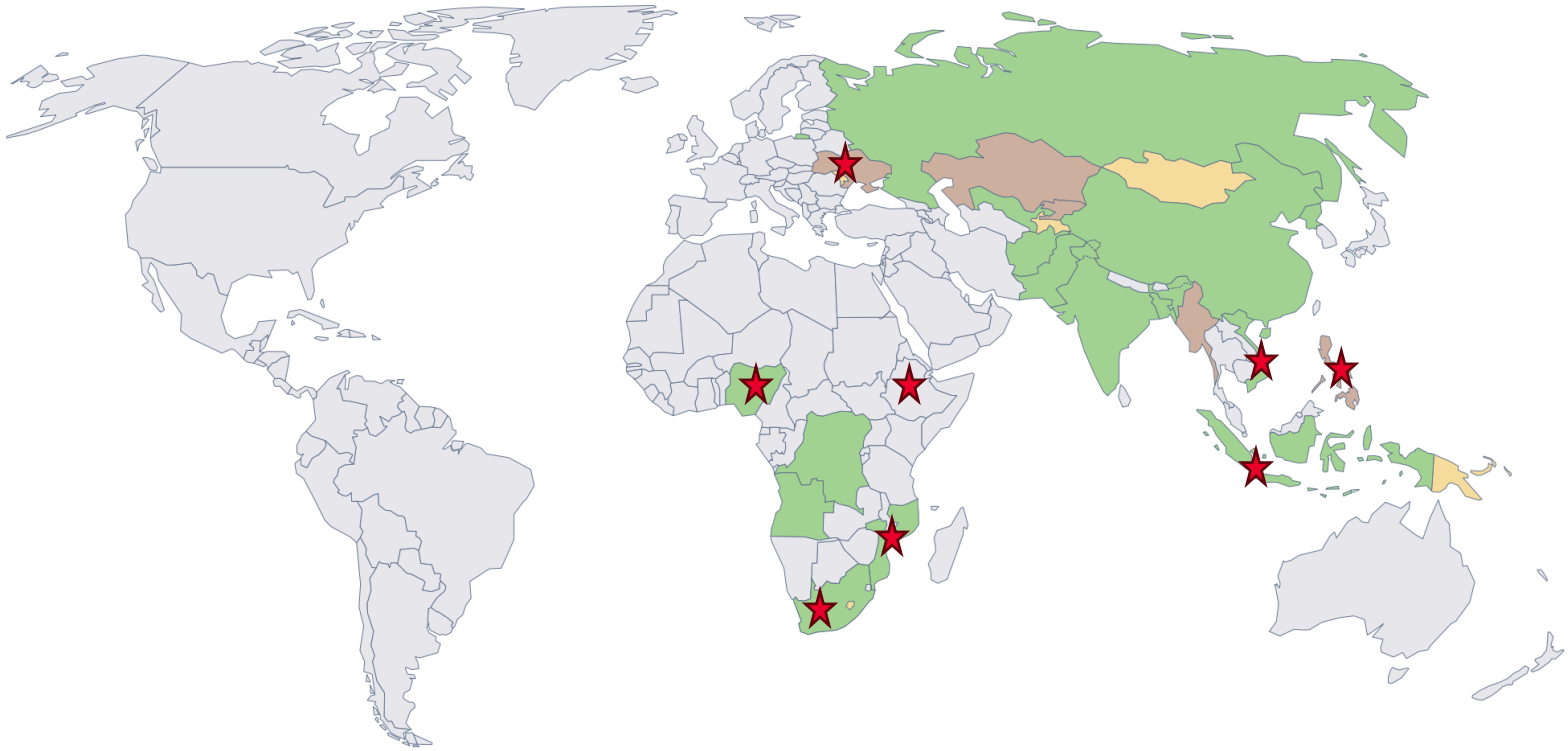
COMMUNITY TRAINING ON DRUG-RESISTANT TB BASICS

Lindsay McKenna
Treatment Action Group
25 July 2024

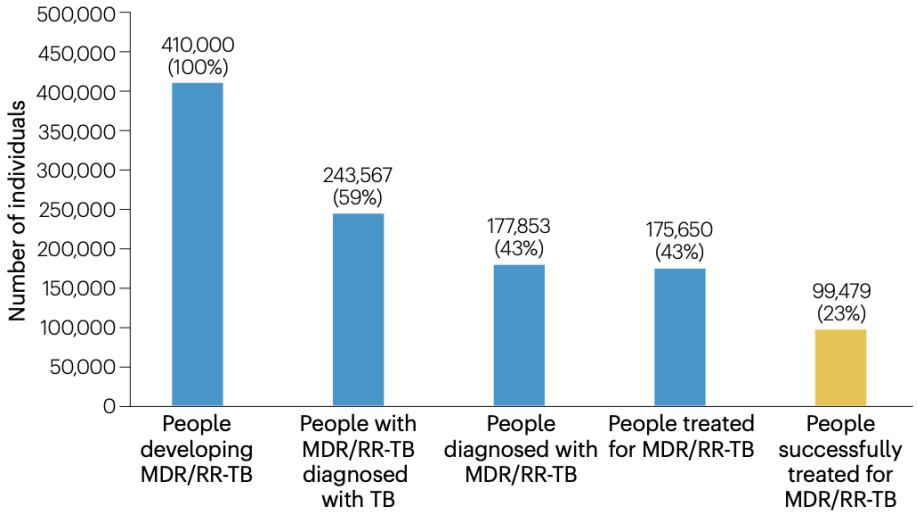
THE 30 COUNTRIES WITH THE HIGHEST BURDEN OF DRUG-RESISTANT TB

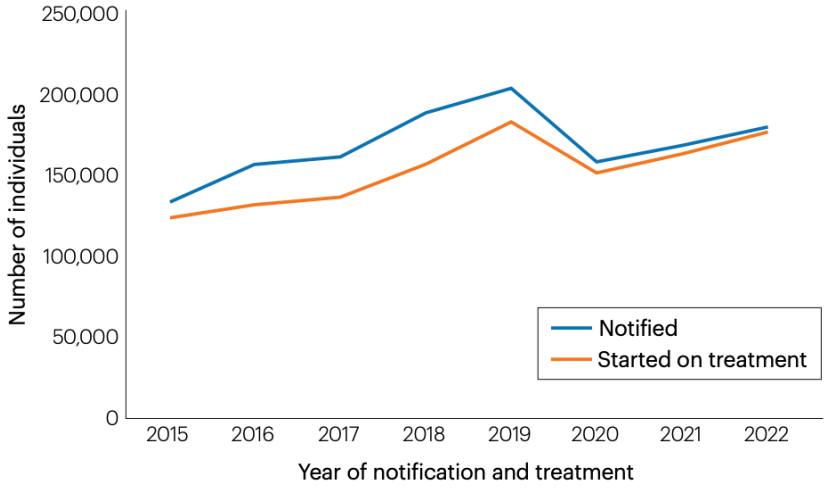


★ ASCENT DR-TB Project focal countries:
Nigeria, Ethiopia, South Africa, Mozambique,
Ukraine, Indonesia, Vietnam, and the Philippines.

Farhat et al. Nat Rev Microbiol (2024)

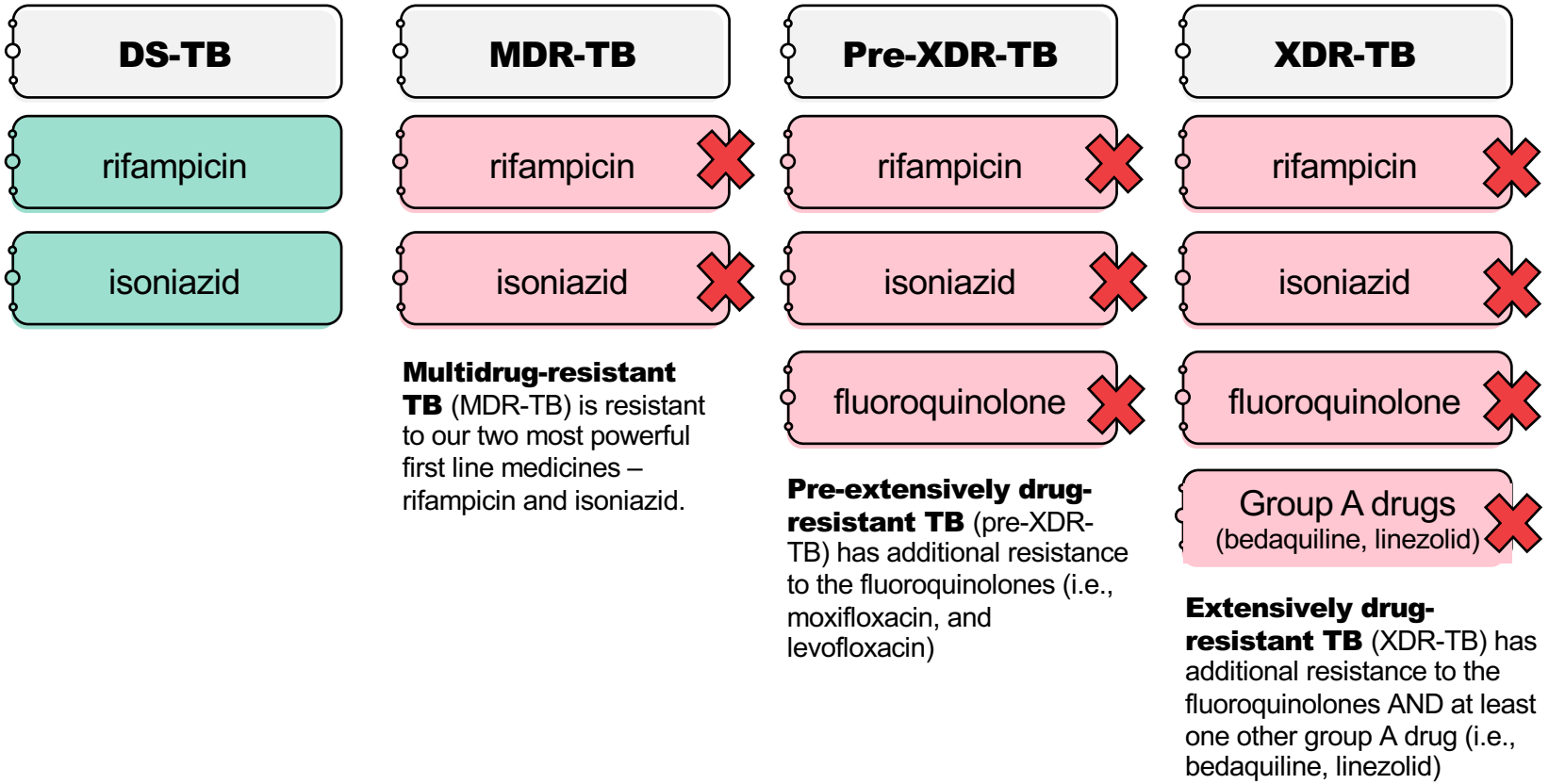
GAPS IN THE CASCADE OF CARE FOR DRUG-RESISTANT TB





Farhat et al. Nat Rev Microbiol (2024)

DEFINING DRUG-RESISTANT TB



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HOW DOES DRUG-RESISTANT TB DEVELOP?

- Each of the medicines used to treat TB has a **mechanism of action** for disabling or killing TB bacteria.
- There are all different method(s) by which TB medicines inactivate or kill TB bacteria, e.g., by inhibiting energy production (bedaquiline) or growth via cell wall synthesis (pretomanid).
- Certain bacterial mutations can prevent a medicine from carrying out its mechanism of action by inactivating it or blocking it from entering or staying inside the TB bacterial cell.
- These **mutations can occur naturally or develop over time** following inadequate or irregular drug exposures.
- Drug-resistant TB can develop due to inadequate treatment because of underdosing, malabsorption, or interrupted or incomplete TB treatment, referred to as **acquired resistance**.
- Drug-resistant TB can also be transmitted from person to person, referred to as **primary or transmitted resistance**.

HOW IS DRUG-RESISTANT TB TREATED?

Until very recently, drug-resistant TB was treated with 18-to-24-month regimens composed of toxic medications that cause permanent disability and don't work very well (treatment success rates used to range from 20-60% globally)

But phase III trials have demonstrated that we can much more safely cure drug-resistant TB in just six-months using regimens composed of 3-4 new and repurposed drugs.

CHEAT SHEET: TB DRUG & REGIMEN ABBREVIATIONS

- Numbers at the beginning of each regimen or after the forward slash (for regimens with intensive and continuation phases) represent the duration of treatment in months
- Letter after forward slash or in brackets represent drugs included situationally (i.e., depending on presence of resistance)
- Letters represent the individual drugs comprising each regimen
- Subscripts indicate dosing in mg

H = isoniazid
R = rifampicin
P = rifapentine
Z = pyrazinamide
E = ethambutol
Lx, Lfx = levofloxacin
M, Mx, Mfx = moxifloxacin

Bdq, B = bedaquiline
Ptd, Pa = pretomanid
Dlm, D = delamanid
L, Lz, Lzd = linezolid
Cfz, C = clofazimine
Cs = cycloserine
Am = amikacin

H_{Hd} = high dose isoniazid
R_{Hd} = high dose rifampicin

SOC = standard of care
IA = injectable agent

DS-TB = drug-sensitive TB
RR-/MDR-TB = rifampicin-/multidrug-resistant TB
pre-XDR-TB = pre-extensively drug-resistant TB
XDR-TB = extensively drug-resistant TB

6HRZE or 2HRZE/4HR

Four months of treatment with isoniazid and rifampicin, given with pyrazinamide and ethambutol for the first two months of treatment.

4HPMZ or 2HPMZ/2HPM

Four months of treatment with isoniazid, rifapentine, and moxifloxacin, given with pyrazinamide for the first two months of treatment.

6BPaL/M or 6BPaL[M]

Six months of treatment with bedaquiline, pretomanid, linezolid, and moxifloxacin, depending on sucseptibility.

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HOW IS DRUG-RESISTANT TB TREATED? (CONTINUED)

The WHO recommends three regimens for the treatment of rifampicin-/multidrug-resistant TB (RR-/MDR-TB), each with slightly different eligibility criteria based on the available data (or lack thereof).

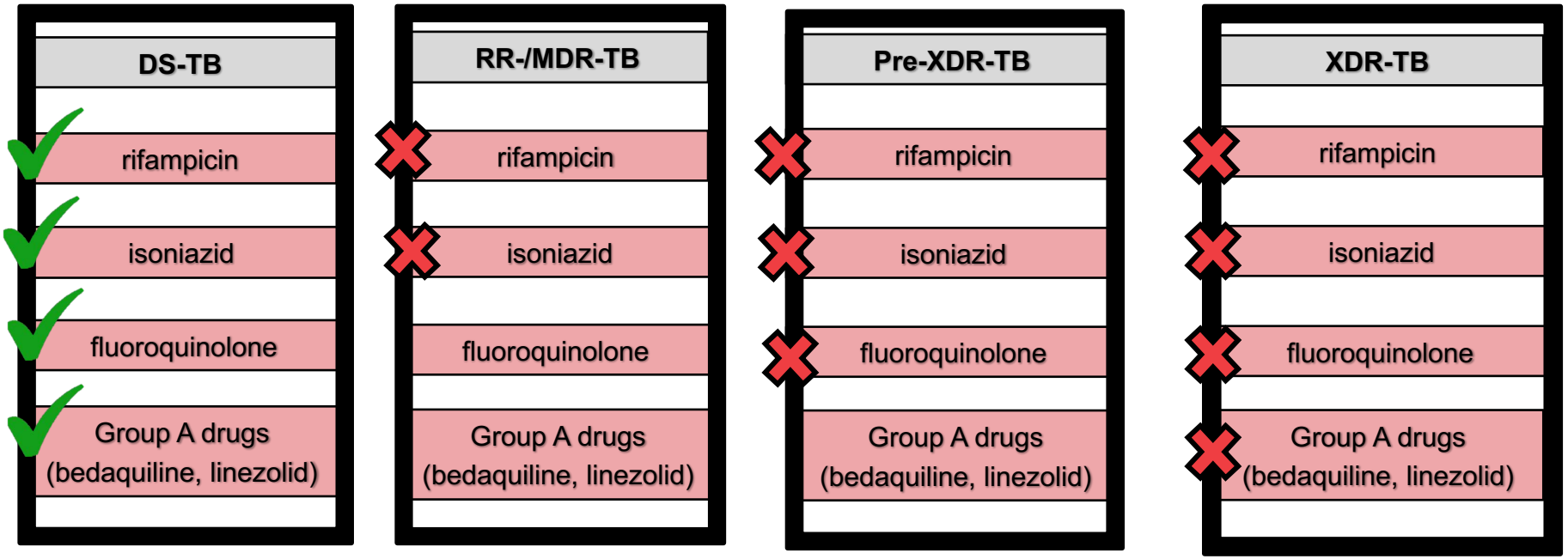
The shorter standardized regimens are prioritized, with the longer individualized regimen recommended for use in populations and individuals otherwise not eligible or able to take the shorter regimens.

1. **Six-month BPaL/M regimen:** six months of bedaquiline, pretomanid, and linezolid given with moxifloxacin for RR-/MDR-TB and without moxifloxacin for pre-XDR-TB.

2. **Nine month standardized, all-oral regimen:** nine months of levofloxacin, clofazimine, pyrazinamide, and ethambutol; supplemented by bedaquiline for the first six months, linezolid for the first two months, and high-dose isoniazid for the first four to six months for RR-/MDR-TB.

3. **18-to-20-month individualized regimen:** 18-to-20-months of a regimen composed of at least four medicines selected from the list of WHO Group A, B, and C medicines according to an individual's drug-susceptibility profile.

QUIZ



Where does an "X" belong? Resistance to which drug(s) or drug class is used to define DS-, RR-/MDR-, pre-XDR-, and XDR-TB?

Bonus: Name a drug in the fluoroquinolone class?

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SHORTER REGIMENS FOR DR-TB (1/2)

A phase III study known as **TB-PRACTECAL** assessed a six-month regimen for multidrug-resistant TB (MDR-TB):

6 B Pa L M

Six months of daily treatment with bedaquiline, pretomanid, linezolid and moxifloxacin.

In this study, bedaquiline was administered 400mg daily for 2 weeks followed by 200mg 3 times per week; and linezolid was administered 600mg daily for 16 weeks followed by 300mg daily (or 600mg thrice weekly).

The phase III study compared this 6-month regimen to longer regimens that were the standard of care / recommended by WHO while the study was enrolling (i.e., 9-to-12-month, seven drug regimens and 18-to-20-month, 4-5 drug regimens).

The study found this 6-month regimen to be non-inferior to (i.e. “not worse than”) the longer regimens, and to have better safety.

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SHORTER REGIMENS FOR DR-TB (2/2)

Two phase III studies known as **Nix-TB and ZeNix-TB** assessed a six-month regimen for pre-extensively drug-resistant TB (pre-XDR-TB):

6 B Pa L

Six months of daily treatment with bedaquiline, pretomanid, and linezolid. *Moxifloxacin is missing from this regimen because the people enrolled in the trials had TB with additional resistance to the fluoroquinolones.

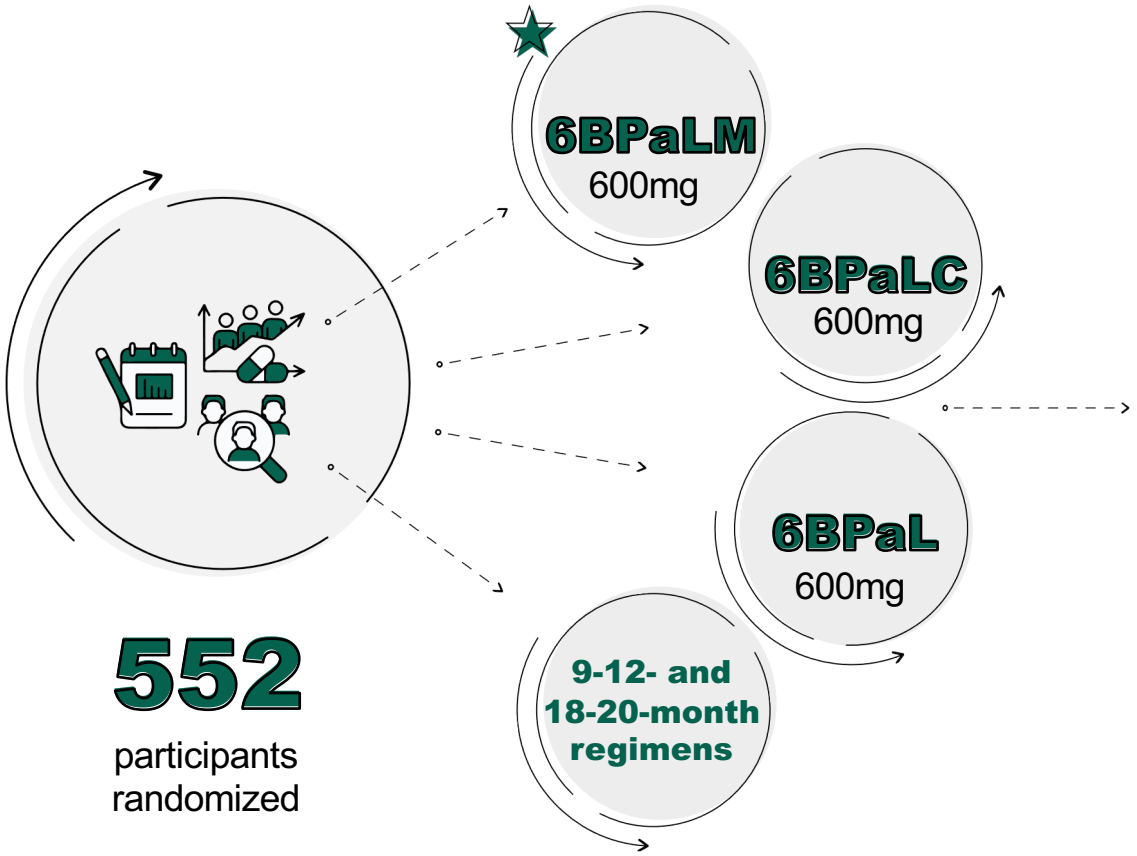
In Nix-TB, bedaquiline was administered 400mg daily for 2 weeks followed by 200mg 3 times per week and linezolid was administered 1200mg daily.

In ZeNix-TB, bedaquiline was administered 200mg daily for 8 weeks followed by 100mg daily and linezolid was administered at 600-1200mg daily for 2-6 months.

These phase III studies did not include any formal comparisons (more on the next few slides).

These studies established the efficacy of the 6-month regimen against pre-XDR-TB (~90% cure rate) and refined the linezolid dose to improve the regimen's safety and tolerability.

A CLOSER LOOK: TB-PRACTECAL



After 1 year of follow-up…

The six-month BPaLM regimen showed favorable efficacy compared to the longer regimens in the control arm – 89% vs. 52% cure rate.

The six-month regimen also showed favorable safety – 80% of participants avoided any major side effects in the BPaLM arm compared to 40% in the control group.

- TB-PRACTECAL enrolled participants from 3 countries (Belarus, South Africa, and Uzbekistan)
- Mostly adults but also adolescents as young as 15 years old; and
- 112 PLHIV irrespective of CD4 T-cell count (median was 250-330 cells/mm^3)

B = bedaquiline | Pa = pretomanid | L = linezolid | M = moxifloxacin | C = clofazimine

A CLOSER LOOK: Nix-TB

109

participants enrolled

6BPaL
1200mg

After 6 months of follow-up…

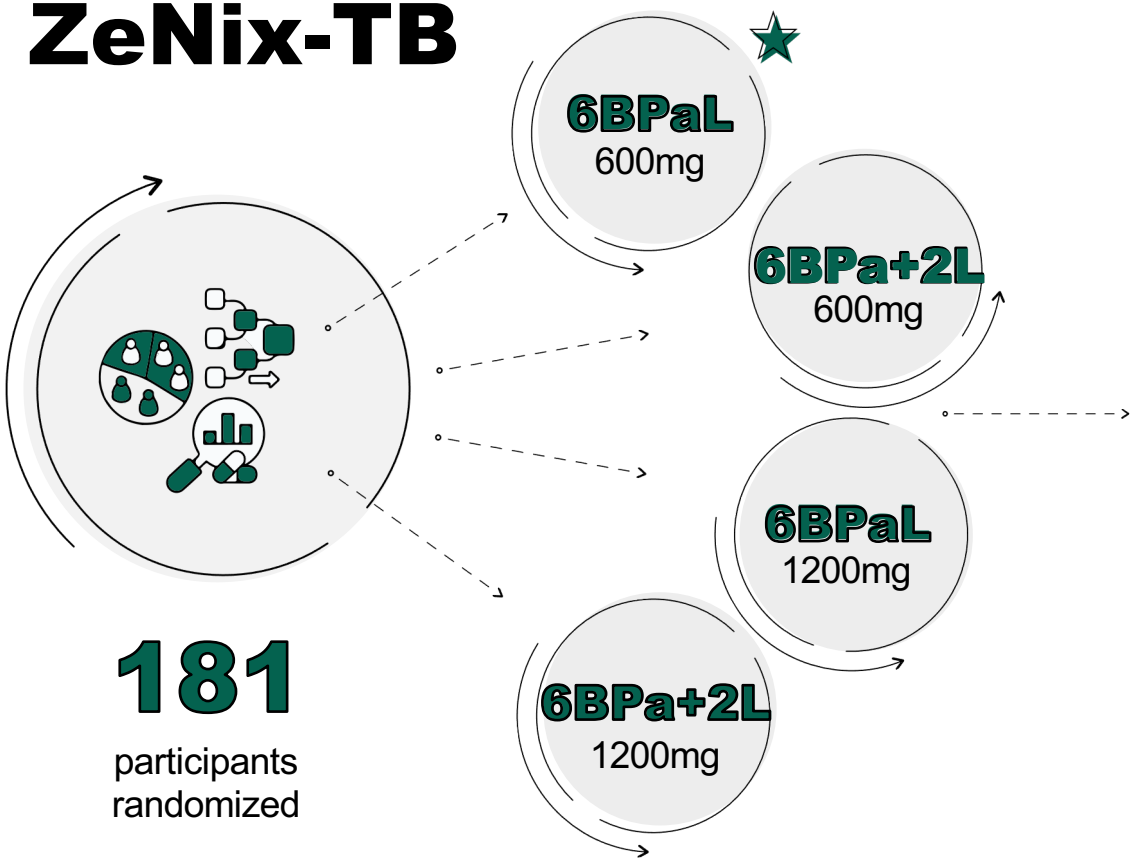
The 6BPaL regimen cured 90% of participants but 57% of participants experienced at least one adverse event.

81% of participants reported peripheral neuropathy (nerve pain) and 48% experienced myelosuppression (blood disorders). Because of these adverse effects, only 34% of participants were able to complete six months of linezolid without interruption

- Nix-TB enrolled participants from 3 sites in South Africa
- Mostly adults but also adolescents as young as 14 years old; and
- 56 PLHIV with a CD4 T-cell count of at least 50 cells/mm^3

B = bedaquiline | Pa = pretomanid | L = linezolid

A CLOSER LOOK: ZeNix-TB



181

participants randomized

After 6 months of follow-up…

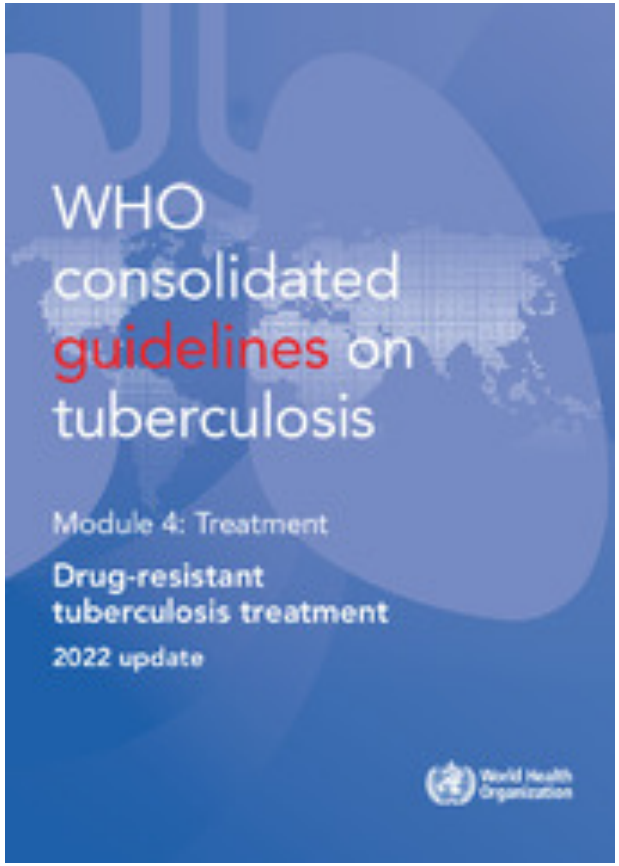
The 6BPaL(600mg) regimen had the best balance of efficacy and safety – 91% cured and 24% experiencing at least one adverse event.

Dosing linezolid at 600 mg is meant to help to balance the power/potency of linezolid against TB with some of its challenging side effects (e.g., nerve pain and blood disorders).

- ZeNix-TB enrolled participants from 4 countries (South Africa Georgia, Moldova, and Russia)
- Mostly adults but also adolescents as young as 14 years old; and
- 36 PLHIV with a CD4 T-cell count of at least 100 cells/mm^3

B = bedaquiline | Pa = pretomanid | L = linezolid

WORLD HEALTH ORGANIZATION RECOMMENDATIONS FOR DR-TB



"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)."

"Either of the bedaquiline dosing schemes may be used for programmatic implementation: daily throughout treatment (200 mg once daily for 8 weeks followed by 100 mg once daily) or daily for loading dose and three times per week thereafter (400 mg once daily for 2 weeks followed by 200 mg three times per week)."

"In cases of fluoroquinolone resistance, moxifloxacin should be dropped, and the regimen continued as the BPaL combination only."

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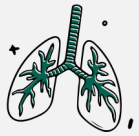
WHO IS ELIGIBLE FOR THE 6 MONTH TREATMENT REGIMENS?

Adults and adolescents above 14 years old



People that have pulmonary TB

People that have RR-/MDR-TB or pre-XD-TB

People living with or without HIV

People with extrapulmonary TB except for TB meningitis, osteoarticular TB or disseminated (miliary) TB

People that have not been previously exposed to bedaquiline, pretomanid and linezolid (for more than one month), unless resistance has been ruled out

All of the above criteria need to be met to be eligible for the BPaL[M] regimens.

No data are available in children, pregnant people, or for the use of the 6-month regimens against more-severe forms of extra pulmonary TB (like TB meningitis).

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WHAT ABOUT EVERYONE ELSE?

1

The 9-12-month standardized regimen: the latest WHO recommended iteration of which includes linezolid in place of ethionamide.

6 Bdq + 2 Lzd + 4-6 hdH Lfx Cfz Z E / 5-6 Lfx Cfz Z E

9-to-12-months of daily clofazimine, levofloxacin (or moxifloxacin), ethambutol, and pyrazinamide; supplemented by bedaquiline for the first 6 months, linezolid for the first 2 months, and high dose isoniazid, for the first 4-to-6-months.

2

18–20-month individualized regimens: composed of at least 4-5 effective drugs selected according to the WHO table that prioritizes TB medicines into groups A, B, and C.

For example:

18-20 Bdq Lzd Cfz Cs +/- E or Dlm

18-20 Bdq Cfz Cs Dlm +/- Z or E or other group C drugs

18-20 Lzd Cfz Cs Dlm +/- Z or E or other group C drugs

18-20 Cfz Cs Dlm +/- Z or E or other group C drugs

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WORLD HEALTH ORGANIZATION RECOMMENDATIONS FOR DR-TB

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	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[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

"WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty of evidence)"

"In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. (Conditional recommendation, very low certainty of evidence)"

"In 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 the 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 of evidence)."

WHAT ABOUT CHILDREN, SPECIFICALLY?

1 **SAME AS ADULTS ON THE PREVIOUS SLIDE**

The 9-12-month standardized regimen: the latest WHO recommended iteration of which includes linezolid in place of ethionamide.

6 Bdq + 2 Lzd + 4-6 hdH Lfx Cfz Z E / 5-6 Lfx Cfz Z E

2

18–20-month individualized regimens: composed of at least 4-5 effective drugs selected according to the WHO table that prioritizes TB medicines into groups A, B, and C.

18-20 Bdq Lzd Cfz Cs +/- E or Dlm

**Pediatric formulations of every drug listed available via the Global Drug Facility!!

3

Shorter regimens tailored to disease severity: composed of at least 4-5 effective drugs selected according to the WHO table that prioritizes TB medicines into groups A, B, and C, given for 6-9 months to children with non-severe TB, and for 9-12 months to children with severe TB.

6-9 or 9-12 Bdq Lfx Cfz Cs [Lzd]

6-9 or 9-12 Bdq Dlm Cfz Cs Lzd

6-to-9-months or 9-to-12-months of daily bedaquiline, levofloxacin (or delamanid, depending on fluoroquinolone resistance), clofazimine, and cycloserine, with linezolid given for the first 8 weeks of treatment.

WE DON'T KNOW THE DOSING OR SAFETY OF PRETOMANID IN KIDS YET, BUT THEY CAN STILL BENEFIT FROM ACCESS TO A SIX-MONTH REGIMEN

QUIZ

1. **Which of the following groups are eligible for the 9-month standardized, all-oral regimen?**

   a) People with resistance to fluoroquinolones (e.g., moxi or levo)
   b) People with TB meningitis
   c) Children
   d) None of the above

2. **What regimen(s) are recommended for a person diagnosed with TB resistant to rifampicin and isoniazid only?**

   a) the six-month BPaL/M regimen
   b) the nine-month standardized all-oral regimen
   c) 18-20-month individualized regimen
   d) none of the above

QUIZ

3. **What regimen(s) are recommended for a person diagnosed with TB resistant to rifampicin, isoniazid, and moxifloxacin?**

a) the six-month BPaL/M regimen
b) the nine-month standardized all-oral regimen
c) 18-20-month individualized regimen
d) none of the above

FACTORS THAT AFFECT ACCESS TO NEW TB DRUGS AND REGIMENS

1. Scientific evidence / WHO Guidelines
2. National Guidelines
3. Inclusion in National Strategic Plans (NSPs), Global Fund Funding Proposals, national and local budgets)
4. Stringent regulatory authority (SRA), National Regulatory Authority (NRA), and WHO PQ approvals ("registration")
5. The availability of fit for purpose formulations (e.g., dispersible tablets for children)
6. Price (often affected by intellectual property barriers to generics competition)
7. ***ACCESS TO TB SCREENING AND DIAGNOSIS, GETTING INTO CARE & PUT ON THE RIGHT REGIMEN!***

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DRUG FORMULATIONS & PRICING

- stand alone formulations of each of the components of 6BPaL[M]
- drug costs for course of a 6-month course of BPaL[M] = $568 – $596 (similar to other longer regimens)
- drug costs for 9-12- or 18-20-month regimens for drug-resistant TB range from $535 – $771 or $7,000 (depending on inclusion of delamanid)
- bedaquiline and pretomanid driving cost of BPaL[M], but prices expected to come down with the availability of generics / additional suppliers
- Other “commodities” are important too…

…for diagnosis and treatment decisions based on safety monitoring and response to treatment.

**Price estimates assume access to GDF pricing.*

PERSON-CENTERED CARE

STAFF

Healthcare & community workers to conduct clinic and community based active case finding; to conduct TB treatment literacy & to support people requiring treatment.

STUFF

Bedaquiline, pretomanid, linezolid, and moxifloxacin; TB tests to diagnose TB and drug-resistance and to monitor treatment and test for adverse effects of medicines.

SPACE

A place for people undergoing TB testing; to collect treatment regimens; to meet with healthcare providers.

SYSTEMS

Updated national guidelines, medicines lists, and healthcare worker trainings; drug registration or waivers via National Regulatory Authorities; updated tenders to procure “stuff” to support treatment.

SUPPORT

Patient-centered models for administering TB treatment, including nutritional, psychosocial and other packages that ensure a holistic approach to treatment support.

For diagnosis, treatment decisions and response monitoring: rapid molecular and phenotypic diagnostics and DST; smear and culture for monitoring

For safety monitoring: psychosocial assessment, peripheral neuropathy screening, visual acuity and color discrimination screening, chest X-ray, ECG, full blood count, liver function tests

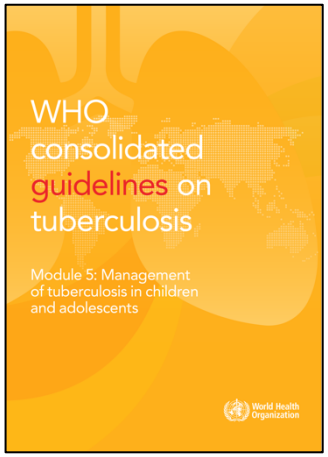
Social protection / material support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowances, housing incentives or financial bonuses

FUTURE COMMUNITY TRAINING TOPICS

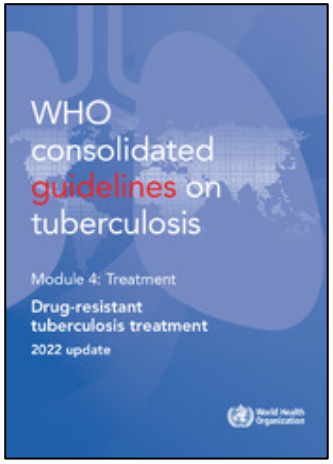
Potential topics for deeper dives into the technical aspects of drug-resistant treatment and care/support…and skills sharing:

1. drug-resistant TB medicines side effects, adverse events, and monitoring tools, and important drug-drug interactions (DDIs)
2. drug-resistant TB treatment in children and other special populations
3. understanding updates to the WHO guidelines (pending any WHO rapid communication or other guidance available on the BEAT Tuberculosis and endTB regimens)
4. Screening and diagnostic tests for TB and drug resistance (with FIND)
5. Treatment accompaniments (e.g., social determinants & social protection programs, patient-centered packages of care (with PIH); stigma interventions (with KNCV, STBP)
6. Advocacy skills, drawing on experiences of Unitaid IMPAACT4TB, TBA FTTC, STBP CSCF grantees (e.g., political advocacy, treatment literacy, CLM, peer support/counseling, etc.)
7. Global Campaigns (with MSF AC)
8. Other topics to support proposed small grant activities??

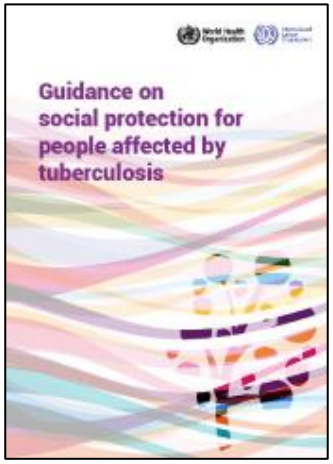
SOME EXISTING RESOURCES



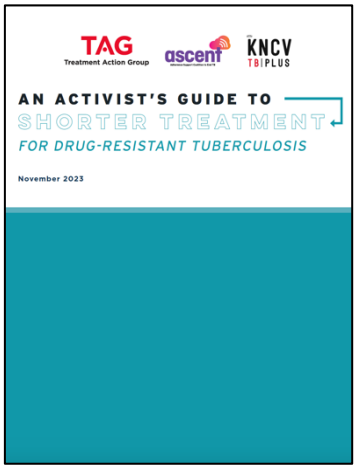
[WHO consolidated guidelines on TB, Module 5: Management of TB in children and adolescents]



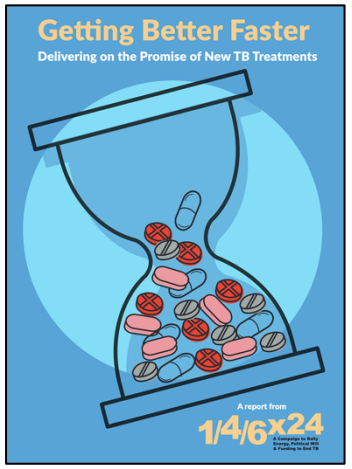
[WHO consolidated guidelines on TB, Module 4: Treatment of DR-TB tuberculosis]



[WHO guidance on social protection for people affected by tuberculosis]

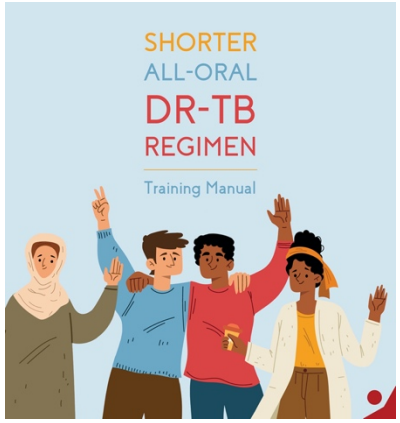


[An Activist's Guide to Shorter Treatment for Drug-Resistant Tuberculosis]



[Getting Better Faster: Delivering on the Promise of New TB Treatments – A Report from the 1/4/6×24 Campaign]

[1/4/6x24 Community Campaign Training Materials]



[GCTA brochure & Training Manual]

[FTTC Advocacy Resources]

[Community Storyboards] (Indonesia, Nigeria)