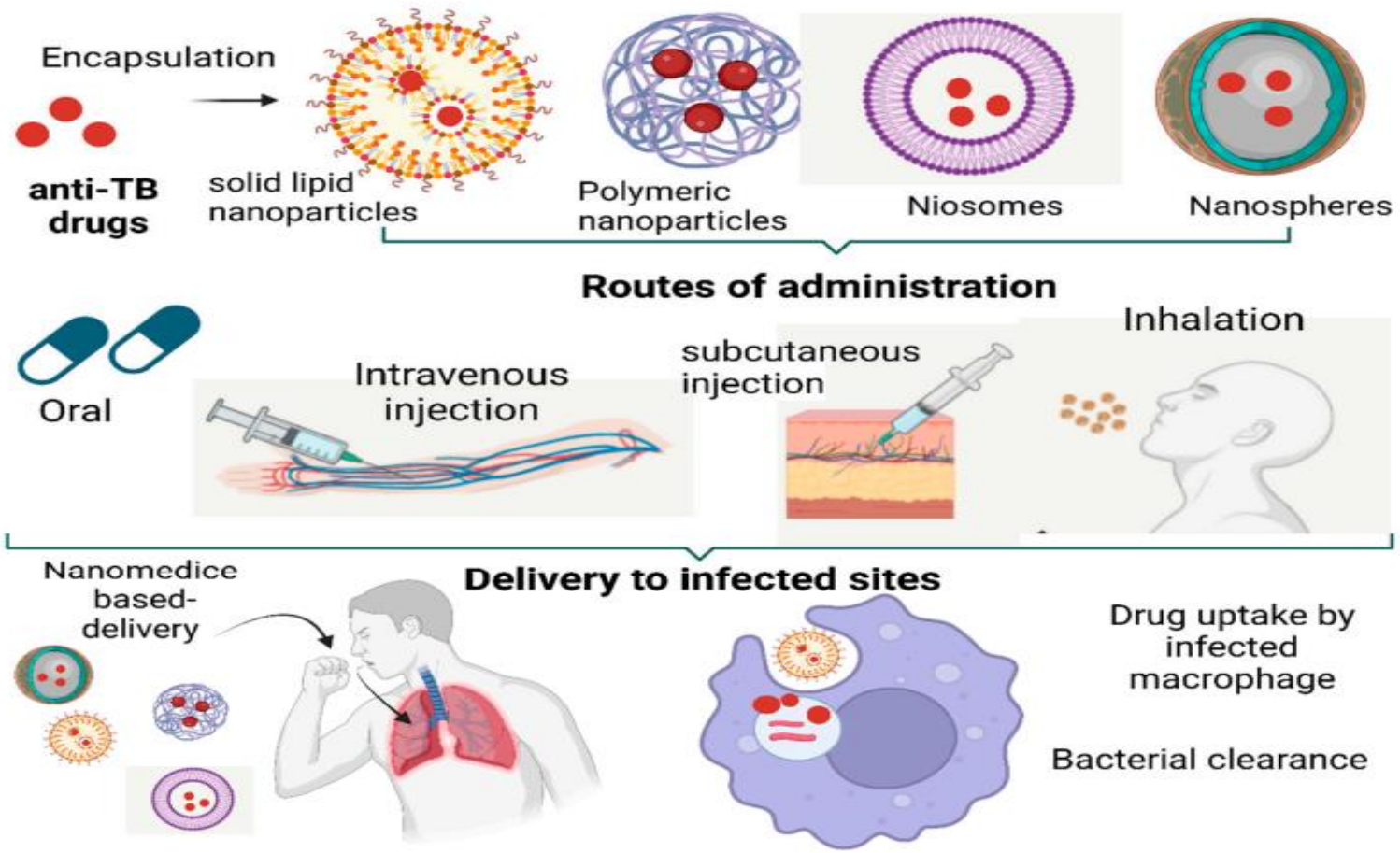
Updated: November 2022

Regimens

Regimen	Developer(s)
2HRZE + experimental drugs	
2HRZE 2HR	
BEAT-TB	USAID
Bedaquiline - Delamanid with MBT for MDR	
Bedaquiline - Linezolid - Levofloxacin with OBR	
Bedaquiline - Pretomanid - Linezolid	TB Alliance
Bedaquiline - Pretomanid - Linezolid - Moxifloxacin	Médecins Sans Frontières
Bedaquiline, Pretomanid, Moxifloxacin, Pyrazinamide	TB Alliance
Bedaquiline-Moxifloxacin-Linezolid-Pyrazinamide	
CC-11050, Auranofin, Everolimus, Vitamin D3 plus Rifabutin-modified TB Therapy	The Aurum Institute NPC, Medicines Development for Global Health
Delamanid with OBR	Otsuka Pharmaceutical Development & Commercialization, Inc.
Delamanid, Bedaquiline, OPC-167832	Otsuka Pharmaceutical Development & Commercialization, Inc.
Delpazolid, Bedaquiline, Delamanid, & Moxifloxacin	PanACEA
INH, RIF, PZA, MOX	
Pravastatin, Rifafour, & Vitamin B6	
Pretomanid - Moxifloxacin - Pyrazinamide Regimen	TB Alliance
Sutezolid, Bedaquiline, Delamanid, & Moxifloxacin	PanACEA

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]

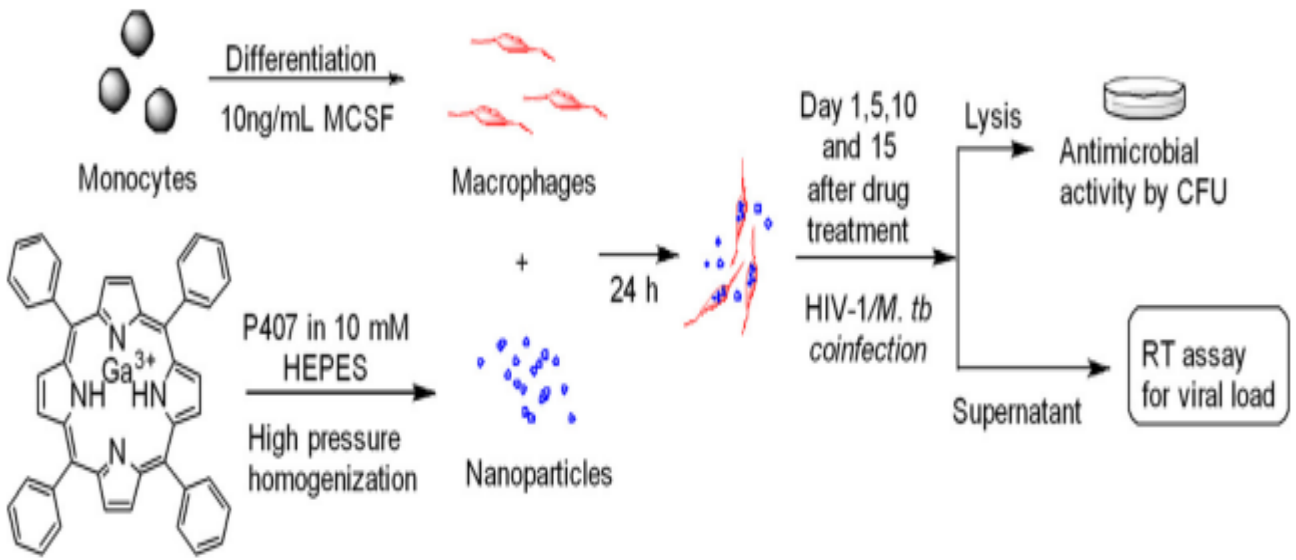


Trop. Med. Infect. Dis. **2023**, *8*, 100

Ga(III) Nanoparticles Inhibit Growth of both *Mycobacterium tuberculosis* and HIV and Release of Interleukin-6 (IL-6) and IL-8 in Coinfected Macrophages

Seoung-ryoung Choi,[a] Bradley E. Britigan,[a,b,c] Prabagaran Narayanasamy[a]

Department of Pathology and Microbiology[a] and Department of Internal Medicine,[b] College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; Research Service, VA Medical Center Nebraska-Western Iowa, Omaha, Nebraska, USA[c]



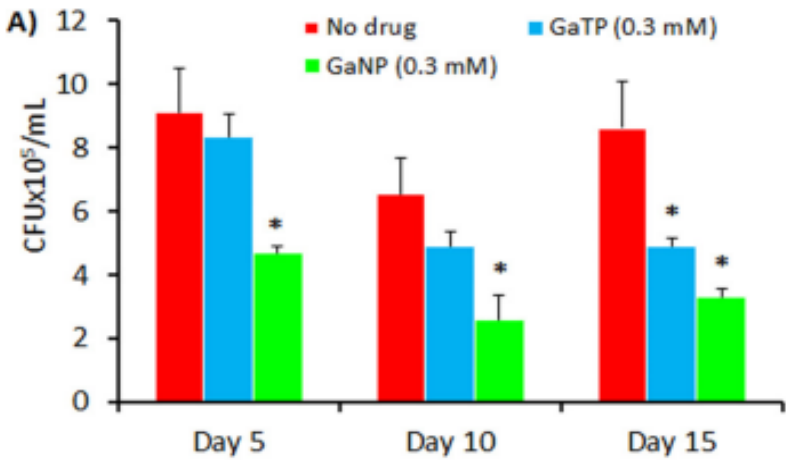


FIG 1 Scheme for testing antimicrobial activities of gallium(III) in *M. tuberculosis* (*M. tb*)- and HIV-infected MDMs.

Stop TB

www.stoptb.it

WHAT WOULD WE NEED TO FIGHT TB?

- ADDRESS and PREVENT SOCIAL DETERMINANTS of TB
- REDUCE and PREVENT MEDICAL COMORBIDITIES (e.g. smoke, diabetis, immunesoppression)
- DIFFERENT DRUGS for LTBI and ACTIVE TB
- SHORTER REGIMENS for SENSITIVE TB
- BETTER TOLERETED REGIMENS (e.g no side effects, no drug-drug interactions, weekly administration, NO FAKE DRUGS)
- PAEDIATRIC FORMULATIONS (e.g. syrup, candies, liquid)
- ORAL REGIMENS for MDR/preXDR/XDR TB
- NEW DELIVERY SYSTEMS (e.g. aerosol, nanoparticols, liposome)
- HIGH GENETIC BARRIERS
- TOTALLY FREE SUPPLY
- "SALVAGE" THERAPY

EFFICIENT, SAFE and FREELY AVAILABLE VACCINE

Good and bad news about new TB vaccines

Candidate TB Vaccine Pipeline (WHO Global TB Report 2021): 9 candidates in Phase 2b/3 (POI/POD/POR)

Phase I	Phase IIa
AdHu5Ag85A[b] McMaster, CanSino	ChAdOx185A-MVA85A[b] (ID/IM/Aerosol) University of Oxford
AEC/BC02[e] Anhui Zhifei Longcom	ID93 + GLA-SE[d] IDRI, Wellcome Trust, IAVI
	TB/FLU-04L[b] RIBSP

[a] Information was self-reported by vaccine sponsors to WHO or to the Stop TB Partnership Working Group on New TB Vaccines.

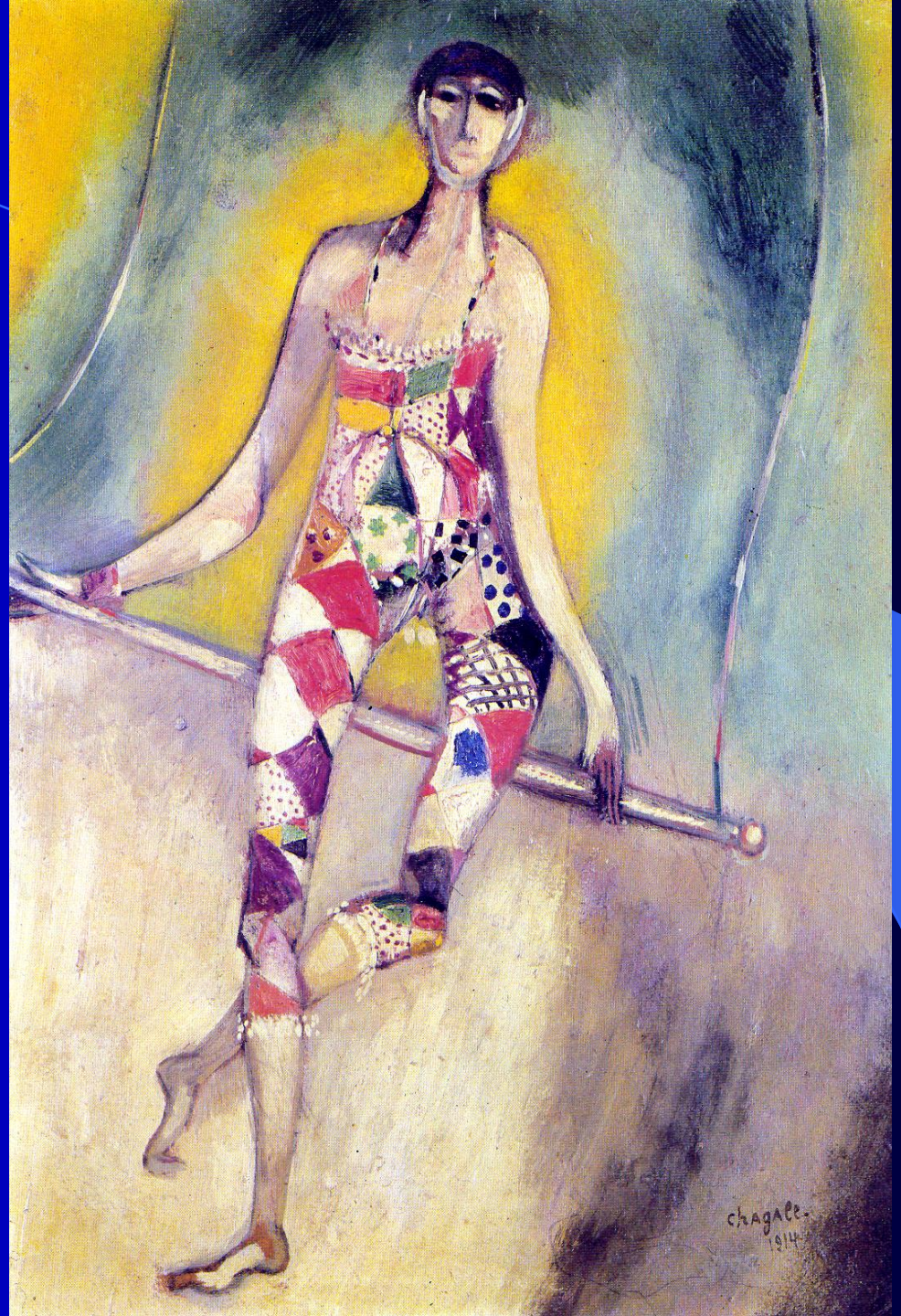
M72/AS01$_E$

M72/AS01$_E$ is a subunit vaccine that pairs two *M. tuberculosis* antigens (32A and 39A) with an adjuvant (AS01$_E$). It was tested in a Phase IIb efficacy trial in HIV-negative adults already infected with *M. tuberculosis* in Kenya, South Africa and Zambia, with the primary end-point being the number of incident cases of active laboratory-confirmed pulmonary TB disease not associated with HIV infection.

The final analysis of this trial showed a 50% (90% CI: 12–71%) point estimate for vaccine efficacy after 3 years of follow-up *(28)*. In terms of the clinical significance and strength of evidence, this result is unprecedented in decades of TB vaccine research. If the findings are confirmed in a Phase III trial, this vaccine has the potential to transform global TB prevention efforts.

Lo specialista di terapia antitubercolare

M Chagall *L'acrobata* 1915

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