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# EVIDENCE FOR 3HP

## Contents

Acronyms and Abbreviations	2
List of tables	3
List of figures	3
1. Background	4
2. The case for treating Latent TB infection	7
3. Why should we use a rifapentine-based regimen for treating Latent TB infection?	11
4. Take home points	26
References	27



## Acronyms and Abbreviations

<b>1HP</b>	One month of daily rifapentine and isoniazid
<b>3HP</b>	Three months of once-weekly rifapentine and isoniazid
<b>6H</b>	Six months of daily isoniazid
<b>9H</b>	Nine months of daily isoniazid
<b>AIDS</b>	Acquired immune deficiency syndrome
<b>ART</b>	Antiretroviral therapy
<b>aHR</b>	Adjusted hazard ratio
<b>aIRR</b>	Adjusted incidence rate ratio
<b>aOR</b>	Adjusted odds ratio
<b>aRH</b>	Adjusted relative hazard
<b>CDC</b>	Center for Disease Control
<b>CI</b>	Confidence interval
<b>DALY</b>	Disability-adjusted life-year
<b>DOT</b>	Directly observed therapy
<b>HCW</b>	Health care worker
<b>HIV</b>	Human immunodeficiency virus
<b>HR</b>	Hazard ratio
<b>IGRA</b>	Interferon-gamma release assay
<b>INH</b>	Isoniazid
<b>IPT</b>	Isoniazid preventive therapy
<b>IR</b>	Incidence rate
<b>IRR</b>	Incidence rate ratio
<b>LTBI</b>	Latent tuberculosis infection
<b>OR</b>	Odds ratio
<b>QALY</b>	Quality-adjusted life-year
<b>RIF</b>	Rifampicin
<b>RPT</b>	Rifapentine
<b>RR</b>	Risk ratio
<b>SAT</b>	Self-administered therapy
<b>TB</b>	Tuberculosis
<b>TST</b>	Tuberculin skin-test
<b>USA</b>	United States of America
<b>WHO</b>	World Health Organization

## List of tables

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- Table 1** Summary of published phase III and IV trials of effectiveness of 1HP/3HP in preventing active TB disease in adults
- Table 2** Summary of published studies evaluating adherence to and/or completion of rifapentine-based therapy for LTBI in adults and children (n = 18 articles)
- Table 3** Summary of published studies describing toxicity and adverse events associated with rifapentine-based regimens for LTBI treatment in adults and children (n = 13)

## List of figures

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- Figure 1** Overview of TB transmission (from Churchyard et al., 2017<sup>3</sup>)
- Figure 2** Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income (from Fox et al. 2013<sup>15</sup>)
- Figure 3** Strategies for (a) eliminating TB (<1 case per million per year) and (b) approaching the elimination phase (<10 deaths per million per year or <1 death per 100,000 per year; from Dye et al., 2013<sup>45</sup>)
- Figure 4** Prospects for TB control and elimination in South Africa (from Dye et al., 2013<sup>45</sup>)
- Figure 5** Incremental TB service costs for each intervention scenario in South Africa, as compared to base case, by model (from Menzies et al., 2016<sup>47</sup>)
- Figure 6** Kaplan–Meier estimates of the risk of tuberculosis or death in the intention-to-treat population, according to treatment group (from Martinson et al., 2011<sup>56</sup>)
- Figure 7** Weighted treatment completion for all participants in the iAdhere study, by study group (from Belknap et al., 2017<sup>72</sup>)
- Figure 8** Number and percentage of patients with medication reactions after any 3HP dose in an observational study in 16 medical centres across the USA (n = 1,174 with symptoms [n = 3,327 receiving treatment]; from Sandul et al.<sup>74</sup>)

## 1. Background

There were an estimated 10 million new cases of tuberculosis (TB) and around 1.6 million deaths attributable to TB in 2017<sup>1</sup>. The World Health Organization (WHO) has set ambitious targets for reducing TB incidence and mortality in the next 10–20 years, with an aim to eliminating TB by 2035<sup>2</sup>. Elimination of TB, however, cannot be considered without discussion of latent TB infection (LTBI) and its diagnosis and treatment. People with TB infection are unlikely to know if they are infected, manifest no symptoms, and, while their disease remains dormant, do not contribute to ongoing disease transmission (see Figure 1 for an overview of transmission)<sup>3</sup>.

Latent TB infection can progress to active disease, and is likely to do so in people with certain risk factors such as reduced immunity. As such, one of the global priority indicators for tracking progress towards the End TB goals, is for  $\geq 90\%$  of people living with HIV and children who are contacts of TB cases to be started on preventive treatment for TB infection<sup>2</sup>. The cost of TB treatment (derived by WHO using national expenditures reported by national TB programmes and costs associated with the use of health services by people with TB), in 2017, was an estimated US\$ 1,224 for each person with drug-susceptible TB and US\$ 7,141 for each person with multidrug-resistant (MDR) TB. Globally, an estimated 40 million disability-adjusted life-years (DALYs) were lost due to illness and death associated with TB in 2016<sup>1</sup>. At present, most high-burden countries follow a two-pronged approach, using the Bacille Calmette-Guérin (BCG) vaccine for all children at birth (to prevent infection and reduce the risk of transmission)<sup>9</sup> and treatment of groups who are high risk for progression to active disease (household contacts aged under five years and HIV-positive people of any age) with 6–36 months of daily isoniazid preventive therapy (IPT)<sup>10</sup>. However, in 2017, only around 23% of eligible household contacts aged under five years and around 36% of HIV-positive people newly enrolled in care were started on TB preventive therapy<sup>1</sup>.

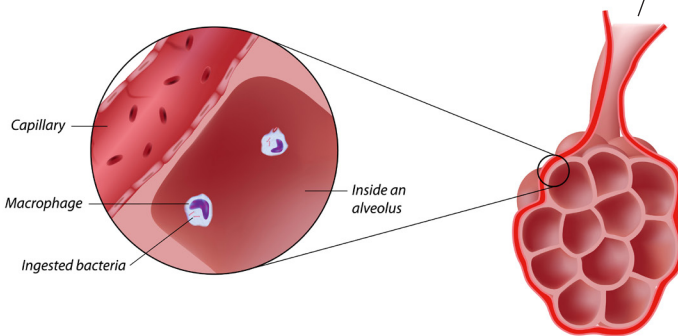
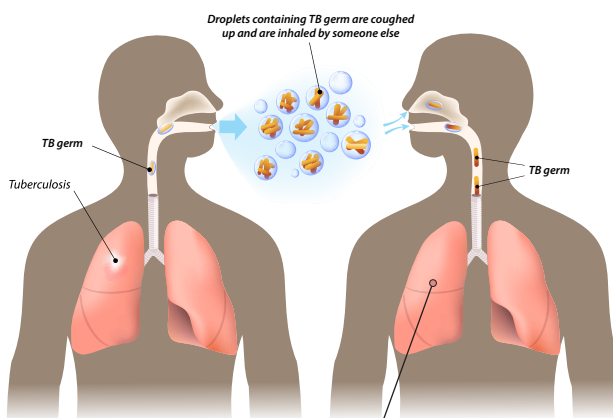
Figure 1. Overview of TB transmission (from Churchyard et al., 2017<sup>3</sup>)

**STAGE 1:**

**Exposure**

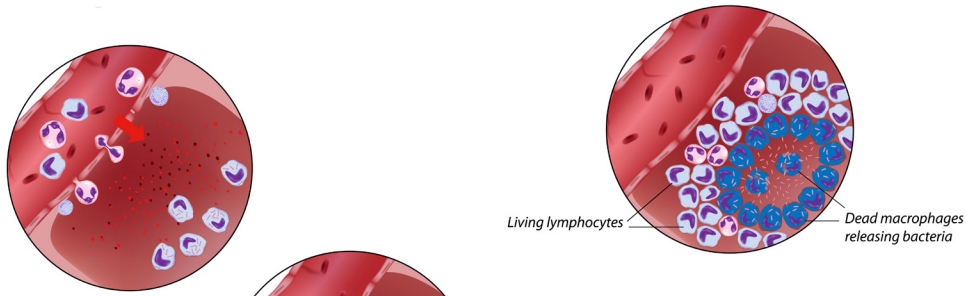
TB Bacilli are inhaled into the lungs of a healthy person via droplets sneezed, coughed or spat by another

**PERSON WHO IS ILL WITH TB**



**STAGE 2:**

TB Bacilli are recognised as invaders and are contained by the healthy immune system (white blood cells - including **CD4 CELLS**) This is known as **LATENT TB infection (LTBI or TB infection)**



**STAGE 3:**

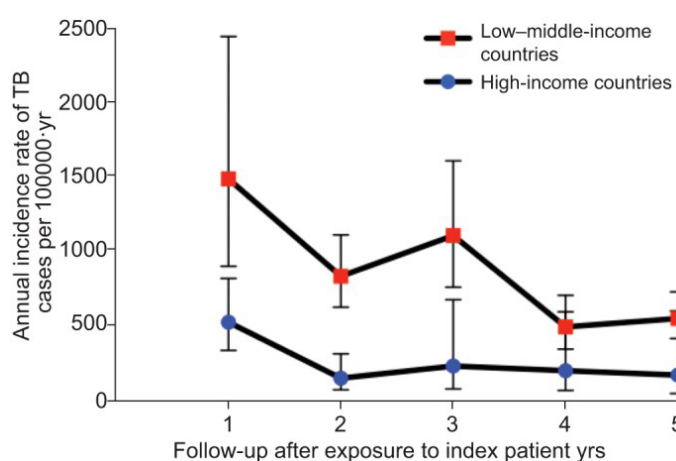
Immune system unable to contain the TB BACILLI which escapes into the rest of the lungs - and possibly other parts of the body causing disease. This is known as **ACTIVE TB DISEASE**

## 1.1 Risk of progression to active disease

HIV is the strongest risk factor for developing TB disease in those with latent or new TB infection<sup>11</sup>; between 11 and 19% of all HIV-positive people are likely have Latent TB infection<sup>12</sup>, though it is probably that this figure is much higher in high-burden settings, as diagnosis of TB infection and TB disease is difficult in people who are living with HIV. Despite greatly increased availability of ART, TB remains a leading cause of morbidity and mortality among HIV-positive people<sup>13,14</sup>; **reducing HIV-associated TB disease and mortality are a central part of the End TB goals**<sup>2</sup>.

**Contacts of people with TB** are also at high risk for developing LTBI and active disease. A 2013 systematic review<sup>15</sup> of 95 studies estimated that the prevalence of active disease in contacts was 3.1% (95% confidence interval (CI) 2–4) and the prevalence of TB infection was 51.5% (95% CI 47–56). This review also found that TB incidence in household contacts of cases varied according to country income (Figure 2).

Figure 2. Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income (from Fox et al. 2013<sup>15</sup>)



TB: tuberculosis; yr: year

A recent (2017) systematic review and meta-analysis of the literature, commissioned by WHO<sup>20</sup> for the guideline update found that **children in high-burden settings who were household contacts of people with active TB, faced an increasing risk of developing LTBI with increasing age**. Compared with children aged 0–5 years, risk of infection was increased in children aged 5–10 years (pooled risk ratio [RR] 1.62 [95% CI 1.25–2.11]; n = 14 studies), was highest in children aged 10–15 years (pooled RR 2.33 [95% CI 1.55–3.50]; n = 11 studies), and was maintained in those aged ≥15 years (pooled RR 2.05 [95% CI 1.53–2.63]; n = 19 studies). In intermediate and low-burden settings, fewer data were available and the risk was less severe, although similar patterns were observed (for children aged 5–15 years vs. 0–5 years, pooled RR 1.18 [95% CI 1.01–1.38] in intermediate-burden settings [n = 4 studies] and pooled RR 1.50 [95% CI 1.14–1.98] in low-burden settings [n = 5 studies])<sup>16</sup>.

This systematic review also examined the risk of **progression to active disease among household contacts with latent TB infection**. In high-burden settings, the risk was highest in child contacts aged 0–5 years (73 cases among 630 contacts [11.6%; n = 4 studies]), lower in child contacts aged 5–15 years (54 cases among 1,329 contacts [4.1%; n = 4 studies]), and lowest in contacts aged ≥15 years (pooled RR 0.22 [95% CI 0.08–0.60] compared with 0–5 years; n = 3 studies)<sup>20</sup>.

## 2. The case for treating Latent TB infection

The primary aim in treating TB infection is to prevent progression to active TB disease<sup>6</sup>; this is well-established within international and national guidelines.

The consolidated 2018 WHO guidelines<sup>20</sup> recommend at least six months of daily INH for HIV-positive children (for HIV-positive children aged <12 months, only if contact with a case of TB; for HIV-positive children aged ≥12 months, even without a case of TB; and for all HIV-positive children after successfully completing treatment for TB), and at least 6 months of daily INH for HIV-positive adolescents and adults with a positive or unknown tuberculin skin-test (TST) result<sup>21,22</sup>. For some time, WHO has recommended preventive treatment for HIV-negative children younger than five years who are household or close contacts of people with TB<sup>23,24</sup> but, importantly, **in the 2018 guidelines, this has been extended to all household contacts of people with TB** in high TB incidence countries<sup>20</sup>. In addition to daily isoniazid (INH or H), the 2018 guidelines also list 3 months of rifampicin and isoniazid (3RH) (in individuals aged <15 years) and 3 months of rifapentine and isoniazid (in adults and children) as suitable regimens for use in countries with high TB incidence. WHO recommendations have been widely incorporated into the national HIV and TB treatment guidelines in many high-burden countries<sup>25,26</sup>.

For countries with a low TB burden, the WHO guidelines<sup>20</sup> recommend the “systematic testing and treatment of LTBI” for people living with HIV, adult and child contacts of TB cases, people initiating anti-tumour necrosis factor-alpha (TNF-) treatment, receiving dialysis, preparing for organ or haematological transplantation, or with silicosis, as well as consideration of the same strategy in prisoners, healthcare workers (HCW), immigrants from high burden countries, homeless persons, and illicit drug users. For treatment, these same guidelines recommend that countries use either six months of daily INH (6H); nine months of daily INH (9H); three months of daily rifampicin (RIF) and INH (3RH); three-to-four months of daily RIF (3R/4R); or three months of once-weekly rifapentine (RPT) and INH (3HP).

### 2.1 LTBI treatment helps reduce TB incidence

Several systematic reviews have been published on the effect of treating latent TB infection on the incidence of TB:

- A wide-ranging review, published in 1970, describes a number of controlled trials of IPT, including several among contacts of people with TB<sup>27</sup>. Studies included were conducted in a wide variety of settings, including Japan, Kenya, and the Philippines. Meta-analysis was not conducted as part of the review, but a number of studies **showed considerably reduced incidence of TB disease among individuals treated with INH, compared with placebo**.
- A 1999 Cochrane review<sup>28</sup> included data on over 73,000 HIV-negative patients in 11 trials, including at least three that were conducted among household contacts (over 28,000 participants in these three trials alone)<sup>29–31</sup>, and **found that the risk of developing TB disease was reduced (for over two years) in people who received treatment with INH (RR 0.40 [95% CI 0.31–0.52])**. It was also estimated that preventive treatment reduced the likelihood of death from TB, but no effect on all-cause mortality was seen.

#### 2.1.1 What about reducing incidence in Persons living with HIV?

- A Cochrane review included results from 12 trials in HIV-positive individuals (n = 8,578 participants)<sup>32</sup> and found that the use of **TB preventive therapy (any drug) was associated with a lower incidence of active TB (RR 0.68 [95% CI 0.54–0.85])**, particularly in people with a positive TST (RR 0.38 [95% CI 0.25–0.57]). This review, however, did not find evidence that TB preventive therapy reduced all-cause mortality among HIV-positive individuals (although some evidence was found for IPT in those with a positive TST and for isoniazid and rifampicin used together
- Another systematic review and meta-analysis of 10 randomised studies (conducted in a variety of settings, from 1993–2014)<sup>33</sup> found that the use of **IPT reduced the incidence of TB among HIV-positive people and that 12 months of IPT reduced the risk of death by 35%**



- A retrospective analysis, in 2005, of medical records of over 11,000 HIV-positive individuals in 29 public health clinics in Brazil<sup>34</sup> found that **the incidence of TB disease in those who had received IPT was lower than in those who had not**. After adjustment for CD4 count, age, and previous TB, IPT alone no longer reduced the risk of TB incidence but IPT in combination with Antiretroviral therapy (ART) was more effective than ART alone
- A prospective cohort of 2,778 HIV-positive individuals in South Africa<sup>35</sup> was followed and the incidence of TB disease measured. In 4,287 person-years (PY) of observation, 267 cases of TB were diagnosed. **Incidence was highest in individuals who did not receive IPT or ART and lowest in those who received ART** after treatment with compared with no IPT or ART
- Another study followed 1,954 HIV-positive adults with positive TST - for up to seven years<sup>36</sup>, with TB incidence the primary outcome. **TB incidence was dramatically lower in those who started IPT (IR 0.53 [95% CI 0.38–0.71] per 100 PY) than in those who did not (IR 6.52 [95% CI 5.21–8.05] per 100 PY.**
- A modelling study by Dowdy et al., published in 2014<sup>37</sup>, used routinely collected data from a cluster-randomised trial of IPT conducted in Brazil to estimate the effects of wider delivery of IPT to the general population and to HIV-positive people in that setting. After five years of implementing an IPT programme (covering around 20% of the ~2,500 individuals eligible per year), the authors estimated a **3.0% (95% CI 1.6–7.2) and 4.0% (95% CI 2.2–10.3) reduction in incidence and mortality in the general population and 15.6% (95% CI 15.5–36.5) and 14.3% (95% CI 14.6–33.7) reduction in incidence and mortality among people living with HIV.**

## 2.2 LTBI treatment also helps reduce all-cause mortality in persons living with HIV

Several studies have demonstrated a mortality benefit from treatment of Latent TB infection:

- An observational cohort study, conducted within a workplace ART programme in South Africa from 2004–2007<sup>38</sup>, examined the impact of IPT on mortality HIV-positive adults taking ART. Among 3,270 adults included, 922 (28%) were started on six months of daily IPT before or within three months of starting ART. After adjustment for age, baseline CD4 count, WHO stage, and year of ART start, **IPT remained associated with reduced mortality** (aHR 0.51 [95% CI 0.32–0.80]).
- The TEMPRANO ANRS 12136 trial<sup>39</sup> assessed the effects of deferred ART vs. deferred ART plus IPT vs. early ART vs. early ART plus IPT on the incidence of AIDS-defining illnesses (and a number of other HIV-related illnesses) or death at 30 months among 2,056 HIV-positive adults in Côte d'Ivoire\*. The investigators found that **the risk of death or severe HIV-related illness was lower with early ART than with deferred ART and lower with IPT than without IPT**. The risk of TB disease was reduced with IPT as well. In a secondary analysis, in which participants were followed up for an extended period (median 4.9 [IQR 3.3–5.8] years; total 9,404 patient-years)<sup>40,41</sup>, the investigators found that **the effect of six months of IPT on reducing mortality risk was maintained, even after adjustment for ART, baseline CD4 count, and study centre.**
- The Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy (REALITY) trial<sup>42</sup>, enrolled 1,805 ART-naïve HIV-positive adults and children (aged >5 years) with CD4 counts <100 cells/μL in Uganda, Zimbabwe, Malawi, and Kenya and randomised them (1:1) to receive either ART plus 'enhanced' antimicrobial prophylaxis (n = 906) or ART plus 'standard' antimicrobial prophylaxis (n = 899). Enhanced prophylaxis consisted of a single dose of albendazole; five days of azithromycin; 12 weeks of fluconazole; and 12 weeks of a combination of co-trimoxazole, isoniazid, and pyridoxine. Standard prophylaxis consisted only of co-trimoxazole. The primary outcome of the trial was death from any cause. At 24 weeks, there were 80 deaths in the 'enhanced' arm vs. 108 in the 'standard' arm (8.9% vs. 12.2%) and this benefit was maintained at 48 weeks. A large reduction in the incidence of TB disease was also seen in the 'enhanced' prophylaxis arm but there was no difference between the two arms in the numbers of deaths attributed to TB.

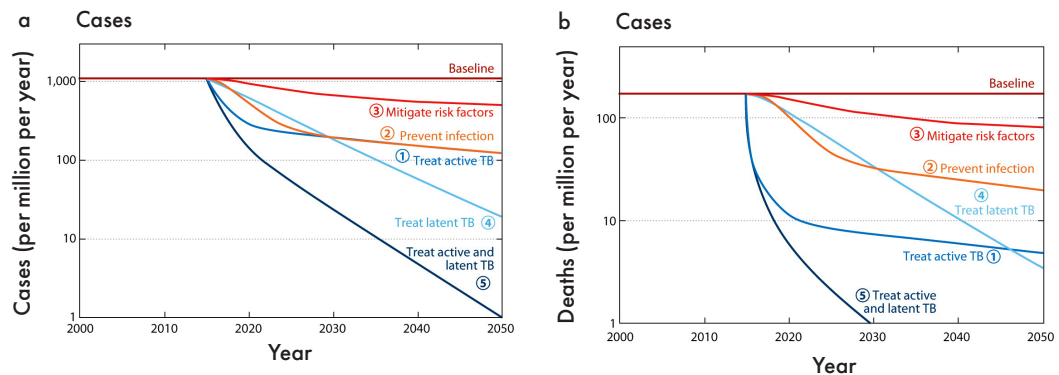
\* NB: Some data from this trial were included in the Ayele 2015 systematic review<sup>33</sup> discussed above.



## 2.3 Preventive treatment is a cost-effective measure to arrive at TB elimination

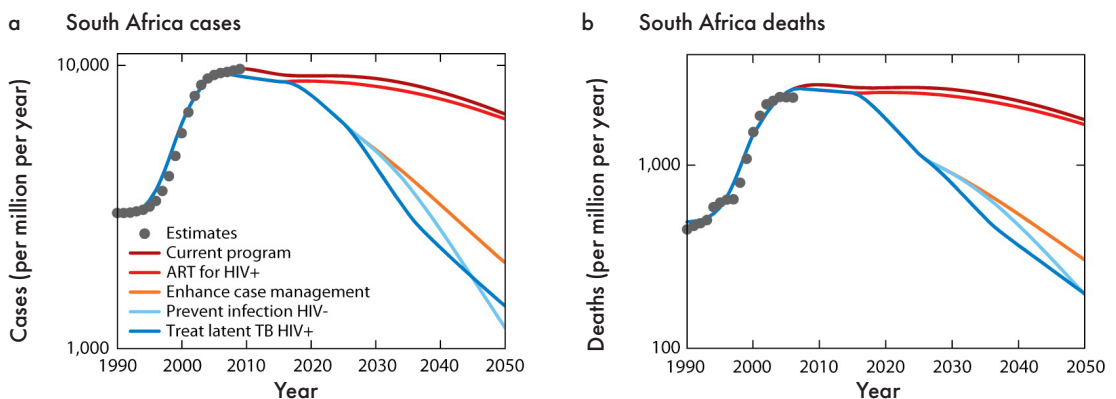
Several reviews<sup>8,12,43,44</sup> and modelling studies have discussed the role of preventive treatment in the efforts to eliminate TB, and the importance of finding cost-effective ways to implement this. In a study published in 2013, Dye et al.<sup>45</sup> suggest that combining multiple strategies is the only way to reduce annual incidence to less than once case per million population by 2050, requiring a 20% annual reduction in incidence and 14% annual reduction in mortality. They also suggest that the most effective way to do this will be to **treat active and latent TB infection (Figure 3), with interventions that work “synergistically and in combination”**. For a country like South Africa, which, in 2010, had the world’s highest per capita incidence of TB disease (almost 1%) and a majority HIV-positive disease burden, the authors suggest that the two major interventions needed are improved case management (to interrupt transmission) and the scale-up of TB preventive therapy (Figure 4).

**Figure 3. Strategies for (a) eliminating TB (<1 case per million per year) and (b) approaching the elimination phase (<10 deaths per million per year or <1 death per 100,000 per year; from Dye et al., 2013<sup>45</sup>)**



Based on a hypothetical high-incidence country with a poorly controlled epidemic (65% case detection, 70% cure) and an initial stable incidence of 1,100 cases and 200 deaths per million per year. TB: tuberculosis

**Figure 4. Prospects for TB control and elimination in South Africa (from Dye et al., 2013<sup>45</sup>)**

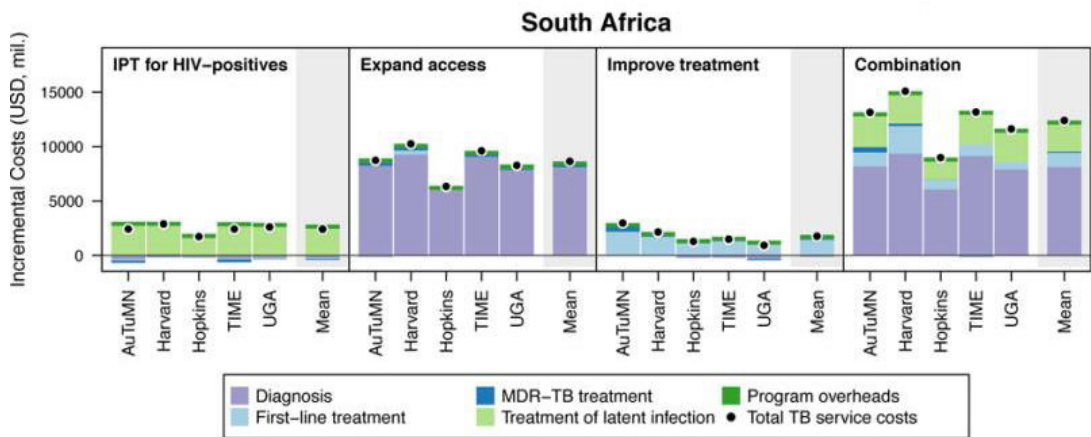


Points are WHO estimates based on the data available for the country.  
ART: antiretroviral therapy; HIV-: HIV-negative; HIV+: HIV-positive; TB: tuberculosis

A more recent study, combining the projections of 11 different models for South Africa, China, and India, reiterated this message, showing that scale-up of any one intervention could not achieve the End TB goals in any of these three countries<sup>46</sup>. For South Africa, however, the authors suggested that a combination of continuous IPT in people on ART along with expanded symptom screening and improved TB care could achieve a 55% (range 31%–62%) reduction in incidence and a 72% (range 64%–82%) reduction in mortality (compared with 2015).

In a separate article, the same group<sup>47</sup>, combining the outputs of nine models, presented projections around the health impacts and resource implications for 2016–2036 for South Africa, India, and China, based on a number of scenarios. Interventions for SA included continuous IPT for all people on ART (with a target of coverage of 80% of people on ART by 2021; Figure 5). **For all countries and for almost all intervention scenarios, the expansion of TB services (access to care, in particular), produced substantial health gains.** The cost per DALY averted for the interventions included was below country per capita GDP (the conventional threshold for identifying highly cost-effective interventions), even before consideration of patient cost-savings.

**Figure 5. Incremental TB service costs for each intervention scenario in South Africa, as compared to base case, by model (from Menzies et al., 2016<sup>47</sup>)**



Costs (2014 USD) represent incremental costs for the period 2016–2035, as compared to base case. IPT: isoniazid preventive therapy; MDR: multidrug-resistant; TB: tuberculosis; USD: United States dollars

### 3. Why should we use a rifapentine-based regimen for treating Latent TB infection?

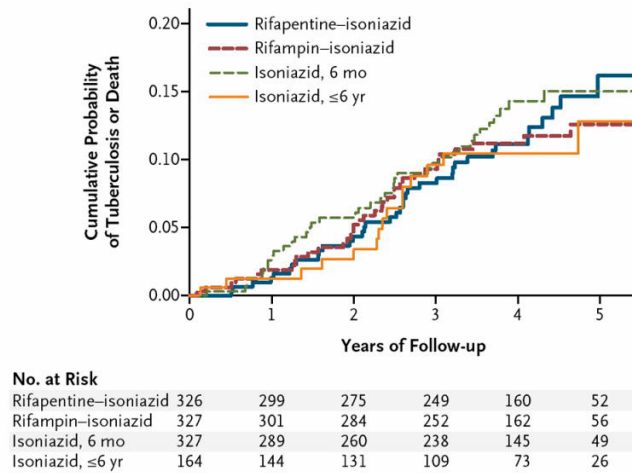
A Cochrane review, published in 2013<sup>48</sup>, compared the effectiveness of rifamycins (rifampicin, rifabutin, and rifapentine) with isoniazid in preventing TB disease in HIV-negative people and concluded that **“A weekly regimen of rifapentine plus INH has higher completion rates, and less liver toxicity, though treatment discontinuation due to adverse events is probably more likely than with INH”**. A subsequent systematic review by Vidal et al., published in 2015<sup>49</sup>, provides a useful summary of some of the literature around the effectiveness and safety of 3HP. A broader review and network meta-analysis of LTBI treatment, published in 2017 by Zenner et al.<sup>50</sup>, found that the **odds of active TB after treatment with 3HP were similar to those after being treated with six or twelve months of isoniazid or three months of rifampicin and isoniazid**, as did a systematic review and network meta-analysis by Pease et al.<sup>51</sup>.

#### 3.1 Is 3HP effective in adults?

Three large trials have attempted to measure the effectiveness of 3HP in preventing TB disease compared with isoniazid monotherapy (and a number of other treatment regimens; Table 1).

- “PREVENT TB”, conducted in Brazil, Canada, Spain, and the USA from 2001–2008 randomised 7,731 individuals aged  $\geq 12$  years to receive 3HP with directly-observed therapy (DOT) or nine months of isoniazid (9H) through self-administered therapy (SAT)<sup>52</sup>. **TB incidence was low in both arms, with 3HP found to be non-inferior to 9H in preventing TB disease.**
- In a recently published analysis of data from HIV-positive individuals enrolled in PREVENT<sup>53</sup>, Sterling et al. present a modified intention-to-treat (MITT) analysis. The incidence rates of TB disease in the MITT analysis were 0.39 per 100 PY and 1.25 per 100 PY in the 3HP and 9H arms, respectively. The difference in cumulative TB rate was  $-2.49\%$ , with the upper bound of the 95% CI at 0.6%, meeting the criteria for non-inferiority.
- In Brazil, from 2001–2005, Schechter et al.<sup>54</sup> randomised 399 adult household contacts to receive either 3HP or eight weeks of rifampicin and pyrazinamide<sup>55</sup>. Due to the high levels of hepatotoxicity observed in the rifampicin/pyrazinamide arm, the trial was stopped early (the original enrolment target was 720), but all 399 individuals enrolled were followed up for two years, with **little difference in the incidence of TB between the two arms.**
- Martinson et al.<sup>56</sup> enrolled 1,150 HIV-positive adults with CD4 counts of  $\geq 200$  cells/ $\mu\text{L}$  who were not on ART and randomised them (2:2:2:1) to receive 3HP (directly observed therapy - DOT); 12 weeks of twice-weekly RIF and INH (DOT); up to six years of daily INH (self administered therapy - SAT); or six months of daily INH (SAT). **TB incidence in all arms was similar**, with 3HP non-inferior to other regimens (Figure 6).

Figure 6. Kaplan–Meier estimates of the risk of tuberculosis or death in the intention-to-treat population, according to treatment group (from Martinson et al., 2011<sup>56</sup>)



Reported very recently at the 2018 Conference on Retroviruses and Opportunistic Infections (CROI), the ACTG 5279 study<sup>57</sup> enrolled 3000 HIV-positive individuals aged  $\geq 13$  years in 10 high TB incidence settings from 2012–2014, randomized them (1:1) to receive one month of daily rifapentine and isoniazid (1HP) or 9H, and followed them up for three years, comparing the incidence of active TB, death due to TB, or death from an unknown cause. **1HP was non-inferior to 9H**: incidence rates of primary endpoints in the 1HP arm were similar to the 9H arm. In both treatment groups, TB incidence rates were higher in those not on ART and those with a positive TST or interferon-gamma release assay (IGRA); similar numbers of serious adverse events were seen in both treatment groups. Importantly, treatment completion rates were higher among those taking 1HP.

Table 1. Summary of published phase III and IV trials of effectiveness of 1HP/3HP in preventing active TB disease in adults

First author, year published	Country/ies	Setting & population	N	Relevant results												
Swindells, 2018 <sup>57</sup>	Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe	HIV-positive, aged ≥13 years	3,000	<p><b>1HP was non-inferior to 9H among HIV-positive individuals, 50% of whom were on ART at enrolment</b></p> <p>34 vs. 35 primary endpoints achieved in 1HP vs. 9H arms (active TB, death due to TB, or death from unknown cause; confirmed or probable TB 29 vs. 24 in 1HP vs. 9H arms) Any endpoint, IR 0.69 vs. 0.72 per 100 PY; IRR 0.025 (95% CI -0.30-0.35)</p>												
Sterling, 2016 <sup>53</sup> †	Brazil, Canada, Hong Kong, Peru, Spain, USA	HIV-positive, aged ≥2 years, 2001–2010	399	<p><b>3HP was non-inferior to 9H among HIV-positive adults, 69% of whom were not taking ART</b></p> <p>2 vs. 6 cases in 3HP vs. 9H arms aHR 0.27 (95% CI 0.05–1.44), p = 0.13</p>												
Sterling, 2011 <sup>52</sup>	Brazil, Canada, Spain, USA	Aged ≥2 years, close contact with TB or HIV-positive, 2001–2008	7,731	<p><b>3HP was non-inferior to 9H</b></p> <p>7 vs. 16 cases/100 PY in 3HP vs. 9H arms aHR 0.38 (95% CI 0.15–0.99), p = 0.05</p>												
Martinson, 2011 <sup>56</sup>	South Africa	HIV-positive adults attending primary care, 2002–2005	1,150	<p><b>3HP was non-inferior to 6H</b></p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>3HP vs. 6H, IRR (95% CI)</th> <th>3RH vs. 6H, IRR (95% CI)</th> <th>≤6y H vs. 6H, IRR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>TB</td> <td>1.05 (0.56–1.97); p = 0.87;</td> <td>1.02 (0.55–1.91); p = 0.94</td> <td>0.74 (0.29–1.73); p = 0.48</td> </tr> <tr> <td>TB or death</td> <td>0.87 (0.54–1.39); p = 0.54</td> <td>0.80 (0.50–1.29); p = 0.34</td> <td>0.75 (0.38–1.38); p = 0.34</td> </tr> </tbody> </table>	Outcome	3HP vs. 6H, IRR (95% CI)	3RH vs. 6H, IRR (95% CI)	≤6y H vs. 6H, IRR (95% CI)	TB	1.05 (0.56–1.97); p = 0.87;	1.02 (0.55–1.91); p = 0.94	0.74 (0.29–1.73); p = 0.48	TB or death	0.87 (0.54–1.39); p = 0.54	0.80 (0.50–1.29); p = 0.34	0.75 (0.38–1.38); p = 0.34
Outcome	3HP vs. 6H, IRR (95% CI)	3RH vs. 6H, IRR (95% CI)	≤6y H vs. 6H, IRR (95% CI)													
TB	1.05 (0.56–1.97); p = 0.87;	1.02 (0.55–1.91); p = 0.94	0.74 (0.29–1.73); p = 0.48													
TB or death	0.87 (0.54–1.39); p = 0.54	0.80 (0.50–1.29); p = 0.34	0.75 (0.38–1.38); p = 0.34													
Schechter, 2006 <sup>55</sup>	Brazil	Adult household contacts of 236 TB patients, 2001–2005	399	<p><b>3HP was non-inferior to and less hepatotoxic than 8 weeks of daily RIF/Pz</b></p> <p>3 vs. 1 case in 3HP vs. 8 weeks of daily RIF/Pz arms IRR 2.8 (95% CI 0.3–26.8); p = 0.66</p>												

†Partially a sub-set of Sterling 2011<sup>52</sup>

1HP: 1 month of daily rifapentine and isoniazid; 3HP: 3 months of once-weekly rifapentine and isoniazid; 3RH: 3 months of twice-weekly rifampicin and isoniazid; 6H: 6 months of daily isoniazid; 9H: 9 months of daily isoniazid; aHR: adjusted hazard ratio; ART: antiretroviral therapy; H: Isoniazid; HR: hazard ratio; IR incidence rate; IRR: incidence rate ratio; m: month(s); MDR: multi drug-resistant; neg.: negative; od: once per day; OR: odds ratio; PY: person-year(s); Pz: pyrazinamide; RIF: rifampicin; TB: tuberculosis; tx: treatment; w: week; y: year(s)

## 3.2 Is 3HP effective in children and adolescents?

Two studies have examined the pharmacokinetics of RPT in children.

- Blake et al. in 2006<sup>58</sup>, gave a single dose of RPT (150 mg or 300 mg) to 24 children aged 2–12 years and found a difference in the dose-normalised area under the concentration-time curve (AUC) between children receiving the two doses, concluding that a larger weight-normalised dose was needed in children, compared with adults.
- PREVENT<sup>59</sup> compared pharmacokinetics in 80 children (aged 2–12 years; doses of 300–900 mg) and 77 adult controls (900 mg), measuring levels of RPT metabolite (C24) in all subjects. Mean AUCs of C24 were 1.3 times higher in children than in adults, 1.3 times higher in children who swallowed whole tablets than crushed tablets, and 1.6 times higher in children who swallowed whole tablets than in adults. The authors concluded that the **use of higher weight-adjusted RPT doses are needed for young children** to achieve exposures associated with successful treatment in adults.
- PREVENT also provided a modified intention to treat analysis in 905 patients aged 2–17 years old<sup>60</sup> which found that 3HP (+ DOT) was non-inferior to 9H.
- A small cohort study in Colorado<sup>61</sup> found no difference in TB incidence between school contacts of a TB case (n = 161 overall; at least 58 children) taking 9H, 4R, or 3HP regimens.

The 2011 CDC guidelines on LTBI treatment recommend the use of 3HP in children aged  $\geq 12$  years<sup>62</sup>. However, they also state that for children aged 2–11 years, the number receiving 3HP was “insufficient for assessing tolerability and efficacy”, and for children aged  $\leq 2$  years, the absence of data on “the safety and pharmacokinetics of rifapentine” meant that it could not be recommended<sup>62</sup>.

Data are still needed around the efficacy, tolerability, and safety of rifapentine and 3HP in children aged  $\leq 2$  years, and, though findings from observational studies in the USA are encouraging more real-world data are also needed around barriers to the implementation of 3HP in paediatric and adolescent populations, particularly in settings outside of the United States<sup>65,66</sup>.

## 3.3 Does 3HP improve adherence and treatment completion?

### 3.3.1 Do shorter regimens improve treatment completion?

Three reviews found that individuals on shorter regimens (most often 3–4 months of rifampicin or rifamycin or rifampicin + isoniazid) were more likely to complete the treatment course:

- Sandgren et al.<sup>67</sup> reviewed 95 studies describing initiation (n = 45 studies) and completion (n = 83 studies) of LTBI treatment published before February 2014
- Stuurman et al.<sup>68</sup> systematically reviewed articles describing determinants of initiation and completion (n = 62 articles) and interventions to improve initiation and completion (n = 23 articles), published before February 2014
- Liu et al.<sup>69</sup> reviewed 54 quantitative and qualitative studies addressing barriers to treatment adherence for LTBI treatment in countries with a low TB burden, published before July 2016.

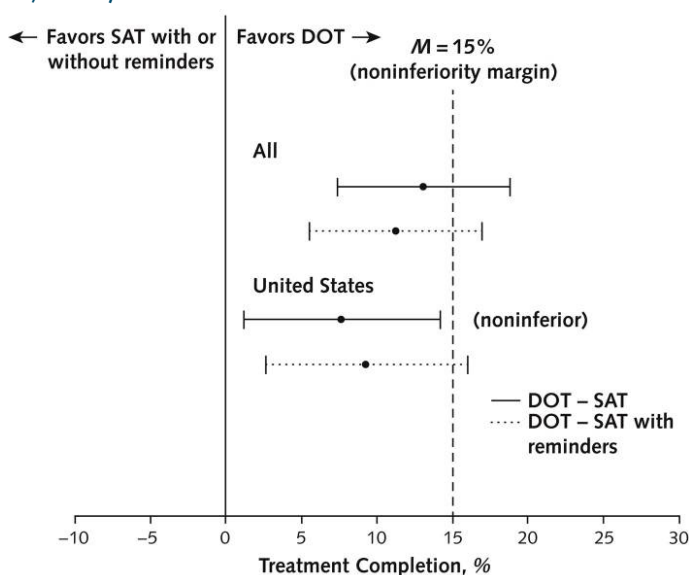
### 3.3.2 Do rifapentine-based regimens improve adherence and treatment completion?

Pease et al.<sup>51</sup> described treatment completion for 3HP in comparison with other treatment regimens. Shorter treatment regimens were associated with higher completion; this association was strongest for rifamycin-based regimens. The odds ratios of completion of 3HP compared with INH for six, nine, and 12–72 months were 2.41 (95% CI 1.26–4.65), 2.19 (95% CI 1.14–4.30), and 3.07 (95% CI 1.37–6.37), respectively.

Many of the large randomised trials reported adherence as a secondary outcome (Table 2):

- The PREVENT TB study (n = 7,731)<sup>52</sup> found that rates of treatment completion were considerably higher for participants taking directly-observed 3HP arm than for those taking nine months of self-administered isoniazid (82.1% vs. 69.0% for 3HP vs. 9H; p < 0.001), as did the paediatric sub-study (n = 1,058; 88.1% vs. 80.9%; p = 0.003)<sup>60</sup>. Martinson et al.<sup>56</sup> and Schechter et al.<sup>55</sup> found no difference in treatment completion between groups taking 3HP or other regimens (except long-term [≤6 years] of daily isoniazid, where 37% of participants stopped treatment).
- Huang et al. studied 691 individuals aged ≥12 years who received 3HP in Taiwan (n = 101) or 9H (n = 590) and found that participants in the 9H arm were four times as likely to not finish their course of treatment (non-completion in 3.0% vs. 12.7% for 3HP vs. 9H; p < 0.001).
- The iAdhere study, conducted in outpatient clinics in Hong Kong, South Africa, Spain, and the USA (77% of participants from the USA) from 2012–2014, randomised 1,002 adults to receive 3HP with either directly observed therapy (DOT), self-administered therapy (SAT) without any reminders, or SAT with weekly text message reminders<sup>72</sup>. Treatment completion in the DOT group (87.2%) was higher than in either SAT group (74.0% without reminders; 76.4% with reminders). When the analysis was restricted to participants in the USA only, 'SAT no reminder' was non-inferior to DOT.

Figure 7. Weighted treatment completion for all participants in the iAdhere study, by study group (from Belknap et al., 2017<sup>72</sup>)



DOT: directly observed therapy; SAT: self-administered therapy

A number of observational studies, all conducted in the USA, have also assessed completion rates of 3HP for LTBI (Table 2). Most have found 3HP (with DOT) to have similar completion rates to other short regimens (such as 4R) and better completion rates than longer INH regimens.



Table 2. Summary of published studies evaluating adherence to and/or completion of rifapentine-based therapy for LTBI in adults and children (n = 18 articles)

First author, year published	Country /ies	Setting & population	N	Relevant findings
<b>Randomised trials</b>				
<b>Swindells, 2018</b> <sup>57</sup>	Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe	HIV-positive, aged ≥13 years	3,000	<b>1HP + SAT:</b> 97% completion <b>9H + SAT:</b> 90% completion
<b>Belknap, 2017</b> <sup>72</sup>	Hong Kong, South Africa, Spain, USA	Adults attending outpatient clinics from 2012–2014	1,002	<b>Overall (n = 1,002)</b> <b>3HP + DOT:</b> 87.2% completion <b>3HP + SAT (no text):</b> 74.0% completion <b>3HP + SAT (with text):</b> 76.4% completion  <b>USA only (n = 774)</b> <b>3HP + DOT:</b> 85.4% completion <b>3HP + SAT (no text):</b> 77.9% completion <b>3HP + SAT (with text):</b> 76.7% completion
<b>Huang, 2016</b> <sup>71</sup>	Taiwan	Aged ≥12 years, contact with drug-sensitive TB, 2014	691	<b>3HP + DOT:</b> 97.0% completion <b>9H + SAT:</b> 87.3% completion 3HP vs. 9H, 25% (95% CI 17–33) difference, p <0.001
<b>Sterling, 2016</b> <sup>53†</sup>	Brazil, Canada, Hong Kong, Peru, Spain, USA	HIV-positive, aged ≥2 years, 2001–2010	399	<b>3HP + DOT:</b> 88.8% completion <b>9H + SAT:</b> 63.7% completion 3HP vs 9H, p <0.001
<b>Villarino, 2015</b> <sup>60</sup>	Brazil, Canada, Hong Kong, Spain, USA	Aged 2–17 years, 2001–2010	1,058	<b>3HP + DOT:</b> 88.1% completion <b>9H + SAT:</b> 80.9% completion 3HP vs. 9H, p = 0.003
<b>Sterling, 2011</b> <sup>52</sup>	Brazil, Canada, Spain, USA	Aged ≥2 years, close contact with TB or HIV-positive, 2001–2008	7,731	<b>3HP + DOT:</b> 82.1% completion <b>9H + SAT:</b> 69.0% completion 3HP vs 9H, p <0.001
<b>Martinson, 2011</b> <sup>56</sup>	South Africa	HIV-positive adults attending primary care, 2002–2005	1,150	<b>3HP + DOT:</b> 98.2% completion <b>3RH:</b> 96.2% completion <b>≤6y daily INH:</b> 63.5% completion <b>6H + SAT:</b> 98.1% completion
<b>Schechter, 2006</b> <sup>55</sup>	Brazil	Adult household contacts of 236 TB patients, 2001–2005	399	<b>3HP + DOT:</b> 93% completion <b>8w daily RIF/Pz:</b> 94% completion 3HP vs. 8w daily RIF/Pz, p = 0.82

First author, year published	Country /ies	Setting & population	N	Relevant findings																		
<b>Observational studies</b>																						
<b>Cruz, 2018<sup>73</sup></b>	USA	Aged ≤18 years, attending one hospital-based TB clinic	667	Seven different regimens/combinations used <table border="1"> <thead> <tr> <th>Regimen</th> <th>Completion, %</th> <th>OR (95% CI)</th> </tr> </thead> <tbody> <tr> <td><b>3HP</b></td> <td>96.8</td> <td>27.4 (12–64)</td> </tr> <tr> <td><b>4R (DOT)</b></td> <td>97.1</td> <td>30.6 (4–239)</td> </tr> <tr> <td><b>4R (SAT)</b></td> <td>83.5</td> <td>4.6 (2–10)</td> </tr> <tr> <td><b>9H (DOT)</b></td> <td>88.8</td> <td>7.1 (4–14)</td> </tr> <tr> <td><b>9H (SAT)</b></td> <td>52.6</td> <td>[Ref]</td> </tr> </tbody> </table>	Regimen	Completion, %	OR (95% CI)	<b>3HP</b>	96.8	27.4 (12–64)	<b>4R (DOT)</b>	97.1	30.6 (4–239)	<b>4R (SAT)</b>	83.5	4.6 (2–10)	<b>9H (DOT)</b>	88.8	7.1 (4–14)	<b>9H (SAT)</b>	52.6	[Ref]
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<b>9H (SAT)</b>	52.6	[Ref]																				
<b>Sandul, 2017<sup>74</sup></b>	USA	Aged ≥2 years, attending 16 clinics from 2011–2013	3,327	<b>Overall:</b> 87.2% completion <b>Recently homeless:</b> 81.2% completion <b>Recently incarcerated:</b> 87.4% completion																		
<b>Holzshuch, 2017<sup>75</sup></b>	USA	High school students and staff	50	<b>3HP + DOT:</b> 96.3% completion <b>4R + SAT:</b> 100% completion <b>9H + SAT:</b> 85.7% completion																		
<b>Jinbo, 2017<sup>76</sup></b>	USA (Hawaii)	Adults attending military clinics, 2014–2015	179	<b>3HP + DOT:</b> 91.6% completion <b>4R + SAT:</b> 82.6% completion <b>9H + SAT:</b> 66.3% completion 3HP vs. 9H, $p < 0.001$ ; 3HP vs. 4R, $p = 0.038$ ; 3HP vs. 9H/4R, $p < 0.001$																		
<b>Eastment, 2017<sup>77</sup> ; McClintock, 2017<sup>78</sup></b>	USA	Adults attending outpatient clinics	393	<b>3HP:</b> 85.1% completion <b>4R:</b> 85.4% completion <b>9H:</b> 52.2% completion																		
<b>Stennis, 2016<sup>79</sup></b>	USA	Aged ≥12 years, attending two TB clinics	394	<b>3HP + DOT:</b> 65% completion <b>Other regimens:</b> 46% completion																		
<b>Cruz 2016<sup>80</sup> ‡</b>	USA	Aged ≤21 years, attending one hospital-based TB clinic	80	<b>3HP + DOT:</b> 98.8% completion																		
<b>Yamin, 2016<sup>81</sup></b>	USA	Adults treated for LTBI at one TB clinic	424	<b>3HP + DOT:</b> 79.2% completion <b>4R + SAT:</b> 70.7% completion <b>9H + SAT:</b> 65.2% completion Between three regimens, $p = 0.18$																		
<b>Hatzenbuehler 2016<sup>82</sup></b>	USA	Adolescents attending two public schools	16	<b>3HP + DOT:</b> 100% completion																		
<b>CDC, 2013<sup>61</sup></b>	USA	School contacts with LTBI	161	<b>3HP:</b> 93.8% completion <b>4R:</b> 96.7% completion <b>9H:</b> 100% completion																		

†Subset of Sterling, 2011<sup>52</sup>

‡Possibly a subset of Cruz, 2018<sup>73</sup>

1HP: 1 month of daily rifapentine and isoniazid; 3HP: 3 months of weekly rifapentine and isoniazid; 3RH: 3 months of twice-weekly rifampicin and isoniazid; 4R: 4 months of daily rifampicin; 6H: 6 months of daily isoniazid; 9H: 9 months of daily isoniazid; DOT: directly observed therapy; INH: isoniazid; LTBI: latent tuberculosis infection; Pz: pyrazinamide; Ref: reference; RIF: rifampicin; SAT: self-administered therapy; TB: tuberculosis; USA: United States of America

### 3.4 Does 3HP cause more toxicity and side effects?

The large randomised trials also reported estimates of treatment-related toxicity, most importantly hepatotoxicity. The PREVENT TB study<sup>52</sup> reported overall adverse events (AEs) attributable to the study drug in 8.4% vs. 5.4% of participants receiving 3HP and 9H, respectively (Table 3). In a post-hoc analysis<sup>83</sup>, however, the investigators describe an increased likelihood of systemic drug reactions in individuals receiving 3HP than in those receiving 9H (aOR 9.4 [95% CI 5.5–16.2]). Most systemic drug-reactions were flu-like events (described as fever or chills with weakness, fatigue, or muscle pain, and any of aches, syncope, heart rate >100 beats per minute, palpitations, flushing, dizziness, conjunctivitis, or sweats), and most were not clinically severe (90.6% and 93.3% of systemic drug reactions were non-severe in 3HP and 9H arms, respectively)<sup>83</sup>. In a second post-hoc analysis, the PREVENT TB team presented hepatotoxicity data, showing that incidence of treatment-limiting hepatotoxicity (symptomatic or asymptomatic) was lower in those receiving 3HP than in those receiving 9H (0.4% [95% CI 0.2–0.6] vs. 1.8% [95% CI 1.4–2.3] in 3HP vs. 9H; RR 4.42 [95% CI 2.52–7.75];  $p < 0.0001$ ).

Table 3. Summary of published studies describing toxicity and adverse events associated with rifapentine-based regimens for LTBI treatment in adults and children (n = 13)

First author, year published	Country /ies	Setting & population	N	Relevant findings
<b>Randomised trials</b>				
Swindells, 2018 <sup>57</sup>	Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe	HIV-positive, aged ≥13 years	3,000	<p><b>Grade 3 or 4 adverse events</b> 16.8% vs. 18.3% in 1HP vs. 9H</p> <p><b>Hepatic adverse events (grade 3 or 4)</b> 1.9% vs. 2.8% in 1HP vs. 9H</p> <p><b>Targeted safety events (liver, GI, neurologic, skin, hypersensitivity)</b> 5.7% vs. 7.2% in 1HP vs. 9H; IRR 9H vs. 1HP 1.59 (95% CI 1.1–2.3), <math>p = 0.016</math></p>
Belknap, 2017 <sup>72</sup>	Hong Kong, South Africa, Spain, USA	Adults attending outpatient clinics from 2012–2014	1,002	<p><b>Any adverse event</b> 15.7% vs. 17.5% vs. 18.9% in DOT vs. SAT, no text vs. SAT+text arms (all ppts received 3HP)</p> <p><b>Any drug-related adverse event</b> 7.1% vs. 8.3% vs. 7.9% in DOT vs. SAT, no text vs. SAT+text arms</p> <p><b>Grade 3 or 4 drug-related adverse events</b> 2.4% vs. 3.0% vs. 4.3% in DOT vs. SAT, no text vs. SAT+text arms</p> <p><b>Adverse events causing treatment discontinuation</b> 3.6% vs. 5.6% vs. 4.3% in DOT vs. SAT, no text vs. SAT+text arms</p>
Huang, 2016 <sup>71</sup>	Taiwan	Aged ≥12 years, contact with drug-sensitive TB, 2014	691	<p><b>Grade 3 or 4 side-effects</b> 4.0% vs. 1.2% in 3HP vs. 9H arms</p> <p><b>Side-effects causing treatment discontinuation</b> 2.0% vs. 4.7% in 3HP vs. 9H arms</p>

First author, year published	Country /ies	Setting & population	N	Relevant findings								
<b>Sterling, 2016</b> <sup>53†</sup>	Brazil, Canada, Hong Kong, Peru, Spain, USA	HIV-positive, aged ≥2 years, 2001–2010	399	<p><b>Grade 3 or 4 adverse events</b> 2.9% vs. 8.6% in 3HP vs. 9H arms</p> <p><b>Adverse events causing treatment discontinuation</b> 3.4% vs. 4.3% in 3HP vs. 9H arms</p> <p><b>Death</b> 2.9% vs. 2.6% in 3HP vs. 9H arms</p>								
<b>Villarino, 2015</b> <sup>60</sup>	Brazil, Canada, Hong Kong, Spain, USA	Aged 2–17 years, 2001–2010	1,058	<p><b>Any adverse event</b> <b>Grade 3:</b> 0.6% vs. 0.2% in 3HP vs. 9H arms; <i>p</i> = 0.49 <b>Grade 4:</b> 0.0% vs. 0.4% in 3HP vs. 9H arms; <i>p</i> = 0.61</p> <p><b>Adverse events attributed to treatment</b> <b>Grade 3:</b> 0.6% vs. 0.2% in 3HP vs. 9H arms; <i>p</i> = 0.63 No Grade 4, 5, or other serious AE attributable to treatment in either arm</p>								
<b>Sterling, 2011</b> <sup>52</sup> ; <b>Bliven-Sizemore, 2015</b> <sup>84</sup> ; <b>Sterling, 2015</b> <sup>83</sup>	Brazil, Canada, Spain, USA	Aged ≥2 years, close contact with TB or HIV-positive, 2001–2008	7,731	<p><b>Adverse events</b> (post-hoc analysis; <i>n</i> = 7,552)<sup>83</sup>: <b>Attributable to study drug</b> 8.4% vs. 5.4% in 3HP vs. 9H arms</p> <p><b>Systemic drug reactions</b> 3.5% vs. 0.4% in 3HP vs. 9H arms; <i>aOR</i> 9.4 (95% CI 5.5–16.2), <i>p</i> &lt; 0.001</p> <p><b>Severe adverse events</b> 0.3% vs. 0.03% in 3HP vs. 9H arms</p> <p><b>Hepatotoxicity</b> (post-hoc analysis; <i>n</i> = 6,862)<sup>84</sup> 0.4% vs. 1.8% in 3HP vs. 9H arms; <i>aRR</i> 4.55 (2.5–8.2), <i>p</i> &lt; 0.0001</p> <p><b>Death</b> 0.8% vs. 1% in 3HP vs. 9H arms; <i>p</i> = 0.22</p>								
<b>Martinson, 2011</b> <sup>56</sup>	South Africa	HIV-positive adults attending primary care, 2002–2005	1,150	<p><b>Any adverse event</b> 66% vs. 64% vs. 84% vs. 66% per 100 enrolled patients in 3HP vs. 3RH vs. ≤6y H vs. 6H arms</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>3HP vs. 6H, IRR (95% CI)</th> <th>3RH vs. 6H, IRR (95% CI)</th> <th>≤6y H vs. 6H, IRR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Death</td> <td>0.66 (0.33–1.26); <i>p</i> = 0.18</td> <td>0.59 (0.30–1.16); <i>p</i> = 0.10</td> <td>0.66 (0.26–1.50); <i>p</i> = 0.31</td> </tr> </tbody> </table>	Outcome	3HP vs. 6H, IRR (95% CI)	3RH vs. 6H, IRR (95% CI)	≤6y H vs. 6H, IRR (95% CI)	Death	0.66 (0.33–1.26); <i>p</i> = 0.18	0.59 (0.30–1.16); <i>p</i> = 0.10	0.66 (0.26–1.50); <i>p</i> = 0.31
Outcome	3HP vs. 6H, IRR (95% CI)	3RH vs. 6H, IRR (95% CI)	≤6y H vs. 6H, IRR (95% CI)									
Death	0.66 (0.33–1.26); <i>p</i> = 0.18	0.59 (0.30–1.16); <i>p</i> = 0.10	0.66 (0.26–1.50); <i>p</i> = 0.31									
<b>Schechter, 2006</b> <sup>55</sup>	Brazil	Adult household contacts of 236 TB patients, 2001–2005	399	<p><b>Grade 3 or 4 hepatotoxicity</b> 1% vs 10% in 3HP vs. RIF/Pz arms; <i>p</i> &lt; 0.001 (Trial stopped early because of hepatotoxicity in RIF/Pz arm)</p>								

First author, year published	Country /ies	Setting & population	N	Relevant findings
<b>Observational studies</b>				
Cruz, 2018 <sup>73</sup>	USA	Aged ≤18 years, attending one hospital-based TB clinic	667	<p><b>Any adverse event</b> 8.5% vs. 4.8% vs. 13.7% in 3HP vs. 4R vs. 9H arms</p> <p><b>Grade 3 or 4 adverse events</b> 0% vs. 0% vs. 0.4% in 3HP vs. 4R vs. 9H arms</p>
Sandul, 2017 <sup>74</sup>	USA	Aged ≥2 years, attending 16 clinics from 2011–2013	3,327	<p><b>Any adverse event/adverse drug reaction</b> 35.7% of participants taking 3HP</p> <p><b>Adverse events causing discontinuation</b> 7.5% of participants taking 3HP (20.9% of those with any adverse event)</p>
Jinbo, 2017 <sup>76</sup>	USA (Hawaii)	Adults attending military clinics, 2014–2015	179	<p><b>Symptom reported</b> Minimum 21.2% of participants taking 3HP‡</p> <p><b>Symptom/s causing treatment discontinuation</b> 6.1% of participants taking 3HP</p>
Stennis, 2016 <sup>79</sup>	USA	Aged ≥12 years, attending two TB clinics	394	<p><b>Any side-effect</b> 13.2% of participants taking 3HP</p> <p><b>Side-effect/s causing treatment discontinuation</b> 4.3% of participants taking 3HP</p>
Yamin, 2016 <sup>81</sup>	USA	Adults treated for LTBI at one TB clinic	424	<p><b>Any adverse event</b> 20.8% vs. 9.7% vs. 21.7% in 3HP vs. 4R vs. 9H arms</p> <p><b>Hepatotoxicity</b> 0% vs. 0.4% vs. 3.5% in 3HP vs 4R vs. 9H arms</p> <p><b>Adverse event causing change in regimen</b> 5.7% vs. 3.9% vs. 15.7% in 3HP vs. 4R vs. 9H arms</p>
Hatzenbuehler 2016 <sup>82</sup>	USA	Adolescents attending two public schools	16	All 16 students were treated with 3HP; no significant adverse events recorded during treatment

†Subset of data presented by Sterling, 2011<sup>52</sup>

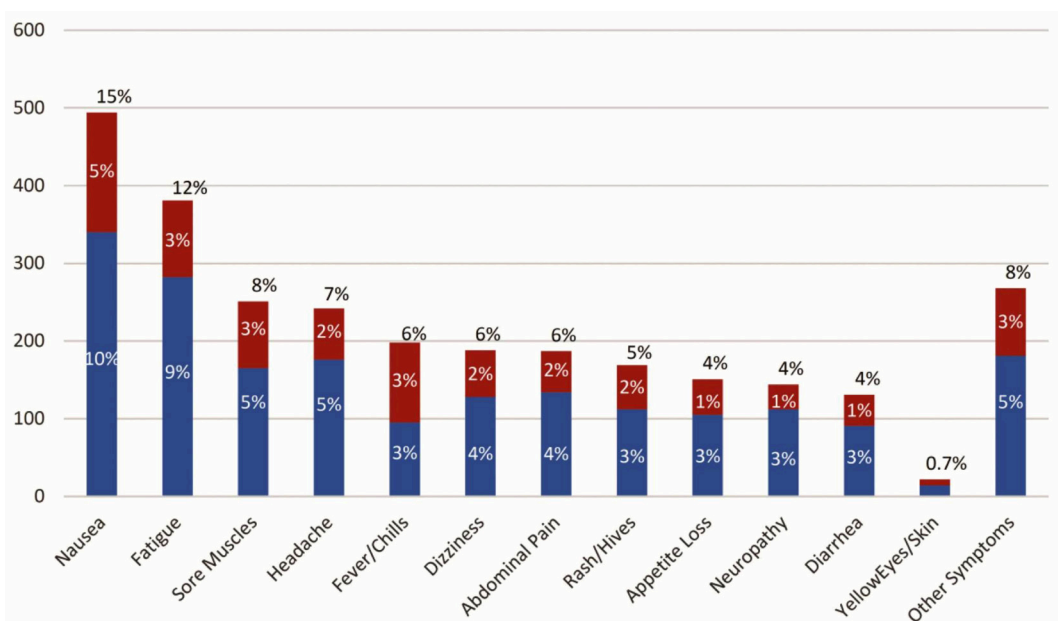
‡Only number experiencing each symptom reported – total number of participants unclear; excludes participants reporting “orange coloured urine”, as this is an expected side-effect of treatment with rifamycins

1HP: 1 month of daily rifapentine and isoniazid; 3HP: 3 months of weekly rifapentine and isoniazid; 3RH: 3 months of twice-weekly rifampicin and isoniazid; 4R: 4 months of daily rifampicin; 6H: 6 months of daily isoniazid; 9H: 9 months of daily isoniazid; DOT: directly observed therapy; INH: isoniazid; LTBI: latent tuberculosis infection; Pz: pyrazinamide; RIF: rifampicin; SAT: self-administered therapy; TB: tuberculosis; USA: United States of America

For children enrolled to PREVENT TB, Villarino et al.<sup>60</sup>, reported similar incidence of Grade 3 AEs in 3HP and 9H arms (0.6% vs. 0.2%;  $p = 0.49$ ) and very low incidence of Grade 4 AEs in both arms (0.0% vs. 0.4%;  $p = 0.61$ ). This relationship was the same when only AEs related to treatment were considered (Grade 3 AEs 0.6% vs. 0.2% in 3HP vs. 9H arms;  $p = 0.63$ ). No hepatotoxicity was reported among children receiving 3HP or 9H<sup>60</sup>.

A number of observational studies have also reported on safety and adverse events recorded with 3HP use (summarised in Table 3). The largest of these, by Sandul et al.<sup>74</sup>, followed up 3,327 adults in 16 medical centres across the USA who were started on 3HP. Of the 3,288 participants eligible to complete treatment, 1,174 (35.7%) reported at least one AE (Figure 8), and 21% of these discontinued treatment as a result (7.5% of all those eligible to complete treatment).

**Figure 8. Number and percentage of patients with medication reactions after any 3HP dose in an observational study in 16 medical centres across the USA (n = 1,174 with symptoms [n = 3,327 receiving treatment]; from Sandul et al.<sup>74</sup>)**



3HP: 3 months of once-weekly rifapentine and isoniazid; No.; Number; Tx: treatment; USA: United States of America

### 3.4.1 Can 3HP be given with Antiretrovirals?

- **Efavirenz and 3HP:** 3HP can be co-administered with efavirenz without clinically meaningful reductions in efavirenz mid-dosing concentrations or virologic suppression supporting the use of rifapentine with EFV, without dose adjustment<sup>67</sup>.
- **Dolutegravir and 3HP:** The DOLPHIN study<sup>119</sup> evaluated the safety and pharmacokinetics of 3HP co-administration with dolutegravir (DTG). 60 PLHIV with undetectable viral loads on EFV-based regimens were switched to a DTG-based regimen for eight weeks. 3HP was co-administered with the DTG-based regimen after the first 8 weeks for 12 weeks, and then participants were followed up for four more weeks. HP decreased DTG bioavailability, and trough levels were decreased by approximately 50%. However, all trough levels but one was above the DTG IC<sub>90</sub>, and viral load remained suppressed in all patients. Overall, co-administration of DTG and 3HP was well-tolerated, safe and did not appear to require any dose-adjustment for DTG. The trough levels observed amongst patients with undetectable viral load in the DOLPHIN study were similar to trough levels observed amongst treatment naïve patients treated with 10mg of DTG in combination with dual-NRTI background regimen

in the SPRING-1 study. These patients achieved viral suppression as rapidly as those receiving 50mg of DTG (Figure 1). Therefore, DTG-based regimens (for example, the tenofovir, lamivudine and dolutegravir fixed dose combination) are recommended as safe and effective for patients newly initiating ART in coadministration with 3HP. This is currently being formally evaluated as a DOLPHIN substudy. However, given the pharmacokinetics of rifamycins in children, these data cannot be extrapolated to children under 15 years of age. Dolutegravir should not be co-administered with 3HP in children until more data is available.

- **Raltegravir and 3HP<sup>86</sup>**: Studies have shown that once-weekly rifapentine can be safely administered with raltegravir.

### 3.5 Cost-effectiveness

In 2009, before robust effectiveness data were available for 3HP, Holland et al.<sup>88</sup> compared the cost-effectiveness of 3HP, 4R, 9H+SAT, 9H+DOT, and no treatment in a range of settings, each corresponding to a different risk of disease reactivation. They found that 4R was the cheapest regimen overall (at US \$495.21 per contact), but **3HP prevented more cases per 1,000 contacts treated (56.3 compared with 43–52 for other regimens) and was the most cost-effective, regardless of risk of disease reactivation**

In 2012, Pho et al.<sup>90</sup>, using data from an HIV/TB clinical trial in India, estimated the cost (which, for IPT, included the cost of the drug, pre-screening for active TB, quarterly clinic visits, and liver function tests every six months) and cost-effectiveness of six months of daily INH and ethambutol (6EH), 36 months of daily INH, and no IPT in HIV-positive individuals in India. In a secondary analysis, they compared their estimates to estimates for 6H, 3RH, and 3HP and found that 3HP was the least cost-effective regimen, costing US\$ 80 more than 36H per person lifetime cost and reducing life expectancy. Estimates of 3HP efficacy and toxicity, however, were based only on the 2011 study by Martinson et al.<sup>56</sup>, and did not include data from the PREVENT TB study.

In 2013, Shepardson et al.<sup>91,92</sup> used data from the PREVENT study and a computational model to estimate the cost-effectiveness of 3HP+DOT compared with 9H+SAT. They found that although 3HP is more expensive to the health system (an extra US\$ 112) and to society (an extra US\$ 23) per person treated, it also prevents an additional 5.2 TB cases and prevents the loss of an extra 25 QALYs per 1000 people treated. Cost-effectiveness calculations suggested that the cost of 3HP would be an extra US\$ 4,565 and US\$ 911 per QALY gained to the health system and society, respectively, but that this was well below the US\$ 50,000 per QALY gained threshold suggested by some health economists for identifying cost-effective interventions in the USA.

After the price of RPT was lowered in the USA (900 mg dose reduced from US\$ 12.31 to US\$ 6.00)<sup>93</sup>, Shepardson et al.<sup>94</sup> published an update to their article using the new prices. They now projected costs of US\$ 8,861 and US\$ 1,879 (down from US\$ 21,525 and US\$ 4,565) to the health system per TB case prevented and per QALY gained, respectively. The authors also predict that 3HP, if administered by SAT, instead of DOT, would then be cost-saving in the USA (saving of US\$ 141 and US\$ 231 per person treated for the health system and society, respectively). This should be used as justification for pricing the drug accessibly<sup>95,96</sup>.

Huang et al.<sup>71</sup> calculated that to use 3HP in their setting (Taiwan) would cost US\$ 261.24 per patient (the bulk of this was due to the cost of RPT, at US\$ 216 per patient). This was cheaper, however, than treating a patient with 9H, the cost of which was an estimated US\$ 717.30 per patient. Using a ratio of one case of TB disease avoided for each 20 people with LTBI treated, they estimated that, in their study, where 98 people were treated with 3HP and 515 with 9H, the cost of avoiding one case of TB disease was US\$ 5,225 and US\$ 15,392 in the 3HP and 9H groups, respectively.

Johnson et al. used data from 1,000 Ugandan patients and a Markov model to estimate the cost effectiveness of 3HP compared with 9H used in HIV-positive people in high TB burden settings<sup>97</sup>. The authors estimate that treatment with 3HP would prevent nine cases of TB and one death that would occur if treatment was with 9H. Overall, the incremental cost-effectiveness ratio (ICER) of 3HP, relative to 9H, was US\$ 9,402 per DALY averted. This was influenced by changes in 3HP treatment completion (reduced to US\$ 6,986 per DALY averted if completion of 3HP at 89% vs. 47% for IPT) and the price of 3HP (reduced to US\$ 535 per DALY averted if the price of 3HP was reduced from US\$ 72 to US\$ 8 per patient course).



## 3.6 Can 3HP be used in other risk groups?

At present there is limited evidence for the use of RPT-based regimens for LTBI treatment in high-risk groups other than those discussed above. A summary of some of the evidence around the burden of TB infection in these individuals, as well as some preliminary evidence around treatment with RPT is presented below.

### 3.6.1 Pregnant women

A systematic review by Malhamé et al.<sup>98</sup> estimated the burden of TB infection in pregnant women. Based on data from 13 studies, the estimated prevalence of TB infection ranged from 14% to 48% of women tested (studies in the USA), with variation based on ethnicity. The authors also found some evidence to suggest that the likelihood of progression to active TB was increased post-partum.

Pregnant women living with HIV are at risk for TB, which can have severe consequences for both the mother and the foetus<sup>112</sup>, and it is well known that women with TB/HIV co-infection have poorer outcomes<sup>113</sup>. Isoniazid and rifampicin are known to be safe for use in pregnant women when used to treat TB disease<sup>114</sup>. The 2018 WHO guidelines consequently recommended that pregnancy should not disqualify women living with HIV from receiving TB preventive treatment, but that sound clinical judgement is recommended to determine the best time to provide it<sup>115</sup>.

Based on the WHO guidance, IPT is currently considered safe for HIV positive pregnant women, regardless of gestational age. However, recent evidence suggests that caution should be exercised in prescribing isoniazid to pregnant women.

At the conference for retroviruses and opportunistic infections (CROI) 2018, the IMPAACT P1078/TB APPRISE Study team presented their results from a phase 4 double-blind, placebo-controlled, non-inferiority trial that randomised 956 women to start 28 weeks of IPT either during pregnancy (immediate arm) or at 12 weeks postpartum (deferred arm) in HIV positive women from TB-endemic areas in Africa, Asia, and Haiti (13 sites across eight countries). Key findings included:

- a. the risk of maternal adverse events, including hepatotoxicity, was similar when IPT was initiated during pregnancy or postpartum and
- b. increased adverse pregnancy outcomes (fetal demise, preterm delivery, low birth weight or congenital anomaly) when IPT was initiated during pregnancy versus postpartum<sup>116</sup>

**The study concluded that the risks associated with IPT initiation during pregnancy may outweigh the benefit.**

At CROI 2019, a secondary analysis of the Tshepiso cohort showed no difference in pregnancy outcomes among 155 pregnant women living with HIV in South Africa with vs without IPT-exposure<sup>117</sup>. This was a prospective observational cohort study, in which pregnancy outcomes were assessed for 155 pregnant women living with HIV and without TB disease. IPT was initiated at public antenatal and HIV clinics for 69 of these women. There were fewer adverse pregnancy outcomes (fetal demise, prematurity, low birth weight, or congenital anomalies) among mother-infant pairs exposed to IPT (16% vs 28%;  $p=0.08$ ). This remained true in multivariable logistic regression after controlling for advanced maternal age, CD4 count, viral load, PMTCT regimen (cART versus AZT monotherapy), body mass index and anemia.

The two studies were conducted in different settings, using different methodologies and providing a different level of evidence. However, the results support the **WHO recommendation that sound clinical judgement (for example, balancing risks against benefits of TPT) should be exercised before recommending IPT during pregnancy.**

There are limited data on the use of 3HP in pregnant and/or post-partum women. A 2018 sub-analysis of data from ( $n = 125$ ) pregnant women enrolled in the PREVENT and iAdhere trials<sup>99</sup> found no unexpected foetal loss or congenital abnormalities among women exposed to the study drugs (either 3HP or 9H).

The IMPAACT 2001 study (principal investigator Jyothi Mathad, Cornell), currently underway in Haiti, Kenya, Malawi, Thailand, the USA, and Zimbabwe, is a phase I/II study evaluating the pharmacokinetics, tolerability, and safety of 3HP in HIV-positive and HIV-negative pregnant and postpartum women with TB infection<sup>100</sup>. Results from the study are expected in early 2020. In the mean time, there is insufficient data to recommend the use of 3HP in pregnant women.

### 3.6.2 Inmates of correctional facilities

A cross-sectional study in two prisons in Brazil<sup>101</sup> used TST to identify TB infection and found a prevalence of 25.2% among the 1,120 inmates tested. A 2011 study by Lopez et al.<sup>102</sup>, conducted in a correctional facility in Spain, did not include an RPT-based regimen, but found that more individuals completed short-course therapy (2–4 months of RIF or RIF/INH) than completed 9H (withdrawal OR 1.56 [95% CI 1.14–2.12] for 9H vs. shorter regimens). Finally, a prospective study in an urban jail in the USA<sup>103</sup> compared completion rates among inmates treated with 3HP or 9H from 2010 and 2014 and found a marked difference between the two groups. Among 154 individuals treated with 9H, only 28 (18.2%) completed treatment, compared with 77/91 (84.6%) who were treated with 3HP. The majority of those not completing either regimen (82% of those who stopped 9H and 79% of those who stopped 3HP) stopped because they were transferred out of the facility before they could complete treatment.

### 3.6.3 Health care workers

A 2016 systematic review by Nasreen et al.<sup>104</sup> estimated that 47% (95% CI 34–60; n = 18 studies; n = 9,545 individuals) of health care workers (HCWs) studied had LTBI. Prevalence varied by country (37% [95% CI 0.17–0.56; n = 6 studies] in Brazil to 64% [95% CI 26–100; n = 2 studies] in South Africa) and by type of HCW (lowest in students [26% {95% CI 6–46}]).

In a retrospective study published in 2017, Arguello-Perez et al.<sup>105</sup> reviewed the health records of 363 HCWs at a health centre in New York who were treated for LTBI between 2005 and 2014. As seen in studies in the general population, HCWs treated with shorter regimens (4R or 3HP) were more likely to complete treatment than those treated with 9H (48/55 [87.3%] completed 3HP, 85/106 [80.2%] completed 4R, and 117/202 [57.9%] completed 9H; 3HP vs. 9H,  $p < 0.0001$ ; 4R vs. 9H,  $p < 0.0001$ ).

### 3.6.4 Transplant candidates/recipients

Two small prospective studies and one larger retrospective study have investigated the use of 3HP in solid-organ transplant candidates. Between March and October 2012, in a transplant centre in the USA<sup>106</sup>, 17 solid-organ transplant candidates received LTBI treatment with 3HP: 13/17 (76.5%) individuals received at least 11 doses of treatment; the remaining four individuals stopped treatment because of drug-related side-effects (n = 2), worsening of their underlying condition (n = 1), or other circumstances (n = 1). In another study in the USA<sup>107</sup>, 12 solid-organ transplant candidates (eight of whom were waiting for liver transplants) were treated with 3HP from 2013–2016. All 12 individuals completed treatment and no hepatotoxicity was associated with 3HP treatment, even in individuals with baseline hepatic impairment.

The largest study in this population is a retrospective review of 153 renal transplant candidates with 3HP (n = 43) or 9H (n = 110)<sup>108</sup>. Individuals receiving 3HP were more likely to complete treatment (93% vs. 47% completion;  $p < 0.001$ ) and less likely to have increases in hepatic transaminases (0% vs. 5% for 3HP vs. 9H). However, a paper by the same group<sup>109</sup> reports an increased incidence of severe hypertension in renal transplant candidates receiving 3HP (8/37 [21.6%]). Although no participants suffered a stroke or myocardial infarction as a result of the hypertension, and only one participant discontinued 3HP due to hypertension, the authors suggest that close monitoring of blood pressure is needed in renal transplant candidates treated with 3HP.

### 3.6.5 Other

Using a Markov model, Tasillo et al.<sup>110</sup> estimated the efficacy and cost-effectiveness of testing (with a range of modalities) and treating (with 3HP+SAT) individuals resident within the USA who were not born in the USA ("non-US born residents"). Across 10,000 simulations, the authors found that testing for LTBI, followed by 3HP with SAT, prevented the incidence of active TB, improved outcomes, and was cost-effective, compared with no testing or no treatment. This did not apply, however, to individuals with end-stage renal disease, in whom the risk of mortality was already very high.

A 2017 review by Zheng et al.<sup>111</sup> suggests that RPT, as it is not nephrotoxic and is eliminated by the kidneys in smaller quantities than rifampicin, may be useful in treating individuals with diabetes and renal impairment, but highlights the likelihood of interactions with oral antidiabetic drugs and states that RPT should only be used in these patients under close supervision until more information on pharmacokinetics and drug interactions becomes available.

## 4. Take home points

### 4.1 Is treatment of TB infection effective?

There is strong evidence to show that the treatment of LTBI (with isoniazid monotherapy, 3HP, and other regimens) **is effective in preventing progression to active disease in adults and children over 2 years of age**. This is reflected in recommendations for best practice made by a number of governing and regulatory bodies, including WHO and CDC.

### 4.2 Is treatment of TB infection necessary?

The treatment of LTBI is **extremely important**, particularly in those at high risk of progression to active TB disease, as it can avert the suffering and catastrophic economic costs associated with developing active TB. From a public health perspective, the treatment of LTBI is also **critical in reducing the enormous burden of premature, preventable mortality attributable to TB**; the massive expenditure imposed on health services by active disease and its complications; the economic damage resulting from the disability and morbidity caused by TB; and in interrupting disease transmission with an aim, eventually, to ending TB.

### 4.3 Is 3HP superior to IPT?

There is no evidence that 3HP is more effective than IPT, but studies have shown **3HP to be equivalent to IPT** in preventing progression to active disease. There is evidence, however, to show that **3HP is less toxic** to the liver than some IPT regimens, although the risk of systemic drug reactions is increased among those taking 3HP. There is strong evidence to show that people taking 3HP (and some other shorter regimens) are much **more likely to complete their course of treatment** than people taking IPT. On the strength of the evidence, WHO now recommend 3HP as an alternative to IPT for use in adults and children in high and low TB incidence countries.

### 4.4 Is 3HP superior to other TB prevention therapy interventions?

In the few studies where 3HP has been compared with other shortened regimens (most studies have compared 3HP with IPT), there has been **no difference in clinical effectiveness** (e.g., compared with three months of twice-weekly rifampicin and isoniazid; see section 5.1); similar or better rates of treatment completion (e.g., compared with four months of daily rifampicin [4R]); higher levels of systemic drug reactions (e.g., compared with 4R); and less hepatotoxicity (e.g., compared with daily rifampicin and pyrazinamide).

### 4.5 Can 3HP be taken with antiretrovirals?

3HP can be taken with most common antiretrovirals such as Dolutegravir, Raltegravir and Efavirenz without dose adjustment. Rifamycins such as rifapentine require dose adjustment for co-administration with protease inhibitors. There is no current data on the pharmacokinetics of co-administration of 3HP with Dolutegravir in children, and therefore should be avoided in anyone under 15 years of age.

### 4.6 Is 3HP cost-effective?

Most studies have found 3HP to be expensive in the short-term, primarily because of the cost of rifapentine, but the **shorter duration of treatment and higher rates of treatment completion make it more cost-effective in the long-term**. Cost-effectiveness would be increased by reducing the cost of rifapentine, switching from directly-observed to self-administered therapy, and/or reducing the duration of treatment (for example from three months to one month), though evidence is limited for the safety and efficacy of the latter two options.

### 4.7 Could (and should) 3HP be used for a wider population?

Other than HIV-positive people and contacts of TB cases (of all ages), the evidence to support this is very limited at present, although the superiority of 3HP (and other shortened regimens) with regard to treatment completion makes it a very attractive option, particularly for use in correctional facilities and other dynamic or unpredictable environments. The results of studies underway in pregnant women will be important to determine the safety and tolerance of 3HP in this group.

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## Endnotes

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