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THERAPY IN PRACTICE

Tuberculosis Preventive Treatment in High TB-Burden Settings: A State-of-the-Art Review

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Abstract

Tuberculosis (TB) is the leading cause of death from a single infectious agent. The burden is highest in some low- and middle-income countries. One-quarter of the world's population is estimated to have been infected with TB, which is the seedbed for progressing from TB infection to the deadly and contagious disease itself. Although some individuals may clear their infections through innate and acquired immunity, many do not. People living with HIV, TB-exposed household contacts, other individuals recently infected, and immunosuppressed individuals are at especially high risk of progressing to TB disease. There have been major advances in recent years to support the programmatic management of TB infection. New tests of infection, including those that predict progression to TB disease, have become available. Numerous World Health Organization-recommended TB preventive treatment (TPT) regimens are available for all ages and for both drug-susceptible and drug-resistant TB infection. All regimens are generally safe, efficacious, and cost effective and have a low risk of generating resistance. TPT is recommended for pregnant women who are at risk for developing TB, but some regimens are associated with an increased likelihood of poor obstetric and fetal outcomes, and newer regimens have not yet been tested in pregnancy. New formulations of rifapentine-based TPT have been developed, and the cost has been radically reduced. Innovative models of delivery to support the scale up of TPT have been developed. Modeling suggests that scaling up TPT, especially regimens with optimal target product profile characteristics, can contribute substantially to ending the TB epidemic. The global uptake of TPT has increased substantially, especially for people living with HIV. Implementation gaps remain, particularly for children, pregnant women, and other household contacts. Further innovation is required to support the continued scale up of TPT and to contribute to ending the TB epidemic.

Key Points

People infected with tuberculosis (TB) are at high risk of progressing to TB disease.

Tests can identify people infected with TB who may benefit from preventive treatment.

Well-tolerated and effective TB preventive treatment regimens are available and recommended in adults, children, and pregnant people.

Extended author information available on the last page of the article

1 Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality from an infectious pathogen [1]. The World Health Organization (WHO) estimated that 10.8 million people developed TB, that 400,000 people developed multidrug-resistant (MDR)/rifampicin-resistant (RR) TB, and there were 161,000 TB-related deaths among people with HIV and 1.09 million TB-related deaths among people without HIV in 2023, respectively [1].

1.1 Natural History of Tuberculosis

TB infection occurs after exposure to a person with infectious TB and inhalation of *Mycobacterium tuberculosis* into the lower respiratory tract, where it infects alveolar macrophages and epithelial cells, which leads to invasion of the

lung interstitial tissue. Inflammatory monocytes and dendritic cells transport the *M. tuberculosis* to pulmonary lymph nodes, which prime T cells and leads to the recruitment of immune cells to the lung parenchyma and the formation of granulomas, which contain the infection. If the immune system fails to contain the infection, dissemination within the lung or to other organs may occur, leading to TB disease [2].

A recent international consensus meeting proposed a new classification of early tuberculosis to guide research and improve care. TB infection is defined as the presence of viable *M. tuberculosis* that are contained by host immune responses. Individuals with infection have no evidence of macroscopic pathology or symptoms or signs consistent with TB and are not infectious [3].

1.2 Burden of Tuberculosis Infection

Approximately 2 billion of the world's population is estimated to have been infected with TB (Fig. 1) [4]. Although some individuals may eliminate the infection through innate and acquired immunity, many do not and harbor viable bacilli that can cause disease [5]. As one in four individuals globally are potentially infected with TB that can progress to TB disease, TB infection represents the largest human reservoir of a highly pathogenic infectious disease [6].

As the drug susceptibility of TB infection cannot be determined, the relative burden of drug-sensitive or drug-resistant TB infection is unknown. Modeling suggests that drug-susceptible TB infection accounts for the majority of TB infection globally [7]. MDR-TB infection is estimated to be present in nearly three in every 1000 people globally, and children with TB infection are more likely than adults to have MDR-TB infection [7].

1.3 Risk of Progression to TB Disease

People infected with TB may contain the initial infection within a granuloma, through innate or adaptive immune responses, without any signs or symptoms of disease. Progression to TB disease may occur in some people within weeks or years later if the immune system fails to contain the infection [2]. Healthy people without HIV who have TB infection have a lifetime risk of progressing to TB disease of 5–15% [8]. Certain people with TB infection have an increased risk of progressing to TB disease, including children aged < 5 years, household and close contacts, and people who are immune-compromised because of HIV, comorbidities, or treatment. People with TB infection are therefore a reservoir of future cases of TB disease, so controlling TB infection is a vital component of the TB elimination strategy.

People living with HIV are at high risk of progressing to TB disease, but this is substantially reduced by antiretroviral therapy (ART) [9]. The risk of TB among people living with HIV well controlled on ART nevertheless remains greater than in people without HIV in the same community [10]. Household contacts of people with TB disease have a high risk of becoming infected with TB, and about 5% develop TB within 2 years of exposure [11]. Infants and children

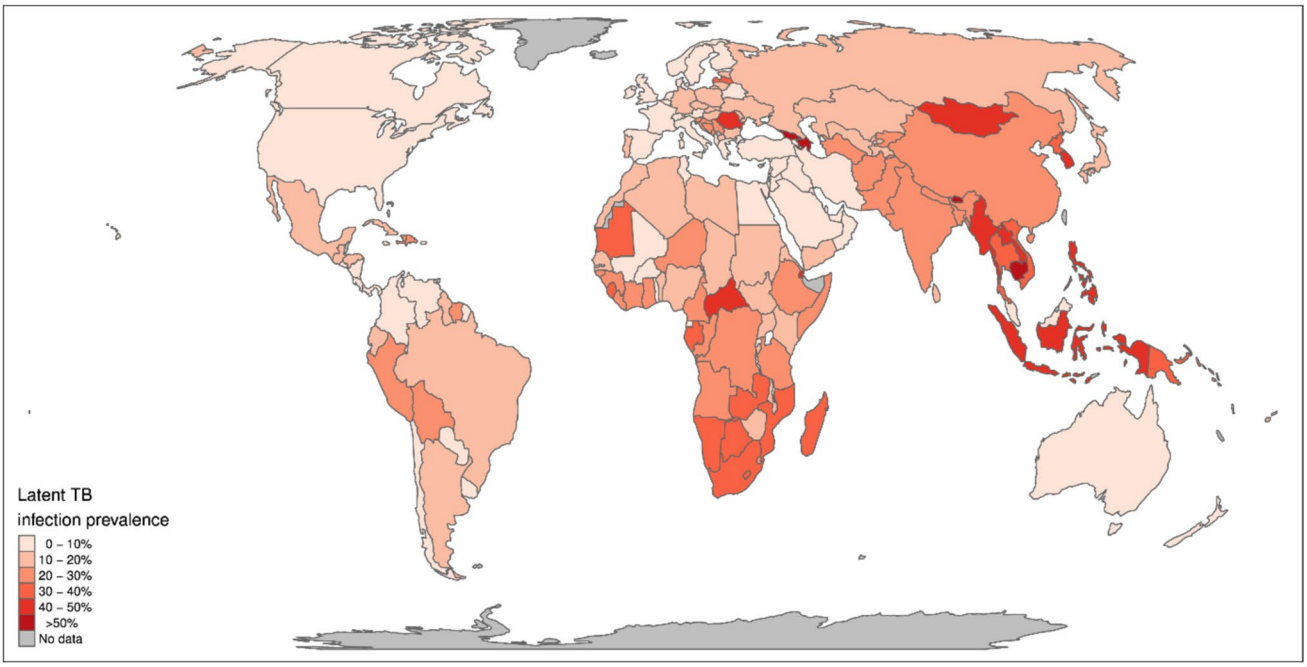

Fig. 1 World map of tuberculosis (TB) infection prevalence [4]

aged < 5 years have a particularly high risk (approximately 10–20% over 2 years) of progressing to TB disease after a household exposure [12]. People with other comorbidities or who are taking immunosuppressive treatment, such as transplant recipients, those with silicosis, and those on chronic renal dialysis or taking anti-tumor necrosis factor-alpha agents, have an increased risk of TB [1]. Other people at high risk of developing TB include homeless people, immigrants from countries with a high TB burden, healthcare workers, prisoners, and people who use drugs [1].

1.4 Rationale for Treating Tuberculosis Infection

People at high risk of developing TB benefit from TB preventive treatment (TPT) and reduce their risk of developing TB and the associated morbidity and mortality. Scaling up TPT, along with other effective TB control program activities, will reduce TB transmission at a population level. Modeling suggests that providing TPT to high-risk groups is cost effective across a wide range of settings and can contribute to ending the TB epidemic [13–21].

1.5 Progress and Targets for Scaling Up TPT

Given the high global burden of TB infection, the risk of progressing to active TB, and the potential individual- and population-level benefit of providing TPT, the WHO has prioritized TPT for people at the highest risk of progression to disease as a key intervention in global TB-control efforts. Toward this goal, the United Nations High-Level Meeting (UNHLM) on TB held in 2018 made several commitments for TB prevention to be achieved between 2018 and 2022 [1]. These included providing 30 million TPT doses overall: 24 million for household contacts, including 4 million children, and 6 million for people living with HIV. The target for scaling up TPT for people living with HIV was met; however, overall targets, and targets for children aged <5 years and for older household contacts were missed [1]. A second UNHLM on TB held in September 2023 set even more ambitious targets to provide TPT to 45 million people at high risk of developing TB, including 30 million household contacts and 15 million people living with HIV by 2027, demonstrating the high-level commitments set by nations highly burdened with TB disease.

The purpose of this review is to provide the latest information to support national control programs and implementing clinicians in scaling up TPT to meet the ambitious 2023 UNHLM targets. The review is focused on moderate to high TB burden and low- and middle-income settings across diverse population groups, including adults, children, and pregnant people.

2 Diagnosis of TB Infection

A test of TB infection can identify people at risk of progressing to TB disease. Diagnosis of TB infection is based on detection of host immune response to *M. tuberculosis* antigens. There is no gold standard for a test of infection; however, the WHO recommends the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), among others. These tests measure the host immune sensitization that occurs following infection but do not directly assess the presence or viability of *M. tuberculosis*.

2.1 Tests for TB Infection

TST has been in use for over a century and is a widely used diagnostic test for TB infection. It measures delayed-type hypersensitivity reaction to intradermally injected purified protein derivative, a mixture of several mycobacterial antigens, including products from *M. tuberculosis*, *M. bovis*, Bacille Calmette Guerrin (BCG), and non-tuberculous mycobacteria (NTM). Induration of 10 mm or 15 mm is classified as positive in healthy HIV-negative people depending on the setting. In people living with HIV or non-HIV immunosuppression, a cut-off of 5 mm is considered positive [22]. Although highly sensitive, the test has low specificity, with false-positive results in those who have had prior BCG vaccination and infection with NTM, and will likely overestimate the proportion with TB infection. Conversely, false-negative results are common in individuals who do not mount immune responses because of immunosuppression [2, 23, 24], underestimating the true burden of infection. There are several operational limitations with the TST in that it requires two clinical encounters 2–10 days apart to place the injection and read the results. Although TST can be performed in the field, it requires a cold chain and trained personnel to administer the test and read and interpret the results. Reader variability also often results in false-positive and false-negative results. The use of different cut-offs for positivity makes it difficult to compare test performance. In the last few years, intermittent supply due to a shortage of purified protein derivative has also limited access to TST testing, underscoring the need for alternative tests.

The IGRA tests are blood based and measure interferon (IFN)-γ production by T lymphocytes following stimulation by specific *M. tuberculosis* antigens. These tests use early secreted antigenic target 6 (ESAT-6) and culture filtrate protein (CFP)-10, which are encoded by genes located on the region of difference 1 segment of the *M. tuberculosis* complex genome, which is absent from the BCG vaccine. Although IGRAs have desirable

performance characteristics such as higher specificity, they are more costly than TST and require appropriate laboratory infrastructure and highly specialized training. The WHO currently endorses QuantiFERON (QFT; Qiagen, Germany) and T-Spot (Oxford Immunotec, UK) IGRA tests. These tests are enzyme-linked immunosorbent assay-based tests performed on whole blood and on separated T lymphocytes, respectively. In addition, QFT also incorporates a third antigen, Rv2654c (TB7.7); to improve the sensitivity of the QFT test, an additional stimulation tube TB2 with ESAT-6 and CFP-10 antigens, optimized for CD4+ and CD8+ T-cell stimulation, has been included in the new-generation test, QFT-Plus. The incorporation of ESAT-6, CFP-10, and TB7.7 antigens, which are found in *M. tuberculosis* but not in *M. bovis* BCG or NTM, greatly improves the specificity of the test [24–26].

Neither TST nor IGRAs can differentiate between different stages of TB infection or have high accuracy for predicting who is likely to progress to TB disease. The pooled positive predictive value for the tests of infection predicting who is likely to get TB after 2 years of follow-up across several studies is low: 1.5% with TST versus 2.7% with IGRAs [27]. A similar trend was reported in a systematic analysis by Hamada et al. [28] even though IGRA appeared to have a higher predictive performance in countries with low TB burden. The positive predictive value of TST and IGRA were similar in countries with a low TB burden (2.7 vs 2.5%) and higher in settings with high TB burdens (7.5 vs 6.0%) [28].

Novel antigen-based skin tests (TBST) using intradermal injection of recombinant *M. tuberculosis*-specific antigens and simplified skin-test platforms have recently been developed and are recommended by the WHO [29]. Combining operational and performance characteristics of IGRAs, TBSTs do not need venipuncture or laboratory facilities and have no safety concerns so have the potential to improve scalability. The Cy-Tb (Serum Institute, India), Diaskintest (Generium, Moscow, Russia), and Creative-TST (C-TST, Anhui Zhifei Longcom, Hefei, China) use ESAT-6 and CFP-10 antigens, as used in IGRAs. The diagnostic accuracy of the TBSTs is similar to that of IGRA and better than with TST, and safety profiles are similar to TST, with minor injection site reactions [30].

The WHO recommends tests of infection using TST, IGRA, or TBST in high-risk groups, including people living with HIV, children, adolescents aged 18 years, and under people who have been vaccinated with BCG [29].

2.2 Ruling Out Active TB Before Initiating TPT

In high-burden settings, the WHO recommends that the absence of a positive test of infection should not preclude initiation of TPT in adults and adolescents living with HIV, regardless of ART status, including pregnant women and those previously treated for TB. TPT should be initiated in those where TB is ruled out based on the WHO four-symptom screen [31]. A similar approach is recommended in individuals who are household contacts of people with bacteriologically confirmed pulmonary TB. Furthermore, where available, a chest radiograph may be used in people living with HIV to rule out TB, and TPT should be offered to those with no abnormality consistent with TB.

2.3 Cost Effectiveness of Tests of Infection

The cost effectiveness of tests of infection varies by test accuracy and setting. In settings with developed laboratory infrastructure, implementing IGRAs may be cost saving. However, in low- and middle-income countries (LMICs) with high TB burden, higher upfront costs for IGRAs than for TST means they are less likely to be cost effective in these settings. In LMICs, TBSTs may be more accurate, cost saving, and likely to improve health equity than TST and IGRA [32]. In countries such as Brazil, a middle-income country with a moderate TB burden, TB infection testing will likely continue to be recommended in people living with HIV using either TST or IGRA [33].

3 Treatment of TB Infection

3.1 TPT for Adults Who are not Pregnant

3.1.1 Current Recommended Regimens

For decades, the only available TPT was 6–9 months of isoniazid (6H, 9H). Although the efficacy of 9H is high, its effectiveness is diminished by low completion rates of 30–64% [34]. Four regimens developed more recently, 3HP (weekly isoniazid and rifapentine for 12 weeks), 1HP (daily isoniazid and rifapentine for 4 weeks), 3HR (daily isoniazid and rifampicin for 3 months), and 4R (rifampicin for 4 months), are shorter, and network meta-analyses indicate they have comparable efficacy and completion rates [35, 36]. Each regimen includes a rifamycin (more active than isoniazid against *M. tuberculosis* in a non-replicating state because it acts independently of cell division). The WHO recommends 9H, 3HP, or 3HR as first-line options and 1HP and 4R as alternative regimens. Key attributes and advantages and disadvantages of the WHO-recommended TPT regimens are summarized in Table 1 [37]. The US Centers for Disease Control recommend 3HP, 4R, and 3HR as first-line regimens and 9H as an alternative [38].

Table 1 Key attributes of the tuberculosis preventive treatment (TPT) regimens recommended by the World Health Organization (WHO)[a]

WHO-recommended TPT regimen	Target population	Regimen duration and frequency	Child-friendly formulation	Regimen advantages	Regimen disadvantages
Preventive treatment for DS-TB					
3HP	Children 0–12 years, adolescents, and adult	12 weekly doses	Dispersible tablet RPT 150 mg available	High completion rates Lower risk of hepatoxicity than 9H	Challenging to remember weekly dose Safety during pregnancy uncertain
3RH	All ages with or without HIV	90 daily doses	Currently available as dispersible FDC for children < 25 kg	Preferred regimen for young children without DDIs Formulated as dispersible tablet High completion rates Low risk of hepatoxicity and other AEs	DDIs with oral contraceptives and ARVs, including DTG, LPV/r, and NVP (prophylaxis and treatment) Not studied in pregnant women for prevention
6-9H	All ages with or without HIV	180–270 daily doses	Dispersible tablet available	Low cost Few DDIs Only regimen that can be used in CLHIV on DTG Dispersible tablet available	Poor completion rates AEs perceived to be too high Increased adverse pregnancy outcomes when used in the first trimester
Alternative preventive treatment for DS-TB					
1HP	Adolescents aged ≥13 years and adults with and without HIV	28 days	Dispersible tablet RPT 150 mg available	High completion rate Lower risk of hepatotoxicity and other AEs than 9H	Dosing for children aged < 13 years uncertain High pill burden per dose Not studied in pregnant women
4R	All ages with or without HIV	120 daily doses	Can be compounded into syrup, not readily available in LMICs	High completion rates Low risk of hepatoxicity and other AEs	Limited availability of rifampicin without coformulation Can be compounded into suspension but requires specialized skills Limited evidence to support dose adjustment in young CLHIV on DTG DDIs with oral contraceptives and ARVs, including DTG, LPV/r, and NVP (prophylaxis and treatment) Not studied in pregnant women for prevention
Preventive treatment for MDR-TB					
6 months Lfx	All ages with or without HIV	180 daily doses	Dispersible formulation available	Low risk of joint pain and tendonitis in children Few AEs	Higher risk of tendonitis in adults Not studied in pregnant women for prevention

ARV antiretroviral, *CLHIV* children living with HIV, *DDI* drug–drug interaction; *DS-TB* drug-susceptible TB, *DTG* dolutegravir, *AE* adverse event, *FDC* fixed-dose combination, *Lfx* levofloxacin, *LMICs* low- and middle-income countries, *LPV/r* lopinavir/ritonavir, *MDR-TB* multidrug resistant-tuberculosis, *NVP* nevirapine, *RPT* rifapentine, *1HP* daily rifapentine and isoniazid for 1 month, *3HP* weekly rifapentine and isoniazid for 3 months, *3RH* daily rifampicin and isoniazid for 3 months, *4R* daily rifampicin for 4 months, *6H* daily isoniazid for 6 months, *9H* daily isoniazid for 9 months

[a]Adapted from Salazar-Austin et al. [39]

3.1.2 Evidence for Efficacy, Safety, and Tolerability

3.1.2.1 Isoniazid TPT One of the first trials to demonstrate the efficacy of isoniazid preventive treatment (IPT) was performed by Comstock et al. [40] in Bethel, Alaska, where there was a 1% annual incidence of TB disease. This community-based trial reported a 60% reduction in TB incidence with IPT given for 12 months [40]. Since then, systematic reviews/meta-analyses of 73,375 people without HIV studied in 11 trials of isoniazid TPT have shown an efficacy of 60% without a significant difference between 6 and 12 months of treatment [41]. IPT was associated with hepatotoxicity in 0.36% of people on 6 months of treatment and in 0.52% of people treated for 12 months. The durability of protection has been estimated to be at least 2 years and depends on risk of reinfection, which in turn is associated with community incidence/burden of disease and host factors. In low-burden countries, the duration of protection is thought to be lifelong. In Alaska, during a period of high community burden, the duration of protection was documented to be longer than 19 years [42]. Among people living with HIV, efficacy has also been extensively studied in clinical trials, largely in the pre-ART era [43, 44]. In low-incidence settings, such as the USA, the preferred duration of IPT is 9 months, whereas the WHO recommends 6 months of IPT [45, 46]. The shorter, 6-month IPT regimen is associated with better completion rates but lower efficacy. Isoniazid inhibits cytochromes and can increase efavirenz exposure, but co-administration is generally safe. Longer courses of IPT are associated with more hepatotoxicity than short-course, rifamycin-based regimens.

In the TEMPRANO trial, ART+IPT had greater efficacy in reducing the incidence of TB disease than either ART or IPT alone [47]. This study also showed a survival benefit of TPT independent of ART [48]. In the REALITY trial, participants in Malawi with advanced HIV and a CD4 count of <100 cells/mm^3 who were starting ART were offered enhanced prophylaxis, which included 3 months of daily IPT and ART compared with standard prophylaxis, which was associated with reduced mortality and a risk of developing TB [49]. In the ART-IPT trial conducted in Cape Town, participants with HIV on or initiating ART were randomized to IPT or placebo [50]. IPT with ART in this population reduced the risk of TB, including in participants who received negative TST or IGRA results. A meta-analysis of the three trials (TEMPRANO, REALITY, ART-IPT) demonstrated that IPT with largely efavirenz-based ART reduced the risk of TB and non-significantly reduced the risk of death [51]. ART with TPT is now the current recommendation for all people living with HIV [46].

3.1.2.2 Shorter TPT Regimens One of the challenges with IPT is adherence to a ≥ 6 month regimen as well as concerns about isoniazid hepatotoxicity. Shorter, efficacious, and more tolerable regimens are therefore desired. In low-incidence settings (< 100 TB cases/100,000), rifamycin-based regimens are preferred because they are efficacious and have a shorter duration and lower hepatoxicity rates than IPT. Increasingly, high-incidence settings are also adopting the use of rifamycin-based regimens. The main issue is the drug interactions with rifamycins, discussed in sect. 3.1.2.5. Rifamycins can also be associated with rash and thrombocytopenia, although these adverse effects are uncommon.

In a randomized trial of more than 6800 adults, 4R was noninferior to 9H [52] and was associated with higher treatment completion (79 vs 63%) and lower adverse event rates. Rifampicin-associated rash or other allergic reactions were observed in 0.2% of those receiving 4R.

3HR is less well studied. Several small studies have been conducted, and a meta-analysis found that 3HR is equally efficacious as and not more toxic than 9H [53].

Rifapentine is a rifamycin with a longer half-life and higher in vitro potency than rifamycin, so it has been studied in treatment-shortening regimens. In a large trial of 7731 people aged ≥ 12 years, the 12-dose, once-weekly regimen of rifapentine and isoniazid (3HP) was noninferior to 9H [54]; TB incidence was 0.19% with 3HP versus 0.43% with 9H. Notably, 3HP had superior completion rates (82 vs 69%). Hepatoxicity was less common with 3HP than in the 9H group (0.4 vs 2.7%), whereas hypersensitivity (flu-like reaction) was more common (3.8 vs 0.5%). Influenza-like reactions associated with 3HP often present after the third or fourth dose of isoniazid and rifapentine [55]. These symptoms are often mild and self-resolving and include fever, fatigue, headache, dizziness, nausea, myalgia, and—rarely—hypotension and syncope. 3HP has also been shown to have similarly high efficacy in people living with HIV and children aged ≥ 2 years [56, 57].

In the WHIP$_3$TB trial, which enrolled 4027 people living with HIV on ART, 3HP was associated with much higher treatment completion than 6H (90.4 vs 50.5%; risk ratio 1.78; 95% confidence interval [CI] 1.61–1.95) [58]. This trial did not find any advantage of repeated annual courses of 3HP in reducing TB incidence in high-transmission settings.

In a network meta-analysis of 63 trials of TPT among people with and without HIV, the odds ratios for risk of TB for patients treated with 4R, 3HR, 3HP, and 6H were 0.25, 0.33, 0.36, and 0.40, respectively, compared with no treatment [38]. For people living with HIV, a systematic review and network meta-analysis found that rifamycin regimens were safer and at least as effective as isoniazid monotherapy in preventing TB and death [59].

In another systematic review and meta-analysis of 175 papers from 277 cohorts reporting TPT-related adverse events in adults and children, all rifamycin-based short-course regimens were safer than IPT, with 4R having the

lowest rate of TPT-related adverse events overall and hepatotoxicity specifically [60].

3.1.2.3 Ultrashort Regimens An ultrashort regimen of 1-month daily rifapentine and isoniazid (1HP) was studied in the BRIEF TB trial and was shown to be noninferior to 9H for TB prevention in 3000 people living with HIV (50% on non-nucleoside reverse transcriptase inhibitor [NNRTI] ART) who had either TB infection or were living in a high-burden setting [61]. The TB incidence was 0.65% in the 1HP arm and 0.67% in the 9H arm. Furthermore, 1HP had superior completion rates (97% vs 90%) and was well tolerated, with few adverse events, including minimal hepatotoxicity and no hypersensitivity reactions.

3.1.2.4 Ongoing Trials Several studies are under way to extend the indication for 3HP for pregnant people (DOLPHIN Moms), and 1HP is being studied in people without HIV (NCT05118490, NCT04703075). A new pan-TB TPT using 4 weeks of oral bedaquiline is being studied in the BREACH-TB trial. These trials will help to expand the indication for short-course regimens for the prevention of TB.

3.1.2.5 Drug–Drug Interactions Between Rifamycins and Antiretrovirals Drug–drug interactions (DDIs) between the rifamycins, including rifampicin and rifapentine, and antiretrovirals are common. Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI) plus the two nucleoside reverse transcriptase inhibitors, tenofovir disoproxil fumarate and lamivudine (or "TLD"), are the most-used ART combinations in high-burden settings for HIV and TB. The WHO recommends TLD as first-line therapy. Biktarvy (tenofovir alafenamide [TAF], emtricitabine, and bictegravir) is a common choice in many settings. The INSIGHT trial is evaluating the safety and virologic efficacy of Biktarvy twice daily with first-line TB therapy versus TLD with an evening dose of DTG. Early results suggest that the two regimens have similar efficacy [62]. Efavirenz, an NNRTI that can be used without dose adjustment with all TPT regimens, is generally reserved for second-line treatment for those who cannot take INSTIs. 3HP is currently recommended in virally suppressed patients receiving DTG, without dose adjustments [63], but recent data suggest it is also effective when started concurrently with once-daily DTG-based ART [64]. Recent data suggest that 1HP with standard-dose TLD is well tolerated and achieves high rates of virological suppression [65]. 3HR and 4R can be used with DTG; current guidelines recommend increasing the dose from 50 mg once daily to 50 mg twice daily during the TPT course [66]. Recent results from the RADIANT-TB randomized trial suggest that DTG once daily provides similar virological activity as DTG twice daily with rifampicin-based TB therapy [67], and the global community awaits WHO guidance to support this dosing strategy. Nucleoside reverse transcriptase inhibitors can largely be used with rifampicin or rifapentine without dose adjustment; clinical data for TAF with rifamycins are limited, but concentrations of tenofovir diphosphate, the active form of the drug, at the site of action following dosing of TAF with rifampicin surpass those achieved with tenofovir disoproxil fumarate given alone, so these combinations (rifamycins with TAF) can be used, with caution [68].

3.1.3 MDR Prevention

In the absence of high-quality evidence, in 2014 the WHO recommended close clinical monitoring for 2 years and no TPT for those exposed to MDR-TB, pre-extensively drug-resistant TB, and extensively drug-resistant TB. In 2017, the WHO updated the guidelines to recommend the use of moxifloxacin or levofloxacin, based on a systematic review and meta-analysis of observational studies that assessed various regimens, including fluoroquinolones. As observational studies identified that fluoroquinolones have benefit in reducing the incidence of TB among those exposed to MDR-TB, two randomized clinical trials were conducted. The VQUIN trial enrolled 2041 household contacts exposed to RR/MDR-TB in Vietnam and compared 6 months of daily levofloxacin versus placebo; the median age was 40 years, and 2.9% were aged < 15 years. The TB CHAMP trial enrolled children, 90% of whom were aged < 6 years, in South Africa, and compared daily levofloxacin with placebo. Both trials observed an efficacy signal; however, incidence rates were lower than expected: the observed efficacy for VQUIN and TB CHAMP was an incidence rate ratio of 0.51 (95% CI 0.18–1.47, $p = 0.21$), and hazard ratio of 0.44 (95% CI 0.15–1.25, $p = 0.121$), respectively. In anticipation of a reduced TB incidence, a pre-specified individual patient meta-analysis combining data from both trials showed an efficacy of 60% over 1 year (hazard ratio 0.40; 95% CI 0.17–0.90) and that levofloxacin was safe overall. In children, there was no indication of tendonitis, arthralgia, or arthritis. However, adults exhibited a higher risk of tendonitis, arthralgia, and arthritis and more treatment discontinuation due to levofloxacin. Based on these results, the WHO released updated 2024 TPT guidelines to recommend levofloxacin for MDR-TB-exposed household and close contacts. The PHOENIx MDR-TB trial (NCT03568383) is an ongoing phase III trial studying 6 months of daily delamanid versus isoniazid

among adult and child household contacts for MDR-TB prophylaxis, the results of which are anticipated in 2027.

3.2 Pediatric TPT

3.2.1 Current Recommended Regimens

The same regimens available for adults are available for children, including the 3HP, 3RH, 4R, and 6-9H regimens. The 3HP regimen has been limited to children aged ≥ 2 years who weigh at least 10 kg. The 1HP regimen has proven effective in adolescents and adults with HIV aged ≥ 13 years, and a study in children in Pakistan found it safe and effective [69]. IMPAACT 2024 will assess the pharmacokinetics, safety, and tolerability of 1HP in children aged ≤ 12 years.

3.2.2 Evidence for efficacy, safety, and tolerability

Isoniazid monotherapy was the mainstay of TB prevention for children exposed to drug-susceptible TB for decades. Meta-analyses have shown that IPT reduces the risk of developing TB disease by over 60% in children [41, 70]. In this population, effectiveness is as high as 90% when analysis is restricted to the adherent population [71]. The long duration and concerns over hepatotoxicity have reduced the uptake of IPT. Hepatotoxicity is rare in children, occurring in only 1% of children who receive IPT, and is fully reversible if identified early. The relative lack of DDIs makes this an attractive option for patients on medications that interact with rifampicin.

The 3HP regimen has been shown to be noninferior to 9H in children aged ≥ 2 years with and without HIV [54, 56, 57]. Completion rates have been high in clinical trials that used directly observed therapy and in programmatic settings that used self-administered treatment [38, 72, 73]. 3HP is well tolerated in children, with lower rates of adverse events than with 9H and than in adults taking 3HP.

The 3RH regimen is safe and widely used in many settings given the presence of a fixed-dose, dispersible formulation that is already procured in many countries for the continuation phase of TB treatment. Among children and adults without HIV, this regimen has efficacy, hepatotoxicity, and adverse events leading to treatment discontinuation similar to those with 6H. Important and less severe side effects include rash and gastrointestinal intolerance. Although 3RH was not studied in children living with HIV, it is anticipated to be effective in this population as long as drug interactions are considered.

The 4R regimen also has noninferior efficacy, an improved safety profile, and higher rates of treatment completion than 9H [52, 72, 74]. Although it has not been studied in children living with HIV, there is no reason to believe this regimen would be any less effective in this population, although DDIs would need to be considered. Drug-induced hepatitis remains the most common severe adverse event, but it is rare and only occurs in 0–2% of children [74]. Common minor side effects include rash and gastrointestinal intolerance. Rifampicin results in temporary orange-red discoloration of bodily fluids, including saliva, urine, sweat, and tears, but this is not problematic.

3.2.3 DDIs

DDIs with rifamycins, particularly with ART, may limit the use of short-course rifamycin-based regimens in some children. Rifampicin has significant drug interactions with antiretroviral agents, including INSTIs, protease inhibitors, and some NNRTIs, including nevirapine. Importantly, this limits the use of rifampicin and rifapentine among both children with HIV and HIV-exposed, uninfected children who remain on nevirapine prophylaxis [75]. Twice-daily dolutegravir was safe and sufficient to overcome the enzyme-inducing effect of daily rifampicin (3RH, 4R) for children with HIV and TB disease [76]. Ongoing studies will assess the appropriateness of once-daily DTG with 3HP and 1HP in children. DOLPHIN Kids (NCT05122767) is assessing once- versus twice-daily DTG with weekly rifapentine as part of the 3HP regimen, and IMPAACT 2024 will assess the drug interactions between daily rifapentine and DTG.

3.2.4 Pyridoxine

Peripheral neuropathy is a known complication of isoniazid caused by a vitamin B_6 deficiency that can be prevented using pyridoxine (vitamin B_6). Use of pyridoxine can be limited to high-risk populations, including exclusively breastfed infants, children with malnutrition, and children living with HIV. Dosing is pragmatic and includes 12.5 mg for children weighing < 25 kg and 25 mg for children weighing ≥ 25 kg [77].

3.2.5 Palatability, Formulations, and Administration to Children

Acceptability of TPT varies by age. Key drivers of TPT acceptability in children are the number, size, and taste of the pills, and side effects; in adolescents, key drivers are clinic waiting times and side effects [78]. Clinical trials and programmatic studies have shown that short-course rifamycin-based TPT regimens are associated with higher completion rates [57, 72, 74].

Implementation of 3HP in children has been hindered by the lack of child-friendly formulations and the lack of dosing for children aged < 2 years. A new 150 mg dispersible tablet with functional scoring is now available on the

market. 3HP dosing for children aged < 2 years will soon be available from TBTC Study 35. Dispersible rifapentine will be co-packaged with isoniazid to help reduce supply chain concerns and ensure drug availability at the decentralized clinics where TPT is dispensed. Whether parents prefer daily medicines with smaller pill burdens per dose or weekly regimens with larger pill burdens per dose but overall fewer pills remains to be seen.

Isoniazid and rifampicin are co-formulated in a dispersible tablet that can be used for TPT or the continuation phase of TB treatment. This formulation lowers the daily pill burden and eases supply chain concerns at the national and clinic level. Although the tablet is dispersible, some families have found it difficult and time consuming to disperse the medication in water and administer it to their child, limiting the family's ability to easily incorporate TPT into their daily routines [79].

There is not currently a child-friendly formulation of rifampicin without isoniazid. Rifampicin can be made into a suspension, but this is often not possible at decentralized clinics where TPT is dispensed. Moreover, the sorbitol component can make the suspension intolerable to some children.

Isoniazid can be obtained in 100 mg tablets that are functionally scored. Both dispersible and non-dispersible tablets exist. Available isoniazid solutions contain sorbitol, which causes significant stomach upset in most children. Due to its long duration, this regimen is rarely used, except when rifamycin allergy, intolerance, or drug interaction prohibits its use.

3.3 TPT in Pregnancy

Large cohort studies demonstrate an approximately two-fold increased risk of TB during pregnancy and early postpartum compared with non-pregnant individuals [80]. The reason for this increased risk is unclear, but a combination of pregnancy-mediated immune changes, including suppression of T-cell immune function [81] and masking of typical TB symptoms [82] during pregnancy, may lead to delays in diagnosis. TB during pregnancy is associated with poor maternal and infant outcomes [83, 84].

Of the currently available regimens for TPT, only 6H, 9H, 4R, and 3HR are recommended in pregnancy [85–87]. Some experts favor rifampicin over isoniazid because of concerns regarding an increased risk of hepatotoxicity during pregnancy and the early postpartum period with isoniazid [88, 89]. However, rifampicin, like many rifamycins, has a long list of DDIs, including with antiretroviral drugs (e.g. integrase inhibitors and protease inhibitors). Therefore, there is not a strong evidence base for TPT during pregnancy. Data for newer TPT regimens (e.g. 3HP, 1HP) in pregnancy are also sparse. Currently, for pregnant people with HIV, isoniazid is still recommended by both the WHO and US HIV treatment guidelines [86, 87].

3.3.1 Studies of TPT in Pregnancy

Only two randomized trials have directly evaluated TPT regimens in pregnant people: TB APPRISE and IMPAACT 2001. TB APPRISE (IMPAACT 1078) randomized pregnant people with HIV to receive 6H either during pregnancy or deferred until 12 weeks after delivery [90]. Participant adverse events were similar between arms. However, a higher rate of composite adverse pregnancy outcomes (including stillbirth or spontaneous abortion, low birth weight, preterm delivery, or congenital anomalies) was experienced among participants randomized to isoniazid during pregnancy and their infants. Similarly, in secondary analyses of BRIEF TB (evaluating 1HP and 9H in people living with HIV), isoniazid exposure in the first trimester in the 9H arm was associated with an increase in composite adverse pregnancy outcomes [91]. No pregnancies occurred in the 1HP arm. The conclusions of TB APPRISE and the BRIEF TB secondary analysis contrast with those from observational studies of pregnant people living with HIV in South Africa [83, 92]. In these studies, isoniazid given for TPT was not associated with an increased risk of adverse pregnancy outcomes. A secondary analysis of participants enrolled in the BOTUSA trial (evaluating 36 months of isoniazid vs 6H for people living with HIV in Botswana) also found that isoniazid exposure during pregnancy did not appear to be associated with increased adverse pregnancy outcomes [93]. Unsurprisingly, a recent systematic review concluded that the relationship between isoniazid and adverse pregnancy outcomes and hepatotoxicity is inconsistent and that more data are needed [94].

IMPAACT 2001 evaluated the pharmacokinetics and safety of 3HP during pregnancy in participants with and without HIV [95]. All people living with HIV were required to be on efavirenz-based ART. The study found that rifapentine clearance was higher in pregnant women with HIV than in women without HIV. However, since target rifapentine and isoniazid exposures were still met, dose adjustment for pregnancy was not required. Although the study was not powered for safety, it did not identify any major safety-related concerns in participants or their infants. A secondary analysis of the WHIP3TB trial, which compared 3HP once or annually, showed that composite pregnancy outcomes (spontaneous abortion and adverse pregnancy outcomes) were similar in 3HP exposed and unexposed women [58, 96].

Neither 3HP nor 1HP are currently recommended in pregnancy because trial data are limited. The DOLPHIN Moms trial is evaluating the safety and pharmacokinetics of these regimens in pregnant people with HIV on dolutegravir-based

ART (NCT05122026) [97]. The study will also determine whether dolutegravir must be given twice daily with these regimens to ensure adequate DTG levels in the setting of rifapentine co-administration and pregnancy.

3.3.2 Lactation and Breastfeeding

Isoniazid and rifampicin are excreted in low concentrations in breastmilk. Like in other body fluids, rifamycins can cause orange color changes to breastmilk. These low levels are considered neither toxic nor therapeutic for the infants [98].

3.3.3 MDR Prevention in Pregnant People

Pregnant people are not currently included in the 2024 WHO rapid update recommending 6 months of levofloxacin as TPT for contacts of patients with MDR/RR-TB [99]. The PHOENIx MDR-TB trial is studying 6 months of daily delamanid versus isoniazid and will follow people who become pregnant while taking delamanid and therefore will inform first-trimester exposure (NCT03568383). The BREACH-TB trial will evaluate a 4-week regimen of bedaquiline as TPT for both drug-resistant and drug-susceptible TB and plans to include pregnant people (https://tbcenter.jhu.edu/wp-content/uploads/2024/02/BREACH-TB-Study-Overview.pdf).

3.3.4 Timing of TPT in Pregnancy

In the setting of recent TB exposure or recent conversion of TB infection tests, TPT should not be delayed during pregnancy, regardless of gestational age [85, 86]. Pregnant people have a high risk of progression to TB disease after recent exposure. In low-burden settings and without a recent known TB contact, TPT may sometimes be delayed until 2–3 months postpartum, although close follow-up should be provided. In the USA, this recommendation is extended to pregnant people living with HIV without a recent contact or TB infection test conversion. In high-burden settings, the WHO recommends TPT be given to pregnant people living with HIV and not be delayed regardless of recent contact, given that deferral may lead to a missed opportunity for TB prevention during a time of potential increased risk for the pregnant person and the fetus.

3.4 Risk of Resistance

The concern that TPT may generate resistant TB is commonly cited as a barrier to scaling up TPT. However, there is no convincing evidence that TPT with isoniazid-, rifapentine-, or levofloxacin-based regimens generates resistance if TB disease is excluded before starting TPT [100, 101]. Among people who develop TB during or after taking TPT, the proportion of drug-resistant cases is likely to be higher than in those who did not receive TPT, as TPT may not effectively treat resistant strains. It is more likely that poor adherence to treatment of TB disease generates resistance. People taking TPT should have regular follow-up to rapidly identify incident cases of TB and should undergo drug-susceptibility testing to tailor treatment accordingly [102]. In countries implementing TPT, national surveillance systems for drug resistance should be strengthened.

4 Delivery of TB-Preventive Treatment: Barriers and Enablers

Despite WHO guidelines for TPT being available since 1991 [103], the scale up of TPT was initially slow globally. Removing the need for a test of infection before starting people living with HIV on TPT only resulted in a modest increase in TPT scale-up [104]. A reduction in the price of rifapentine and the development of fixed-dose and child-friendly formulations contributed to the adoption of short-course, rifapentine-based TPT in national guidelines for people living with HIV and household contacts. Updated WHO guidelines, advocacy, and the UNHLM on TB in 2018 shifted policy and increased scale-up of TPT for people living with HIV globally but minimally for child and other household contacts. The US President's Emergency Plan for AIDS Relief included TPT as a performance indicator, and other funders tied funding to TPT provision and reporting, which further contributed to TPT scale-up. Barriers and enablers to the scale up of TPT are shown in Fig. 2 and described specifically for people living with HIV and household contacts in the following sections.

4.1 Delivery of TPT to People Living with HIV

Despite recent advances, various health system and individual client-level barriers remain. The increased availability of TPT in clinics has not been sufficient to achieve the desired levels of provision. Without overcoming patient- and provider-related barriers to TPT delivery, the benefits of TPT will never be fully realized.

Healthcare worker concerns regarding TPT adverse effects, effectiveness, and assessing eligibility are important barriers to providing TPT to people living with HIV. These concerns include TPT-associated drug-induced liver injury, especially among individuals who may have additional liver injury risks, such as alcohol use; providing TPT to a client with unrecognized TB disease and generating resistance; hesitancy of clients to accept or adhere to taking TPT; and addressing competing clinical priorities during (often) short encounters in busy clinic settings [107–114].

Efforts to overcome these clinic-level barriers and increase TPT provision include added training for clinic

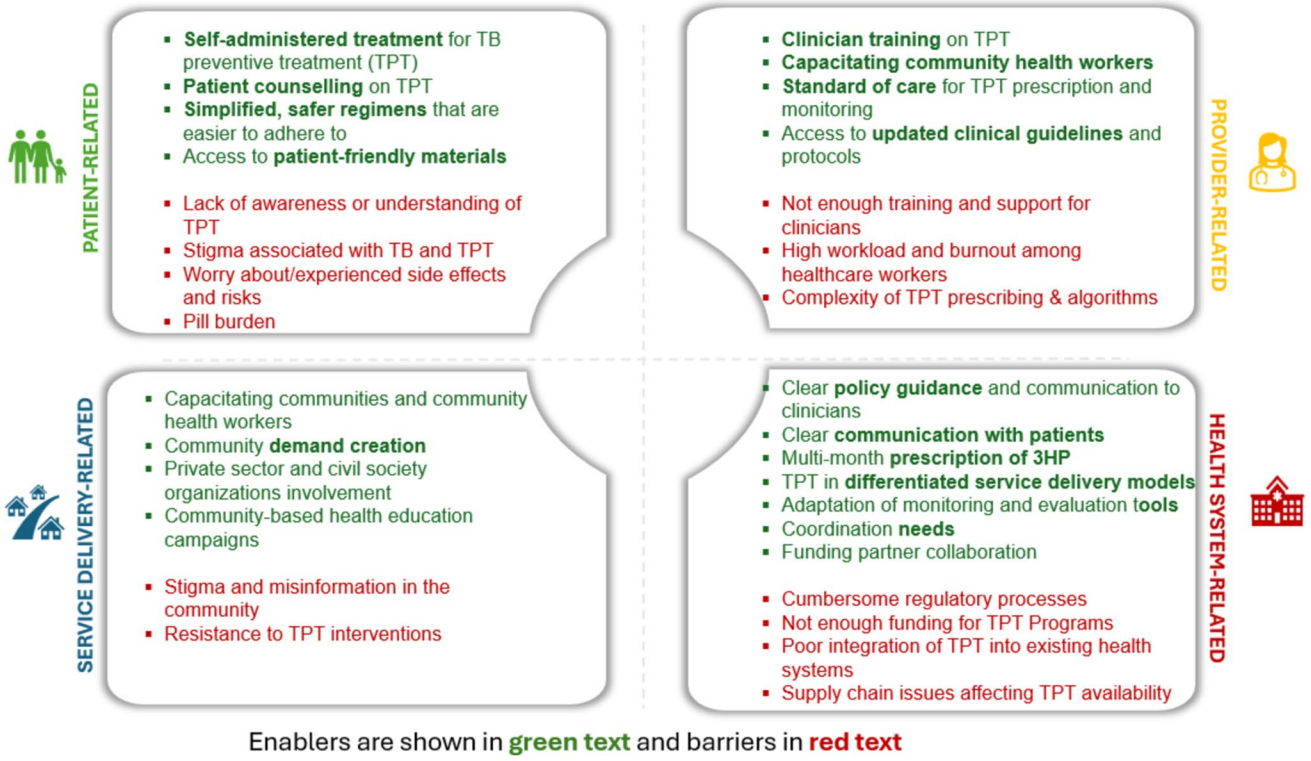

Fig. 2 Barriers and enablers for tuberculosis (TB) preventive treatment (TPT) implementation [105, 106]

managers and staff, standardizing TPT eligibility screening, quality improvement projects, and choice architecture approaches that make TPT the default choice (or opt-out choice) for people living with HIV initiating ART (supported by electronic or paper-based systems) [115–122]. Success with these approaches has been mixed, with ongoing concerns about missing diagnosis of TB disease a remaining barrier. Ameliorating these concerns with added reports of the consequences (minimal generally) of TB diagnosis after TPT initiation may help to shift health program and clinician concerns.

Patient-related barriers to TPT uptake and completion are a further impediment to maximizing TPT benefit. Added pill burden, perceived and real TPT side effects, fears of severe adverse reactions, TB-related stigma, and user fees or medication charges all contribute to hesitancy to initiate or complete treatment [123–126]. The quality and delivery of counseling and demand creation at the clinic level may be further impediments.

Efforts to overcome these client-level barriers include eliminating user fees payment for TPT medications, shorter and better tolerated TPT regimens, and health communication to improve understanding of the risk-benefit balance.

Novel community-based approaches to TPT delivery may help overcome some clinic and client barriers to TPT delivery for people living with HIV. In the DO-ART trial, IPT delivery was embedded in ART delivery models of care in South Africa. Initiation and continuation of IPT were 4.5- and 2-fold higher with community versus clinic-based ART delivery [127].

4.2 Delivery of TPT to Household Contacts

Traditionally, contact investigation and management of child contacts has occurred in facilities. People living with TB are asked to bring their household members to the clinic for evaluation and treatment. Time, cost of transportation, lost income, stigma, absence of symptoms, fear of long waits, and fear of exposures to TB and other infectious diseases often prevent household members from going to the clinic for evaluation. Despite decades of recommendation, in 2019 only one-third of household contacts aged < 5 years are initiated on TPT, improving to 55% in 2022 [1]. Similarly, data from a systematic review of evidence for child contact management in high-burden settings in Africa, Southeast Asia, and South America suggested that, although TPT initiation rates in some countries are high, 38% of the countries included had rates < 50% [128].

Simple reminders and the use of community health workers to encourage household members to seek facility-based care have been used with some success [129–132]. Community-based models of care may help alleviate many of these

barriers and are increasingly being studied for contact investigation and management. TB symptom screening and sputum collection are already accomplished through integrated community-based approaches and are sometimes followed by clinic referral for TPT services. These hybrid approaches have been effective at identifying more contacts; 50% more child contacts are identified with a community-based versus facility-based approach [133]. When integrated into existing community-based services, only a modest increase in cost would be expected [134]. Multiple cohort studies and trials of community-based TPT initiation in the Gambia, eSwatini, Cameroon, Uganda, South Africa, and Ethiopia have all demonstrated high acceptability and TPT completion [135–138]. Moreover, TPT initiation and follow-up has been shown to be safe and effective when conducted by both nurses and community health workers [138, 139]. Community-based models of care may be one option to improve TPT uptake and completion among household child contacts. Most of these approaches would also be effective in improving TPT uptake and completion among adolescent and adult household contacts. A community-randomized trial in Brazil showed that incorporating TPT for contacts into the DOTS program resulted in a significant reduction of TB incidence in the community over 5 years [140].

4.3 Delivery of TPT to High-Burden Communities

The WHO does not currently recommend community-wide TPT for high-burden communities because this approach is deemed to be infeasible and costly and because of concerns of serious and potentially fatal side effects in people at low risk of TB [102]. However, community-wide TPT has been implemented in high-burden settings and serves as a model of delivering TPT at scale. Community-wide IPT was first implemented among Alaskan Natives living in the Bethel district, villages in Greenland, and housing blocks in Tunisia and showed modest to large effects in reducing the incidence of TB at a population level [40, 141–143]. In gold mining communities with a high force of TB infection coupled with high rates of HIV infection and exposure to silica dust, community-wide screening for TB disease simultaneously linked to IPT or TB treatment did not reduce TB incidence or prevalence at a population level; however, TB incidence at the individual level was reduced by 58% while on 9 months of IPT [144]. Modeling suggests that a combination of strategies, including improved rapid diagnostics and effective preventive treatment regimens in addition to strengthening health systems and ensuring high uptake of ART, was needed to achieve population-level impact [145]. School-wide implementation of TPT among Tibetan refugee school children reduced the risk of TB infection and disease among the children and adolescents [146]. Community-wide TPT has also been implemented in the Marshal Islands and Kiribati [147, 148].

5 Cost Effectiveness of TPT Regimens

In addition to the individual-level benefits of TPT preventing disease and death, TPT may also reduce downstream TB treatment costs to both health systems and households by preventing future TB cases and averting transmission. Published studies, including those that did not account for averted future transmission benefits, overwhelmingly indicated that TPT is likely to be cost effective and impactful among people living with HIV [21, 149, 150] and both child and adult household contacts [15, 151] of people recently diagnosed with TB (including contacts of patients with rifampicin-resistant TB) [19, 152, 153]. There is less evidence, particularly from high-burden settings, on the cost effectiveness of TPT for other high-risk groups who may benefit from TPT, such as healthcare workers, incarcerated populations, people with diabetes, homeless individuals, and non-household close contacts [149, 154–157].

Short-course regimens are likely to be cost effective (at current prices) compared with longer IPT. However, the cost effectiveness may vary based on factors such as the choice of short-course regimen (3HP, 1HP, 3HR, 4R), the modality for ruling out TB disease, and whether a test of infection is required to start TPT. Although model-based analyses can be used to explore these details, the available evidence limits the extent to which these questions can be answered in a modeling framework. Assessment of cost effectiveness would benefit from more implementation research and programmatic data [158] and evidence of patient and clinician preferences (e.g., prioritization between regimen characteristics, such as duration, dosing frequency, and side effect profile) [159].

6 Novel Tests of Infection and TPT Regimens

Recent advances in diagnostics and TPT regimens and formulations will contribute to the scale up and impact of TPT. However, further innovation is still required to develop better tests of TB infection and safer, shorter, more effective TPT regimens that are programmatically easier to implement and are scalable and to provide more options for programs and patients. To guide the development of novel tests of infection and TPT regimens, the WHO has issued target product profiles for each.

Table 2 Attributes for developing novel tuberculosis preventive treatment (TPT) regimens

Attributes	
Priority	Minimum and optimal criteria are defined for priority attributes that include efficacy, duration of treatment, safety and tolerability, drug–drug interactions, barrier to the emergence of resistance, target population, formulation, dosage, frequency and route of administration, stability and shelf life
Desirable	Desirable attributes, such as cost of regimen, special populations, treatment adherence and completion, and drug susceptibility of index patients, may be traded off against priority attributes
Cross-cutting	TPT should be extremely safe, including in vulnerable groups New TPT regimens should be useable in all settings, including whether or not the drug susceptibility of the infection strain is known Self-administered treatment is desirable. Strategies to support adherence should be developed and long-acting formulations considered Only clinical monitoring for TB disease, adverse events and drug–drug interactions should be required Health equity, access and scalability are essential considerations. Consideration should be given to factors associated with implementation

6.1 Target Product Profiles for TPT Regimens

The WHO target product profile for TPT regimens identifies priority, desirable, and cross-cutting attributes of novel TPT regimens (see Table 2) [160, 161]. Minimum and optimal requirements are defined for priority attributes. The minimum requirements should be met for all priority attributes, whereas trade-offs can be made between priority and desirable attributes, for example, a potent, efficacious regimen that has a high pill count may be acceptable. Cross-cutting aspects should be considered for all potential regimens. Optimal oral TPT regimens should be indicated for all individuals and age groups, be safe and efficacious, have no or few drug–drug interactions, be self-administered, and be simple to implement, including in decentralized settings. Modeling suggests that efficacy and ease of adherence were the priority attributes of a new TPT regimen that are most likely to have the largest population-level impact [161]. Scaling up TPT regimens meeting the optimal attributes can contribute substantially to TB control, but the epidemiological impact

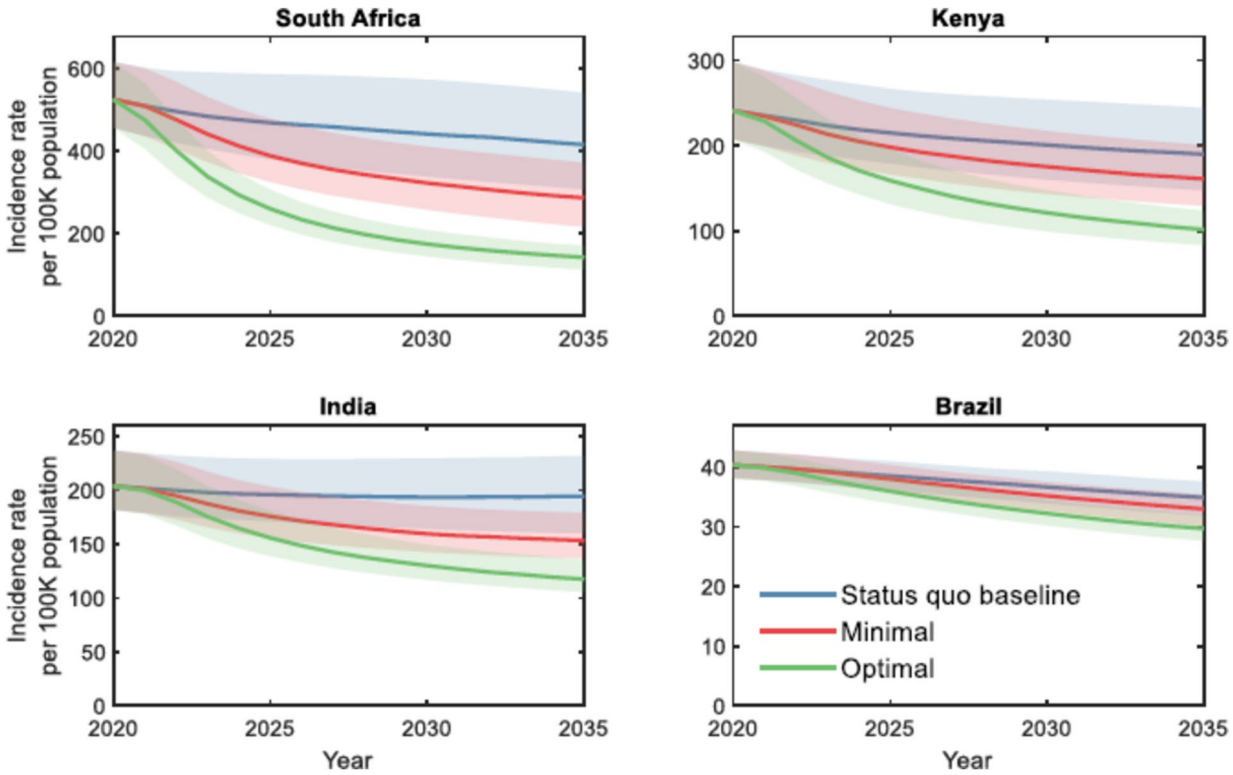

Fig. 3 Modelled impact of future tuberculosis (TB) preventive regimens scaled up to people living with HIV and household contacts [161]

varies widely by country according to the proportion of TB that is attributable to reactivation versus recent transmission (Fig. 3) [162]. Furthermore, modeling suggests that scaling up a novel TPT regimen would be cost effective in most settings, as the savings from TB cases averted would offset the cost of scaling up a new TPT regimen [161].

6.2 Long-Acting Formulations

Certain drugs have physicochemical properties that enable the development of long-acting and extended-release formulations that may allow less frequent dosing, thereby improving patient convenience, adherence, and treatment completion rates. Long-acting formulations would simplify TPT regimens and reduce the burden on health programs.

Diarylquinolines have physicochemical properties that allow them to be formulated as long-acting injectables. Bedaquiline is a potent sterilizing drug that is used in short-course treatment of MDR-TB and is being evaluated in novel short-course regimens for drug-susceptible TB. A long-acting injectable formulation of bedaquiline has demonstrated activity for up to 12 weeks in a validated mouse model [163, 164]. One or more doses of long-acting bedaquiline with or without a 2-week oral course of bedaquiline alone or with rifapentine could substantially reduce treatment duration and improve adherence [163]. A phase I trial of a human formulation of long-acting bedaquiline injectable has recently begun (EUCT:2023-508810-41-00).

A single intramuscular injection of a long-acting injectable formulation of a next-generation diarylquinoline (TBAJ-876 LAI) was highly efficacious in a validated paucibacillary mouse model of TB infection [165].

Rifapentine is a key drug in short- and ultra short-course TPT. Rifapentine also has properties that allow the drug to be formulated as a long-acting injectable. In a paucibacillary mouse model, various doses and dosing schedules of long-acting injectable rifapentine had similar efficacy as 1 month of daily oral isoniazid and rifapentine (1HP) [166]. Given the pharmacokinetic characteristics of long-acting injectable rifapentine, it may be possible to achieve efficacy similar to that of 1HP with a single injection of rifapentine.

Although isoniazid has a short half-life, it may be possible to develop a sustained-release injectable formulation of isoniazid using poly (DLlactide-co-glycolide) microparticles [167, 168]. Development of long-acting injectable formulations of both rifapentine and isoniazid may allow the two drugs to be administered together as an injectable version of 3HP or 1HP [168]. Development of new long-acting technologies, such as microneedle patches, may overcome some of the current challenges in developing long-acting injectable rifapentine and isoniazid.

Although long-acting injectable formulations hold great promise for TPT, they are not without concerns. Managing adverse effects when drugs are administered as long-acting injectables may be challenging. Some long-acting injectables of antiretroviral drugs require an oral lead in, which may not be possible with TPT when the duration of oral treatment may only be 1 month long [169]. The acceptability of long-acting injectable TPT regimens by patients requiring TPT is unknown. However, from a patient-centered perspective, it will be important to have options. It is likely that some patients may prefer long-acting injectables and others oral tablets [169].

6.3 Pan-TPT Regimens

A TPT regimen comprising novel drugs that are safe and effective against both drug-susceptible and drug-resistant TB infection could be used as a pan-TPT regimen. Such a regimen would be useful in settings with a high prevalence of drug-resistant TB and poor access to drug-susceptibility testing and would allow TPT to be started immediately, particularly in household contacts where the drug-susceptibility pattern of the index patient is not known.

A potent pan-TPT regimen that can be formulated as a long-acting injectable would meet many of the priority attributes of an optimal TPT regimen. Such a regimen would simplify programmatic implementation, reduce treatment duration, and improve adherence. Bedaquiline and TBAJ-876 given orally or as long-acting injectables could potentially be used as pan-TPT regimens. Long-acting formulations of pan-TPT regimens, particularly those that can be given as a single dose, could further increase the individual-level effectiveness and population-level impact of pan-TPT regimens.

6.4 Tests to Rule Out TB

The WHO currently recommends that the WHO 4 symptom screen, which can only detect symptomatic TB, should primarily be used to rule out TB. However, asymptomatic TB (previously called subclinical TB) is prevalent in people living with HIV, and household contacts and should be ruled out before starting TPT. The WHO also recommends the use of symptom-agnostic TB screening tests such as CXR, C-reactive protein, and WHO-approved molecular rapid diagnostic tests to rule out both clinical and asymptomatic TB before starting TPT. Better tests to rule out both clinical and subclinical TB before starting TPT are required.

6.5 Tests to Select the Appropriate TPT Regimen for Household Contacts

To select the appropriate TPT regimen for contacts living in a TB-affected household, a rapid molecular test should be used to determine the drug-susceptibility pattern of

the index patient with TB. A molecular test for at least rifampicin should be available but may also include tests for isoniazid and fluoroquinolone resistance if resistance is suspected. Better tests to select the appropriate TPT regimen for household contacts is required.

6.6 Tests of Infection

There is no gold standard for diagnosing TB infection. The current tests of infection (TST, IGRAs, skin tests) cannot distinguish between current and past infection, and all have a low predictive value for identifying those at greatest risk of progressing to TB disease and are poor at determining response to treatment [3]. Developing novel tests that can distinguish between current and past TB infection is a high priority. Better predictive tests that would allow treatment to be targeted to those who would benefit most from TPT would reduce the numbers needed to treat to prevent a case of TB.

Tests of host response can only identify current or past TB infection, and molecular tests for TB antigen, such as lipoarabinomannan or DNA, can only identify the presence of antigen and not whether mycobacteria are viable. Host response tests using *M. tuberculosis*-specific T-cell activation markers, such as the ΔHLA-DR biomarker and CD38-based TAM-TB test, may be able to detect T cells that are actively responding to viable *M. tuberculosis* infection and distinguish between current and past infection [170, 171]. In contrast, tests that identify ongoing pathological processes using transcriptional signatures, such as the Cepheid 3-gene blood test and RISK11 biomarker, may identify individuals at high risk of progressing to clinical TB disease [172, 173]. To provide guidance to developers of tests that will predict progression to TB disease, the WHO published target product profiles with minimal and optimal characteristics [160].

7 Conclusion

Over the past decade, there have been major advances in developing new tests of infection, including those that predict progression to TB disease, and new, shorter, safer TPT regimens. New formulations of rifapentine-based TPT have been developed, and the price of these regimens has been radically reduced through market-shaping interventions. Implementing TPT is cost effective, and global scale-up can contribute to ending the TB epidemic. Setting targets for scale up of TPT in people living with HIV and child and other household contacts as part of the UNHLM on TB catalyzed the global scale up of TPT, particularly for people living with HIV. Substantial gaps exist in scaling up TPT for child and other household contacts. Addressing barriers to TPT delivery is required to support TPT scale-up. Further innovation is required to develop even shorter and safer regimens.

Declarations

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Ethics approval Not applicable. The manuscript is a review and does not report results of a study that involved human participants, their data, or biological material.

Consent for publication Not applicable. The manuscript does not contain identifiable patient data.

Consent for publication Not applicable. The article does not contain clinical photos of patients or patient data that could be identifiable.

Author contributions VC and GC conceptualized and designed the outline of the paper. All authors (VC, MG, AG, NSA, TR, CJM, SL, JSM, VM, KED, REC, GC) contributed to specific sections of the manuscript and reviewed the paper. All authors read and approved the final version.

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