
TB Europe Coalition
15 June 2023
1/4/6x24
A Campaign to Rally Energy, Political Will & Funding to End TB

& SUPPORTIVE DIAGNOSTICS

David Branigan, Treatment Action Group
TB Europe Coalition Webinar
15 June 2023
WHAT DOES IT MEAN?

1. one-month or once weekly treatment regimens for TB prevention.

4. four-month treatment regimens for drug-sensitive TB.

6. six-month treatment regimens for drug-resistant TB.

$\times 24$ by the end of 2024.

A deadline for having in place the “staff, stuff, space, systems, and support” needed for shorter TB regimens to be made accessible to everyone, everywhere as a human right.

& priority research to extend the benefits of short treatment and prevention regimens to any groups who cannot currently use them due to data gaps or research exclusions.
### Why Do We Need This Campaign?

<table>
<thead>
<tr>
<th>Why we need the campaign</th>
<th>After 20+ YEARS (!!) of research and development, we can finally treat TB infection in as little as one month and most forms of drug-sensitive and drug-resistant TB in four and six months.</th>
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<tbody>
<tr>
<td>The COVID-19 pandemic and other concurrent global health, economic, social, and political crises have rolled back and continue to threaten progress in the fight against TB.</td>
<td>Yet relatively few people have access to these shorter regimens – <strong>the lack of access to these advances is a human rights issue that should inspire outrage.</strong></td>
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<tr>
<td>We’ve already missed nearly all the treatment and prevention targets set during the United Nations High Level Meeting on TB in 2018.</td>
<td><strong>To get back on track to ending TB by 2030, we need an infusion of energy, political will, and funding – the generation of which requires something inspiring to rally around.</strong></td>
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“If everyone has a right ‘to share in scientific advancement and its benefits,’ where are our pragmatic efforts to improve the spread of these advances? … even as our biomedical interventions become more effective, our capacity to distribute them equitably is further eroded.”

— Pathologies of Power: Rethinking Health and Human Rights, AJPH 1999

The right of everyone to enjoy the benefits of scientific progress and its applications i.e., the right to science.

Governments have “a duty to make available and accessible to all persons, without discrimination, especially to the most vulnerable, all the best available applications of scientific progress necessary to enjoy the highest attainable standard of health.”

— General Comment 25, Committee on Economic, Social and Cultural Rights
NOW AND THEN

TB Prevention
6+ → 1 month

MONTH 1  MONTH 2  MONTH 4
X  X  X
MONTH 5  MONTH 6
X  X

Treatment (DS-TB)
6 → 4 months

MONTH 1  MONTH 2  MONTH 3
X  X  X
MONTH 4  X  X

Treatment (DR-TB)
18 → 6 months
(+no more hearing loss!)

MONTH 1  MONTH 2  MONTH 3  MONTH 4
MONTH 5  MONTH 6  MONTH 7  MONTH 8
MONTH 9  MONTH 10
MONTH 11  MONTH 12
MONTH 13  MONTH 14
MONTH 15  MONTH 16
MONTH 17  MONTH 18

X  X  X  X  X  X  X  X  X  X  X  X
SHORTER REGIMENS MEAN...

People and families affected by TB can get back to work, school, etc. and recover economically sooner.

People affected by TB find treatment more safe, tolerable and acceptable, leading to fewer interruptions that can generate resistance, higher rates of treatment completion, and better outcomes.

Human resources and other health program savings from shorter duration of prevention and treatment regimens can be repurposed to improve active screening and case finding, and psychosocial and other supportive services and programs.
STAFF, STUFF, SPACE, SYSTEMS, SUPPORT

STAFF
Staff being all care providers, including doctors, nurses, community health workers (e.g., public, private, informal, community-based, etc.)

STUFF
Stuff being diagnostic tests and corresponding consumables, imaging technologies, medications, other equipment

SPACE
Space being appropriate, dignified care facilities for patients within a clinic, hospital, or community care setting

SYSTEMS
Systems being policymaking and regulatory mechanisms, active case finding outreach programs, referral services

SUPPORT
Support being accompaniments for patients to get better, such as food, housing, counselling, and other psychosocial services. This approach requires a multi-sector and fully financed TB response.
In 2021, 40% of the 10.6 million people who developed active TB were not diagnosed or notified to the health system.

Most people with TB symptoms first seek care in primary health centers or in the private sector, where they are often not offered TB testing or are only tested using smear microscopy, an outdated diagnostic that is only about 50% sensitive and does not test for drug resistance.

Even though several rapid molecular diagnostics have been endorsed by WHO, only 38% of all people diagnosed and notified with TB in 2021 received a WHO-recommended rapid diagnostic (WRD).

Of the 450,000 people estimated to have developed RR/MDR-TB in 2021, just one in three was linked to DR-TB treatment.

Testing for TB infection is not required to start TB preventive treatment (TPT) for people at higher risk of developing disease, but limited access to tests for TB infection makes it hard to scale TPT.
1 = TB Preventive Treatment (TPT)

**1HP**
1 month of daily isoniazid (H) + rifapentine (P)

**3HP**
3 months of once-weekly isoniazid (H) + rifapentine (P)

**3HR**
3 months of daily isoniazid (H) + rifampicin (R)

### Supportive Diagnostics

<table>
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<tr>
<th>Tests for TB infection (not required for people living with HIV or TB contacts under 5 years)</th>
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<tr>
<td>• Interferon-gamma release assays (IGRAs)</td>
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<td>• TB-specific skin tests (TBST)</td>
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### Screening tests to rule out active TB, prior to starting TPT

• Chest X-ray +/- computer-aided detection (CAD)
• C-reactive protein (CRP) tests for people living with HIV (PLHIV)
• Rapid molecular tests for PLHIV

### State of access

| Limited availability of IGRAs due to complexity and cost. |
| TBST pending quality assurance by Global Fund ERP; no WHO Prequalification pathway yet for these products. |
| Limited scale-up of chest X-ray devices due to high cost of hardware. |
| Scale up of CAD dependent on access to digital chest X-ray. |
| CRP tests widely available. |
| Limited scale-up of rapid molecular tests due to cost and placement. |
**4 = DS-TB Treatment**

### Study 31 / ACTG A5349

Adults and adolescents down to 12 years old are eligible for the **4-month rifapentine- and moxifloxacin-containing regimen** from TBTC Study 31 / ACTG A5349

**4 H P M Z** – four months of daily treatment with isoniazid, rifapentine, moxifloxacin + pyrazinamide for the first two months.

### SHINE

Children 0-16 years old with “non-severe” TB are eligible for the **4-month regimen from the SHINE trial**

**4 H R Z [E]** – four months of daily treatment with isoniazid and rifampicin + pyrazinamide (and ethambutol in certain situations) for the first two months.

### Supportive Diagnostics

#### Screening tests for TB and to diagnose non-severe TB in children
- Chest X-ray +/- CAD

### Diagnostic tests for TB
- Rapid molecular tests for TB (including use of stool and other non-invasive samples for children who cannot produce sputum)
- Broader use of WHO-recommended clinical diagnostic algorithms
- Urine LAM tests for PLHIV

### Drug-susceptibility testing
- Rapid and high-throughput molecular tests for RIF, INH and FQ resistance
- Line probe assays for PZA and EMB resistance

### State of access

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<td>Screening tests for TB and to diagnose non-severe TB in children</td>
<td>Limited scale-up of chest X-ray devices due to high cost of hardware.</td>
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<tr>
<td>Diagnostic tests for TB</td>
<td>Scale up of CAD dependent on access to digital chest X-ray; research gap of CAD performance among young children must be addressed.</td>
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<tr>
<td>Drug-susceptibility testing</td>
<td>Limited scale-up and decentralization of rapid molecular tests due to cost and infrastructure requirements.</td>
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Need to implement standard operating procedures for testing non-sputum samples that are easy to obtain from children.

Limited scale-up of urine LAM tests due to insufficient prioritization and action to update national algorithms.

Limited scale-up of molecular tests for RIF, INH and FQ resistance due to cost.

Limited access to line probe assays due to centralized placement and cost.
6 = DR-TB Treatment

**6 B P a L [M]** – six months of daily treatment with bedaquiline, pretomanid, linezolid, and moxifloxacin.

Linezolid is given at 600 mg daily, with further dose reduction as needed. The regimen can be given without moxifloxacin (6BPaL) if there is fluoroquinolone resistance (pre-XDR-TB).

Treatment is extended to nine months if culture conversion (the amount of time it takes for TB cultures to turn negative, indicating TB bacteria are no longer replicating) is slow.

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<tr>
<td><strong>Drug-susceptibility testing</strong></td>
<td>Limited scale-up of molecular tests for RIF, INH, and FQ resistance due to cost.</td>
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<tr>
<td>• Rapid or high-throughput molecular tests for RIF, INH, and FQ resistance</td>
<td>Limited access to mycobacterial culture for BDQ, PTD, and LZD resistance due to centralized placement and long turnaround time to results (2-6 weeks); need for a WHO-recommended critical concentration for PTD phenotypic DST.</td>
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<tr>
<td>• Mycobacterial culture for BDQ, PTD, and LZD susceptibility testing</td>
<td>tNGS pending WHO recommendation; likely high cost and initial placement in central labs requiring sample transport.</td>
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<tr>
<td>• Targeted next-generation sequencing (tNGS) susceptibility testing for all TB drugs</td>
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Scaling up access to the shorter, safer 1/4/6 regimens and implementing the WHO standard for universal access to rapid diagnostics requires urgently expanding access to currently available tools for TB screening and diagnosis and increasing investments in TB diagnostics research and development, including children as a priority population. This will require increased donor and domestic funding for implementation and R&D, along with more affordable pricing and improved supply of drugs and diagnostics.
Program Essentials include 1/4/6 regimens

“Treatment and care services should be designed and delivered considering the needs and preference of people with TB rather than that of the health care system… Use of shorter, all-oral and patient-friendly treatment regimens recommended by WHO… are important elements to support a person with TB to access and complete their treatment successfully.”

Also:

“The new, 4-month DS-TB regimen (2HPMZ/2HPM) for people aged ≥12 years may be considered when the needs justify the additional costs over the existing standard regimen.”

Table 4: Program Essentials for Global Fund Supported Services

<table>
<thead>
<tr>
<th>2. TB treatment and care</th>
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<tr>
<td>2.1 Child-friendly formulations, all-oral regimens for DR-TB, and 4-month regimen for non-severe, DS-TB are used for TB treatment in children.</td>
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<tr>
<td>2.2 People with DR-TB receive shorter, all-oral regimens or individualized longer treatment regimens as recommended by WHO and people-centered support to complete their treatment.</td>
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<thead>
<tr>
<th>3. TB prevention</th>
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<tbody>
<tr>
<td>3.1 TB preventive treatment (including shorter regimens) is available for all eligible people living with HIV (adults and children) and for all eligible household contacts of people with bacteriologically confirmed pulmonary TB.</td>
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https://www.theglobalfund.org/media/4762/core_tuberculosis_infonote_en.pdf
“To improve early TB diagnosis, applicants are encouraged to implement intensified case finding in health facilities, conduct active case finding and surge campaigns targeting key and vulnerable populations and high TB prevalence settings. The use of molecular WHO-recommended rapid diagnostics (mWRD), as the initial diagnostic test to replace sputum microscopy should be prioritized. Testing non-sputum-based samples of children, improving bacteriological confirmation of pulmonary TB, and universal rapid drug-susceptibility testing (DST) are other priorities.”

Table 4: Program Essentials for Global Fund Supported Services

<table>
<thead>
<tr>
<th>1. TB screening and diagnosis</th>
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<tbody>
<tr>
<td>1.1 Systematic TB screening is provided for those at highest risk (key and vulnerable populations), including using Chest X-rays with or without computer-aided detection (currently recommended for people aged 15 years and older).</td>
</tr>
<tr>
<td>1.2 Multiyear plan to achieve universal use of rapid molecular assays as the initial test to diagnose TB for all people with presumptive TB, with implementation on track.</td>
</tr>
<tr>
<td>1.3 All people with bacteriologically confirmed TB are tested for at least rifampicin resistance and for those with RR-TB further tests are conducted to rule out resistance to other drugs.</td>
</tr>
<tr>
<td>1.4 TB diagnostic network operates efficiently to increase access to testing and includes specimen transportation, maintenance of equipment, connectivity solutions, biosafety, quality assurance and supply system.</td>
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https://www.theglobalfund.org/media/4762/core_tuberculosis_infonote_en.pdf
Global Fund funding request development, and the country dialogues that precede it, is a crucial time to ensure that the Global Fund invests in the latest advances in diagnostics and treatment in the next funding cycle.

https://www.globalfundadvocatesnetwork.org/resource/advocacy-guides-to-1-4-6x24-shorter-regimens-for-tb/
# KEY OPPORTUNITIES & NEXT STEPS

1. **Take stock of where your national government is with respect to introducing and implementing the short-course 1/4/6 prevention and treatment regimens and what the barriers are – what are they not doing yet, and why?**

2. **Elevate the campaign to the attention of the Minister of Health and other duty bearers – what advocacy, communications, and other strategies can be used to generate political commitments and to address known barriers?**

3. **National Strategic Plan (NSP) Development – what is the timeframe, who is involved, and how can you influence its contents or get directly involved in the development process?**

4. **National Health & Research Budget Appropriations – what is the calendar / process for developing and passing annual appropriations bill(s)? Are there any legislators that can champion domestic funding increases for TB programs and research (e.g., to ensure a fully funded NSP)?**

5. **Global Fund Portfolio Optimization/Catalytic Investments and NFM4 – what is the timeframe, who is involved in the country coordinating mechanism (CCM), how can you influence the TB priorities or get directly involved in these discussions and decisions?**

6. **Are there other important stakeholders and/or funding mechanisms to engage with in your national context?**
CAMPAIGN ASKS & ACTORS: NATIONAL GOVERNMENTS

- Expedite uptake of new innovations through 1) rapid updates of national guidelines, strategic plans, and essential medicines lists; and 2) healthcare worker trainings on short course TB prevention and treatment regimens.

- Increase domestic and international investments in TB programming.

- Leverage legal and other strategies that can help improve access to TB medicines and diagnostic technologies.

- Develop patient-centered models of treatment and prevention that deliver care through differentiated, community-based systems, including for post-TB support.
CAMPAIGN ASKS & ACTORS:
DONORS / FUNDING MECHANISMS

Increase investments in TB programs, to support higher medicines costs and increased health systems, human resources, and laboratory infrastructure and diagnostic technology needs.

Establish new, and expand existing, sources of funding for civil society and community organizations to work on national 1/4/6x24 campaigns and accountability initiatives.

Expand resources and capacity to accelerate research to fill data gaps and shorten treatment even further.
CAMPAIGN ASKS & ACTORS: PHARMA & DIAGNOSTICS COMPANIES

Develop fit-for-purpose formulations for short-course prevention and treatment regimens, including fixed-dose combinations and formulations appropriate for children.

Commit to rapid registration with stringent regulatory authorities and other national regulatory authorities as needed and early submission to the World Health Organization Pre-Qualification Program.

Develop fit-for-purpose diagnostic technologies, including rapid molecular tests that can detect TB and resistance to key medicines (rifampicin, isoniazid, fluoroquinolones, bedaquiline) at the point of care.

Commit to transparent, evidence-based pricing determined by the cost-of-goods-sold (COGS) plus a reasonable profit margin or to patent non-enforcement.

Commit to addressing outstanding research priorities (see next slide).
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<tr>
<th>CAMPAIGN ASKS &amp; ACTORS: RESEARCH NETWORKS / INSTITUTIONS</th>
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| **Design and implement studies that address remaining research and data gaps**  
| **Advance fit-for-purpose quantitative and qualitative research to support the introduction and scale up of the shorter regimens and supportive technologies.**  
| **Ensure regimens are safe and dose optimized for PLHIV, younger adolescents, children, and pregnant people.**  |
| **Evaluate risk factors or populations that would benefit from treatment extensions**  
<p>| <strong>Evaluate preferences and needs of the target populations to see what they want and will use</strong>  |
| <strong>Invest in developing better point of care TB diagnostics and new TB vaccines</strong> |</p>
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<tr>
<td>Demand access to new innovations through rapid updates of national guidelines, strategic plans, and essential medicines lists. Expedite uptake of new innovations through healthcare worker trainings on short course TB prevention and treatment regimens.</td>
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<tr>
<td>Mobilize through healthcare professional associations to network, inform, learn and build commitment to implementing 1/4/6 by the end of 2024.</td>
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CAMPAIGN RESOURCES (1/3)

ACTIVIST GUIDES

An Activist’s Guide to Rifapentine for TB Infection:

An Activist’s Guide to Shorter Treatment for Drug-Sensitive Tuberculosis:

GFAN Advocacy Briefs:
https://www.globalfundadvocatenetwork.org/resource/advocacy-guides-to-1-4-6x24-shorter-regimens-for-tb/

More Campaign Resources:
https://www.treatmentactiongroup.org/1-4-6-x-24/
CAMPAIGN RESOURCES (2/3)

WORLD HEALTH ORGANIZATION GUIDELINES+

WHO consolidated guidelines on tuberculosis, Module 1: Prevention: Tuberculosis preventive treatment: https://www.who.int/publications/i/item/9789240001503

WHO consolidated guidelines on tuberculosis, Module 4: Treatment: Drug-susceptible tuberculosis treatment: https://www.who.int/publications/i/item/9789240048126

WHO consolidated guidelines on tuberculosis, Module 5: Management of tuberculosis in children and adolescents: https://www.who.int/publications/i/item/9789240046764

WHO consolidated guidelines on tuberculosis, Module 4: Treatment of drug-resistant tuberculosis: https://www.who.int/publications/i/item/9789240063129

CAMPAIGN RESOURCES (3/3)
LANDMARK STUDIES


CAMPAIGN COORDINATOR CONTACTS

Treatment Action Group (TAG)
Lindsay.McKenna@treatmentactiongroup.org
Mike.Frick@treatmentactiongroup.org
David.Branigan@treatmentactiongroup.org

Partners In Health (PIH)
LPalazuelos@pih.org
COswald@pih.org

Médecins Sans Frontières (MSF)
Amanda.Banda@geneva.msf.org
Manuel.Martin@geneva.msf.org