IMPAACT4TB

Literature review to support the public health case for the scale-up of 3HP

Version 3.1
12 March 2018
Contents

1. Introduction.................................................................................................................. 6
   1.1. Aims and objectives............................................................................................... 7
2. Methods and results of literature search..................................................................... 8
   2.1. Methods .................................................................................................................. 8
   2.2. Results .................................................................................................................... 8
3. The global burden of TB.............................................................................................. 9
   3.1. Risk of progression to active disease..................................................................... 9
4. The case for treating LTBI .......................................................................................... 12
   4.1. Reducing TB incidence......................................................................................... 13
   4.2. Reducing all-cause mortality among HIV-positive people.................................... 14
   4.3. Cost-effectiveness and eliminating TB effectiveness and eliminating TB........... 16
5. Rifapentine-based regimens for treating LTBI............................................................. 19
   5.1. Effectiveness in adults ......................................................................................... 19
   5.2. Effectiveness in children and adolescents............................................................. 23
   5.3. Adherence and treatment completion..................................................................... 24
   5.3.1. Reviews of adherence to and/or completion of LTBI treatment ....................... 24
   5.3.2. Studies describing adherence to and/or completion of rifapentine-based regimens .......................................................................................................................... 24
   5.4. Toxicity and adverse events................................................................................... 29
   5.5. Cost-effectiveness ................................................................................................. 33
   5.6. Potential expansion to other high-risk groups....................................................... 37
   5.6.1. Pregnant women .............................................................................................. 37
   5.6.2. Inmates of correctional facilities ...................................................................... 38
   5.6.3. Health care workers ....................................................................................... 38
   5.6.4. Transplant candidates/recipient ...................................................................... 39
   5.6.5. Other.................................................................................................................. 40
6. Summary ....................................................................................................................... 41
   6.1. Is LTBI treatment effective? .................................................................................. 41
   6.2. Is LTBI treatment necessary? ............................................................................... 41
   6.3. Is 3HP superior to IPT? ....................................................................................... 41
   6.4. Is 3HP superior to other TB prevention therapy interventions?.......................... 41
   6.5. Is 3HP cost-effective? ......................................................................................... 42
   6.6. Could (and should) 3HP be used for a wider population? .................................... 42
7. References .................................................................................................................... 43
8. Appendices ........................................................................................................................................ 49

8.1. Appendix 1. Ongoing trials ........................................................................................................... 49
8.2. Appendix 2. Details of studies with findings included in this report ........................................... 51

List of tables

Table 1. Summary* of published phase III and IV trials of effectiveness of 1HP/3HP in preventing active TB disease in adults ................................................................................................................................. 22
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) ........................................................................................................ 27
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) .............................................................................. 29

List of figures

Figure 1. Overview of TB transmission (from Churchyard et al., 2017) ......................................................... 6
Figure 2. Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income (from Fox et al. 2013) ............................................................................................................... 10
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) ............................................................................................................................................................................ 17
Figure 4. Prospects for TB control and elimination in South Africa (from Dye et al., 2013) ......................... 17
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) .................................................................................................................. 18
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) ............................................................... 20
Figure 7. Weighted treatment completion for all participants in the iAdhere study, by study group (from Belknap et al., 2017) ............................................................................................................................... 26
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.) .................................................................................................................. 32
Figure 9. Cost-effectiveness plots for 3HP vs. 4R vs. 9H+DOT vs. 9H+SAT vs. no treatment under different relative risk* of disease activation (from Holland et al., 2009) ........................................................................................................... 34
Figure 10. Cost-effectiveness of 1HP+SAT vs. 3HP+SAT vs. 3HP+DOT vs. 9H+SAT vs. no treatment (ICERs are represented by the inverse slope of the dotted and dashed lines between strategies; in 2011 US$; from Holland et al., 2011) ........................................................................................................... 35
Figure 11. Cost of a complete course of treatment* for LTBI with 3HP+DOT or 9H+SAT (in 2010 US$; from Shepardson et al., 2013) .................................................................................................................................................. 36

List of supplementary tables

Supplementary table 1. List of active trials of rifapentine registered on ClinicalTrials.gov in February 2018 (n = 6) .................................................................................................................................................................................. 49

Supplementary table 2. List of articles reporting primary data included in this report (n = 41; listed alphabetically by first author) .................................................................................................................................................... 51

Supplementary table 3. List of review articles included in this report (n = 19; listed alphabetically by first author) ........................................................................................................................................................................... 57

Supplementary table 4. List of modelling studies included in this report (n = 12; listed alphabetically by first author) ...................................................................................................................................................................... 59
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1HP</td>
<td>one month of daily rifapentine and isoniazid</td>
</tr>
<tr>
<td>3HP</td>
<td>three months of once-weekly rifapentine and isoniazid</td>
</tr>
<tr>
<td>6H</td>
<td>six months of daily isoniazid</td>
</tr>
<tr>
<td>9H</td>
<td>nine months of daily isoniazid</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>aHR</td>
<td>adjusted hazard ratio</td>
</tr>
<tr>
<td>aIRR</td>
<td>adjusted incidence rate ratio</td>
</tr>
<tr>
<td>aOR</td>
<td>adjusted odds ratio</td>
</tr>
<tr>
<td>aRH</td>
<td>adjusted relative hazard</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DALY</td>
<td>disability-adjusted life-year</td>
</tr>
<tr>
<td>DOT</td>
<td>directly observed therapy</td>
</tr>
<tr>
<td>HCW</td>
<td>health care worker</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IGRA</td>
<td>interferon-gamma release assay</td>
</tr>
<tr>
<td>INH</td>
<td>isoniazid</td>
</tr>
<tr>
<td>IPT</td>
<td>isoniazid preventive therapy</td>
</tr>
<tr>
<td>IR</td>
<td>incidence rate</td>
</tr>
<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
</tr>
<tr>
<td>LTBI</td>
<td>latent tuberculosis infection</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>RIF</td>
<td>rifampicin</td>
</tr>
<tr>
<td>RPT</td>
<td>rifapentine</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>SAT</td>
<td>self-administered therapy</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TST</td>
<td>tuberculin skin-test</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1. Introduction

There were an estimated 10.4 million new cases of tuberculosis (TB) and around 1.7 million deaths attributable to TB in 2016.¹ 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 2035.² Elimination of TB, however, cannot be considered without discussion of latent TB infection (LTBI) and its diagnosis and treatment. People with LTBI are unlikely to know themselves to be 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).³ Latent disease can progress to active disease, however, and is likely to do so in people with certain risk factors (such as reduced immunity; see Section 3.1). As such, one of the global priority indicators for tracking progress towards the End TB goals is for ≥90% of people with living with HIV and children who are contacts of TB cases to be started on preventive treatment for LTBI.²

Figure 1. Overview of TB transmission (from Churchyard et al., 2017³)
1.1. Aims and objectives

The aim of this review is to summarise the evidence around the treatment of LTBI with three main objectives:

1. To establish the case for the treatment of LTBI;
2. To summarise the evidence for the use of three months of once-weekly rifapentine and isoniazid (henceforth referred to as 3HP) in preference to other treatment regimens; and
3. To explore the potential for extending the use of 3HP to high-risk groups other than HIV-positive people and household contacts and to other parts of the population.
2. Methods and results of literature search

2.1. Methods

A search of Medline (via PubMed) was carried out using the broad terms “rifapentine” OR “3HP” AND “tuberculosis”. Results were sifted by title and abstract (articles that described the results of animal experiments, described the use of rifapentine in the treatment of active TB disease, or were published in a language other than English were excluded) and the full texts of relevant articles sought. Reference sections of related systematic reviews (found through the search and identified prior to starting the search) were sifted for relevant articles. Additional articles, both published and in-press, were included after consultations with experts.

The US National Library of Medicine (NLM) clinical trials database (https://clinicaltrials.gov/) was searched, using the terms: “tuberculosis” (condition or disease) AND “rifapentine” (other terms) and then “tuberculosis” AND “3HP”. PubMed was then searched for published results of relevant trials if none were described as part of the trial record. Details of ongoing trials were also recorded.

2.2. Results

The initial search of Medline yielded 312 unique results. Of these, 85 (27.2%) were included for further review and full-text articles were available for 75/85 (88.2%). A further 25–30 articles were included through the review of reference sections of included and other articles and expert recommendation.

The searches of the NLM clinical trials database yielded a total 29 unique results, of which 15 (51.7%) had ‘completed’ recruitment, nine (31.0%) were ‘recruiting’, two (6.9%) were ‘not yet recruiting’, two (6.9%) were ‘terminated’, and one (3.4%) was ‘active, not recruiting’. A total six active studies were considered relevant to this review and are listed in Appendix 1 (Supplementary table 1).
3. The global burden of TB

There were an estimated 1.7 billion people with LTBI in 2014, with 50–60 million people infected in the preceding two years. Once infected, individuals without effective immunity (such as young children and people living with HIV) are at high risk of progression to active TB disease. Active disease, in addition to drastically increasing the likelihood of transmission to other individuals, brings with it considerably increased morbidity, a high risk of premature death (particularly in people who are HIV-positive), and often catastrophic economic costs. 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 2016, was an estimated US$ 1,253 for each person with drug-susceptible TB and US$ 9,529 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.

Treatment of LTBI, particularly in those people who are at high risk of progression to active disease (see section 3.1, below), is a crucial part of reducing transmission, morbidity, and mortality, and eventually eliminating TB. At present, most high-burden countries follow a two-pronged approach, using the Bacille Calmette-Guérin (BCG) vaccine of all children at birth (to prevent infection and reduce the risk of transmission) 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). However, in 2016, only around 13% of eligible household contacts aged under five years and around 42% of HIV-positive people newly enrolled in care were started on TB preventive therapy.

3.1. Risk of progression to active disease

HIV is the strongest risk factor for developing TB disease in those with latent or new TB infection; between 11 and 19% of all HIV-positive people likely have LTBI, though this figure is likely to be much higher in high-burden settings, as diagnosis of LTBI and TB disease is difficult in people who are HIV-positive. Despite
greatly increased availability of ART, TB remains a leading cause of morbidity and mortality among HIV-positive people\textsuperscript{13,14}; reducing HIV-associated TB disease and mortality are a central part of the End TB goals.\textsuperscript{2}

Contacts of people with TB are also at high risk for developing LTBI and active disease. A 2013 systematic review\textsuperscript{15} of 95 studies estimated that the prevalence of active disease in contacts was 3.1\% (95\% CI 2–4) and the prevalence of latent 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).

\textbf{Figure 2. Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income (from Fox et al. 2013\textsuperscript{15})}

![Graph showing annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income.](image)

TB: tuberculosis; yr: year

A recent (2017), as yet unpublished, systematic review and meta-analysis of the literature commissioned by WHO\textsuperscript{16} 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]).

The WHO-commissioned systematic review also examined the risk of progression to active disease among household contacts with LTBI. 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).
4. The case for treating LTBI

The primary aim in treating LTBI is to prevent progression to active disease; this is well-established within international and national guidelines. For countries with a low TB burden, the 2015 WHO guidelines 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-α) treatment, receiving dialysis, preparing for organ or haematological transplantation, or with silicosis, as well as consideration of the same strategy in prisoners, health care workers (HCW), immigrants from high burden countries, homeless persons, and illicit drug users. For treatment, these same guidelines recommend that countries use any of six months of daily INH (isoniazid; 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). The use of TB preventive therapy is also recommended by the US Center for Disease Control (CDC; since at least 1994) and the British HIV Association (BHIVA; since at least 2005).

In high burden settings, 2018 WHO guidelines 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 36 months of daily INH for HIV-positive adolescents and adults with a positive or unknown tuberculin skin-test (TST) result. 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 but, importantly, in the 2018 guidelines, this has been extended to all household contacts of people with TB (children aged ≥5 years, adolescents, and adults; high TB incidence countries only). In addition to daily INH, the 2018 guidelines also list 3RH (in individuals aged <15 years) and 3HP (in adults and children) as suitable regimens for use in countries with high TB incidence (but not 3R or 4R). WHO recommendations have been widely incorporated into the national HIV and TB treatment guidelines in many high-burden countries, including South Africa.
4.1. Reducing TB incidence

A wide-ranging review, published in 1970, describes a number of controlled trials of IPT, including several among contacts of people with TB. 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 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), 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.

Two systematic reviews, published in the last eight years, have examined the effectiveness of TB preventive therapy in preventing disease in HIV-positive people. A Cochrane review, published in 2010, included results from 12 trials in HIV-positive individuals (n = 8,578 participants) 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 [RR 0.74 [95% CI 0.55–1.00]] and for isoniazid and rifampicin used together [RR 0.69 [95% CI 0.50–0.95]]). In 2015, a systematic review and meta-analysis of 10 randomised studies (conducted in a variety of settings, from 1993–2014) found that the use of IPT reduced the incidence of TB among HIV-positive people (pooled RR 0.65 [95% CI 0.51–0.84]; n = 10 studies) and that 12 months of IPT reduced the risk of death by 35% (pooled RR 0.65 [95% CI 0.47–0.90]).

In addition, a retrospective analysis, in 2005, of medical records of over 11,000 HIV-positive individuals in 29 public health clinics in Brazil found that the incidence of TB disease in those who had received IPT was
lower than in those who had not (incidence 1.4% vs. 3.8% for IPT vs. no IPT; IRR 0.48 [0.39–0.59] ART only vs. no treatment; IRR 0.32 [0.10–0.76] IPT only vs. no treatment; IRR 0.20 [95% CI 0.09–0.91] ART plus IPT vs. no treatment). After adjustment for CD4 count, age, and previous TB, IPT alone no longer reduced the risk of TB incidence (adjusted relative hazard [aRH] 0.57 [95% CI 0.18–1.82]), but IPT in combination with ART was more effective than ART alone (aRH 0.24 [95% CI 0.11–0.53] vs. 0.41 [95% CI 0.31–0.54], ART plus IPT vs. ART only). Two additional studies by the same group also provide strong support for the use of IPT in HIV-positive people. The first\textsuperscript{35} followed a prospective cohort of 2,778 HIV-positive individuals in South Africa and measured the incidence of TB disease. In 4,287 person-years of observation, 267 cases of TB were diagnosed (IR 6.2 [95% CI 5.5–7.0] per 100 PY). Incidence was highest in individuals who did not receive IPT or ART (IR 7.1 [95% CI 6.2–8.2] per 100 PY) and lowest in those who received ART after treatment with IPT (IR 1.1 [95% CI 0.02–7.6] per 100 PY; IRR 0.15 [95% CI 0.005–0.85] compared with no IPT or ART). In the second study\textsuperscript{36}, 1,954 HIV-positive adults with positive TST were followed-up for up to seven years, with TB incidence the primary outcome (1,601 [82%] started IPT; total 9,117 PY of observation). 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; aHR 0.17 [95% CI 0.11–0.25]).

A modelling study by Dowdy et al., published in 2014,\textsuperscript{37} 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.

### 4.2. Reducing all-cause mortality among HIV-positive people

An observational cohort study, conducted within a workplace ART programme in South Africa from 2004–2007\textsuperscript{38}, 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]).

Two recent, large, prospective, randomised trials of composite interventions among HIV-positive adults in high-burden settings showed a large reduction in mortality (and TB incidence) among participants who also received treatment for LTBI. The TEMPRANO ANRS 12136 trial\(^3^9\) 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 (adjusted hazard ratio [aHR] 0.56 [95% CI 0.41–0.76]) and lower with IPT than without IPT (aHR 0.65 [95% CI 0.48–0.88]). IPT also reduced, considerably, the risk of TB disease in these individuals (aHR 0.44 [95% CI 0.28–0.69] overall; aHR 0.47 [95% CI 0.23–0.97] if CD4 count ≥500 cells/µL; and aHR 0.42 [95% CI 0.23–0.76] if CD4 count <500 cells/µL). 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),*\(^4^0\), 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 (aHR 0.63 [95% CI 0.41–0.97]).

The second study, the Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy (REALITY) trial\(^4^2\), 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 (in some study sites, depending on national guidelines, isoniazid and pyridoxine were continued for longer than 12 weeks).

\(^*\)NB: Some data from this trial were included in the Ayele 2015 systematic review\(^3^3\) discussed above.
Standard prophylaxis consisted only of co-trimoxazole. The primary outcome of the trial was death from any cause within 24 weeks of randomisation; secondary outcomes included adverse events and incidence of key diseases, including TB. At 24 weeks, there were 80 deaths in the ‘enhanced’ arm vs. 108 in the ‘standard’ arm (8.9% vs. 12.2%; hazard ratio [HR] 0.73 [95% CI 0.55–0.98]) and this ratio was maintained at 48 weeks (98 [11.0%] deaths vs. 127 [14.4%] deaths; HR 0.76 [95% CI 0.58–0.99]). A large reduction in the incidence of TB disease was also seen in the ‘enhanced’ prophylaxis arm (HR 0.67 [95% CI 0.49–0.93]), but there was no difference between the two arms in the numbers of deaths attributed to TB (2.3% vs. 2.5%), although the authors do not describe procedures for assigning causes of death.

4.3. Cost-effectiveness and eliminating TB
Several reviews\textsuperscript{8,12,43,44} and modelling studies have discussed the role of LTBI 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.\textsuperscript{45} 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 (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).

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)

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. 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\textsuperscript{47}, 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.

\textbf{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\textsuperscript{47})}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Incremental TB service costs* for each intervention scenario in South Africa, as compared to base case, by model (from Menzies et al., 2016\textsuperscript{47})}
\end{figure}

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
5. Rifapentine-based regimens for treating LTBI

A Cochrane review, published in 2013\textsuperscript{48}, 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\textsuperscript{49}, 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.\textsuperscript{50}, 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.\textsuperscript{51} (summary rate ratios of TB incidence after treatment with 3HP compared with six and nine months of INH 0.83 [95% CI 0.29–2.02] and 0.71 [95% CI 0.25–3.08], respectively).

The rest of this section aims to summarise the important findings of the phase III/IV trials of 3HP, categorised into four main areas of interest: effectiveness (in adults and in children/adolescents), adherence/treatment completion, toxicity/side-effects, and cost-effectiveness.

5.1. Effectiveness 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). The largest of these, “PREVENT TB”, conducted in Brazil, Canada, Spain, and the USA from 2001–2008 randomised 7,731 individuals aged ≥12 years to receive 3HP with directly-observed therapy (DOT) or nine months of isoniazid (9H) through self-administered therapy (SAT).\textsuperscript{52} TB incidence was low in both arms, with 3HP found to be non-inferior to 9H in preventing TB disease (aHR 0.38 [95% CI 0.15–0.99], \(p = 0.05\)). In a recently published analysis of data from HIV-positive individuals enrolled in PREVENT\textsuperscript{53}, Sterling et al. present a modified intention-to-treat (MITT) analysis (\(n = 399\)), with 206 individuals randomised to receive 3HP and 193 to receive 9H. 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.

Two studies were conducted entirely in high-burden\textsuperscript{54} settings. In Brazil, from 2001–2005, Schechter et al. randomised 399 adult household contacts to receive either 3HP or eight weeks of rifampicin and pyrazinamide.\textsuperscript{55} 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 (incidence rate ratio [IRR] 2.8 [95% CI 0.3–26.8]; \( p = 0.66 \)). Finally, in South Africa, from 2002–2005, Martinson et al.\textsuperscript{56} enrolled 1,150 HIV-positive adults with CD4 counts of \( \geq 200 \) cells/\( \mu L \) who were not on ART and randomised them (2:2:2:1) to receive 3HP (DOT); 12 weeks of twice-weekly RIF and INH (DOT); up to six years of daily INH (SAT); or six months of daily INH (SAT). TB incidence in all arms was similar, with 3HP non-inferior to other regimens (incidence rate [IR] of TB disease 2.0 vs. 2.0 vs. 1.4 vs. 1.9 per 100 PY for the four arms, respectively; IR of death 1.4 vs. 1.3 vs. 1.4 vs. 2.1 per 100 PY, respectively; 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\textsuperscript{56})
Reported very recently at the 2018 Conference on Retroviruses and Opportunistic Infections (CROI), the ACTG 5279 study\textsuperscript{57} enrolled 3000 HIV-positive individuals aged ≥13 years in 10 high TB incidence settings from 2012–2014, randomised 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 (IR 0.69 vs. 0.72 per 100 PY for 1HP vs. 9H; IRR 0.026, upper 95% CI 0.31). 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 (5.6% vs. 7.1%, 1HP vs. 9H; \( p = 0.1 \)). Importantly, treatment completion rates were higher among those taking 1HP (97% vs. 90%, 1HP vs. 9H; \( p < 0.01 \)).
# Table 1. Summary* of published phase III and IV trials of effectiveness of 1HP/3HP in preventing active TB disease in adults

<table>
<thead>
<tr>
<th>First author, year published</th>
<th>Country /ies</th>
<th>Setting &amp; population</th>
<th>N</th>
<th>Relevant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swindells, 2018⁷⁷</td>
<td>Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe</td>
<td>HIV-positive, aged ≥13 years</td>
<td>3,000</td>
<td>1HP was non-inferior to 9 months of daily isoniazid among HIV-positive individuals, 50% of whom were on ART at enrolment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any endpoint, IR 0.69 vs. 0.72 per 100 PY; IRR 0.025 (95% CI −0.30–0.35)</td>
</tr>
<tr>
<td>Sterling, 2016⁶¹⁺</td>
<td>Brazil, Canada, Hong Kong, Peru, Spain, USA</td>
<td>HIV-positive, aged ≥2 years, 2001–2010</td>
<td>399</td>
<td>3HP was non-inferior to 9 months of daily isoniazid among HIV-positive adults, 69% of whom were not taking ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 vs. 6 cases in 3HP vs. 9H arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>aHR 0.27 (95% CI 0.05–1.44), p = 0.13</td>
</tr>
<tr>
<td>Sterling, 2011⁵²</td>
<td>Brazil, Canada, Spain, USA</td>
<td>Aged ≥2 years, close contact with TB or HIV-positive, 2001–2008</td>
<td>7,731</td>
<td>3HP was non-inferior to 9 months of daily isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 vs. 16 cases/100 PY in 3HP vs. 9H arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>aHR 0.38 (95% CI 0.15–0.99), p = 0.05</td>
</tr>
<tr>
<td>Martinson, 2011⁵⁶</td>
<td>South Africa</td>
<td>HIV-positive adults attending primary care, 2002–2005</td>
<td>1,150</td>
<td>3HP was non-inferior to 6 months of daily isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TB 1.05 (0.56–1.97); p = 0.87; IR 1.02 (0.55–1.91); p = 0.94; IRR 0.74 (0.29–1.73); p = 0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TB or death 0.87 (0.54–1.39); p = 0.54; IR 0.80 (0.50–1.29); p = 0.34; IRR 0.75 (0.38–1.38); p = 0.34</td>
</tr>
<tr>
<td>Schechter, 2006⁵⁵</td>
<td>Brazil</td>
<td>Adult household contacts of 236 TB patients, 2001–2005</td>
<td>399</td>
<td>3HP was non-inferior to and less hepatotoxic than 8 weeks of daily RIF/Pz</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 vs. 1 case in 3HP vs. 8 weeks of daily RIF/Pz arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IRR 2.8 (95% CI 0.3–26.8); p = 0.66</td>
</tr>
</tbody>
</table>

*For detailed summary of population, inclusion/exclusion criteria, and other methods, see Appendix 2 (Supplementary table 2)

⁺Partially a sub-set of Sterling 2011⁵²

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)
5.2. Effectiveness in children and adolescents

Two studies have examined the pharmacokinetics of RPT in children. The smaller, published by Blake et al. in 2006, 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. A second, larger study, nested within PREVENT, 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.

The most robust estimate of effectiveness come from a paediatric sub-study nested within the PREVENT trial (n = 905 participants aged 2–17 years in the modified intention-to-treat analysis, recruited in Brazil, Canada, Hong Kong, Spain, and the USA from 2001–2010), which aimed primarily to measure safety and adherence, but also found that 3HP (+ DOT) was non-inferior to 9H (incidence rate [IR] 0.00 vs. 0.27 per 100 PY for 3HP vs. 9H). In addition, a small cohort study in Colorado 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 (zero cases in any group).

The 2011 CDC guidelines on LTBI treatment recommend the use of 3HP in children aged ≥12 years. 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 ≤2 years, the absence of data on “the safety and pharmacokinetics of rifapentine” meant that it could not be recommended.

Two reviews by Cruz et al., published in 2013 and 2014, have explored some of the issues around diagnosis and treatment of LTBI in children and adolescents. In the first, the authors review 29 randomised
trials of various combinations of INH, RIF, RPT, and Pyrazinamide, and cite summary evidence of 20–30% increased effectiveness of 9H, compared with 6H; equivalent effectiveness of 4R or 3RH, compared with 6–12 H; and equivalence of 3HP and 9H (though data for this last statement come only from the PREVENT trial).63

Data are still needed around the efficacy, tolerability, and safety of rifapentine and 3HP in children aged ≤2 years, and, though findings from observational studies in the USA are encouraging (see Section 5.3), 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.65,66

5.3. Adherence and treatment completion

5.3.1. Reviews of adherence to and/or completion of LTBI treatment

At least three systematic reviews have examined this issue: Sandgren et al.67 reviewed 95 studies describing initiation (n = 45 studies) and completion (n = 83 studies) of LTBI treatment published before February 2014; Stuurman et al.68 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; and Liu et al.69 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. All 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. In random-effects meta-analysis conducted by Stuurman et al., shorter treatment regimens improved adherence among case contacts (summary odds ratio [sOR] 1.5 [95% CI 1.0–2.3]; n = 2 studies) and improved completion rates in the general population (sOR 1.9 [95% CI 1.1–3.5]; n = 2 studies).68

5.3.2. Studies describing adherence to and/or completion of rifapentine-based regimens

The systematic review and network meta-analysis by Pease et al., published in 2017 and referred to in Section 5.1,51 also described treatment completion for 3HP in comparison with other treatment regimens
(14 studies included for this outcome). As with previous meta-analyses, 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. A less systematic, narrative synthesis of adherence and resistance data, with a similar conclusion, is presented in a 2012 review by Person & Sterling.70

Many of the large randomised trials discussed in Section 5.1 also reported adherence as a secondary outcome (Table 2). The PREVENT TB study (n = 7,731)52 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).60 Martinson et al.56 and Schechter et al.55 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).

Two other trials have attempted to assess adherence to 3HP in a number of settings (Table 2). In Taiwan, in 2014, Huang et al. studied 691 individuals aged ≥12 years who received 3HP (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).71 In addition, 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.72 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 (85.4% vs. 77.9% vs. 76.7% for DOT vs. SAT no reminder vs. SAT with reminder; Figure 7). Both the Huang et al. and iAdhere studies did not recruit HIV-positive individuals who were taking (or were about to take) ART.
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)

<table>
<thead>
<tr>
<th>First author, year published</th>
<th>Country /ies</th>
<th>Setting &amp; population</th>
<th>N</th>
<th>Relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Swindells, 2018**            | Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe | HIV-positive, aged ≥13 years | 3,000 | 1HP + SAT: 97% completion  
9H + SAT: 90% completion |
| Belknap, 2017**              | Hong Kong, South Africa, Spain, USA | Adults attending outpatient clinics from 2012–2014 | 1,002 | Overall (n = 1,002)  
3HP + DOT: 87.2% completion  
3HP + SAT (no text): 74.0% completion  
3HP + SAT (with text): 76.4% completion  
USA only (n = 774)  
3HP + DOT: 85.4% completion  
3HP + SAT (no text): 77.9% completion  
3HP + SAT (with text): 76.7% completion |
| Huang, 2016**                | Taiwan       | Aged ≥12 years, contact with drug-sensitive TB, 2014 | 691   | 3HP + DOT: 97.0% completion  
9H + SAT: 87.3% completion  
3HP vs. 9H, 25% (95% CI 17–33) difference, p <0.001 |
| Sterling, 2016**†            | Brazil, Canada, Hong Kong, Peru, Spain, USA | HIV-positive, aged ≥22 years, 2001–2010 | 399   | 3HP + DOT: 88.8% completion  
9H + SAT: 63.7% completion  
3HP vs. 9H, p <0.001 |
| Villarino, 2015**            | Brazil, Canada, Hong Kong, Spain, USA | Aged 2–17 years, 2001–2010 | 1,058 | 3HP + DOT: 97.1% completion  
9H + SAT: 80.9% completion  
3HP vs. 9H, p = 0.003 |
| Sterling, 2011**             | Brazil, Canada, Spain, USA | Aged ≥2 years, close contact with TB or HIV-positive, 2001–2008 | 7,731 | 3HP + DOT: 98.2% completion  
9H + SAT: 96.2% completion  
3HP vs. 9H, p <0.001 |
| Martinson, 2011**            | South Africa | HIV-positive adults attending primary care, 2002–2005 | 1,150 | 3HP + DOT: 98.2% completion  
3RH: ≤6y daily INH: 96.2% completion  
≤6H + SAT: 98.1% completion |
| Schechter, 2006**            | Brazil       | Adult household contacts of 236 TB patients, 2001–2005 | 399   | 3HP + DOT: 93% completion  
8w daily RIF/Pz  
3HP vs. 8w daily RIF/Pz, p = 0.82 |
| **Observational studies**    |              |                      |       |                   |
| Cruz, 2018**                | USA          | Aged ≤18 years, attending one hospital-based TB clinic | 667   | Seven different regimens/combinations used  
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Completion, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3HP</td>
<td>96.8</td>
<td>27.4 (12–64)</td>
</tr>
<tr>
<td>4R (DOT)</td>
<td>97.1</td>
<td>30.6 (4–239)</td>
</tr>
<tr>
<td>4R (SAT)</td>
<td>83.5</td>
<td>4.6 (2–10)</td>
</tr>
<tr>
<td>9H (DOT)</td>
<td>88.8</td>
<td>7.1 (4–14)</td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country /ies</td>
<td>Setting &amp; population</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Sandul, 2017⁷⁴</td>
<td>USA</td>
<td>Aged ≥2 years, attending 16 clinics from 2011–2013</td>
</tr>
<tr>
<td>Holzhuch, 2017⁷⁵</td>
<td>USA</td>
<td>High school students and staff</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jinbo, 2017⁷⁶</td>
<td>USA (Hawaii)</td>
<td>Adults attending military clinics, 2014–2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastment, 2017⁷⁷; McClintock, 2017⁷⁸</td>
<td>USA</td>
<td>Adults attending outpatient clinics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stennis, 2016⁷⁹</td>
<td>USA</td>
<td>Aged ≥12 years, attending two TB clinics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cruz 2016⁸⁰‡</td>
<td>USA</td>
<td>Aged ≤21 years, attending one hospital-based TB clinic</td>
</tr>
<tr>
<td>Yamin, 2016⁸¹</td>
<td>USA</td>
<td>Adults treated for LTBI at one TB clinic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hatzenbuehler 2016⁸²</td>
<td>USA</td>
<td>Adolescents attending two public schools</td>
</tr>
<tr>
<td>CDC, 2013⁸¹</td>
<td>USA</td>
<td>School contacts with LTBI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For detailed description of population, inclusion/exclusion criteria, and other methods, see Appendix 2 (Supplementary table 2)
†Subset of Sterling, 2011⁵²
‡Possibly a subset of Cruz, 2018⁷³

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
5.4. Toxicity and adverse events

The large randomised trials also reported estimates of treatment-related toxicity, most importantly hepatotoxicity. The PREVENT TB study\(^{52}\) 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\(^{83}\), 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).\(^{83}\) 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)

<table>
<thead>
<tr>
<th>First author, (year) published</th>
<th>Country /ies</th>
<th>Setting &amp; population</th>
<th>(N)</th>
<th>Relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swindells, (2018^{17})</td>
<td>Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe</td>
<td>HIV-positive, aged ≥13 years</td>
<td>3,000</td>
<td><strong>Grade 3 or 4 adverse events</strong>&lt;br&gt;16.8% vs. 18.3% in 1HP vs. 9H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Hepatic adverse events (grade 3 or 4)</strong>&lt;br&gt;1.9% vs. 2.8% in 1HP vs. 9H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Targeted safety events (liver, GI, neurologic, skin, hypersensitivity)</strong>&lt;br&gt;5.7% vs. 7.2% in 1HP vs. 9H; IRR 9H vs. 1HP 1.59 (95% CI 1.1–2.3), (p = 0.016)</td>
</tr>
<tr>
<td>Belknap, (2017^{17})</td>
<td>Hong Kong, South Africa, Spain, USA</td>
<td>Adults attending outpatient clinics from 2012–2014</td>
<td>1,002</td>
<td><strong>Any adverse event</strong>&lt;br&gt;15.7% vs. 17.5% vs. 18.9% in DOT vs. SAT, no text vs. SAT+text arms (all pts received 3HP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Any drug-related adverse event</strong>&lt;br&gt;7.1% vs. 8.3% vs. 7.9% in DOT vs. SAT, no text vs. SAT+text arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Grade 3 or 4 drug-related adverse events</strong>&lt;br&gt;2.4% vs. 3.0% vs. 4.3% in DOT vs. SAT, no text vs. SAT+text arms</td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country /ies</td>
<td>Setting &amp; population</td>
<td>N</td>
<td>Relevant findings</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>----------------------</td>
<td>----</td>
<td>------------------</td>
</tr>
</tbody>
</table>
| **Huang, 2016**<sup>73</sup> | Taiwan       | Aged ≥12 years, contact with drug-sensitive TB, 2014 | 691 | **Grade 3 or 4 side-effects** 4.0% vs. 1.2% in 3HP vs. 9H arms  
**Side-effects causing treatment discontinuation** 2.0% vs. 4.7% in 3HP vs. 9H arms |
| **Sterling, 2016**<sup>73†</sup> | Brazil, Canada, Hong Kong, Peru, Spain, USA | HIV-positive, aged ≥2 years, 2001–2010 | 399 | **Grade 3 or 4 adverse events** 2.9% vs. 8.6% in 3HP vs. 9H arms  
**Adverse events causing treatment discontinuation** 3.4% vs. 4.3% in 3HP vs. 9H arms  
**Death** 2.9% vs. 2.6% in 3HP vs. 9H arms |
| **Villarino, 2015**<sup>60</sup> | Brazil, Canada, Hong Kong, Spain, USA | Aged 2–17 years, 2001–2010 | 1,058 | **Any adverse event**  
| **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); p = 0.18 | 0.59 (0.30–1.16); p = 0.10 | 0.66 (0.26–1.50); p = 0.31 |
| **Schechter, 2006**<sup>65</sup> | Brazil | Adult household contacts of 236 TB | 399 | **Grade 3 or 4 hepatotoxicity** 1% vs 10% in 3HP vs. Rif/Pz arms; p <0.001  
(Trial stopped early because of hepatotoxicity in Rif/Pz arm) |
<table>
<thead>
<tr>
<th>First author, Country /ies</th>
<th>Setting &amp; population</th>
<th>N</th>
<th>Relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational studies</strong></td>
<td>patients, 2001–2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cruz, 2018</strong>&lt;sup&gt;73&lt;/sup&gt; USA</td>
<td>Aged ≤18 years, attending one hospital-based TB clinic</td>
<td>667</td>
<td>Any adverse event 8.5% vs. 4.8% vs. 13.7% in 3HP vs. 4R vs. 9H arms</td>
</tr>
<tr>
<td><strong>Sandul, 2017</strong>&lt;sup&gt;74&lt;/sup&gt; USA</td>
<td>Aged ≥2 years, attending 16 clinics from 2011–2013</td>
<td>3,327</td>
<td>Any adverse event/adverse drug reaction 35.7% of participants taking 3HP</td>
</tr>
<tr>
<td><strong>Jinbo, 2017</strong>&lt;sup&gt;76&lt;/sup&gt; USA (Hawaii)</td>
<td>Adults attending military clinics, 2014–2015</td>
<td>179</td>
<td>Symptom reported Minimum 21.2% of participants taking 3HP‡</td>
</tr>
<tr>
<td><strong>Stennis, 2016</strong>&lt;sup&gt;79&lt;/sup&gt; USA</td>
<td>Aged ≥12 years, attending two TB clinics</td>
<td>394</td>
<td>Any side-effect 13.2% of participants taking 3HP</td>
</tr>
<tr>
<td><strong>Yamin, 2016</strong>&lt;sup&gt;81&lt;/sup&gt; USA</td>
<td>Adults treated for LTBI at one TB clinic</td>
<td>424</td>
<td>Any adverse event 20.8% vs. 9.7% vs. 21.7% in 3HP vs. 4R vs. 9H arms</td>
</tr>
<tr>
<td><strong>Hatzenbuehler 2016</strong>&lt;sup&gt;82&lt;/sup&gt; USA</td>
<td>Adolescents attending two public schools</td>
<td>16</td>
<td>All 16 students were treated with 3HP; no significant adverse events recorded during treatment</td>
</tr>
</tbody>
</table>

*For detailed description of population, inclusion/exclusion criteria, and other methods, see Appendix 2 (Supplementary table 2)
‡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; 3R: 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.⁶⁰, 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.⁸⁰

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.⁷⁴, 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.⁷⁴)**

![Figure 8](image)

3HP: 3 months of once-weekly rifapentine and isoniazid; No.; Number; Tx: treatment; USA: United States of America
Most recently, a drug-drug interaction study that gave 3HP and dolutegravir, a first-line antiretroviral agent and integrase inhibitor, to four healthy volunteers was forced to stop early because of toxicity in two of the participants, who experienced the rapid-onset of a flu-like syndrome and raised inflammatory markers liver enzymes. Further investigation is needed to establish the safety of co-administration of 3HP and dolutegravir; previous studies have shown that once-weekly rifapentine can be safely administered with raltegravir, and 3HP with efavirenz.

5.5. Cost-effectiveness
In 2009, before robust effectiveness data were available for 3HP, Holland et al. 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 (Figure 9).
Figure 9. Cost-effectiveness plots for 3HP vs. 4R vs. 9H+DOT vs. 9H+SAT vs. no treatment under different relative risk* of disease activation (from Holland et al., 2009)

The base assumptions for the four panels are: (A) Base-case lifetime risk of 6%; (B) Patients with double the baseline relative risk of disease; (C) Patients with 5.2 times the baseline relative risk of disease; and (D) Patient with 10 times the baseline relative risk of disease.

Authors’ explanation: “(A) In this scenario, 4R is less expensive and more effective than all regimens except 3HP, which is more effective at a cost of $48,997 per QALY (shown in the figure as the inverse slope of the solid line connecting 4R and 3HP). 3HP is more effective than 9H, at a cost of $20,207 per QALY (dotted line). (B) In this scenario, 4R and 3HP dominate other options, and 3HP is more effective than 4R, at a cost of $20,099 per QALY (solid line). (C) Here, 4R and 3HP are equivalent in cost, but 3HP is more effective. (D) 3HP dominates all strategies.”

3HP: three months of once-weekly rifapentine and isoniazid; 4R: four months of daily rifampicin; 9H: nine months of daily isoniazid; DOT: directly observed therapy; QALY quality-adjusted life-year; SAT: self-administered therapy; US$: United States dollars

In 2011, the same group used a Markov model to compare the costs of 9H+SAT, 3HP+SAT, 3HP+DOT, and one month of daily rifapentine and isoniazid (1HP) + SAT. Estimates of costs other than drugs were taken from US literature or approximated using clinical judgement. The authors estimated that the cost per month of 9H+SAT was US$ 27.72 (range 20–34), of 3HP+DOT was US$ 176.50 (range 133–221), of 3HP+SAT was US$ 80.20 (range 60–100) and of 1HP+SAT was US$ 293.81 (range 220–367). However, after cost-effectiveness (US$ per quality-adjusted life year [QALY]) was calculated, 1HP+SAT emerged as more cost-effective than all other regimens (Figure 10), as long as adherence was above 83%, efficacy above 81%, and toxicity below 7%.
Both 3HP+SAT and 3HP+DOT were more cost-effective than 9H+SAT. 3HP+SAT remained dominant to 9H+SAT as long as adherence remained above 70% and toxicity below 10%.

**Figure 10.** Cost-effectiveness of 1HP+SAT vs. 3HP+SAT vs. 3HP+DOT vs. 9H+SAT vs. no treatment (ICERs are represented by the inverse slope of the dotted and dashed lines between strategies; in 2011 US$; from Holland et al., 2011⁸⁹)

![Cost-effectiveness graph](image)

1HP: one month of daily rifapentine and isoniazid; 3HP: three months of once-weekly rifapentine and isoniazid; 9H: nine months of daily isoniazid; DOT: directly observed therapy; ICER: incremental cost-effectiveness ratio; SAT: self-administered therapy; US$: United States dollars

In 2012, Pho et al.⁹⁰, 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.⁵⁶, and did not include data from the PREVENT TB study.
In 2013, Shepardson et al.\textsuperscript{91,92} 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 [95% CI 99–129]; Figure 11) and to society (an extra US$ 23 [95% CI 7–41]) per person treated, it also prevents an additional 5.2 (95% CI 4.5–5.9) TB cases and prevents the loss of an extra 25 (95% CI 21–29) 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.

**Figure 11. Cost of a complete course of treatment* for LTBI with 3HP+DOT or 9H+SAT (in 2010 US$; from Shepardson et al., 2013\textsuperscript{91})**

*"Patients receiving 9H have an initial clinic visit and eight later clinic visits; those receiving 3HP have an initial clinic visit, two later clinic visits and 12 visits by a health care worker for DOT. Patient costs include out-of-pocket expenses and lost productivity; other costs are costs to the health system."\textsuperscript{91} 

3HP: three months of once-weekly rifapentine and isoniazid; 9H: nine months of daily isoniazid; DOT: directly observed therapy; LTBI: latent tuberculosis infection; SAT: self-administered therapy; US$: United States dollars

After the price of RPT was lowered in the USA (900 mg dose reduced from US$ 12.31 to US$ 6.00),\textsuperscript{93} Shepardson et al.\textsuperscript{94} 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 update was welcomed by activists, stating that significant public investments were made in the development of RPT, and that this should be used as justification for pricing the drug accessibly.95,96

More recently, in 2016, Huang et al.71 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.

Most recently, 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.97 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).

5.6. Potential expansion to other high-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 LTBI in these individuals, as well as some preliminary evidence around treatment with RPT is presented below.

5.6.1. Pregnant women

A systematic review by Malhamé et al.98 estimated the burden of LTBI in pregnant women. Based on data from 13 studies, the estimated prevalence of LTBI 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.

Few studies appear to have examined the effect of LTBI treatment 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 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 LTBI. Results from the study are expected in early 2019 (see Appendix 1).

5.6.2. Inmates of correctional facilities
A cross-sectional study in two prisons in Brazil used TST to identify LTBI and found a prevalence of 25.2% among the 1,120 inmates tested. A 2011 study by Lopez et al. 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 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.

5.6.3. Health care workers
A 2016 systematic review by Nasreen et al. 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.\textsuperscript{105} 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, \( p < 0.0001 \)).

5.6.4. Transplant candidates/recipient

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,\textsuperscript{106} 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\textsuperscript{107}, 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).\textsuperscript{108} 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\textsuperscript{109} 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.
5.6.5. Other

Using a Markov model, Tasillo et al.\textsuperscript{110} 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.\textsuperscript{111} 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.
6. Summary

6.1. Is LTBI treatment 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. This is reflected in recommendations for best practice made by a number of governing and regulatory bodies, including WHO and CDC.

6.2. Is LTBI treatment 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.

6.3. Is 3HP superior to IPT?
There is no evidence that 3HP is more effective than IPT, but studies have shown 3HP to be equivalent effective as IPT in preventing progression to active disease (see sections 5.1–5.4). 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.

6.4. 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], see section 5.3); higher levels of systemic drug reactions (e.g., compared with 4R, see section 5.4); and less hepatotoxicity (e.g., compared with daily rifampicin and pyrazinamide; section 5.4).

6.5. 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 (see section 5.5). 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.

6.6. 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 (see section 5.6), 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.
7. References


16. World Health Organization. Update of three systematic literature reviews on the prevalence of latent tuberculosis infection, the risk of progression to active TB disease, and cumulative prevalence of active TB among contacts in different age groups. Personal communication (A. Kanchar). 2017.


Marais BJ. Twelve-Dose Drug Regimen Now Also an Option for Preventing Tuberculosis in Children and Adolescents. JAMA Pediatr. 2015;169(3):208.


8. Appendices

8.1. Appendix 1. Ongoing trials

Supplementary table 1. List of active trials of rifapentine registered on ClinicalTrials.gov in February 2018 (n = 6)

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Status</th>
<th>Intervention(s)</th>
<th>Main outcome measures</th>
<th>Locations</th>
<th>Sponsor / collaborators</th>
<th>Enrolment target</th>
<th>Start / completion dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02208427</td>
<td>Active, not recruiting</td>
<td>RPT and INH for 3 months vs. INH for 9 months</td>
<td>Completion rate, Side effects, Interruption, Active TB</td>
<td>Taiwan</td>
<td>National Taiwan University Hospital</td>
<td>283</td>
<td>Aug 2014 / Dec 2016</td>
</tr>
<tr>
<td>NCT02430259</td>
<td>Recruiting</td>
<td>Weekly INH/RPT given by DOT</td>
<td>TB disease, Drug discontinuation, Grade 3 or 4 drug toxicities, Deaths associated with 3HP, Treatment completion</td>
<td>China</td>
<td>Huashan Hospital</td>
<td>566</td>
<td>Mar 2015 / Dec 2018</td>
</tr>
<tr>
<td>NCT02651259</td>
<td>Recruiting</td>
<td>RPT, INH, &amp; pyridoxine (vitamin B6)</td>
<td>Clearance, absorption, and volume of distribution of RPT and metabolite SAES in pregnant and postpartum women, SAES in infants born to women</td>
<td>United States, Haiti, Kenya, Malawi, Thailand, Zimbabwe</td>
<td>NIAID</td>
<td>82</td>
<td>Feb 2017 / Dec 2018</td>
</tr>
<tr>
<td>NCT02689089</td>
<td>Recruiting</td>
<td>3HP</td>
<td>Completion of treatment</td>
<td>Canada</td>
<td>OHRI, Government of Nunavut, Government of Canada</td>
<td>450</td>
<td>Apr 2016 / Sep 2018</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Status</td>
<td>Intervention(s)</td>
<td>Main outcome measures</td>
<td>Locations</td>
<td>Sponsor / collaborators</td>
<td>Enrolment target</td>
<td>Start / completion dates</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>NCT02735590</td>
<td>Not yet recruiting</td>
<td>INH &amp; RPT</td>
<td>Treatment efficacy</td>
<td></td>
<td>UCT, SATVI, The Aurum Institute, CAPRISA, University of Stellenbosch, LSHTM, Fred Hutchinson Cancer Research Center</td>
<td>3200</td>
<td>Jul 2016 / NS</td>
</tr>
<tr>
<td>NCT02980016</td>
<td>Recruiting</td>
<td>RPT + INH vs. INH</td>
<td>Treatment completion</td>
<td>South Africa</td>
<td>KNCV Tuberculosis Foundation, The Aurum Institute, LSHTM, Johns Hopkins University</td>
<td>4000</td>
<td>Nov 2016 / Sep 2019</td>
</tr>
</tbody>
</table>

CAPRISA: Centre for the AIDS Programme of Research in South Africa; COR: correlate of risk; DALY: disability adjusted life year; INH: isoniazid; LSHTM: London School of Hygiene & Tropical Medicine; OHRI: Ottawa Hospital Research Institute; RPT: rifapentine; NIAID: National Institute of Allergy and Infectious Diseases; NS: Not specified; SAE: serious adverse event; SATVI: South African Tuberculosis Vaccine Initiative; TB: tuberculosis; UCT: University of Cape Town
8.2. Appendix 2. Details of studies with findings included in this report

Supplementary table 2. List of articles reporting primary data included in this report (n = 41; listed alphabetically by first author)

<table>
<thead>
<tr>
<th>First author, year published</th>
<th>Country/ies</th>
<th>Year(s) active</th>
<th>Population</th>
<th>Sample size</th>
<th>Demographics</th>
<th>Summary of methods</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arguello-Perez, 2017&lt;sup&gt;105&lt;/sup&gt;</td>
<td>USA</td>
<td>2005–2014</td>
<td>HCW treated for LTBI</td>
<td>3927 (363 treated)</td>
<td>Mean age 36 (±10); 50% female; 74% with previous BCG treated with 3HP, 4R, or 9H, looking mainly at treatment completion.</td>
<td>Retrospective review of health records of HCW treated with 3HP, 4R, or 9H, looking mainly at treatment completion.</td>
<td></td>
</tr>
<tr>
<td>Badje, 2017&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Côte d’Ivoire</td>
<td>2008–2015</td>
<td>HIV-positive adults</td>
<td>2,056</td>
<td>Median age 35 years; 78.5% female</td>
<td>Long-term follow-up of TEMPRANO study, looking at outcomes after a median 4.9 years.</td>
<td></td>
</tr>
<tr>
<td>Belknap, 2017&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Hong Kong, South Africa, Spain, USA</td>
<td>2012–2014</td>
<td>Outpatient clinics; Adults (≥18 years)</td>
<td>1,002</td>
<td>Median age 36 years; 48% female</td>
<td>Randomised to receive 3HP + one of DOT, SAT without reminders, or SAT with weekly text message reminders.</td>
<td></td>
</tr>
<tr>
<td>Blake 2006&lt;sup&gt;58&lt;/sup&gt;</td>
<td>USA</td>
<td>NS</td>
<td>Children aged 2–12 years</td>
<td>24</td>
<td>54% female</td>
<td>Measured pharmacokinetics of rifapentine after administration of a single dose of 150 mg or 300 mg.</td>
<td></td>
</tr>
<tr>
<td>Bliven-Sizemore, 2015&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Brazil, Canada, Spain, USA</td>
<td>2001–2008</td>
<td>≥18 years; enrolled in PREVENT TB</td>
<td>6,862</td>
<td>Median age ~45 years; 67% cases female, 44% controls female</td>
<td>Objective: to evaluate the hepatotoxicity risk associated with 3HP compared to 9H, and factors associated with hepatotoxicity. Nested case-control study within PREVENT TB; cases experienced hepatotoxicity after taking at least one dose of 3HP or 9H.</td>
<td></td>
</tr>
<tr>
<td>Brooks, 2018&lt;sup&gt;85&lt;/sup&gt;</td>
<td>USA</td>
<td>2016</td>
<td>Healthy adults</td>
<td>4</td>
<td>Age range 21–44 years; 25% female</td>
<td>Aim to examine pharmacokinetic drug-drug interactions between 3HP and dolutegravir. Single-centre, open-label, fixed-sequence, drug-drug interaction study in healthy volunteers.</td>
<td></td>
</tr>
<tr>
<td>CDC, 2013&lt;sup&gt;61&lt;/sup&gt;</td>
<td>USA</td>
<td>2011</td>
<td>School contacts with LTBI</td>
<td>161</td>
<td>Not reported</td>
<td>Compared completion of treatment in contacts treated with 3HP, 4R, or 9H.</td>
<td></td>
</tr>
<tr>
<td>Charalambous, 2010&lt;sup&gt;58&lt;/sup&gt;</td>
<td>South Africa</td>
<td>2004–2007</td>
<td>ART-naive, HIV-positive adults starting ART; employed in one of ART</td>
<td>3,752</td>
<td>Mean age 44.9 years; median baseline CD4 155 (IQR 87–221) cells/µL; 7% female</td>
<td>Prospective cohort; followed up for 12 months. Primary outcome was death; looked for associations between IPT use and mortality.</td>
<td></td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country/ies</td>
<td>Year(s) active</td>
<td>Population</td>
<td>Sample size</td>
<td>Demographics</td>
<td>Summary of methods</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------</td>
<td>--------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Cruz, 2018&lt;sup&gt;73&lt;/sup&gt;</td>
<td>USA</td>
<td>2014–2017</td>
<td>Aged ≤21 years attending one hospital-based TB clinic</td>
<td>80</td>
<td>Median age 8.0 (IQR 3.6–13.8) years; 50.8% female</td>
<td>Describing completion rates in participants receiving 3HP + DOT for LTBI.</td>
<td>selected companies; not on TB treatment</td>
</tr>
<tr>
<td>de Castilla, 2014&lt;sup&gt;106&lt;/sup&gt;</td>
<td>USA</td>
<td>2012</td>
<td>Adult candidates for solid organ transplants</td>
<td>17</td>
<td>Median age 57 (range 33–75) years; 17.6% female</td>
<td>Aim: to assess the safety and tolerability of 3HP in this group. Prospective cohort study describing completion rates and toxicity in 17 transplant candidates treated with 3HP.</td>
<td></td>
</tr>
<tr>
<td>Eastment, 2017&lt;sup&gt;77&lt;/sup&gt;</td>
<td>USA</td>
<td>2009; 2013–2014</td>
<td>Adults attending five outpatient clinics</td>
<td>393</td>
<td>Mean age ~43 years; 44.5% female</td>
<td>Retrospective cohort estimating treatment completion in adults receiving 3HP, 4R, or 9H</td>
<td>Same dataset as McClintock 2017&lt;sup&gt;78&lt;/sup&gt;</td>
</tr>
<tr>
<td>Golub, 2007&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Brazil</td>
<td>2003–2005</td>
<td>HIV-positive adults attending 29 public clinics</td>
<td>11,026</td>
<td>38.1% female; 74% taking ART before or during follow-up</td>
<td>Retrospective cohort; data collected through review of medical notes. Estimated rates of TB disease in patients who received no ART or IPT vs. only ART vs. ART and IPT.</td>
<td></td>
</tr>
<tr>
<td>Golub, 2009&lt;sup&gt;35&lt;/sup&gt;</td>
<td>South Africa</td>
<td>2003–2007</td>
<td>HIV+ adults attending primary care (urban and rural)</td>
<td>2,778</td>
<td>Median age 33 (IQR 29–39) years; 80% female; median BMI 23.6 (IQR 20–28) kg/m²; median baseline CD4 266 (IQR 139–439) cells/µL; 30% initiated ART</td>
<td>Prospective cohort estimating incidence of active TB in individuals receiving ART or IPT or both or neither. Total follow-up of 42,87 person-years.</td>
<td></td>
</tr>
<tr>
<td>Golub, 2015&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Brazil</td>
<td>2003–2009</td>
<td>HIV+ adults, TST+</td>
<td>1,954</td>
<td>38% female; median age ~40 years; ≥50% with CD4 ≥500 cells/µL</td>
<td>Sub-analysis within a cluster-randomised, phased implementation trial of IPT (“THRIO” study). Followed TST+, HIV+ patients until incidence of TB, death, or administrative censoring.</td>
<td></td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country/ies</td>
<td>Year(s) active</td>
<td>Population</td>
<td>Sample size</td>
<td>Demographics</td>
<td>Summary of methods</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Hakim, 2017</td>
<td>Kenya, Malawi, Uganda, and Zimbabwe</td>
<td>2013–2015</td>
<td>HIV-positive, aged ≥5 years; ART naïve; starting ART; CD4 count ≤100 cells/µL</td>
<td>1,805</td>
<td>Median age 36 (IQR 29–42) years; 47% female; median BMI 19.2 (IQR 17–21) kg/m²; median CD4 37 (IQR 16–63) cells/µL; 15% with active TB at enrolment</td>
<td>Factorial open-label trial; randomised to receive 'enhanced' (CPT, IPT, flucanazole, azithromycin, albendazole) vs. ‘standard’ (CPT) antimicrobial prophylaxis, adjunctive raltegravir vs. no raltegravir, and supplementary vs. no supplementary food. Primary endpoint was mortality at 24 weeks.</td>
<td>“Reduction of early mortality in HIV-infected adults and children starting ART (REALITY)”</td>
</tr>
<tr>
<td>Hatzenbuehler 2016</td>
<td>USA</td>
<td>NS</td>
<td>Adolescents attending two public schools</td>
<td>16</td>
<td>Not reported for students receiving treatment.</td>
<td>Students with positive IGRA were treated with 3HP; estimated toleration and completion of regimen.</td>
<td></td>
</tr>
<tr>
<td>Holzshuch, 2017</td>
<td>USA</td>
<td>2015</td>
<td>Contacts of an individual with TB who were IGRA+</td>
<td>50</td>
<td>41 students and staff members, 4 household contacts, five social contacts</td>
<td>Treatment of IGRA+ contacts of a person with TB with 9H + SAT, 4R + SAT, or 3HP + DOT. 15/27 individuals receiving 3HP opted for video DOT instead of conventional DOT.</td>
<td></td>
</tr>
<tr>
<td>Huang, 2016</td>
<td>Taiwan</td>
<td>2014</td>
<td>≥12 years; people on ART not given 3HP</td>
<td>691</td>
<td>Mean age ~34 years; 48.5% female</td>
<td>3HP vs. 9H; randomisation process not described (101 [14.6%] received 3HP vs. 590 [85.4%] 9H)</td>
<td></td>
</tr>
<tr>
<td>Jinbo, 2017</td>
<td>USA</td>
<td>2014–2015</td>
<td>Adults with LTBI attending two military clinics; negative CXR</td>
<td>365</td>
<td>Median age 30 (IQR 25–36) years; 30% female; 44% IGRA+; 46% TST+</td>
<td>Retrospective cohort of people with LTBI taking 3HP, INH monotherapy, or RIF monotherapy. Primary outcome was completion of treatment.</td>
<td></td>
</tr>
<tr>
<td>Juarez-Reyes, 2016</td>
<td>USA</td>
<td>2010–2011</td>
<td>Individuals incarcerated in an urban county jail; TST+ and IGRA+</td>
<td>245</td>
<td>Median age ~36 years; 2.9% female</td>
<td>Retrospective cohort – chart review of individuals receiving 3HP vs. 9H for treatment of LTBI. Primary endpoint: treatment completion; secondary endpoint: permanent treatment discontinuation due to adverse drug reactions.</td>
<td></td>
</tr>
<tr>
<td>Knoll, 2017</td>
<td>USA</td>
<td>2013–2016</td>
<td>Candidates for solid organ transplant; IGRA+</td>
<td>12</td>
<td>Median age 60 (range 44–72) years; 8.3% female; median MELD score 17 (range 10–31)</td>
<td>Prospective monitoring of safety and tolerability of 3HP in transplant candidates.</td>
<td></td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country/ies</td>
<td>Year(s) active</td>
<td>Population</td>
<td>Sample size</td>
<td>Demographics</td>
<td>Summary of methods</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Lopez, 2011</td>
<td>Spain</td>
<td>2000–2009</td>
<td>Inmates at a medium-sized prison; TST+ or other risk factor for LTBI</td>
<td>810</td>
<td>Median age ~39 years; 15% HIV-positive</td>
<td>Retrospective longitudinal study comparing adherence and completion rates of 9H, 2 months of twice-weekly RIF and Pz, 3 months of daily INH and Rif, or 4R.</td>
<td></td>
</tr>
<tr>
<td>Martinson, 2011</td>
<td>South Africa</td>
<td>2002–2005</td>
<td>HIV+ adults; CD4 ≥200 cells/µL; not on ART; TST+; no active TB</td>
<td>1,150</td>
<td>Median age 30.4 y; 83% female; median CD4 484 cells/µL; median VL 4.2 log copies/ml; median BMI 24.9 kg/m²</td>
<td>Randomised 2:2:2:1 to receive 3HP + DOT vs. 3 months of twice weekly RH + DOT vs. ≤6y H vs. 6H; followed up for ~4 years</td>
<td></td>
</tr>
<tr>
<td>McClintock, 2017</td>
<td>USA</td>
<td>2009; 2013–2014</td>
<td>Adults attending five outpatient clinics</td>
<td>393</td>
<td>Mean age ~43 years; 44.5% female</td>
<td>Retrospective cohort estimating treatment completion in adults receiving 3HP, 4R, or 9H</td>
<td>Same dataset as Eastman 2017</td>
</tr>
<tr>
<td>Moro, 2018</td>
<td>Brazil, Canada, Hong Kong, South Africa, Spain, USA</td>
<td>2001–2014</td>
<td>Pregnant women who received at least 1 dose of 3HP or 9H</td>
<td>125</td>
<td>126 pregnancies; 100% female</td>
<td>Analysis of data from PREVENT TB and iAdhere trials, reporting foetal loss and/or congenital abnormalities in the children of pregnant women who received 3HP or 9H.</td>
<td>Analysis of PREVENT TB and iAdhere data</td>
</tr>
<tr>
<td>Navarro, 2016</td>
<td>Brazil</td>
<td>2013</td>
<td>Inmates of two prisons; no previous TB; no previous TST</td>
<td>1,120</td>
<td>Mean age 27 (± 7) years; 8.9% female</td>
<td>Cross-sectional cohort study that used TST to estimate the prevalence of LTBI in two prisons in Brazil.</td>
<td></td>
</tr>
<tr>
<td>Podany, 2015</td>
<td>Botswana, Peru, South Africa, Thailand, USA</td>
<td>2012–2013</td>
<td>HIV+; ≥13 years; ≥30 kg; no active TB</td>
<td>87</td>
<td>Median age 35 (IQR 29–44 years); 54% female</td>
<td>Measured interactions and pharmacokinetics of 3HP and efavirenz in HIV-positive individuals enrolled to ACTG 5279.</td>
<td></td>
</tr>
<tr>
<td>Sandul, 2017</td>
<td>USA</td>
<td>2011–2014</td>
<td>16 health programmes across the people with LTBI taking 3HP</td>
<td>3,288</td>
<td>46.5% female; 60.6% US-born; 3.8% “immunocompromised”</td>
<td>Observational cohort of LTBI patients receiving 3HP through 16 US programmes. Assessed treatment completion, adverse drug reactions, and factors associated with treatment discontinuation.</td>
<td></td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country/ies</td>
<td>Year(s) active</td>
<td>Population</td>
<td>Sample size</td>
<td>Demographics</td>
<td>Summary of methods</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Schechter, 2006</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Brazil</td>
<td>2001–2005</td>
<td>Household contacts of 236 TB patients, ≥18 years; TST+, no TB symptoms; negative CXR</td>
<td>399</td>
<td>Mean age 37.4 y; 60% female; &lt;1% HIV+</td>
<td>Randomised 1:1 to receive 3HP or 8 weeks of daily RIF (450 mg) + Pz (750 mg) if &lt;50 kg OR RIF (600 mg) + Pz (1500 mg) if ≥50 kg. Followed up for 2 years</td>
<td></td>
</tr>
<tr>
<td><strong>Simkins, 2017</strong>&lt;sup&gt;108&lt;/sup&gt;</td>
<td>USA</td>
<td>2012–2014</td>
<td>Renal transplant candidates; IGRA+; treated for LTBI</td>
<td>153</td>
<td>Mean age ~57 years; 30.1% female</td>
<td>Retrospective study among renal transplant candidates treated with 3HP or 9H, estimating adherence, treatment completion, and adverse events.</td>
<td></td>
</tr>
<tr>
<td><strong>Simkins, 2017</strong>&lt;sup&gt;109&lt;/sup&gt;</td>
<td>USA</td>
<td>2012–2015</td>
<td>Renal transplant candidates; IGRA+, treated with 3HP</td>
<td>37</td>
<td>Mean age 56 (±14) years; 22% female; all stage 5 CKD; 92% on dialysis</td>
<td>Estimation of the incidence of severe hypertension in renal transplant candidates treated with 3HP. Severe hypertension defined as blood pressure ≥180/110 mmHg.</td>
<td></td>
</tr>
<tr>
<td><strong>Stennis, 2016</strong>&lt;sup&gt;79&lt;/sup&gt;</td>
<td>New York, USA; Canada</td>
<td>2013;</td>
<td>Aged ≥12 years; attending two TB clinics</td>
<td>394</td>
<td>Median age ~33 years; 53% female</td>
<td>Prospective cohort estimating treatment completion in patients treated with 3HP, 4R, or 9H.</td>
<td></td>
</tr>
<tr>
<td><strong>Sterling, 2016</strong>&lt;sup&gt;113&lt;/sup&gt;</td>
<td>Brazil, Canada, Hong Kong, Peru, Spain, USA</td>
<td>2001–2010</td>
<td>HIV+; TST+ or close contact of person with TB</td>
<td>399</td>
<td>Median age ~36 years; 31% female; median CD4 ~500 cells/µL; median BMI ~25 kg/m²; 31% reported ART</td>
<td>Prospective, open-label, randomised trial; 1:1 randomisation to receive 3HP + DOT (n = 206) or 9H + SAT (n = 193). Part of PREVENT TB data</td>
<td></td>
</tr>
<tr>
<td><strong>Sterling, 2015</strong>&lt;sup&gt;113&lt;/sup&gt;</td>
<td>Brazil, Canada, Spain, USA</td>
<td>2001–2008</td>
<td>≥2 years AND close contact with TB (last 2y) and TST+ OR HIV+ and TST+/contact OR TST+ with CXR fibrosis</td>
<td>7,552</td>
<td>Median age ~36 y; ~45% female; ~2.7% HIV-positive; median BMI ~26 kg/m²</td>
<td>Identification of systemic drug reactions and estimation of severity and risk factors for their development.</td>
<td>Analysis of PREVENT TB data</td>
</tr>
<tr>
<td><strong>Sterling, 2011</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Brazil, Canada, Spain, USA</td>
<td>2001–2010</td>
<td>HIV+; TST+ or close contact with TB (last 2y) and TST+ OR HIV+ and TST+/contact OR TST+ with CXR fibrosis</td>
<td>7,731</td>
<td>Median age ~36 y; 4% female; 3% reported ART</td>
<td>Randomised 1:1 to receive 3HP + DOT or 9H + SAT; followed up for 33 months. “PREVENT TB”</td>
<td></td>
</tr>
<tr>
<td><strong>Swindells, 2018</strong>&lt;sup&gt;117&lt;/sup&gt;</td>
<td>Botswana, Brazil, Haiti, Kenya, Malawi,</td>
<td>2012–2014</td>
<td>HIV-positive, aged ≥13 years</td>
<td>3,000</td>
<td>Median age 35 (IQR 28–43) years; 54% female; median BMI 23.5 (IQR 20.9–27.1)</td>
<td>Randomised 1:1 to receive 1HP or 9H; followed up for 3 years. Primary endpoints were incidence of active TB, death due to TB, and death due to unknown “ACTG 5279”</td>
<td></td>
</tr>
<tr>
<td>First author, year published</td>
<td>Country/ies active</td>
<td>Year(s) active</td>
<td>Population</td>
<td>Sample size</td>
<td>Demographics</td>
<td>Summary of methods</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Peru, South Africa, Thailand, USA, and Zimbabwe</td>
<td>2008–2015</td>
<td>HIV-positive adults</td>
<td>2,056</td>
<td>Median age 35 years; 78.5% female</td>
<td>Assessed the effects of deferred ART vs. deferred ART + IPT vs. early ART vs. early ART + IPT on the incidence of HIV-related illnesses or death at 30 months post-enrolment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEMPRANO ANRS39</td>
<td>Côte d'Ivoire</td>
<td>2008–2015</td>
<td>HIV-positive adults</td>
<td>1,058</td>
<td>Median age 11 years; 49% female; 2.3% HIV-positive</td>
<td>Randomised 1:1 to receive 3HP + DOT or 9H + DOT/SAT; followed up for ~3 years</td>
<td>Partially PREVENT TB data</td>
</tr>
<tr>
<td>Villarino, 201540</td>
<td>Brazil, Canada, Hong Kong, Spain, USA</td>
<td>2001–2010</td>
<td>Children aged 2–17 years, HIV+ and HIV-neg.; mostly TST+</td>
<td>80 children, 77 adults</td>
<td>Children: median age 4.5 years; Adults: median age 40 years</td>
<td>Nested within PREVENT TB. Measured pharmacokinetics of rifapentine in children (300–900 mg) and adult controls (900 mg).</td>
<td>Part of PREVENT TB</td>
</tr>
<tr>
<td>Weiner 201448</td>
<td>USA</td>
<td>NS</td>
<td>Children aged 2–12 years and adult controls</td>
<td>21</td>
<td>Median body weight 75 (IQR 64–80) kg; ethnicity 52% non-Hispanic white</td>
<td>Open-label, fixed-sequence, three-period study estimating the pharmacokinetics and interactions of rifapentine and raltegravir in healthy volunteers.</td>
<td></td>
</tr>
<tr>
<td>Weiner 201446</td>
<td>USA</td>
<td>NS</td>
<td>Healthy adult volunteers</td>
<td>424</td>
<td>Median age 42 years; 35% female</td>
<td>A retrospective cohort comparing completion of treatment in adults receiving 3HP vs. 4R vs. 9H</td>
<td></td>
</tr>
<tr>
<td>Yamin, 201641</td>
<td>USA</td>
<td>2012–2013</td>
<td>Adults treated for LTBI in one TB clinic</td>
<td>424</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1HP: 1 month of daily rifapentine and isoniazid; 3HP: 3 months of once-weekly rifapentine and isoniazid; 4R: 4 months of daily rifampicin; 4RH: 4 months of daily rifampicin and isoniazid; 6H: 6 months of daily isoniazid; 9H: 9 months of daily isoniazid; ACTG: AIDS Clinical Trials Group; AE: adverse event; aHR: adjusted hazard ratio; AIDS: acquired immune deficiency syndrome; aOR: adjusted odds ratio; aR: adjusted risk ratio; ART: antiretroviral therapy; BMI: body mass index; CKD: chronic kidney disease; CPT: cotrimoxazole preventive therapy; CXR: chest x-ray; DOT: directly-observed therapy; H: isoniazid; HCW: health care workers; HIV+: HIV-positive; HR: hazard ratio; IGRA: interferon-gamma release assay; IGRA+: IGRA-positive; IPT: isoniazid preventive therapy; IQR: interquartile range; IR: incidence rate; IRR: incidence rate ratio; LTBI: latent TB infection; m: month(s); MELD: model for end-stage liver disease; MDR: multi drug-resistant; neg.: negative; NS: not stated; od: once per day; OR: odds ratio; PY: person-year(s); Pz: pyrazinamide; Rif: rifampicin; Rpt: rifapentine; RR: risk ratio; SAT: self-administered therapy; TB: tuberculosis; TST: tuberculin skin-test; TST+: TST-positive; tx: treatment; USA: United States of America; w: week; VL: viral load; y: year(s)
Supplementary table 3. List of review articles included in this report (n = 19; listed alphabetically by first author)

<table>
<thead>
<tr>
<th>First author, year published</th>
<th>Summary of aims &amp; objectives</th>
<th>Number of studies included</th>
<th>If meta-analysis, method used</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akolo, 2010</td>
<td>To determine the effectiveness of TB preventive therapy in reducing the risk of active tuberculosis and death in HIV-infected persons.</td>
<td>12</td>
<td>Fixed-effects</td>
<td>Cochrane review</td>
</tr>
<tr>
<td>Ayele, 2015</td>
<td>To synthesize effect estimates of IPT for TB prevention in adult HIV patients and to assess the effect of IPT on HIV disease progression, all-cause mortality and adverse drug reactions</td>
<td>10</td>
<td>Random-effects</td>
<td></td>
</tr>
<tr>
<td>Cruz 2013</td>
<td>Discussion of available treatment regimens for children with LTBI, as documented by either the TST or IGRA. For each regimen, discussion of data for safety and tolerability, efficacy, adherence, and scenarios in which a clinician might consider using the regimen.</td>
<td>29</td>
<td>n/s</td>
<td>Summary estimates presented, but methods not clear</td>
</tr>
<tr>
<td>Cruz 2014</td>
<td>To review guidance on the testing and treatment of LTBI in children</td>
<td>n/s</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Ferebee, 1970</td>
<td>To review the present knowledge of chemoprophylaxis in human tuberculosis</td>
<td>n/s</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Fox, 2013</td>
<td>Conducted as a part of a GRADE review for an expert panel that was convened to contribute to the development of international guidelines on contact investigation for the WHO</td>
<td>203</td>
<td>The weighted average estimates of incidence rate and prevalence calculated using the exact binomial method.</td>
<td></td>
</tr>
<tr>
<td>Getahun, 2015</td>
<td>To review the pathogenesis, epidemiology, diagnosis, and treatment of LTBI; to address critical gaps in its understanding and propose the necessary research agenda</td>
<td>n/s</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Liu, 2018</td>
<td>To better understand treatment behaviour of individuals with LTBI to address four policy-relevant research questions: what proportion of people who are recommended treatment (a) initiate and (b) complete (i.e., adhere to) treatment; what factors explain nonadherence to treatment; and what are the effective, including cost-effective, strategies to improve adherence to LTBI treatment</td>
<td>54</td>
<td>n/a</td>
<td>Narrative synthesis</td>
</tr>
<tr>
<td>Malhame, 2016</td>
<td>To further understand the prevalence, natural history, screening and management of LTBI in pregnancy</td>
<td>22</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Title and Details</td>
<td>Study Methodology</td>
<td>GRADE: g.</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------</td>
<td>------------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Nasreen, 2016</td>
<td>To estimate the prevalence of LTBI among health care workers in high burden countries</td>
<td>18</td>
<td>Random-effects</td>
<td></td>
</tr>
<tr>
<td>Pease, 2017</td>
<td>To examine the efficacy and completion rates of treatments for LTBI</td>
<td>16</td>
<td>Network meta-analysis</td>
<td></td>
</tr>
<tr>
<td>Person, 2012</td>
<td>To review data, particularly those published since 2011, on the diagnosis and treatment of LTBI</td>
<td>n/s</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Sandgren, 2016</td>
<td>To assess initiation and completion rates of LTBI treatment and to identify determinants and interventions for adherence and completion, in the general and in specific populations with LTBI</td>
<td>39</td>
<td>Not done for the first review question (heterogeneity)</td>
<td></td>
</tr>
<tr>
<td>Sharma, 2013</td>
<td>To compare the effects of rifampicin monotherapy or rifamycin-combination therapy versus INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB</td>
<td>10</td>
<td>Random-effects model, if heterogeneity was significant.</td>
<td>Cochrane review</td>
</tr>
<tr>
<td>Smieja, 1999</td>
<td>To estimate the effect of six- and 12-month courses of INH for preventing TB in HIV-negative people at increased risk of developing active TB</td>
<td>11</td>
<td>Der Simonian and Laird random effects model</td>
<td>Cochrane review</td>
</tr>
<tr>
<td>Stuurman, 2016</td>
<td>To systematically review data on determinants of initiation, adherence and completion of LTBI treatment, and on interventions to improve initiation and completion</td>
<td>62</td>
<td>Random effects</td>
<td></td>
</tr>
<tr>
<td>Vidal, 2015</td>
<td>To assess and to synthesize evidence on the effectiveness and safety of rifapentine-isoniazid combination therapy in LTBI chemoprophylaxis in the general and HIV-positive population to support national recommendations for TB control</td>
<td>10</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Zenner, 2017</td>
<td>To evaluate the comparative efficacy and harms of LTBI treatment regimens aimed at preventing active TB among adults and children</td>
<td>61</td>
<td>Random-effects and network meta-analysis</td>
<td></td>
</tr>
<tr>
<td>Zheng, 2017</td>
<td>To review all clinical and pharmacological data relevant for the concurrent use of rifapentine and oral hypoglycaemic agents/insulin, to compare them with those of rifampicin, and to potentially identify optimal combinations of rifapentine and hypoglycaemic drugs in terms of patient safety</td>
<td>n/s</td>
<td>n/a</td>
<td>Narrative review</td>
</tr>
</tbody>
</table>

GRADE: grading of recommendations, assessment, development, and evaluation; HIV: human immunodeficiency virus; IGRA: interferon gamma release assay; INH: isoniazid; IPT: isoniazid preventive therapy; LTBI: latent tuberculosis infection; n/a: not applicable; n/s: not specified; TB: tuberculosis; TST: tuberculin skin test; WHO: World Health Organization
## Supplementary table 4. List of modelling studies included in this report (n = 12; listed alphabetically by first author)

<table>
<thead>
<tr>
<th>First author, year published</th>
<th>Summary of aims</th>
<th>Summary of methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dowdy, 2014&lt;sup&gt;47&lt;/sup&gt;</td>
<td>To model the epidemiological impact of IPT, delivered at levels that could be feasibly scaled up among people living with HIV in modern, moderate-burden settings.</td>
<td>Used routine surveillance and implementation data from a cluster-randomised trial of IPT among HIV-positive clinic patients with good access to ART in Brazil to populate a parsimonious model of TB/HIV. Modelled IPT delivery as a constant process capturing a proportion of the eligible population every year. Projected feasible reductions in TB incidence and mortality in the general population and among HIV-positive people at the end of five years of implementing an IPT programme.</td>
</tr>
<tr>
<td>Dye, 2013&lt;sup&gt;46&lt;/sup&gt;</td>
<td>To model the interventions needed to reduce the global incidence rate of TB to levels that will lead to the elimination of TB by 2050.</td>
<td>Present estimates from several models using data from a wide variety of sources, including WHO and national TB programmes.</td>
</tr>
<tr>
<td>Holland, 2009&lt;sup&gt;88&lt;/sup&gt;</td>
<td>To evaluate the costs and cost-effectiveness of regimens for the treatment of LTBI</td>
<td>Used a computerised Markov model to estimate total societal costs and benefits associated with four regimens used to treat LTBI: 9H + SAT; 9 months of twice-weekly INH + DOT; 3HP + DOT; and 4R + SAT.</td>
</tr>
<tr>
<td>Holland, 2011&lt;sup&gt;89&lt;/sup&gt;</td>
<td>To inform clinical trial design by estimating the potential costs and effectiveness of rifapentine-based regimens for treatment of LTBI</td>
<td>Used a Markov model to estimate cost and societal benefits for three regimens used to treat LTBI: 1HP; 3HP + DOT/SAT; and 9H. Used a ‘no treatment’ strategy for comparison; calculated costs, QALYs gained, and instances of active TB averted.</td>
</tr>
<tr>
<td>Houben, 2016&lt;sup&gt;4&lt;/sup&gt;</td>
<td>To re-assess the global burden of LTBI</td>
<td>Constructed trends in annual risk of infection for countries between 1934 and 2014 using a combination of direct estimates from LTBI surveys and indirect estimates from WHO estimates of smear-positive TB prevalence from 1990–2014. Used Gaussian process regression to generate annual risk of infection for country-years without data and to represent uncertainty. Applied estimated annual risk of infection time-series to the demography in each country to calculate the number and proportions of individuals infected, recently infected (infected within 2 years), and recently infected with INH-resistant strains. Resulting estimates were aggregated by WHO region.</td>
</tr>
<tr>
<td>Houben, 2016&lt;sup&gt;46&lt;/sup&gt;</td>
<td>To assess the feasibility of the End TB Strategy targets for reductions in TB incidence and mortality in China, India, and South Africa</td>
<td>Used 11 independently developed mathematical models of TB transmission to project the epidemiological impact of currently available TB interventions for prevention, diagnosis, and treatment. Models calibrated with data on TB incidence and mortality in 2012. Representatives from national TB programmes and the advocacy community provided country-specific intervention scenarios.</td>
</tr>
<tr>
<td>Johnson, 2018&lt;sup&gt;97&lt;/sup&gt;</td>
<td>To compare the contexts in which 3HP may be cost effective compared with IPT among people living with HIV</td>
<td>Used a Markov state transition model to estimate the incremental cost-effectiveness of 3HP relative to IPT in high-burden settings, using data from a cohort of 1,000 patients in a Ugandan HIV clinic. Explored conditions under which 3HP would be considered cost-effective relative to IPT.</td>
</tr>
<tr>
<td>First author, year published</td>
<td>Summary of aims</td>
<td>Summary of methods</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Menzies, 2016&lt;sup&gt;47&lt;/sup&gt;</td>
<td>To assess resource requirements and cost-effectiveness of strategies to achieve the End TB strategy targets in China, India, and South Africa</td>
<td>Examined intervention scenarios developed in consultation with country stakeholders, which scaled-up existing interventions by 2025. Nine independent TB modelling groups collaborated to estimate policy outcomes; costed each scenario by synthesising service utilisation estimates, empirical cost data, and expert opinion on implementation strategies. Estimated health impact and resource implications for 2016–2035, including patient-incurred costs.</td>
</tr>
<tr>
<td>Pho, 2012&lt;sup&gt;30&lt;/sup&gt;</td>
<td>To assess the cost-effectiveness of IPT and other treatment regimens among HIV-positive people in India</td>
<td>Used an HIV/TB model to project TB incidence, life expectancy, cost, and incremental cost-effectiveness of six months of isoniazid plus ethambutol (6EH), 36H, and no IPT. Model input parameters included a median CD4 count of 324 cells/µL, and a rate ratio of developing TB of 0.35 for 6EH and 0.22 for 36H at three years as compared with no IPT. Results of 6EH and 36H were also compared to 6H, 3RH, and 3HP.</td>
</tr>
<tr>
<td>Shepardson, 2013&lt;sup&gt;31&lt;/sup&gt;</td>
<td>To assess the cost-effectiveness of 3HP compared to 9H</td>
<td>Used a computational model to simulate individuals with LTBI treated with 9H or 3HP. Estimated costs and health outcomes to determine incremental costs per active TB case prevented and per QALY gained by 3HP compared to 9H.</td>
</tr>
<tr>
<td>Shepardson, 2014&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Update to 2013 paper</td>
<td>Re-calculated the cost of 3HP vs. 9H using the updated price of rifapentine.</td>
</tr>
<tr>
<td>Tasillo, 2017&lt;sup&gt;110&lt;/sup&gt;</td>
<td>To estimate health outcomes, costs, and cost-effectiveness of LTBI testing and treatment among non-US born residents with and without medical comorbidities</td>
<td>Used a decision analytic tree and Markov cohort simulation model among non-US born residents with no comorbidities, with diabetes, with HIV infection, or with end-stage renal disease using a health care sector perspective with 3% annual discounting. Strategies compared included no testing, TST, and IGRA, among others. All strategies coupled to treatment with 3HP.</td>
</tr>
</tbody>
</table>

3HP: 3 months of once-weekly rifapentine and isoniazid; 3RH: 3 months of daily rifampicin and isoniazid; 4R: 4 months of daily rifampicin; 4RH: 4 months of daily rifampicin and isoniazid; 6H: 6 months of daily isoniazid; 9H: 9 months of daily isoniazid; 36H: 36 months of daily isoniazid; ART: antiretroviral therapy; DOT: directly-observed therapy; IGRA: interferon-gamma release assay; IGRA+: IGRA-positive; INH: Isoniazid; IPT: isoniazid preventive therapy; LTBI: latent TB infection; QALY: quality-adjusted life year; SAT: self-administered therapy; TB: tuberculosis; TST: tuberculin skin-test; TST+: TST-positive; WHO: World Health Organization