

A review of rifapentine for treating active and latent tuberculosis

Background: Nearly 1/3 of the world's population is infected with *Mycobacterium tuberculosis* (Mtb). Simple, effective treatment regimens could improve global tuberculosis (TB) treatment and prevention. We review the literature on the use of isoniazid and rifapentine for the treatment of TB infection. **Methods:** We performed a literature search with the terms 'rifapentine' and 'tuberculosis' and 'treatment.' **Results:** We identified and summarized the data for five randomized controlled trials for latent TB infection (LTBI) and seven randomized controlled trials for use in active pulmonary TB. **Conclusion:** Isoniazid and rifapentine given once weekly for 12 weeks is an effective, well-tolerated short course regimen for latent tuberculosis. It is also an effective combination in the continuation phase of active TB treatment in HIV-negative individuals without cavitary disease.

Keywords: isoniazid • latent • prevention • rifapentine • tuberculosis

Background Epidemiology of tuberculosis infection & disease

Nearly 1/3 of the world's population is infected with *Mycobacterium tuberculosis* (Mtb), with millions developing active disease and dying annually [1]. Most people with active tuberculosis (TB) are infected for months or years before developing disease making TB one of the leading causes of preventable disease and death globally. Individuals from countries with higher TB incidence, people who are immunocompromised, those who experience homelessness or incarceration, contacts to patients with active TB, children, and individuals who use intravenous drug are all disproportionately affected by TB. Ensuring individuals who are at risk for TB infection have full access to TB care and treatment is a critical strategy for reducing TB disease and progressing toward elimination, defined as one case per million. The WHO recently published guidelines for the diagnosis and treatment of latent TB infection (LTBI) in recognition of the importance of TB prevention [2]. While

there are currently many challenges in fully implementing these guidelines globally, they represent a step forward towards the ultimate goal of eliminating TB.

Diagnosis of LTBI

The diagnosis of LTBI is defined as evidence of TB infection without any symptoms or radiographic evidence of active disease. TB infection is identified by a positive tuberculin skin testing (TST) or interferon gamma release assay (IGRA) [2–4]. Once active disease has been carefully excluded through the absence of symptoms or chest radiograph abnormalities, the risks and benefits of LTBI therapy should be evaluated.

Treatment of LTBI

For maximum efficacy, LTBI treatment needs to be well tolerated and as short as possible to achieve a high completion rate. Isoniazid (INH) is a bactericidal agent which disrupts cell wall synthesis, primarily acting on cells which are rapidly dividing. Point mutations in the *inhA* or *katG* regions can be identified in 85% of patients with phenotypic resistance

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to INH. The efficacy of INH in preventing progression from latent to active TB is well established in low burden countries [5–8]. Efficacy in middle burden countries among immunocompromised individuals is also sustained over time but may wane in hyperendemic settings due to reinfection [9,10]. While acceptance rates of LTBI therapy can be as high as 90%, both acceptance [11] and completion rates vary widely, ranging from 30 to 90% [12–15]. The recommended treatment duration for INH is 9 months although 6 months is considered acceptable for patients who have difficulty tolerating treatment. The long duration of therapy and limited tolerability are major limitations for treatment completion that decrease the overall efficacy of INH [8,16,17].

Rifampin (RIF) is a rifamycin which is bactericidal against *Mtb* by disrupting protein synthesis in both actively replicating mycobacteria and dormant or persisting mycobacteria and thus has excellent sterilizing activity. The ability of rifamycins to target dormant mycobacteria is critical for achieving a stable cure with a 6 month treatment course for active TB. This also makes rifamycins ideal candidates for treatment of latent TB. Resistance is mediated in more than 95% of cases through point mutations in the *rpoB* gene. It can be given for 3–4 months' duration with less toxicity and better treatment completion than 6–9-month INH regimens [16–18]. The combination of INH and RIF taken daily for 3 months is another alternative that was shown to be comparable to INH alone for 6 months [19]. A large randomized clinical trial is currently ongoing that will evaluate the efficacy and safety of 4 months of RIF compared with 9 months of INH [20].

Rifapentine (RPT) is a rifamycin that was first described in 1978, with similar mechanism of action and emergence of resistance compared with rifampin. It has a half-life which is four- to five-times longer than other rifamycins [21,22]. After absorption, rifapentine is converted to a slightly less active metabolite, desacetyl rifapentine. Bioavailability can be increased by taking it with food that has a relatively high fat content [23]. Animal models and human studies suggest RPT may have increased bactericidal activity compared with rifampin [24–27]. This has led to interest in its use for treatment of TB infection and disease, initially by using intermittent dosing as part of directly observed therapy (DOT). Recently, there has been interest in evaluating the safety and efficacy of daily dosing of rifapentine to shorten treatment duration which could improve adherence and treatment completion [28]. While rifapentine has activity to treat other mycobacteria such as *Mycobacterium avium*, it is currently only US FDA-approved for treating *M. tuberculosis* [24].

Methods

We performed a literature search on PubMed with the search terms 'rifapentine' and 'tuberculosis' and 'treatment' which yielded 200 articles and reviewed conference presentations from 2015. We excluded animal model data, nonoral formulations, reviews and meta-analyses as well as *in vitro* studies. We identified seven randomized controlled trials in active pulmonary TB (Table 1) and five randomized controlled trials for LTBI (Table 2). We summarize the data for use in active tuberculosis and discuss in greater detail the clinical trial data for use in LTBI.

Results

Rifapentine for use in active TB

Table 1 summarizes the clinical trials of the use of rifapentine for the treatment of active TB. The first clinical trial evaluating the use of rifapentine for treating tuberculosis was conducted in Hong Kong, the initial results of which were published in 1998 [29]. A total of 672 individuals were enrolled to receive standard therapy for 2 months consisting of thrice weekly streptomycin, INH, RIF and pyrazinamide (PZA). Of these, a total of 592 were included in the intention to treat analysis. During the continuation phase of treatment, patients received either INH and RIF thrice weekly ($n = 190$), INH and RPT once weekly ($n = 199$) or INH and RIF for two weeks followed by INH and RPT ($n = 203$). The continuation phase treatment regimens were given for an additional 4 months and the total treatment duration was 6 months. Patients were followed for 5 years and assessed for relapse as well as adverse events. Relapse rates were higher in the INH and RPT arm (9%) compared with the INH and RIF (4%), $p = 0.04$. There was concern about the bioavailability of the rifapentine used in the trial but whether this affected relapse rates is uncertain. Multivariate proportional hazard analysis of risk factors associated with relapse identified increased pretreatment extent of disease being associated with relapse [30]. Notably, 35% of the cohort receiving INH and RPT presented with cavitary disease which was later shown to be a risk factor for relapse with weekly INH and RPT in the continuation phase [31].

In 2002, the results from a larger multicenter trial in the USA and Canada were published which compared INH and RPT once weekly to INH and RIF twice weekly during the 4-month continuation phase of a 6-month course [31,32]. Patients initiated treatment with INH, RIF, PZA, and ethambutol (EMB) daily for 2 weeks and then could receive daily, thrice weekly or twice weekly therapy thereafter for a total of 2 months. Of note, the dose of RPT used in the continuation phase was 600 mg, which is lower than

Table 1. Randomized controlled trials using rifapentine for active tuberculosis.

Study (year)	Location(s)	Participants	Active TB continuation phase therapies evaluated	Proportion with relapse of active TB	Adverse outcomes	Ref
Tam <i>et al.</i> (1998, 2002)	Hong Kong	Aged 15 years or older, n = 692, diagnosis of pulmonary TB. 37% overall with cavitory disease	After thrice weekly SHRZ for 2 months, participants were randomized to 4 months of: 1) thrice weekly HR vs 2) H/RPT weekly vs 3) H/R for 2 weeks followed by H/P on week 3	HR = 4%; H/P = 9% (difference significant p = 0.04), HR x 2 weeks followed by H/P x 1 week = 10%	Any adverse effect: HR = 14%, H/RPT = 9%, HR x 2 weeks followed by H/RPT x 1 week 10%	[29,30]
Benator <i>et al.</i> (2002, 1999)	USA, Canada	Aged 18 years or older, HIV-negative adults [†] , n = 1004. 57% with cavitory disease in the H/P, 51% in the twice weekly H/R	IREZ x 2 months, then participants randomized to twice weekly H/R vs once weekly H/P	HR = 5.6%; H/P = 9.2%. When excluding individuals with cavitation, risk of relapse was 2.5% in HR, 2.9% in H/P	Grade 3 or 4 toxic event: H/R 14%; H/RPT 8.7%	[31,32]
RIFAQUIN (2014)	South Africa, Zimbabwe, Botswana, Zambia	Aged 18 years or older, n = 827. 28% HIV-positive, 65% with cavitory disease	IREZ daily x 2 months, followed by: 1) H/R daily x 6 months vs 2) Moxi/REZ daily for 2 months, followed by moxi and rifapentine twice weekly x 2 months, vs 3) Moxi/REZ daily for 2 months, followed by weekly moxi with rifapentine x 4 months	HR = 4.9%; Moxi and rifapentine twice weekly x 2 months = 18.2%; moxi and rifapentine once weekly x 4 months = 3.2%	Low. Total number that changed treatment due to adverse event was five	[35]

[†]The trial originally enrolled HIV-seropositive individuals, but was stopped early due to increased rates of relapse with rifamycin resistance in the rifapentine arm.

E: Ethambutol; H: Isoniazid; H/P: Isoniazid and rifapentine; H/R: Isoniazid and rifampin; TB: Tuberculosis; Moxi: Moxifloxacin; R: Rifampin; RPT: Rifapentine; S: Streptomycin; Z: Pyrazinamide.

Table 2. Randomized controlled trials using rifapentine for latent tuberculosis infection.

Study (year)	Location(s)	Participants	LTBI therapies evaluated	Incidence of active TB	Adverse outcomes	Ref.
Schecter <i>et al.</i> (2006)	Brazil	Adult household contacts, n = 399*	INH and RPT vs RIF and PZA	INH and P: 1.45%, RIF and PZA 0.52%	Hepatotoxicity: 10% RIF and PZA, 1% INH and RPT, p < 0.001	[36]
Martinson <i>et al.</i> (2011)	South Africa	HIV-positive adults, n = 1150	INH and RPT vs INH and RIF vs INH daily x 6 months vs INH daily x 6 years	1.9/100 person years; continuous INH arm had 58% lower risk of active TB while on treatment p = 0.02	Grade 3 or 4 toxic event: INH and RPT = 6.4%, INH and RIF = 4.8%, INH x 6 months = 9.5%, INH continuous = 32.3%	[41]
PREVENT TB (2011)	USA, Brazil, Canada, Spain	Aged 12 years or older, n = 3986	INH and RPT vs INH x 9 months	INH and RPT: 0.19% INH x 9 months, 0.43%	Any adverse event: INH and RPT, 1.6% INH x 9 months, 2.9%, p < 0.001	[42]
Villarino <i>et al.</i> (2015)	USA, Brazil, Canada, Spain	Children aged 2–17 years, n = 1058	INH and RPT vs INH x 9 months	INH and RPT: 0 INH x 9 months, 0.6%	Any adverse event: INH and RPT, 2.6% INH x 9 months, 1.2%	[43]
iAdhere (2015)	USA, Spain, South Africa, China	Adults aged 18 years or older, n = 998	INH and P: 1) DOT, 2) SAT, 3) eSAT	Adherence: DOT = 87%, SAT = 74%, eSAT = 76%	Treatment discontinuation due to adverse event: DOT = 3.6%, SAT = 5.4%, eSAT = 4.3%	[44]

DOT: Directly observed therapy; eSAT: Enhanced self-administered therapy; INH: Isoniazid; LTBI: Latent tuberculosis infection; PZA: Pyrazinamide; RIF: Rifampin; RPT: Rifapentine; SAT: Self-administered therapy.

the dose used in more recent trials in both active and latent TB. The study included HIV-seropositive individuals and was stopped early due to an increased risk of relapse with rifamycin resistance in the INH and RPT arm in these individuals [32]. However, the HIV-negative cohort was allowed to continue follow-up per protocol. Among those without cavitory disease, relapse was no different: 2.9% for weekly INH and RPT compared with 2.5% in the INH and RIF twice weekly arm. Therefore, this study established that INH and RPT in the continuation phase is a reasonable alternative to twice weekly INH and RIF for HIV-negative individuals without cavitory disease. Within the entire cohort however relapse rates were higher for INH and RPT (9.2%) compared with INH and RIF twice weekly (5.6%).

The next few studies in patients with active TB were to identify the optimal dose of RPT given the evidence for safety and tolerability along with mouse-model data showing increased efficacy with higher doses [28,33,34]. RPT in doses ranging 900–1200 mg appeared to be reasonably well tolerated whether given intermittently or daily. At daily doses of 15–20 mg/kg in the continuation phase increased sterilization was seen compared with rifampin [34].

In the RIFAQUIN trial, INH was replaced with moxifloxacin throughout treatment and RPT was given in the continuation phase at a dose of 1200 mg weekly for 4 months or 900 mg twice weekly for 2 months. These were compared with 6 months of daily treatment with the standard therapy [35]. Importantly, this multicenter trial included 28% HIV-seropositive individuals and 65% of the cohort had underlying cavitory disease. The unfavorable response rates were not different between the standard therapy arm (4.9%) and once-weekly moxifloxacin with rifapentine for 4 months (3.2%) but were worse in the twice-weekly treatment shortening arm (18.2%). The report did not include information on relapse rates among subpopulations traditionally at higher risk such as HIV-seropositive individuals or those with cavitory disease. While the study failed to show efficacy with a 4-month treatment regimen, it is encouraging that the once-weekly regimen without INH was comparable to a standard daily treatment course.

Rifapentine in combination with isoniazid for LTBI Treatment

Table 2 summarizes the randomized controlled trials of the use of RPT for LTBI all of which have been conducted in combination with INH. The first study published in 2006 was conducted in Brazil and recruited adult household contacts to individuals with active pulmonary TB [36]. Individuals were randomized to

receive 12 weekly doses of INH 900 mg and RPT 900 mg by DOT compared with RIF and PZA daily. This study was stopped early due to an increased rate of hepatotoxicity with the RIF and PZA combination [37–40]. A total of 399 individuals were enrolled, 206 in the RIF and PZA arm, 193 in the INH and RPT arm. Of those receiving RIF and PZA, 10% developed grade 3 or 4 hepatotoxicity, compared with 1% of those receiving INH and RPT; $p < 0.001$. Incidence of TB was similar in either arm, 1.45% in the INH and RPT, 0.52% in the RIF and PZA. The estimated rate of TB among household contacts in Brazil who did not receive LTBI therapy was 8%. This was the first study to demonstrate the efficacy and tolerability of INH and RPT as a therapy for LTBI.

The next published study in 2011 evaluated the same 12-dose regimen of once-weekly INH 900 mg and RPT 900 mg by DOT in HIV-seropositive individuals in Soweto, South Africa [41]. It was compared with twice weekly INH and RIF by DOT for 3 months, INH daily continuously for 6 years and INH daily \times 6 months. HIV-seropositive patients had to have a CD4 count of >200 cells/ μ L and could not be receiving antiretroviral therapy. 1150 individuals underwent randomization, with 328 in the INH and RPT, 329 in the INH and RIF arm, 327 in the INH for 6-month arm and 164 in the INH for 6 years. Patients were followed for a minimum of 3 years. The primary end point was diagnosis of TB or death. Adverse reactions were also assessed. The cohort was overwhelmingly female (83%) with a median CD4 count of 484 cells/ μ L. Adherence to medications was higher in the INH and RPT and INH and RIF groups (95%) compared with the INH alone arms (approximately 85%). Leading reasons for treatment discontinuations included pregnancy, initiation of antiretroviral therapy and withdrawal due to conflicts with work. Grade 3 or 4 hepatotoxicity was higher among the continuous INH (28%) and 6 month INH arm (5.5%) compared with the other regimens ($<2.5\%$). Overall incidence of tuberculosis was 1.9/100 person-years with little differences among regimens other than continuous INH. In this arm, there was a 58% lower risk of developing TB ($p = 0.02$). However, the rate of TB increased markedly upon treatment cessation. There were two cases of INH resistant TB and three cases of rifampin monoresistance. Multidrug resistant TB was detected in 2 individuals, one who was taking INH and RPT and the other was taking INH continuously. This study demonstrated that INH and RPT was not inferior to 6 months of INH alone in HIV-seropositive individuals. Importantly, this trial was conducted in South Africa, which has an estimated incidence of TB of 860/100,000.

In the PREVENT TB trial which was also published in 2011, the CDC funded TB Trials Consortium (TBTC) performed a multicenter international randomized controlled trial comparing 12 once-weekly doses of INH 900mg and RPT 900 mg by DOT to INH 300 mg daily self-administered for 9 months [42]. A total of 3986 were enrolled in the INH and RPT arm and 3745 in the INH arm. Enrollment was limited to individuals at least 12 years of age at the onset of the study. Later, enrollment was extended to include children at least 2 years of age when pharmacokinetic data on rifapentine in children became available. Approximately 71% reported close contact and 25% had recent conversion to a positive tuberculin skin test. Nearly 3% in each arm had underlying HIV disease or hepatitis C, with just under 2% with hepatitis B. The vast majority of enrollees were in the USA and Canada, with the remainder from Brazil and Spain. Study subjects were followed for 33 months.

The primary end point was confirmed tuberculosis and the study was designed to evaluate if the experimental regimen was noninferior to the standard therapy. Secondary end points were adverse events and treatment completion. The proportion of subjects developing tuberculosis was 0.19% in the INH and RPT group versus 0.43% in the INH group. INH and RPT was consistently noninferior, with a trend towards superiority by the end of the 33-month follow-up period. Subjects receiving INH and RPT were significantly more likely to complete treatment compared with INH alone (82 vs 69%; $p < 0.001$). Discontinuation of therapy due to adverse events was higher in the INH and RPT group compared with the INH alone group (4.9 vs 3.7%; $p = 0.009$). However, the proportion of those with any adverse event was lower in the INH and RPT group, including hepatotoxicity. Of those who were subsequently diagnosed with active TB, two were INH resistant, both of which were randomized to the INH arm. There was one rifampin resistant case in an HIV-seropositive subject who had several treatment interruptions. This is the largest study of the use of INH and RPT for treatment of LTBI to date and firmly established this regimen as a well-tolerated and effective therapy in HIV-negative adolescents and adults. Notably INH and RPT was also associated with significantly higher adherence compared with 9 months of INH monotherapy.

While the PREVENT TB trial established the safety and efficacy of once weekly INH and RPT for 12 weeks, the cost and challenges associated with DOT are barriers to wider usage. As a follow-up to that study, the TBTC recently completed a multicenter trial in the USA, Spain, Hong Kong and

South Africa comparing weekly INH and RPT given by DOT versus standard self-administered therapy (SAT) or enhanced SAT (eSAT) with weekly text message reminders, the I-Adhere study [43]. The primary end point was treatment completion using a 15% noninferiority margin based on cost-effectiveness modeling and multiple secondary objectives including an evaluation of adverse events. A total of 1002 adults were enrolled and randomized into the study. The majority were enrolled at US sites (77%) and in contrast to the PREVENT TB trial, only 34% were contacts to active TB. Treatment completion for the DOT arm was 87% compared with 74% in the SAT arm and 76% in the eSAT arm. When restricting analysis of adherence to US sites, adherence in the DOT, SAT and eSAT arms was 85, 78 and 77%, respectively. Among US sites, SAT was noninferior to DOT, and adverse events were low (less than 6%) but similar in either arm. Importantly, completion with once-weekly INH and RPT by SAT was higher than historical results with daily INH for 9 months and should be considered a reasonable option for treating LTBI.

Rifapentine & INH for LTBI treatment in special populations

Within the PREVENT TB trial, enrollment was expanded to children aged 2–11 years after pharmacokinetic studies were completed. A subanalysis was performed among children aged 2–18 years [44]. Sites were allowed to give INH monotherapy as DOT depending upon the local protocol for managing LTBI in children. The primary end point was to determine equivalence of safety between the two study arms. Secondary end points included treatment effectiveness, assessing noninferiority of INH and RPT compared with INH. There were 1058 children enrolled between June 2001 and December 2010 and the majority (93%) were contacts to a patient with active TB. Only five individuals (<1%) were HIV-positive and there were larger than expected differences in age and sex between the two groups. The median age for INH and RPT was 10 years compared with 12 years for the INH monotherapy group. Within the INH and RPT arm, 54% were male compared with 48% in the INH monotherapy group. Treatment completion was significantly higher in the INH and RPT arm (88%), compared with 81% in the INH monotherapy arm; $p = 0.003$. The rates of discontinuation due to adverse events were similar in each group and included rash, influenza-like illness and gastrointestinal events. There were no events attributed to hepatotoxicity in either arm. There were no diagnoses of active TB in the INH and RPT arm,

and only three in the INH monotherapy arm, none of which were reported to have resistance. Thus INH and RPT was shown to be well tolerated in this largely HIV-negative cohort of children who were contacts to active TB. While there were differences noted in age and sex between the INH and RPT arm compared with the INH monotherapy arm, Monte Carlo sampling distribution simulation performed by the study team failed to identify any bias in study outcomes. Overall children have few adverse effects, including very young children so it is unlikely that there could have been age related differences in tolerability. Notably, the INH and RPT regimen was again associated with higher adherence than INH monotherapy with comparable efficacy.

Individuals with LTBI undergoing solid organ transplants are at high risk for reactivation TB and are a high priority for treatment of LTBI prior to transplant. There has been one prospective observational cohort study of 17 individuals awaiting solid organ transplant. Adherence to INH and RPT was 76% and two (12%) discontinued therapy for adverse events.

Patients with LTBI who undergo hemodialysis are also at high risk for developing active TB disease. Scheduled dialysis sessions and thus frequent contact with healthcare providers are an ideal context for the provision of weekly INH and RPT by DOT. However, no studies to date have evaluated the use of INH and RPT in hemodialysis patients and there are no pharmacokinetic data on the use of RPT in the context of renal impairment. In the case series of solid organ transplant patients, one individual on hemodialysis had to discontinue INH and RPT due to adverse effects [45]. It is uncertain whether dosing in the context of hemodialysis contributed to this patient's significant adverse effects but this cannot be excluded. Therefore, use of INH and RPT in patients undergoing hemodialysis should be monitored carefully.

There have been no studies evaluating the use of INH and RPT in pregnant and lactating women. The trial in HIV-seropositive individuals in South Africa primarily recruited women, and pregnancy was noted as an adverse event in 24.7% ($n = 81$) [41]. Within the entire cohort, only 34 reported discontinuing study drug due to pregnancy, and it is unclear how many were on INH and RPT. Adverse outcomes among pregnant women in this trial were not reported. Within the trial conducted in Brazil, there were three pregnant women during the study period and five during follow-up and no adverse outcomes were noted [36]. Therefore, INH and RPT cannot be recommended as a therapy for LTBI in pregnancy unless there are no other options and treatment is considered urgent.

Cost of providing TB treatment through use of RPT-containing regimens

While DOT has been shown to be cost effective compared with daily, self-administered therapy, there has never been a study evaluating the cost-effectiveness of rifapentine containing regimens compared with other DOT regimens for active TB [46]. Once weekly therapy with either moxifloxacin with rifapentine or isoniazid with rifapentine for active TB has the potential to decrease costs and burden for programs and patients associated with DOT. Despite the higher costs of rifapentine compared with isoniazid, use of rifapentine with INH weekly for 12 doses has been shown to be cost effective in the treatment of latent TB [47,48].

Conclusion

Isoniazid and rifapentine once weekly in the continuation phase of active TB treatment is an option for individuals with noncavitary pulmonary TB who are HIV negative. In these individuals the risk of relapse was comparable to a twice weekly regimen of INH and rifampin. While data are limited, moxifloxacin and rifapentine once weekly in the continuation phase of active TB treatment could be considered for patients with resistance or intolerance to INH. While HIV-seropositive patients and patients with cavitary disease were included in that study, the numbers were small and use of highly intermittent treatment should be approached with caution in populations traditionally at higher risk for relapse, failure and acquired drug

resistance. None of the rifapentine trials for active TB included individuals who had undergone solid organ transplantation, and data on the use in pregnancy remain very limited. Thus, use in these populations for active TB treatment should also be approached with caution.

For latent tuberculosis, isoniazid in combination with rifapentine given once weekly for 12 weeks is an effective, well-tolerated short course regimen for LTBI. This regimen is comparable to a variety of other LTBI regimens, including 3 months of isoniazid and rifampin given twice weekly, isoniazid for 6 months and isoniazid for 9 months. Adverse effects are similar to those seen with isoniazid monotherapy and emergence of drug resistant active TB is uncommon. When assessed, adherence is significantly better to INH and RPT compared with 9 months of INH which should increase its effectiveness in clinical practice. Isoniazid and rifapentine has also been shown to be effective in children as young as 2 years of age and in HIV-seropositive individuals not on antiretroviral therapy. Data in other special populations such as solid organ transplant candidates, individuals with advanced kidney disease and pregnant/lactating women are very limited. Finally while data have shown it to be effective in low- and middle-burden countries over time, as with other LTBI regimens, long-term efficacy remains uncertain in high-burden countries, likely due to high rates of reinfection. INH and RPT has also been shown

Executive summary

- Nearly a third of the world's population is infected with *Mycobacterium tuberculosis*.
- Ensuring individuals who are at risk for tuberculosis (TB) infection have full access to TB care and treatment is a critical strategy for reducing TB disease.
- The diagnosis of latent TB infection (LTBI) is defined as evidence of TB infection without any symptoms or radiographic evidence of active disease.
- The recommended LTBI treatment duration for isoniazid (INH) is 9 months although 6 months is considered acceptable. The long duration of therapy and limited tolerability are major limitations for treatment completion that decrease the overall efficacy.
- Rifampin (RIF) is a rifamycin that can be given for 3–4 months duration with less toxicity and better treatment completion than 6–9 month INH regimens.
- Rifapentine is a rifamycin that was first described in 1978. It has a longer half-life than other rifamycins which led to interest in exploring its use for shortening LTBI therapy and simplifying active TB treatment regimens.
- Isoniazid in combination with rifapentine once weekly is a reasonable alternative to twice weekly INH with RIF for the continuation phase of TB treatment in HIV-negative individuals without cavitary disease.
- In the RIFAQUIN trial, there was no difference in treatment failure and relapse for the 6-month arm that included once-weekly moxifloxacin and rifapentine during the 4-month continuation phase and this may be a reasonable alternative to daily INH and RIF.
- The recent randomized controlled trials evaluating the use of INH and rifapentine for latent TB treatment have demonstrated that it is a safe, effective regimen for HIV-seropositive individuals not on antiretroviral therapy as well as HIV-negative individuals.
- INH and rifapentine can be safely administered to children as young as 2 years of age for latent TB treatment.
- Gaps remain regarding safety and efficacy in pregnancy and lactation, solid organ transplant and hemodialysis patients.

to be a potentially cost-savings therapy for LTBI in the USA, a key consideration for implementation by public health programs [47,48]. Furthermore, data are emerging that this regimen by SAT may be a reasonable option when DOT is not feasible. This in combination with its shorter duration, and tolerability should allow more patients with LTBI to successfully complete treatment, inching us further on the path towards TB elimination.

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