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VIEWPOINTS

Preventing Multidrug-Resistant Tuberculosis: The Dawn of a New Era

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Multidrug-resistant tuberculosis (MDR-TB) remains a global health threat and accounts for a quarter of deaths due to antimicrobial resistance. Individuals infected with MDR-TB are at risk of progressing to TB disease. Treatment of drug-resistant TB infection to prevent progression to disease and avert the associated morbidity and mortality is a global priority. Randomized evidence to inform TB preventive treatment (TPT) guidelines has been lacking. Two recently completed trials provide the first randomized evidence that treatment of household contacts exposed to people with MDR-TB with daily levofloxacin for 6 months is safe and efficacious in preventing TB. Based on these results, the World Health Organization updated its TPT guidelines to make a strong recommendation for use of levofloxacin for 6 months in MDR-TB exposed contacts. Novel, shorter regimens in development will usher in a new era for the treatment of MDR-TB infection if shown to be safe and efficacious.

Keywords. tuberculosis infection; preventive treatment; levofloxacin; delamanid; bedaquiline.

Tuberculosis (TB) is an ancient disease that has caused more deaths globally than any other infectious agent in human history, despite being curable and preventable since the 1950s. To accelerate progress toward ending the TB epidemic, the United Nations (UN) High-Level meeting on TB in 2018 prioritized scaling up effective interventions and set bold targets for implementation; at the 2023 UN high-level meeting, there was a renewed call to action to scale up TB preventive treatment (TPT) [1].

Global Burden of Multidrug-Resistant/Rifampicin-Resistant (RR) Tuberculosis Disease and Infection

Antimicrobial resistance is an important global health threat; multidrug-resistant (MDR) TB, which is resistant to two of the primary antituberculosis drugs, rifampin and isoniazid, accounting for a quarter of all deaths attributed to antimicrobial-resistant infections [2]. In 2023, the World Health Organization (WHO) estimated that there were 400 000 MDR/RR-TB cases, only 43% of whom were started on appropriate treatment [3].

Recent evidence suggests that a high proportion of MDR/RR-TB is acquired through recent transmission and infection rather than acquired during treatment of drug-susceptible TB [3, 4]. Mathematical modeling estimates that the global prevalence of MDR-TB infection was 0.3%, accounting for 19.1 million people infected with MDR-TB [5].The prevalence of MDR-TB infection varies widely across WHO regions with the European, Western Pacific, African, and Southeast Asia regions having the highest burden [5]. Compared with adults, children have a greater risk of progressing to TB disease if exposed and infected and are less likely to be diagnosed with MDR-TB disease [6, 7]. Modeling suggests that the prevalence of MDR-TB infection is increasing in all regions, particularly among children [5]. The rising burden of MDR-TB infection is concerning due to the human toll in unnecessary illness and death, as well as undermining the End TB Strategy. To end, the MDR-TB epidemic requires finding MDR-TB, through active case finding, improving access to drug-susceptibility testing, and treating MDR-TB with effective regimens, in addition to using TPT.

Risk of Developing Multidrug-Resistant/RR Tuberculosis Among Close Contacts

Household and other close contacts of people with infectious pulmonary MDR/RR TB have a high probability of being exposed and becoming infected [8, 9]. In a systematic review of 25 studies of household contacts of people with MDR-TB in

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low-, middle-, and high-burden countries, the proportion of household contacts with TB disease or infection in high-burden countries was 8.7% (12 studies) and 52.5% (5 studies), respectively. For all studies, TB organisms from more than 50% of secondary TB cases with drug-susceptibility testing were concordant with those from the index people with TB; the majority of secondary cases were detected within a year of diagnosis of the adult index patient [8]. In a recent systematic review, the pooled concordance for isoniazid and rifampicin resistance only between index and secondary cases within MDR-TB exposed households was 54.3% overall and 82.6% for isoniazid and rifampicin resistance only [10]. Children not yet of school-going age have close contact with adults in the home (particularly parents or other caregivers) and are at particularly high risk of exposure compared with other household contacts. In addition, the risk of progressing to active TB once infected is higher in children than in adults, particularly infants and very young children [11]. The number of adults diagnosed with MDR-TB has increased with the rollout of rapid molecular diagnostic tools and is associated with a commensurate increase in the numbers of child and adult household contacts (HHCs) identified [12].

A prospective observational study conducted in eight high TB burden countries showed that over three-quarters of household contacts of people with MDR/RR-TB were at high risk of progressing to TB disease [12, 13]. Risk factors for TB infection among household contacts >15 years old included living in poorer-quality homes, being highly exposed to the index patient, ever having been incarcerated, currently using substances or alcohol, or having COPD/asthma [13]. Over 1 year, a fifth of household contacts without evidence of infection at initial screening converted their test of TB infection to positive, which increased by age but not with HIV-positive status [6]. Furthermore, only 5% of high-risk household contacts had taken TPT, underscoring the enormous need for novel therapies and TPT scale up among this very high-risk population [6]. A high proportion (79%) of high-risk household contacts were willing to participate in a TB preventive therapy trial [14].

Emerging Evidence for Treating Multidrug-Resistant/RR Tuberculosis Infection

There is a substantial body of observational evidence that treatment of close contacts of people with MDR-TB reduces the risk of developing active TB disease [15, 16]. Different regimens have been used to treat close contacts with presumed MDR-TB infection, which include fluoroquinolones (levofloxacin, moxifloxacin, ciprofloxacin, ofloxacin), isoniazid (standard and high dose), ethionamide, ethambutol, and pyrazinamide [15, 16]. Historically, clinicians have tailored the TPT regimen based on the drug susceptibility pattern, when available, of the index people with MDR-TB, particularly when treating exposed children. Alternatively, a standardized, public health approach has been used with a fluoroquinolone (levofloxacin or moxifloxacin) with or without ethambutol or ethionamide.

A systematic review evaluated 21 papers on MDR TPT, 5 of which (3 prospective and 2 retrospective) compared treatment versus nontreatment outcomes [17]. The estimated reduction in risk of TB was 90%, but treatment discontinuation due to adverse events was high overall, particularly for pyrazinamide-based regimens [17]. A more recent systematic review and meta-analysis identified 11 studies (5 prospective and 6 retrospective) and found that TPT reduced the risk of TB, with variation by study type, age, and treatment strategy (standardized or individualized) [18]. Treatment completion rates were relatively high, and treatment limiting adverse effects were low [18]. In low TB incidence settings, TPT with a fluoroquinolone with or without ethambutol compared with no treatment was estimated to be cost-effective [19]. However, among index people with MDR-TB enrolled into an MDR TPT trial from 28 sites (13 countries) in Africa, Asia, Central, and South America, 20% (164/801) had fluoroquinolone resistance and hence has important implications for rolling out fluoroquinolone-based TPT in settings with a high prevalence of fluoroquinolone resistance [20].

The TB CHAMP [21] and VQUIN [22] trials recently evaluated the efficacy of levofloxacin given once daily for 6 months compared with placebo in preventing TB among adult and child household contacts exposed to MDR-TB. The TB CHAMP was conducted in South Africa and enrolled index people with MDR-TB; 922 child contacts were enrolled, and 91% were age <5 years. Follow–up time was censored at 54 weeks. Levofloxacin was very safe in child contacts. The proportion of participants who developed TB in the levofloxacin and placebo arms was 1.1% and 2.6% through 54 weeks, respectively (HR: 0.44; 95% CI: .15–1.25; $P = .121$) [21]. The VQUIN trial was conducted in Vietnam and enrolled index people with RR/MDR-TB; 2041 HHCs were enrolled, the median age was 40 years, and 2.9% were <15 years of age. Participants were followed for 30 months postentry.

Bacteriologically confirmed incident TB occurred among 0.6% of adult participants in the levofloxacin arm and 1.1% in the placebo arm through 30 months (IRR: 0.55; 95% CI: 0.19–1.62) [22]. No acquired resistance to levofloxacin was observed among those developing incident TB [22]. Almost a third of adult participants on levofloxacin reported adverse events, and ∼7% stopped treatment early, suggesting that low-grade symptoms may be a barrier to completing treatment.

The TB CHAMP and VQUIN trials shared several limitations, which were that the incidence of TB in the placebo group was lower than the assumed rate in the sample size calculation, and each trial was only conducted in a single country, thereby limiting generalizability. Transmission of MDR-TB in the household may have been reduced by the widespread roll out of XPERT MTB/RIF in South Africa, leading to earlier

detection, and initiation of treatment, which may render patients noninfectious sooner. A preplanned individual patient meta-analysis using data from both trials was conducted to provide a more precise estimate of effect. Levofloxacin was safe and significantly reduced the risk of TB (relative difference in cumulative incidence: 0.41 [95% CI: 0.18–0.92]) [23].

In children, there was no indication of tendinitis, arthralgia, and arthritis. In adults, there was a higher risk of tendinitis, arthralgia and arthritis and more treatment discontinuation due to levofloxacin, which increased with age.

Evolving Guidelines for Treating Multidrug-Resistant/RR Tuberculosis Infection

Tuberculosis preventive treatment for drug-susceptible TB infection is highly effective and is recommended by the WHO for people with HIV and all household contacts [24]. Guidelines for treating MDR/RR TB have evolved as new evidence has emerged. In 2018 and 2020, the WHO made a conditional recommendation for MDR/RR-TPT based on poor-quality evidence [24]. No specific regimen was recommended, but use of later generation fluoroquinolones (levofloxacin, moxifloxacin) with close clinical monitoring for adverse events while on treatment and for active TB for at least 2 years after MDR-TB exposure was advised [24]. The uptake and implementation of these guidelines have been poor [24]. The WHO identified the need for randomized controlled trials to generate quality evidence to inform MDR TPT guidelines and to evaluate the potential role of newer antituberculosis drugs. The WHO issued updated TPT guidelines in September 2024, which included a strong recommendation, with moderate certainty of the estimate of effects, to use 6 months of levofloxacin as TPT for contacts of all ages exposed to persons with MDR/RR-TB, based on the results of the TB CHAMP and VQUIN trials, taking into considerations their strengths and limitations and stakeholder input [24]. The updated WHO TPT guidelines further recommend that moxifloxacin may be used as an alternative if levofloxacin is not available, even though there are no trial data to support the use of moxifloxacin.

Novel Multidrug-Resistant Tuberculosis Preventive Treatment Regimens

Further innovation is required to develop alternative MDR TPT regimens that are safer, shorter, and more effective. Regimens that address fluroquinolone-resistant drug-resistant TB are also urgently needed as many low- and middle-income countries with a high incidence of MDR-TB have substantial resistance to fluroquinolones with some settings reporting more than 25% resistance [20, 25]. Novel MDR TPT regimens in development are discussed.

Long (6-Month) Tuberculosis Preventive Treatment Regimens

Delamanid is a dihydronitroimidazooxazole derivative that impairs mycolic acid synthesis of *Mycobacterium tuberculosis* (*M.tb*), and is active against drug-susceptible and drug-resistant TB and actively dividing and dormant *M.tb* [26]. In a phase III trial, delamanid was safe but did not contribute to an optimized background regimen in treating MDR-TB [27]. Delamanid has minimal drug–drug interactions, can be dosed as a single daily dose, and is available in child and infant formulations. In mouse studies, PA-824 (pretomanid), also a nitroimidazole, had comparable activity to isoniazid and levofloxacin in treating drug-susceptible TB infection [28]. Delamanid was selected for evaluation as an MDR TPT regimen as delamanid had shown potent anti-TB activity in mouse studies and the study team had access to delamanid donated by Otsuka [29]. A5300B/IP2003B/PHOENIx is a cluster randomized trial that is evaluating the use of oral daily delamanid for 6 months versus oral daily isoniazid for 6 months (as an active control) for treating high-risk household contacts (children <5 years and household contacts 5 years or older and diagnosed with HIV or with non-HIV immunosuppression or have a positive test of TB infection) of adult people with MDR-TB (NCT03568383).

Isoniazid preventive treatment was selected as an active control arm after careful review of the epidemiological and ethical considerations. A proportion of MDR-TB-exposed household contacts may benefit from standard dose isoniazid treatment, particularly adolescents and adults, if infected with drug-susceptible TB acquired in the community, and if infected with MDR-TB with *inhA* mutations associated with low-level isoniazid resistance. Furthermore, providing isoniazid in the control arm would be assessed as equitable. The intriguing results from Huang et al [30] further support the justification to include an active isoniazid control arm. In a large cohort study of household contacts <19 years of age in Peru, household contacts exposed to index people with MDR-TB that received standard dose isoniazid preventive treatment had a lower risk of developing TB compared with those that were not treated [30]. The potential mechanism for the protective effect is not clear, but may include host immune modulation of isoniazid [30, 31]. Evidence from randomized controlled trials showing that isoniazid is effective in preventing TB in MDR-TB-exposed contacts will be required to inform global policy and practice. The results of Huang et al support the use of isoniazid as an active control arm in trials evaluating TPT regimens for presumed MDR/RR TB infection.

Recruitment into the A5300B/IP2003B/PHOENIx trial evaluating delamanid versus isoniazid for MDR TPT is complete. Although there is now a strong WHO recommendation for use of levofloxacin for MDR TPT, there is also clear justification for completing the PHOENIx and other ongoing trials of MDR TPT [24]. First, the adoption of the new MDR TPT guidelines and achieving high coverage is likely to occur slowly. Second, fluoroquinolone resistance is relatively high and levofloxacin may not be effective in preventing MDR-TB in people with fluoroquinolone-resistant TB infection [25], and the uptake

Table 1. Summary of MDR TPT Trials

	TB-CHAMP	V-QUIN	PHOENIX	BREACH-TB	TMC207TBC1006
TPT regimen evaluated	Levofloxacin (oral) daily for 6 m	Levofloxacin (oral) daily for 6 m	Delamanid (oral) daily for 6 m	Bedaquiline (oral) daily for 1 m	Bedaquiline long- acting injectable (intramuscular) given once
Dose	15 to 20 mg per kilogram. Maximum dose 750 mg/d	10 to 15 mg per kilogram for adults. Maximum dose 750 mg/d	Adults and children ≥30 kg: delamanid 200 mg/d Children ≥2.5 to <30 kg: weight-band dosing	>30 kg: 200 mg <30 kg: Weight-banded	Three doses being evaluated: 500, 1000, and 2000 mg
Trial phase	Phase III (completed)	Phase III (completed)	Phase III (ongoing)	Phase II/III (planned)	Phase I (ongoing)
Design	Superiority design	Superiority design	Superiority design	Noninferiority design	Descriptive
Target population	Child contacts, 91% were <5 y of age	TST-positive household contacts, 2.9% were <15 y of age	High-risk household contacts (children <5 y, or 5 y and older with HIV or TST/IGRAs positive	People with HIV and close contacts of all ages	Healthy people without HIV
Safety	No indication of tendinitis, arthralgia, and arthritis	Increased risk of tendinitis, arthralgia, arthritis, and more treatment discontinuation	Safety data not yet available	Not started	No results yet
Drug interactions	No interactions with antiretroviral therapy	No interactions with antiretroviral therapy	No major interactions with antiretroviral therapy	Avoid with CYP3A4 inducers (rifamycins, efavirenz). Can be used without dose adjustment with dolutegravir	Avoid with CYP3A4 inducers (rifamycins, efavirenz). Can be used without dose adjustment with dolutegravir

of molecular tests to rapidly diagnose fluoroquinolone resistance to guide treatment of persons with MDR-TB and exposed household contacts is limited. Third, in adults, low-grade adverse events were common. Fourth, the active control arm with isoniazid (INH) improves the ethical conditions of the study. All these reasons justify the continued development of alternative TPT regimens to levofloxacin. The results of the PHOENIx trial are anticipated in 2027.

Ultrashort Tuberculosis Preventive Treatment Regimens

Experience from TPT regimens for drug-susceptible TB suggests that short (3–4-month) and ultrashort (1-month) regimens are associated with better adherence and treatment completion rates [32, 33]. In the BRIEF TB trial, among people with HIV or with evidence of TB infection, the ultrashort-course TPT regimen of 1 month of isoniazid and rifapentine for drug-susceptible TB was noninferior to 9 months of isoniazid and had better safety profile and treatment completion [33]. Multidrug-resistant tuberculosis preventive treatment with levofloxacin or delamanid (if efficacious) requires 6 months of daily dosing, which is likely to have similar rates of adherence and treatment completion as 6 months of isoniazid. Effective ultrashort-course MDR TPT regimens are therefore desirable.

Bedaquiline is a potent sterilizing drug that is safe and active against drug-susceptible and drug-resistant TB and actively dividing and dormant *M.tb*. Bedaquiline is a key drug in short-course treatment of MDR-TB disease and is being evaluated in novel short-course regimens for drug-susceptible TB. In a validated paucibacillary mouse model, 1 month of daily oral bedaquiline was as effective as 1 month of daily isoniazid and rifapentine and achieved a greater reduction in $\log_{10}$ colony-forming units per lung than daily isoniazid and weekly isoniazid and rifapentine for treating drug-susceptible TB infection [34]. The BREACH-TB trial is planning to evaluate oral, daily, bedaquiline for 1 month in MDR/RR TB-exposed household contacts and people with HIV (BREACH-TB; NCT06568484).

Completed, ongoing, and planned trials of MDR TPT are summarized in Table 1.

Long-acting Injectable Tuberculosis Preventive Treatment Regimens

Some of the newer TB drugs have properties that may allow them to be developed as long-acting injectables (LAIs). Long-acting injectable TPT could potentially be a game changer for scaling up TPT by reducing pill burden and dosing frequency and improving adherence and treatment completion rates. Long-acting injectable formulations could potentially have an additional benefit in that they may be less affected by drug–drug interactions that induce first-pass hepatic metabolism [35]. Bedaquiline, a diarylquinoline, has been formulated as an LAI. In a validated mouse model, LAI bedaquiline has activity for up to 12 weeks [36, 37]. One or more doses of long-acting bedaquiline could substantially reduce treatment

duration and ensure treatment completion [36]. A phase I trial of LAI bedaquiline is currently in progress (EUCT:2023–508810-41-00). A next-generation diarylquinoline (TBAJ-876 LAI) has also been formulated as an LAI and shown to be highly efficacious in a validated paucibacillary mouse model of TB infection [38]. There appears to be high-level acceptance of LAI TPT regimens by patients and healthcare providers if shown to be safe and cost concerns are addressed [39]. Community engagement is, however, required to better understand values and preferences for LAI TPT.

Risk of Resistance

The risk of generating resistance is commonly cited as a barrier to scaling up TPT for drug-susceptible TB. Similar concerns have been expressed for MDR TPT. There is no convincing evidence from clinical trials that TPT with isoniazid, rifapentine, rifampicin, or levofloxacin is associated with an increased risk of developing resistance. Symptom agnostic screening to exclude asymptomatic TB prior to starting TPT would further reduce the risk of generating resistant TB. Potentially, the use of fluoroquinolones for TPT may also promote antimicrobial resistance in other bacteria. In countries where levofloxacin-based TPT is being implemented, surveillance systems for drug resistance to fluoroquinolones should be strengthened

Priority Attributes for Novel Tuberculosis Preventive Treatment Regimens

Priority attributes for novel TPT regimens have been described and 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 [40]. Mathematical modeling of priority attributes of novel TPT regimens suggests that efficacy (potency) and ease of adherence are the most important attributes required to achieve epidemiological impact [41]. Tuberculosis preventive treatment regimens using 1 month of daily, oral bedaquiline, or LAI formulations of diarylquinolines (bedaquiline or TBAJ-876 LAI) meet many of the desirable attributes of a novel TPT regimen. Long-acting injectables–tuberculosis preventive treatment regimens, particularly if they can be given as a single dose, have the added benefit of ensuring adherence and maximizing individual- and population-level effectiveness [36, 38].

CONCLUSIONS

There is a high estimated burden of MDR-TB infection globally. However, there are reasons for optimism as we enter a new era for managing MDR-TB infection. We have updated WHO guidelines for use of levofloxacin for treating MDR-TB infection based on high-quality evidence. An ongoing trial will provide evidence for an alternative regimen (delamanid) for MDR TPT. New ultrashort-course oral or single-dose LAI TPT regimens are being evaluated. Scale up of safe, potent TPT regimens that are ultrashort or can be administered as a single-dose injection, in combination with other effective interventions to find and treat MDR-TB, has the potential to substantially contribute to ending the global MDR-TB epidemic.

Notes

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