WHO's recommendations on TB preventive therapy

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Prevalence of *M. tuberculosis* infection in the world

One-quarter of the global population is infected with *M. tuberculosis*

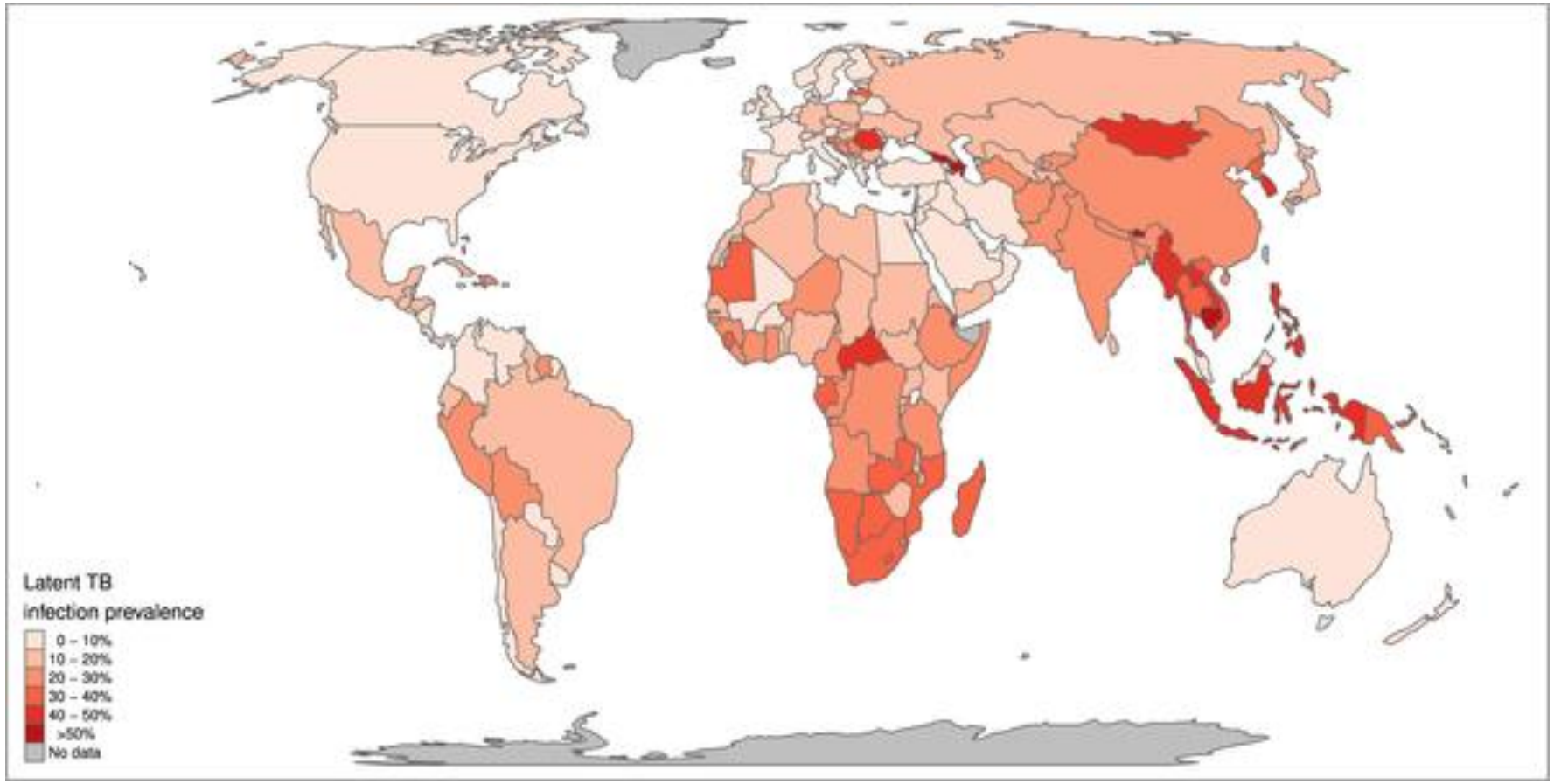
- Global population March 2026: 8.3 billion
- Approximately 2 billion people infected
  - Raviglione M. JAMA 1995;273:220. Dye C et al. JAMA 1999;282:677. Houben R PLoS Med 2016.

- Prevalence of *M. tuberculosis* infection varies by location
  - High TB incidence setting: (Kampala, Uganda): 49% (95% CI: 44-55)
    - Kizza FN. BMC Infect Dis 2015:165
  - Low TB incidence setting (United States): ~5%
    - Miramontes R. PLoS ONE 2015:10 (11):e0140881
    - Mancuso JD. Am J Respir Crit Care Med 2016 Feb 11.
    - Ghassemieh BJ. Am J Respir Crit Care Med 2016 Feb 18.

Active TB arises from this pool of M.tb-infected persons

Global map of prevalence of *M. tuberculosis* infection

From this reservoir of ~2 billion infected persons, 100-200 million TB cases could develop



Houben RMGJ, Dodd PJ (2016) The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLOS Medicine 13(10): e1002152. https://doi.org/10.1371/journal.pmed.1002152
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002152

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Treatment of *M. tuberculosis* infection

World Health Organization

Whom to Treat

- People living with HIV
  - Adults and adolescents who are unlikely to have active TB
    - Includes persons on ART, pregnant women, those previously treated for TB, irrespective of CD4, and if TST or IGRA testing is unavailable
  - Infants < 12 months who are TB close contacts and unlikely to have active TB
  - Children ≥ 12 months in a setting of high TB transmission, regardless of TB contact
  - Children who have completed TB treatment
- Household contacts, regardless of HIV status
  - Children < 5 years who are contacts of microbiologically confirmed pulmonary TB, regardless of TST/IGRA status
  - Children ≥ 5 years, adolescents, and adults who are contacts of microbiologically confirmed pulmonary TB who do not have active TB
  - Contacts of MDR-TB
- Other people at risk for TB:
  - Anti-TNF agents, hemodialysis, organ transplant, silicosis
  - Consider LTBI testing and treatment for prisoners, health workers, immigrants from high TB burden countries, homeless people, people who use drugs

WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020.

Treatment of *M. tuberculosis* infection

World Health Organization

Treatment Regimens

- Regardless of HIV status or local TB burden
  - Recommended:
    - 6-9INH: 6-9 months of daily isoniazid
    - 3HP: 3 months of weekly isoniazid + rifapentine
    - 3HR: 3 months of daily isoniazid + rifampin
  - Alternatives:
    - 4R: 4 months of daily rifampin
    - 1HP: 1 month of daily isoniazid + rifapentine
- If HIV+ in settings of high M.tb transmission, 36 months of INH regardless of LTBI status, antiretroviral therapy, CD4 count, history of prior TB, pregnancy

Treatment of *M. tuberculosis* Infection

Current Regimens

Regimen	Efficacy	Effectiveness	Comments
3 months INH + rifapentine once-weekly	90% (estimated)	90% (estimated)	≥82% completion Lower rates when self-administered than DOT
4 months rifampin daily	---	50-90% (estimated)	Limited data in persons with HIV
3 months INH + rifampin daily	---	41-59%	Concern re: hepatoxicity
6-9 months INH daily	90%	25-88% (median:60%)	6 and 12 months well-studied; 30-60% completion

3 months of weekly INH + rifapentine

Recent Updates

- The regimen is rolling out in high TB burden settings
  - IMPAACT4TB (UNITAID): in persons with HIV and children < 5 years old
  - Project countries: Brazil, Cambodia, Ethiopia, Ghana, India, Indonesia, Kenya, Malawi, Mozambique, South Africa, Tanzania and Zimbabwe
    - G Churchyard, R Chaisson
- Pregnancy did not ↑ RPT clearance, but HIV did; appears safe (n=50)
    - Mathad JS. 2022 May 3;74(9):1604-1613; Hibma JE AJRCCM 2020;202(6):866-877.
- Can be given with dolutegravir without dose adjustments; also in pregnancy
    - Dooley KE et al. DOLPHIN Study. Lancet HIV 2020 Jun 7 (6):e401-9. DOLPHIN-Moms CROI 2026 Abstract 147.
- Possible flu syndrome
  - Risk 4-19%. Risk factors: race (white; Asian), female sex, ↑ age, ↓ BMI, NAT2 genotype
    - Sterling TR. CID 2015; Jo KW. Respir Med 2019; Huang HL. CID 2020 Nov; Ruan QL. Clin Microbiol Infect 2020; Feng JY. IJID 2020; Lee MR. J Clin Med 2019
- Lower hepatotoxicity risk than with 9INH
    - Bliven-Sizemore E. IJTLD 2015; Sun Tuberculosis 2018.
- Completion rate lower when self-administered vs. directly-observed
  - 74-76% vs. 87%
    - Belknap B. Ann Intern Med 2017
- Safe and effective in several patient populations
  - Health departments, clinics, high school contacts, jails, homeless, renal transplant candidates. Higher completion rates than in trials.
    - Bargman MMWR 2014, Stennis CID 2016, Juarez-Reyes OFID 2016, Yamin OFID 2016, Lines G JHCPU. Simkins J Transpl 2016. Sandul CID 2017. Moro Ann Am Thorac Soc 2018. Schmit CID 2020

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

- Population: HIV-positive persons ≥ 13 years old in high TB incidence settings
  - ≥ 60 / 100,000 population
- Intervention: daily INH + rifapentine for 1 month
- Comparator arm: daily INH for 9 months
- Antiretroviral therapy: efavirenz or nevirapine-based
- Follow-up: 3 years after last participant enrolled
- Primary endpoint: TB (confirmed or probable), TB death, death due to unknown cause
- Non-inferiority design:
  - Expected TB rate in 9H arm: 2.0 per 100 person-years
  - Non-inferiority margin: 1.25 per 100 person-years

Swindells S. N Engl J Med 2019;380:1001-1011

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
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Characteristic	9H N=1504	1HP N=1496
Median age (years)	35	35
Male sex	692 (46%)	694 (46%)
Median BMI	23.5	23.6
Median CD4	469	473
ART at entry	749 (50%)	747 (49%)
TST-positive	21%	21%

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4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
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Endpoint	9H N=1504	1HP N=1496	IRR (95% CI)
Primary endpoint All-comers	33/4896 p-y 0.67 / 100 p-y	32/4926 p-y 0.65 / 100 p-y	0.023 (-0.30, 0.35)
Primary endpoint CD4 ≤ 250	1.275 / 100 p-y	1.931 / 100 p-y	-0.656 (-2.06, 0.75)
Active TB, confirmed	14	18	
Active TB, probable	10	11	
Death due to TB	2	0	
Death-unknown cause	7	3	

Swindells S. N Engl J Med 2019;380:1001-1011

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
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Endpoint	9H N=1498	1HP N=1488
Grade ≥ 3 adverse event	274 (18%)	250 (17%)
Treatment completion (self-report)	90%	97%
Premature drug discontinuation	2%	1%

Swindells S. N Engl J Med 2019;380:1001-1011

Ultra-Curto

Randomized Controlled Trial

- 1HP vs. 3HP in Brazilian adolescents and adults
  - Recent TB exposure; positive test for *M. tuberculosis* infection; HIV-seronegative
- Primary outcomes:
  - Completion of > 90% of medication (self-report, pill counts, pharmacologic monitoring)
  - Safety (Grade ≥ 2 events, or drug discontinuation due to adverse effects)

Results

	1HP (n=249)	3HP (n=251)	Risk difference
Age (median; IQR)	40.0 (28 – 54)	38.0 (25 – 52)	
Female sex	67.1%	55.8%	
Body mass index (BMI; median)	27.8	27.8	
Treatment completion	89.6%	84.1%	
Grade ≥ 2 events or d/c	16.1%	10.4%	6.1% (site-adjusted; P = 0.05) 3.4% (site, demogr/clin; P=0.24)
Discontinuation due to adverse event	7.2%	4.4%	

- No TB cases during 6 months of study follow-up
- The study was not designed/powered to assess efficacy/effectiveness

Durovni B. PLoS Med 2026;23(2): e1004758

1HP vs. 3HP South Africa, India

The One-to-Three Trial

- 1HP vs. 3HP in persons with HIV in South Africa and India
  - Median age 43; 68% female; on dolutegravir, with HIV-1 RNA < 50
- Primary outcome: composite of treatment completion (self-report, pill count, opening of electronic med device)

Results

	1HP (n=250)	3HP (n=250)
Treatment completion (composite)	75.6%	87.6%
Treatment completion (self-report)	>90%	>90%
Treatment completion (pill count)	>90%	>90%
Treatment completion (device)	79.2%	96.4%
Treatment-limiting AE	3.2%	0%
Grade > 2 AE	10%	9.6%
Grade > 3 AE (study drug)	0.4%	0.8%
Hepatotoxicity	0%	0%
Hypersensitivity/flu-like	0%	0%

No TB cases during 6 months of follow-up

Moodley J. CROI 2026. February 24. Abstract 148

1HP vs. 3HP Thailand

Randomized controlled trial

- 1HP vs. 3HP in persons with HIV in Thailand
  - Median CD4 = 349; on efavirenz or dolutegravir
- Primary outcome: composite of TB or death from any cause
- Non-inferiority study design: margin: 2.5%

Results

	1HP (n=748)	3HP (n=752)	Risk difference
TB	2	1	
Deaths	2	2	
Proportion	0.27%	0.13%	0.13% (-0.32 – 0.58)
Rate per 1,000 person-years	1.7	1.0	
HIV-1 RNA < 50 copies	96%	95.5%	
Grade 3-4 adverse event	2.4%	2.4%	
Serious adverse event	1.1%	0.9%	
Hepatotoxicity	1.5%	1.7%	
Hypersensitivity/flu-like	0.3%	0.5%	
Treatment discontinuation	1.5%	1.3%	

Avihingsanon A. CROI 2026. February 24. Abstract 145

Conclusions

- Focus TB preventive therapy on persons at high risk of progressing to TB disease

- Use short, safe, and effective TB preventive therapy regimens