REVIEW

Demanding an end to tuberculosis: treatment of tuberculosis infection among persons living with and without HIV

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Purpose of review
More than two billion people are infected with *Mycobacterium tuberculosis* and few of them are ever offered therapy in spite of such treatment being associated with reduced rates of morbidity and mortality. This article reviews the current recommendations on the diagnosis and treatment of TB infection (or what is commonly referred to as 'prophylaxis' or 'preventive therapy' of latent TB) and discusses barriers to implementation that have led to low demand for this life-saving therapeutic intervention.

Recent findings
Treatment of infection for both TB and drug-resistant TB is well tolerated and effective, and several new, shorter regimens – including rfiapenitine-based regimens of 1 month and 12 weeks duration – have been shown to be effective. Not all persons infected with TB go on to develop disease and the risk is the highest in the first 2 years after infection. Given this, additional work is needed to better identify those at the highest risk of developing active TB.

Summary
Practitioners should offer newer, shorter regimens to persons who are infected with TB and at high risk of developing disease, including people living with HIV and household contacts of people living with TB who are age 5 years and under. This includes individuals who have been exposed to drug-resistant forms of disease. Socioeconomic risk factors may play a key role in the development of TB disease and should also be addressed.

Keywords
demand, infection, preventive therapy, prophylaxis, tuberculosis

INTRODUCTION

It is estimated that one out of every three people living in the world today is infected with *Mycobacteria tuberculosis*, the bacteria that causes tuberculosis (TB) disease, the leading infectious cause of death globally [1]. Of those infected, 5–10% will develop signs and symptoms of TB disease in their lifetime [2]. This progression from infection to active disease can be avoided when the infection is treated, sometimes referred to as 'prophylaxis' or 'preventive therapy,' the efficacy of which has been shown to be between 60 and 90% [3]. Preventive therapy is not only effective at limiting individual disease, but also allows elimination of this important *M. tuberculosis* reservoir, thus bringing us closer to the global goal of 'ending TB' [4]. However, the lack of treatment actually offered to people infected with *M. tuberculosis* is not only a clinical and public health failure, but also a major market failure leading to limited therapeutic products, which are only available from a small number of manufacturers at high prices [5]. How can this be, given the potential benefits to the more than two billion people with TB infection today and the 10 million people who develop TB each year? This article will review barriers to the treatment of TB infection and discuss recent developments in the field that show why such treatment should be demanded in order to end TB.

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KEY POINTS

- Treatment of TB infection in high-risk persons is the only way to reach the 'End TB' goal of TB elimination by 2030.

- Better diagnostic and prognostic tests of infection and likelihood of development of disease are in the pipeline, with data showing socioeconomic factors are also predictive of who will develop the disease.

AQ4
- Shorter, rifamyicn-based regimens – including 4 months of rifampin, 12 weeks of weekly INH and rifapentine, and 1 month of daily INH and rifapentine – should improve treatment adherence without sacrificing efficacy.

- Data show that when persons exposed to drug-resistant TB are treated for infection with fluoroquinolone-based regimens, there is a 90% risk reduction for developing active TB.

- Human-rights-based approaches to TB require that persons who have been exposed to and infected with all forms of TB be told about their risks and offered treatment of infection: an informed affected community is the best way to increase demand.

TERMINOLOGY

The term 'latent TB' is often used to describe people who have been infected with the TB bacteria but who have no evidence of clinical TB disease [6]. This is contrasted with people who have 'active TB' with physical signs and symptoms, the ability to transmit *M. tuberculosis* bacteria, and who need treatment with multiple antituberculous agents. Recent data on the pathophysiology of TB show this to be a false dichotomy perpetuated by both a public health approach to TB and a limited understanding of the processes of disease [7]. Instead, TB is now understood as occurring along a spectrum ranging from infection to mild, moderate and severe disease depending on bacillary burden and host immune response [8■]. Thus, rather than referring to 'latent TB' and using the terms 'preventive therapy' or 'prophylaxis,' we use the term 'treatment of TB infection' [9].

> Possible impact on demand: people may be reluctant to take medication to 'prevent' a disease as opposed to taking medication to treat an infection.

WHO RECOMMENDATIONS

In 2018, the WHO issued an updated guideline on the treatment of TB infection, with a focus on 'consolidated guidelines for programmatic management.' [10■] The document focuses on GRADE-

based recommendations in the areas of testing for TB infection, managing high-risk contacts, selecting a TB infection treatment regimen, monitoring people on these regimens, and treating TB infection in persons exposed to drug-resistant forms of TB (DR-TB). Of concern, the recommended strategies differ for people living in low-incidence countries (i.e. wealthier countries) and high-incidence countries (i.e. poorer countries) [11]. For example, it is recommended that all persons in low-incidence countries with household exposure to TB be offered treatment of infection, whereas in high-incidence countries only those who are living with HIV and children under the age of 5 years with exposure to TB in the household be offered such therapy. With such double standards, it will be impossible to meet the goals set out in the WHO's 'End TB' Strategy [12]. In addition, the algorithms in the guidelines differ for certain subpopulations, which can be confusing for clinicians, and policy and program makers [13].

> Possible impact on demand: conflicting recommendations have led to inadequate demand from high-burden settings where the majority of those who would benefit from treatment reside.

HEATH SYSTEM CHALLENGES

The current contradictory WHO guidance has set a very low bar in the rollout out of treatment of TB infection, which coupled with significant health system challenges, has further stifled access. Data show that fewer than 15% of people in need of treatment of TB infection according to WHO recommendations actually receive it [14]. There are multiple reasons for this, including lack of awareness on the part of affected populations, limited treatment literacy materials, perceptions and attitudes of healthcare workers, adherence challenges with lengthy and complicated regimens, challenges interpreting tests diagnosing TB infection, interruptions in drug and diagnostic test supply, lack of dedicated funds and human resources, and limited policies for prioritizing treatment of infection [15]. Add to this the concerns about stigma and discrimination for people attending TB services, the heavy workload of healthcare providers in high TB burden settings, difficulties ruling out active TB disease, and the perceived risks of drug toxicity, and it is not surprising that treatment of infection is perceived by many to be a low priority health intervention [16].

> Possible impact on demand: those with TB infection do not know that they may benefit from treatment and health systems are not structured

to prioritize treatment of TB infection, leading to low uptake of treatment.

DIAGNOSTIC TESTS FOR TUBERCULOSIS INFECTION

One major reason for the lack of treatment of TB infection is the limited availability of sensitive and specific diagnostic tests. Currently, the available tests include skin testing with tuberculin/purified protein derivative and blood testing with interferon-gamma releasing assays [17]. Although the benefit of treatment of infection seems to be increased in people in whom these tests are positive, neither of these tests is able to exclude TB infection and both perform poorly in populations of people at highest risk for developing TB disease [18]. The poor performance of existing tests coupled with their limited availability led the WHO to recommend that no test of TB infection is needed prior to offering treatment after household exposure in high-risk populations [19].

Although there are several promising tests on the horizon – including both PET scanning and skin tests using ESAT-6 and CFP-10 proteins – many of them are still immune-based or are in very early stages of development [20,21]. Such testing could be validated and brought to the market sooner if there is increased investment in the research and development of these diagnostic tests [22].

Possible impact on demand: in the absence of a sensitive, specific, affordable, and easy-to-use diagnostic test, many people with TB infection remain undiagnosed and are therefore not offered treatment.

PREDICTING WHO WILL PROGRESS FROM TUBERCULOSIS INFECTION TO DISEASE

It is imperative that better tools are developed to predict, which persons and populations are at high risk of disease progression. This is especially so considering that in most instances of TB infection, the immune system will be able to clear the infection [23■■], and that adverse events can occur with the treatment of TB infection.

In those who are not HIV infected, there is an estimated 10% chance that TB infection will progress to disease [24]. Data from those living with HIV show that risk to be 10% per year, and this is the reason – along with the high rates of mortality from TB – why this high-risk group are offered treatment of TB infection [25]. This data has been extrapolated to other immunocompromised populations for whom treatment of infection is recommended, most notably those receiving tumor necrosis factor-alpha

blockers. However, other potentially immunocompromised populations, such as those with malnutrition, diabetes mellitus and alcohol use disorder, have not been included in recommendations because of a lack of data on their risks for disease development [26].

Age has also been viewed as an important criterion for treatment of TB infection, considering children under the age of 5 years are at high risk of developing severe forms of TB. It bears mentioning, however, that there is also a high rate of TB cases among persons aged 10–14 years of age [27]. Socioeconomic factors could also play a role in determining who is at risk for developing TB disease once infected [28]. One key study assessing progression from TB infection to disease in a Peruvian slum found that a composite score including measures of poverty – such as indoor air pollution, a low number of windows, and lower household economic position – was an excellent predictor of 10-year risk for developing TB. This evidence, coupled with the fact that many high-burden TB settings are low-income settings again raises the question of why more aggressive treatment of infection is not recommended in these contexts.

Other individual physical factors – including the specific immune responses to *M. tuberculosis* – can be predictive of progression of infection to active disease. Researchers have identified host protein/metabolomics markers, microRNA signals, and host genomic expressions that appear to correlate with development of active TB disease [29■].

Possible impact on demand: without an accurate and valid way to predict who is at risk of developing TB disease after being infected with M. tuberculosis, a number of people in need of treatment are not offered it.

TREATMENT REGIMENS AND ASSOCIATED CHALLENGES

There are currently multiple possible regimens that can be offered to a patient diagnosed with TB infection. Historically these regimens, summarized in Table 1, have been long (3–6 months) and use drugs, which can lead to the development of both nonserious and serious adverse events, including liver failure, peripheral neuropathy, hypersensitivity, or thrombocytopenia [30]. These are important factors that can impact adherence, and thus the clinical benefits of treatment [31]. An additional challenge for the high-risk group of people living with HIV is that both rifampin and rifapentine are not recommended with nevirapine or protease inhibitors because of drug–drug interactions [32].

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Table 1. WHO recommended treatment regimens for tuberculosis infection

Treatment regimen	Duration	Advantages	Disadvantages	Comments
Isoniazid	6 months daily	Single drug Shorter duration	Adverse effects of isoniazid (peripheral neuropathy, liver toxicity) May not adequately protect people with HIV	Pyridoxine co-administration required
Isoniazid	9 months daily	Single drug	Adverse effects of isoniazid (peripheral neuropathy, liver toxicity)	Pyridoxine co-administration required
Isoniazid	36 months daily	Single drug May improve protection for people with HIV	Adverse effects of isoniazid (peripheral neuropathy, liver toxicity) Adherence challenges given long duration	Pyridoxine co-administration required
Isoniazid and rifampin	3–4 months daily	Shorter duration	Two medications (co-formulation could decrease pill burden) Adverse effects of isoniazid (peripheral neuropathy, liver toxicity) and rifampin (hypersensitivity, thrombocytopenia) Cannot administer with nevirapine or protease inhibitors	
Rifampin	3–4 months daily	Single drug	Adverse effects of rifampin (hypersensitivity, thrombocytopenia). Cannot administer with nevirapine or protease inhibitors.	Fears of development of rifampin resistance have led to hesitancy to use this regimen
Isoniazid and rifapentine	3 months, once weekly	Shorter duration Once weekly administration	Adverse effects of isoniazid (peripheral neuropathy, liver toxicity) and rifapentine (gastrointestinal problems, rash). Cannot administer with dolutegravir. High costs and poor availability of rifapentine.	
Isoniazid and rifapentine	4 weeks, daily	Short duration	Adverse effects of isoniazid (peripheral neuropathy, liver toxicity) and rifapentine (gastro intestinal problems, rash). Cannot administer with dolutegravir. High costs and low availability of rifapentine.	Not yet recommended by WHO as results only recently made available
Fluoroquinolones	6 months daily	Treatment of DR-TB infection	Adverse effects of fluoroquinolones (arthralgia, arthritis, tendon rupture). Not effective in fluoroquinolone-resistant TB.	Often given in conjunction with other medications – based on the drug-susceptibility pattern of the index case

DR-TB, drug-resistant tuberculosis; TB, tuberculosis.

In persons living with HIV, three randomized controlled trials from high-burden settings suggest that continuous treatment of infection (defined as 36 months) with isoniazid results in a statistically significant reduction in TB-related mortality among persons with a positive test of infection compared with only 6 months of isoniazid [33]. Thus, some have called for persons living with HIV to receive

ongoing treatment with isoniazid, and there is now a tablet with a fixed-dose combination of isoniazid, vitamin B6, and co-trimoxazole available to lighten the pill burden [34].

The high-pill burden and lengthy treatment regimens has led to significant interest in shorter, simpler regimens for treatment of TB infection. A recent study found that a 4-month regimen of daily rifampin therapy was noninferior to a 9-month regimen of daily isoniazid treatment and that treatment completion rates were significantly higher among those on the rifampin regimen (15.1% more people treated with the shorter rifampin regimen compared with the 9-month isoniazid treatment) [35▪]. The shorter rifmapin regimen was also found to be well tolerated in children [36▪]. Two studies also support the use of shorter, rifapentine-containing regimens for treatment of TB infection. The first is a once-a-week regimen of high-dose isoniazid and rifapentine over a 12-week period [37]. The second option is a 1-month, daily regimen of isoniazid and rifapentine [38]. Both of these regimens have been shown to be noninferior to a 9-month regimen of daily isoniazid. Both these regimens were assessed in people living with HIV and found to have a sustained protective effect for as long as 36 months after treatment completion. This is consistent with results from the TEMPRANO trial showing a sustained mortality benefit among people living with HIV who were given 6 months of isoniazid for treatment of TB infection [39]. Given the concern for re-infection and continued risk in persons with HIV, a trial of repeated cycles of the 12-week isoniazid/rifapentine regimen is currently underway. Despite these promising developments, pricing and availability of rifapentine are serious challenges to uptake in the field. Another challenge in using these shorter, rifapentine-based regimens among people living with HIV is that rifapentine is not yet recommended for use with dolutegravir, a drug, which is expected to form the basis of most HIV treatment regimens in the next 2–3 years [40].

Possible impact on demand: expensive, complicated and lengthy regimens with drugs that can cause toxicity limit recommendations for use of treatment of TB infection. Limited availability and high-price of rifapentine coupled with concerns about co-administration with dolutegravir are a further limit.

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS INFECTION

It is estimated that half a million people develop DR-TB disease each year, and it is therefore, likely that at least a million people are newly infected with DR-TB [41]. Cohort studies report fewer than 500 people ever being treated for DR-TB infection globally. This gap is particularly significant as household studies have shown that persons exposed to DR-TB have a higher rate of TB disease than those exposed to drug-susceptible disease [42].

A 2017 meta-analysis of studies in which persons with DR-TB infection were offered treatment – largely with fluoroquinolone-based regimens – found a 90% reduction in the development of TB disease and a cost-saving to the health system [43▪▪]. This led to the first-ever WHO recommendation for the treatment of DR-TB infection in high-risk individuals, which advises selection of the treatment of infection regimen be based on the drug resistance profile of identified index case(s). Surprisingly– after presenting compelling evidence on the shortcomings on tests of infection – the WHO recommends that treatment of DR-TB should only be offered to those with a positive IGRA or TST, and only to high-risk individuals. Without specifying who is in this group, it is likely that treatment of DR-TB infection will only be offered to those under the age of 5 years and those living with HIV – as is recommended for treatment of drug-susceptible TB infection. Considering the consequences of DR-TB disease, which includes a long treatment (9–24 months) consisting of multiple toxic agents, and only results in success in slightly more than half of those treated all persons exposed to DR-TB, this group could be considered high risk [44]. **AQ5**

Possible impact in demand: conditional recommendations from the WHO coupled with a required positive test of infection could lead to low uptake of treatment of DR-TB infection by programs and limited demand among persons infected with DR-TB.

CONCLUSION AND GENERATING DEMAND **AQ6**

Achieving the public health goal of 'ending TB' will only be possible if development of TB disease is prevented amongst the two billion people living with *M. tuberculosis* infection. In view of limitations with the tests of TB infection and possible toxicity of drug regimens, guidance on treatment of infection needs to balance the potential risks and benefits of treatment at the individual and community level. The current guidance for treatment of TB infection are exceptionally limited and has ultimately contributed to a lack in demand for treatment resulting in costly and limited therapeutic options. Broadening access for more individuals is a significant economic opportunity, which would reduce cost and may encourage the much needed research and development into

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Table 2. Overcoming barriers and generating demand

Barrier	Proposed solutions
People may be reluctant to take medication to 'prevent' a disease as opposed to treating an infection.	Medical community to use the terminology 'treatment of TB infection' and not ''TB prophylaxis.' Awareness and education on treatment of TB infection amongst health providers, individuals and communities at risk.
Conflicting recommendations have led to inadequate demand from high-burden settings where the majority of those who would benefit from treatment reside.	High-burden settings prioritized for access to treatment of infection. Streamline recommendations across contexts; treatment of infection based on risk benefit to individuals and communities.
People do not know they may benefit from treatment of TB infection and health systems are not structured to prioritize treatment of TB infection.	Health systems structured to prioritize contact tracing, screening and treatment of TB infection. Adequate resources dedicated to treatment of infection including human resources, budget for drugs and appropriate facilities depending on what is acceptable to the community. Context dependent differentiated models of care for delivering treatment including at schools, work places and through home visits Contact tracing and case finding to be prioritized.
Without a sensitive, specific, affordable, and easy-to-use diagnostic test, many people with TB infection are unaware of their status and are not offered treatment. Providers are also unable to diagnose TB infection among people seeking care and offer them therapy and this too contributes to low demand.	Investment into the research, development and validation of diagnostic tests.
The absence of a sensitive, specific, affordable, and easy-to-use diagnostic test, has led to many people with TB infection remaining undiagnosed, and are therefore, not offered treatment.	Research, development and validation of tests and scores to predict progression of TB infection to disease Adapt guidance on treatment of TB infection to include additional categories of risk such as 10–14 year olds, other immunosuppressive conditions in addition to HIV, socioeconomic conditions that can predispose to development of TB
Complicated and lengthy regimens with drugs that can cause toxicity limit recommendations for use of treatment of TB infection. The limited availability and high-price of rifapentine coupled with concerns about co-administration with dolutegravir are a further limit.	Investment in the research and development of an ideal regimen for treatment of infection Improve access to rifapentine and other drug options Policy makers to consolidate and simplify guidance on exclusion of active TB disease depending on context and treatment of infection
Conditional recommendations from the WHO coupled with a required positive test of infection could lead to low uptake of treatment of DR-TB infection by programs and limited demand among persons infected with DR-TB.	Offer the option of treatment of DR-TB infection for all close contacts – regardless of age, HIV status and result of test of infection. Fast track trials on the use of new DR-TB drugs (bedaquiline and delamanid) for the treatment of infection.

DR-TB, drug-resistant tuberculosis; TB, tuberculosis.

both diagnostic and therapeutic interventions. More importantly, improving access to treatment for TB infection is a fundamental part of a human-rights-based approach to TB elimination. Pledges to 'End TB' by 2030 are merely hollow promises if they do not include urgent access to the treatment of TB infection for all individuals, regardless of where they live in the world. The task is daunting and will require unprecedented efforts along with unprecedented commitment of both human and financial resources in order to overcome the barriers described here. There is, however, a clear path forward (see Table 2) and it is time to demand it be taken.

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<AQ10>	Please define the two-letter abbreviation 'PK.'	