# Can short-term treatment of tuberculosis be effective in controlling the disease?

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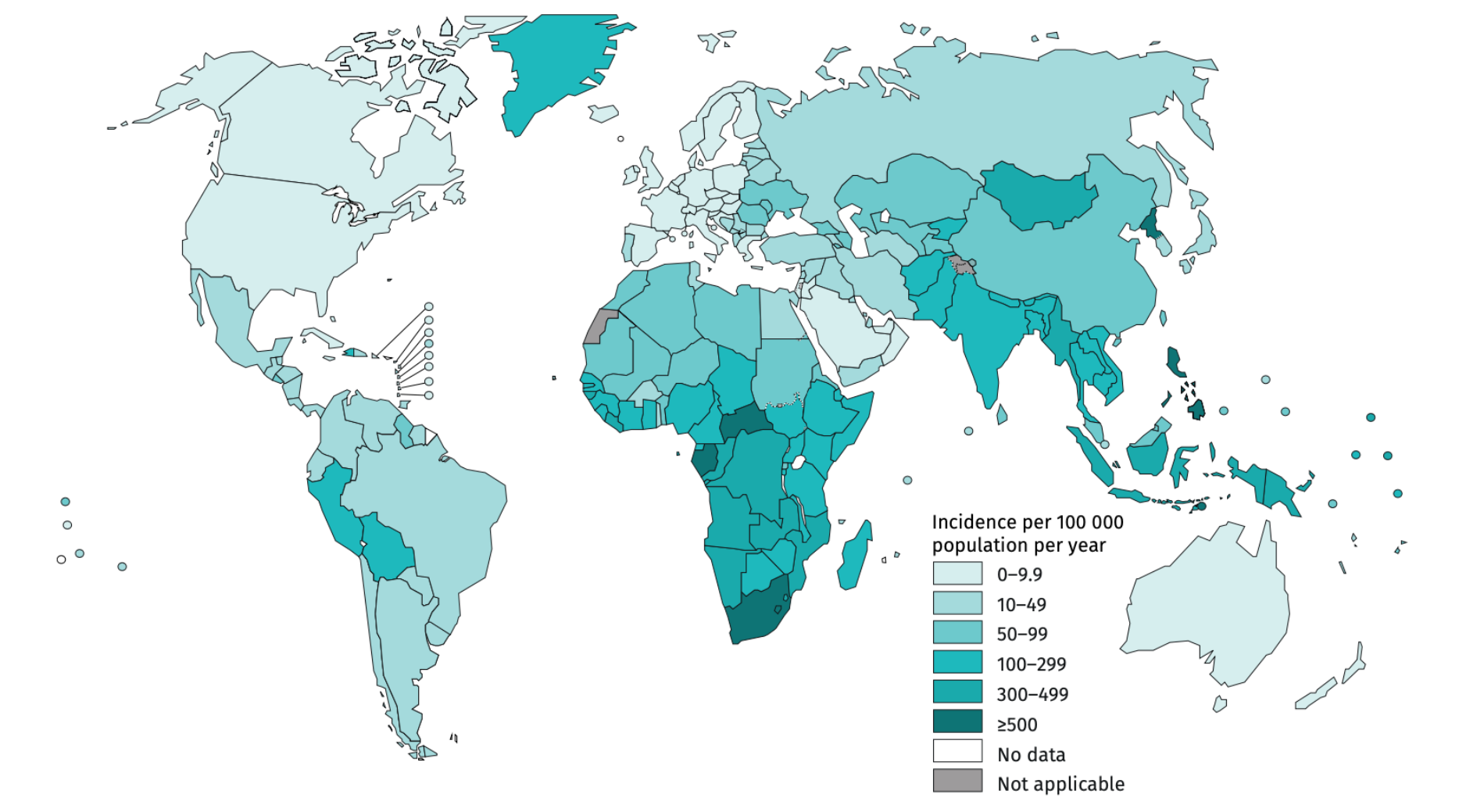
# Estimated tuberculosis incidence rates across the world in 2020




About a quarter(1/4) of the global population is estimated to have been infected with TB bacteria.

About 5–10% of people infected with TB will eventually get symptoms and develop TB disease.


- TB is present in all countries and age groups. But TB is curable and preventable.
- MDR-TB remains a public health crisis and a health security threat.
  Only about 1 in 3 people with drug resistant TB accessed treatment in 2021.
- An estimated 74 million lives were saved through TB diagnosis and treatment between 2000 and 2021.
- US$ 13 billion is needed annually for TB prevention, diagnosis, treatment and care to achieve the global target agreed at the 2018 UN high level-meeting on TB.


- Although preventable and treatable, TB remains one of the world's deadliest infectious diseases, taking the lives of 1.6 million people annually.

- nearly **11 million** people **becoming ill** with TB in 2021 (**Six million men**, **3.4 million women** and **1.2 million children**.)

- A total of **1.6 million people died from TB in 2021** (including 187 000 people with HIV).

- Worldwide, **TB is the 13th leading cause of death** and **the second leading infectious killer after COVID-19 (above HIV and AIDS).**


**Each year on March 24, CDC joins the global community to observe World Tuberculosis (TB) Day – an important moment to unite in support, attention, and energy to end TB.**

Ending the TB epidemic by 2030 is among the health targets of the United Nations Sustainable Development Goals (SDGs)


The year 2023 is going to be critical for all of us engaged in tuberculosis (TB) work and should be championed as the ‘year of hope’ to get full support, attention, and energy for a collective **‘YES! We Can End TB’**.


The Global Plan to End TB, 2023–2030 (Global Plan) is a plan for ending tuberculosis (TB) as a public health challenge by 2030—the year by which governments around the world have committed to achieving the United Nations (UN) Sustainable Development Goals.

- With the advent of the COVID-19 pandemic, the world lost some of the gains made previously in the fight against TB.

- Global deaths from tuberculosis increased for the first time in more than a decade, rising from 1.4 million to 1.5 million.

- This is due to **the socioeconomic impact of the pandemic**, with impacts including **worsening poverty**, **malnutrition** and **the diversion of health resources initially used for TB to fight COVID-19**, among others.

- Other effects suffered globally were a reduction in tuberculosis diagnoses due to lockdown, poor adherence to treatment, and an increasing incidence of drug-resistant TB.

# Areas to focus on to End TB

- There are several key areas to focus on such as financial needs to scale up implementation and speed up, research and development of new tools including:
  - ✓ A new TB vaccine,
  - ✓ Access to new rapid molecular diagnosis and
  - ✓ **To new shorter and more efficient treatment regimens**,
  - ✓ TB prevention,
  - ✓ TB in children,
  - ✓ Strengthening and funding Communities, Rights and Gender (CRG) work.

- For more than four decades, the global standard treatment for drug-susceptible pulmonary TB has been **a 6-month rifampin-based regimen**.

- This treatment has **cured >95% of persons** with tuberculosis in the context of clinical trials but has underperformed in national treatment programs, in which **long-term adherence is difficult for some persons** and **resource constraints limit the provision of adherence support.**

- The unsatisfactory outcomes associated with standard treatment have contributed to the ongoing failure to meet global tuberculosis targets and to **the generation of drug resistance**.

- Shorter, effective TB treatments could enable more rapid cure and improve patient quality of life.

- Exploration of new treatment approaches is essential.

- In clinical trials, **at least 85% of participants** have been **cured with 3-month and 4-month regimens**, and the percentage is likely to be **higher** when these regimens **contain Fluoroquinolones or Rifapentine**.

- **A similar probability of cure** has also been observed **with 2-month regimens** that are administered for the **treatment of smear-negative tuberculosis.**

- Thus, the current 6-month regimen may lead to overtreatment in the majority of persons in order to prevent relapse in a minority of persons.

- This approach may be misaligned with the desires of persons who have tuberculosis and with efficient functioning of programs, thereby impairing outcomes.

# Ongoing clinical trials evaluating shortened regimens for drug-susceptible

| ClinicalTrials.gov Identifier (study name) | Phase | Study population | Study groups | Status | Results expected in (year) |
|---|---|---|---|---|---|
| NCT02410772 (TBTC 31/A5349) | 3 | 2,500 adults and children (≥ 12 years), HIV+ and HIV- | 2 months of isoniazid, rifapentine, ethambutol, and pyrazinamide, followed by 2 months of isoniazid and rifapentine, or 2 months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by 2 months of isoniazid, rifapentine, and moxifloxacin vs. standard 6-month therapy | Active, not recruiting | 2020 |
| NCT03474198 (TRUNCATE-TB) | 2/3 | 900 adults, HIV+ and HIV- | Standard 6-month therapy vs. Regimen B: rifampin (35 mg/kg), isoniazid, pyrazinamide, ethambutol, and linezolid; or Regimen C: rifampin (35 mg/kg), isoniazid, pyrazinamide, ethambutol, and clofazimine; or Regimen D: rifapentine, isoniazid, pyrazinamide, linezolid, and levofloxacin; or Regimen E: isoniazid, pyrazinamide, ethambutol, linezolid, and bedaquiline | Recruiting | 2022 |
| NCT02581527 (RIFASHORT) | 3 | 654 adults, HIV- | 2 months of ethambutol, isoniazid, rifampin (1,200 mg or 1,800 mg), and pyrazinamide daily, followed by 2 months of isoniazid and rifampin (1,200 mg or 1,800 mg) daily vs. standard 6-month therapy | Recruiting | 2021 |
| NCT03338621 | 2c/3 | 450 adults, HIV+ and HIV- | BPaMZ regimen: bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1,500 mg daily for 17 weeks (total treatment duration: 4 months) vs. standard 6-month therapy | Recruiting | 2022 |
| NCT03561753 | 2b | 300 adults, HIV- | PRS regimen: 4 months of daily clofazimine, ethambutol, prothionamide, and high dose pyrazinamide vs. standard 6-month therapy | Enrolling by invitation | 2021 |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Treatment Strategy for Rifampin-Susceptible Tuberculosis

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# Methods

## Trial Population

Persons were eligible for inclusion in the trial if they were 18 to 65 years of age, had symptoms of tuberculosis or evidence of tuberculosis on a chest radiograph, and had a nucleic acid amplification test (Xpert MTB/RIF test, Cepheid) that was positive for tuberculosis without rifampin resistance.

## Participants

From March 21, 2018, through January 20, 2020, a total of 1179 participants were screened and 670 were enrolled at 18 sites in Indonesia, the Philippines, Thailand, Uganda, and India.

All 660 participants who were alive and undergoing follow-up were evaluated at week 96;

## Randomization and Treatment Strategy

Participants were randomly assigned to undergo either standard treatment or a strategy involving initial treatment with an 8-week regimen, Extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse.

There were four strategy groups with different initial regimens; participants were randomly assigned to the standard-treatment group or to one of the four strategy groups in equal proportions.

Current evidence from **in vitro**, **animal**, and **human studies** suggests that **high-dose rifampin can shorten the duration of tuberculosis treatment.**

**Higher rifampin doses** were associated with **more rapid sputum sterilization**, and **toxicity was similar to that of the standard dose**.

# Methods

Standard treatment consisted of a standard dose of Rifampin and Isoniazid for 24 weeks in combination with pyrazinamide and ethambutol for the first 8 weeks.

In the four strategy groups, initial treatment consisted of the following 8-week regimens:

**1-high dose of Rifampin(20mg/kg) and Linezolid** (+INH+ ETM+PZA)

**2-high dose of Rifampin and Clofazimine**, (+INH+ ETM+PZA)

**3-Rifapentine and Linezolid**, (+INH+ Levofloxacin +PZA)

**4-Bedaquiline and linezolid**, (+INH+ ETM+PZA)

When a participant had persistent clinical disease (symptoms and a positive sputum smear) at week 8 or had missed doses, treatment with the five-drug regimen could be extended through week 12.

When a participant had persistent clinical disease at week 12 or had adverse events at an earlier point, the five-drug regimen could be switched to standard treatment to complete a 24-week course of treatment.

## Methods

The trial steering committee **discontinued enrollment in two strategy groups** (the **rifampin–clofazimine** and the **rifapentine–linezolid strategy** group) to ensure that sample-size requirements could be met for the formal evaluation of non-inferiority in the two remaining strategy groups.

Participants who met prespecified criteria for relapse were retreated for at least 24 weeks with standard treatment, which was adjusted according to the participant's resistance profile.

## Conclusion

- The results of the TRUNCATE-TB trial showed that a strategy involving initial treatment with an 8-week regimen that **contained Bedaquiline and linezolid** was **non-inferior to standard treatment** with respect to the risk of a composite clinical outcome at week 96.

- This treatment strategy was associated with a shorter initial course and with a shorter total duration of treatment than was standard treatment.

- Also, participants who were treated according to this strategy reported a **higher level of motivation to adhere to an 8-week initial course** than to standard treatment.

- **One risk that is associated with a shorter course** could be the **development of antibiotic resistance**.

- There were **two cases** of acquired drug resistance **in the bedaquiline–linezolid** group and **none in the standard-treatment group**.

- **Bedaquiline has a long terminal half-life** that generates **lingering sub-therapeutic concentrations for several months after the end of therapy,** which results in **de facto monotherapy** and a prolonged window for the potential acquisition of drug resistance in cases of relapse.

- Although a much larger number of patients would need to be treated to detect any significant difference, the small number of cases of drug resistance

## Conclusion

- Of the two strategy groups that were formally evaluated for noninferiority, **only** the group that was assigned to receive initial treatment with a **bedaquiline–linezolid regimen** met the **noninferiority criterion at week 96.**

- **Bedaquiline may be well-suited for a 2-month initial course** because its long half-life may extend efficacy beyond treatment completion, **with a low risk of drug resistance.**

## Conclusion

- The 13-week reduction in the total treatment duration could allow program resources (both financial and human) — which are currently consumed by procuring, distributing, and supervising additional months of treatment — to be redeployed to enhance adherence support during a shorter period.

- This support may synergize with the increased individual motivation to better sustain adherence and thereby prevent the decrease in effectiveness that has been seen with standard treatment in its translation from clinical trials to programs

# WHO consolidated guidelines on tuberculosis

## Module 4: Treatment

## Drug-susceptible tuberculosis treatment

24 May 2022
Guideline

- Sponsored by CDC and conducted in collaboration with the NIH-sponsored ACTG, Study 31/A5349 was an international, open label, phase 3 non-inferiority clinical trial that randomized 2,516 participants **at 34 clinical sites** in **13 countries.**
- The trial confirmed that a **4-month daily treatment regimen containing high-dose RPT and MOX**, as well **as INH and PZA**, is **as effective as** (noninferior to) **the standard daily 6-month regimen in curing drug-susceptible TB**

# Four-month Rifapentine-Moxifloxacin TB treatment regimen:

Considerations for specific groups of people with TB disease

CDC recommends the 4-month Rifapentine-Moxifloxacin regimen as an option for treating drug-susceptible pulmonary TB disease for:

1) People who are **≥12 years**
2) People with a body **weight ≥40 kg**
3) People with **HIV with CD4 >100**, who are receiving or planning to **start efavirenz as part of their ART** regimen (In the absence of any other known drug-drug interactions between anti-TB and ARV medications)
4) People who have **no contraindications to this regimen**
5) People with a **negative sputum culture** who in the judgment of the clinician likely represent **paucibacillary** or **low mycobacterial burden TB disease** unless the person is included in one of the non-recommended groups

# Four-month Rifapentine-Moxifloxacin TB treatment regimen:

CDC recommends that clinical consultation be obtained to determine if the 4-month rifapentine-moxifloxacin regimen is an acceptable treatment option for

1) People at increased **risk of MTB resistance to any drug in the 4-month regimen**

2) People who received **more than 5 doses of TB treatment in the prior 6 months**

3) People who received **more than 5 doses of latent TB infection treatment in the prior 6 months**

4) People who **received more than 5 doses of treatment with any one or more of the following drugs** for any reason (e.g., UTI, pneumonia) in the **prior 30 days**:
   (Isoniazid (INH), rifampin (RIF), rifabutin, rifapentine (RPT),pyrazinamide (PZA), or any FQ)

5) People who have serum or plasma **ALT or AST> 3 ULN** or **total bili>2.5 ULN**, or with **preexisting advanced liver disease**

# Four-month Rifapentine-Moxifloxacin TB treatment regimen:

Considerations for specific groups of people with TB disease

CDC recommends that clinical consultation be obtained to determine if the 4-mo rifapentine-moxifloxacin regimen is an acceptable treatment option for

6) People who have **renal insufficiency** or **ESRD**, or **Serum or plasma Cr >2 ULN**, or **Plasma K <3.5mEq/L**

7) People who have types of **extrapulmonary TB that are likely to be paucibacillary**, **not pose a substantial risk of death or disability**, and **not require prolonged treatment (i.e., pleural or lymph node TB)**

8) People with a sputum specimen that is **unable to be submitted for any M.TB resistance testing prior to initiating the 4-month treatment regimen**

# Four-month Rifapentine-Moxifloxacin TB treatment regimen:

Considerations for specific groups of people with TB disease

CDC Does NOT Recommend the 4-month Rifapentine-Moxifloxacin regimen for

1) People who are **aged <12 years**
2) People with a **body weight <40 kg**
3) People who are **pregnant or breastfeeding**
4) People who have most types of **suspected or documented extrapulmonary TB**
5) People who have a **history of prolonged QT syndrome or concurrent use of one or more QT-prolonging medications** (in addition to moxifloxacin)
6) People who are receiving medications with known **clinically relevant drug-drug interactions** with INH, RPT, PZA, or MOX

# Four-month Rifapentine-Moxifloxacin TB treatment regimen

- The 4-month daily treatment regimen consists of:

  **A-Intensive phase** composed of 8 weeks of daily treatment with **RPT, MOX, INH, and PZA**,

  **B-Continuation phase** of 9 weeks of daily treatment with **RPT, MOX, and INH** .

- Anti-TB drugs should be administered:
  - **A. once daily with food**,
  - **B. 7 days per week**,
  - C. for **a total of 119 treatment doses;** similar to the standard 6-month regimen**, at least 5 of 7 weekly doses should be administered under direct observation**

# Dosing recommendation for a 4-month Rifapentine-Moxifloxacin regimen for patients aged ≥12 years with pulmonary TB caused by drug-susceptible organisms

| Medication* | Body weight, kg | Dose | Intensive phase | Continuation phase | Total doses |
|---|---|---|---|---|---|
| Rifapentine | ≥40 | 1,200 mg | 7 days/wk for 56 doses (8 wks) | 7 days/wk for 63 doses (9 wks) | 119 |
| Moxifloxacin | ≥40 | 400 mg | | | |
| Isoniazid† | ≥40 | 300 mg | | | |
| Pyrazinamide | 40–<55 | 1,000 mg | | NA | |
| | ≥55–75 | 1,500 mg | | | |
| | >75 kg | 2,000 mg | | | |

# Baseline and follow-up evaluations for patients treated with a 4-month rifapentine-moxifloxacin regimen

| Evaluation | Baseline | Week 4 | Week 8 (end of intensive phase) | Week 12 | Week 17 (end of treatment) |
|---|---|---|---|---|---|
| **Microbiology** | | | | | |
| Sputum for rapid molecular test† | Y | NA | NA | NA | NA |
| Sputum for AFB smear and culture§ | Y | Y | Y | Y¶ | Y¶ |
| Drug susceptibility testing** | Y | NA | Y¶ | NA | NA |
| **Imaging** | | | | | |
| Chest radiograph†† | Y | NA | Y¶ | NA | Y¶ |
| **Clinical assessment** | | | | | |
| Weight§§ | Y | Y | Y | Y | Y |
| Symptoms, adverse events, and adherence¶¶ | Y | Y | Y | Y | Y |
| **Laboratory testing** | | | | | |
| ALT, AST, bilirubin, and alkaline phosphate*** | Y | Y¶ | Y¶ | Y¶ | Y¶ |
| Platelet count | Y | Y¶ | Y¶ | Y¶ | Y¶ |
| Creatinine | Y | Y¶ | Y¶ | Y¶ | Y¶ |
| Potassium, calcium, and magnesium††† | Y | Y¶ | Y¶ | Y¶ | Y¶ |
| HIV | Y | NA | NA | NA | NA |
| CD4 count and HIV RNA load (if HIV infection)§§§ | Y¶ | NA | NA | NA | NA |
| Hepatitis B and C screen¶¶¶ | Y¶ | NA | NA | NA | NA |
| Diabetes screen**** | Y¶ | NA | NA | NA | NA |
| Pregnancy testing for persons who might become pregnant†††† | Y | NA | NA | NA | NA |

# FINAL CONSIDERATIONS

- Many observational studies and clinical trials have demonstrated the potential of shortened regimens for the treatment of both DS-TB and MDR-TB.

- In addition to **reducing costs**, the use of shorter regimens can **improve adherence** and, consequently, **treatment completion** and reduces risk of development of drug resistant tuberculosis.

- However, further studies, especially randomized clinical trials and pragmatic clinical trials, are needed to evaluate regimens including newer drugs, drugs drugs proven to be or highly likely to be efficacious, and all-oral drugs in an effort to eliminate the need for injectable drugs.

## FINAL CONSIDERATIONS

New approaches need to be identified to shorten treatment duration, including the possibility of administering new drugs (e.g., Bedaquiline and Delamanid) together, as recent evidence suggests that it can be safer than it was initially considered


WORLD TB DAY
24 MARCH
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نعم!
YES!
OUI!
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