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Evidence Summaries

Rifampicin compared to isoniazid for preventing active TB in HIV-negative people at risk of developing active TB: Implications for public health

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ABSTRACT

A Cochrane systematic review summarized the evidence for the effects of four regimens containing short courses of rifampicin or rifamycin-combinations compared to isoniazid (INH) given for six to nine months on the development of active tuberculosis (TB), adherence, treatment-limiting adverse events, and hepatotoxicity in HIV-negative people with latent TB infection (LTBI) or at risk of developing active TB. The review included 10 randomized controlled trials that enrolled 10,717 HIV-negative (2% HIV-positive) adults and children (older than two years) that were conducted in Brazil, Canada, Germany, Hong Kong, Saudi Arabia, Spain, Taiwan, and USA. Participants were recruited from clinics in general hospitals or university-affiliated hospitals, pneumoconiosis clinics, homeless shelters, or in prison. The regimens compared were: rifampicin mono-therapy (three to four months) versus isoniazid (INH) mono-therapy (six months); rifampicin plus INH (three months) versus INH (six months); rifampicin plus pyrazinamide (two months) versus INH (six months); and rifapentine (900 mg) plus INH (900 mg) combination therapy, once-weekly, directly-observed (DOT) for three months versus self-administered INH (300 mg) for nine months. Follow-up ranged from two to five years.

The review concluded that four months of rifampicin and the standard INH treatment for six or nine months may not differ in the incidence of active TB in HIV-negative people at risk of active TB. Rifampicin probably increases treatment completion compared to INH in adults. While it is uncertain if treatment-limiting adverse events are any different, rifampicin probably results in significantly less hepatotoxicity in adults than INH. No instances of rifampicin resistance were observed in people who developed active TB while on rifampicin in the included trials. The review also concluded that two months of rifampicin plus INH may offer no advantage over longer INH treatment, and rifampicin combined with pyrazinamide is associated with more liver toxicity and treatment-limiting adverse events with uncertain benefits for TB incidence, or adherence compared to INH. A weekly regimen

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of supervised rifapentine plus INH for three months has higher completion rates, is probably as effective and a safer option than nine months of self-administered INH, though more data on its effects in adults in high TB burden countries, and in children are needed. Copyright © 2013, INDIACLEN. Publishing Services by Reed Elsevier India Pvt Ltd. All rights reserved.

1. The evidence

A Cochrane systematic review of 10 randomized controlled trials that enrolled 10,717 mostly HIV-negative (2% HIV-positive) adults and children at risk of developing TB and followed-up for two to five years concluded that:

- Rates of active TB were not higher with rifampicin mono-therapy (three to four months) compared to isoniazid (INH) mono-therapy (six months). Treatment completion was probably higher and adverse events, particularly liver toxicity, may be fewer with shorter regimens of rifampicin compared to INH (1781 participants, five trials).
- Rifampicin plus INH (three months) may offer no advantage over INH mono-therapy (six months) since rates of active TB, adherence, serious adverse events and hepatotoxicity did not significantly differ between the two regimens (536 participants, two trials).
- Rifampicin plus pyrazinamide (two months) is associated with more treatment-limiting adverse events compared to INH mono-therapy (six months), and probably more liver toxicity, and may have no significant benefits in the incidence of active TB or for adherence rates (661 participants, four trials).

- Rifapentine (900 mg) plus INH (900 mg) combination therapy, once-weekly, directly-observed (DOT) for three months, has higher completion rates, and less liver toxicity compared with nine months of self-administered daily INH (300 mg), though treatment discontinuation due to adverse events is probably more likely with the rifapentine-INH combination than with INH (7799 participants, one non-inferiority trial).

Review on which this evidence summary is based: Sharma SK, Sharma A, Kadiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD007545. <http://dx.doi.org/10.1002/14651858.CD007545.pub2>.

This evidence summary presents an overview of the findings and the implications for low- and middle-income countries. For further details, please read the latest version of the full review that can be downloaded, free of charge (through various funded provisions) in most parts of the world, from the *Cochrane Database of Systematic Reviews* that is published in *The Cochrane Library* (www.thecochranelibrary.com).

Table 1 – Rifampicin (3–4 months) compared to isoniazid (6–9 months) for preventing active tuberculosis (TB) in HIV-negative people at risk of TB infection: summary of effects – follow-up 2 years to 5 years.

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative risk (RR) (95% CI)	No of participants (studies)	Overall evidence quality
	Assumed risk	Corresponding risk			
	Isoniazid	Rifampicin			
Active TB Follow-up: 5 years	150 per 1000	121 per 1000 (70 to 210)	RR 0.81 (0.47–1.4)	332 (1) ^{b, c}	Very low (due to serious indirectness and very serious imprecision)
Adherence	690 per 1000	822 per 1000 (697 to 884)	RR 1.19 (1.01–1.3)	1768 (5)	Moderate (due to serious inconsistency)
Treatment-limiting adverse events	93 per 1000	45 per 1000 (21 to 93)	RR 0.48 (0.23–1)	1674 (4)	Very low (due to serious study limitations, inconsistency, and imprecision)
Hepatotoxicity: Grade 3 and 4 toxicity	46 per 1000	7 per 1000 (3 to 16)	RR 0.15 (0.07–0.4)	1774 (5)	Moderate (due to serious study limitations)

^a The basis for the assumed risk is the control group risk in single studies, and the median risk in the control group for pooled data. The corresponding risk (and its 95% CI) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI). CI: confidence interval.

^b In the placebo arm of this four-arm trial of adults with silicosis, 36/159 (23%) developed active TB.

^c In another trial in children, data for comparative effectiveness could not be used for the outcome of developing active TB (no cases detected in 100 children over two years of follow-up).

Table 2 – Rifampicin plus isoniazid (3 months) compared to isoniazid (6–9 months) for preventing active tuberculosis (TB) in HIV-negative people: summary of effects – follow-up ~16 months to 5 years.

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative risk (95% CI)	No of participants (studies)	Overall evidence quality
	Assumed risk	Corresponding risk			
	INH	Rifampicin plus INH			
Active TB Follow-up: 5 years	150 per 1000	162 per 1000 (97–268)	RR 1.08 (0.65–1.79)	328 (1) ^{b, c}	Very low (due to serious indirectness and very serious imprecision)
Adherence	758 per 1000	812 per 1000 (743–887)	RR 1.07 (0.98–1.17)	524 (2)	High
Treatment-limiting adverse events	114 per 1000	133 per 1000 (85–208)	RR 1.16 (0.74–1.82)	536 (2)	Low (due to very serious imprecision)
Hepatotoxicity	55 per 1000	49 per 1000 (24–100)	RR 0.88 (0.43–1.81)	536 (2)	Low (due to very serious imprecision)

^a The basis for the assumed risk is the control group risk in single studies, and the median risk in the control group for pooled data. The corresponding risk (and its 95% CI) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI). CI: confidence interval.

^b In the placebo arm of this four-arm trial of adults with silicosis, 36/159 (23%) developed active TB.

^c In another trial, one participant from among 196 adults and children developed TB; however, the allocated treatment was not reported.

2. Why is this question important?

- Preventing active tuberculosis (TB) from developing in people with latent TB infection (LTBI) is important for global TB control.
- The risk of progression to active TB in people with LTBI is much higher in certain high-risk groups including HIV-positive people, and in others on immunosuppression, or with diseases that suppress immunity. At moderately high risk are young children (below five years) who are close contacts of people with pulmonary TB, those with diabetes mellitus, silicosis, and with severe malnutrition.

Incarcerated prisoners and certain categories of healthcare workers are also at higher risk of developing TB than the general population.

- Since the risk of progression to active TB is far greater in HIV-positive than in HIV-negative people, LTBI preventive treatment in HIV-negative people is less of a priority, particularly in resource-constrained settings. However, TB in people with HIV is more likely to be due to new infections (re-infection), particularly in high-transmission settings, while reactivation of LTBI is the major concern in HIV-negative people. Most of the active TB cases in low TB incidence countries, and in high TB incidence countries outside Africa, such as China and India, arise from this pool of HIV-negative individuals with LTBI. In addition, in

Table 3 – Rifapentine plus isoniazid weekly for 3 months (12 doses by DOT) compared to self-administered isoniazid daily for 9 months (270 doses) for preventing active TB in HIV-negative people with latent TB infection: summary of effects – Follow up 33 months.

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative risk (95% CI)	No of participants (studies)	Quality evidence quality
	Assumed risk	Corresponding risk			
	Isoniazid	Rifapentine plus isoniazid			
Active TB Follow-up: 33 months after enrolment	4 per 1000	2 per 1000 (1 to 4)	RR 0.44 (0.18–1.07)	7731 (1)	Moderate (due to serious indirectness)
Adherence	690 per 1000	821 per 1000 (801 to 842)	RR 1.19 (1.16–1.22)	7731 (1)	Moderate (due to serious indirectness)
Treatment-limiting adverse events	37 per 1000	49 per 1000 (40 to 61)	RR 1.32 (1.07–1.64)	7731 (1)	Moderate (due to serious imprecision)
Hepatotoxicity Follow-up: 5–11 months	27 per 1000	4 per 1000 (3 to 7)	RR 0.16 (0.1–0.27)	7799 (1)	High

^a The basis for the assumed risk is the risk in the control group. The corresponding risk (and its 95% CI) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval. DOT: directly-observed treatment.

countries with a high TB incidence, the duration of protection with LTBI treatment may be reduced due to the increased incidence of re-infection, even in HIV-negative people.

- Isoniazid (INH) for six to nine months has 60%–90% protective efficacy in people with LTBI, but the treatment period is long, liver toxicity is a problem, and completion rates outside trials are only around 50%.
- Rifampicin or rifamycin-combination treatments are shorter and may result in higher completion rates.
- However, alternative drugs used for treating TB also have the potential to cause adverse events, particularly liver

toxicity; and the risk of drug-resistant TB following treatment with regimens other than the conventional INH mono-therapy is also currently unknown.

What did the systematic review seek and what did they find?

Review objectives: to compare the effects of rifampicin mono-therapy or rifamycin-combination therapy versus INH mono-therapy for preventing active TB in HIV-negative people at risk of developing active TB.

	What did the review authors search for?	What did the review find?
Types of studies	Randomized controlled trials (RCTs) that randomized individuals or clusters of individuals. Quasi-RCTs (where allocation to intervention arms could be predicted) were excluded.	Of the 10 studies that met the review's criteria, eight randomized individuals, one randomized households (by index case), and one randomized households and individuals. Of 48 excluded studies, two were not interventional studies; seven were not RCTs; three were quasi-RCTs, and 36 RCTs did not fulfil the inclusion criteria. Three ongoing trials were identified that aim to recruit over 6920 participants randomized to rifampicin given daily for four months versus INH for nine months and anticipate completing recruitment between 2013 and 2016. One RCT awaiting assessment for inclusion was conducted in prisoners and evaluated INH 900 mg DOT given twice weekly for nine months with daily rifampicin 600 mg; but attrition was high and complete data were unavailable at the time of completing this review.
Setting	Any setting	The trials were conducted in Brazil, Canada, Germany, Hong Kong, Saudi Arabia, Spain, Taiwan, and USA. One trial was conducted in prison, two recruited adults attending pneumoconiosis clinics, one recruited homeless people attending government hospitals or from charitable shelters, and in the remaining trials recruitment was from among clinic attendees in university-affiliated hospitals or general hospitals in these middle- and high-income countries.
Participants	HIV-negative people at risk of developing active TB and without active TB at the time of enrolment, irrespective of the degree of risk of developing TB, and including trials of children at risk for active TB (e.g.: asymptomatic children of patients with pulmonary TB).	Four trials included a few participants (2% overall) who were HIV-positive, with two trials stratifying randomized participants by HIV status. Of the four trials, two included adult males with silicosis, one trial included male prisoners, and one trial included only children (<18 years). The remainder included participants of both genders. The trials differed in the methods used to diagnose LTBI.
Interventions	<i>Intervention:</i> treatment with rifampicin or rifamycin-containing drug combinations (any dose or duration). <i>Control:</i> INH mono-therapy for six to twelve months.	1. Rifampicin mono-therapy versus INH mono-therapy: five trials randomized 1781 participants to rifampicin ($N = 891$) given daily for three or for four months versus INH mono-therapy ($N = 890$) given daily for six or for nine months. 2. Rifampicin plus INH versus INH: two trials randomized 536 people to receive a combination of rifampicin plus INH ($N = 265$) given daily for three months versus daily INH ($N = 271$) for six months or for nine months.

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	What did the review authors search for?	What did the review find?
		<p>3. Rifampicin plus pyrazinamide versus INH: four trials that randomized 661 participants evaluated rifampicin and pyrazinamide ($N = 347$) given daily for two months or to INH daily ($N = 384$) for six months.</p> <p>4. Rifapentine plus INH once a week (DOT) for three months versus daily INH daily (self-administered) for nine months: one, open-label, randomized, non-inferiority trial, compared three months of once-weekly, directly-observed treatment (DOT), with rifapentine (900 mg) plus INH (900 mg) versus nine months of self-administered daily INH (300 mg) in 7799 people at high risk for TB who fulfilled eligibility criteria (from 8053 initially randomized) from 26 centres in four high-income countries. (Rifapentine is rifamycin drug that is as effective as rifampicin, but whose serum half-life is five times that of rifampicin, thus permitting weekly dosing). This trial is ongoing and is expected to complete recruitment in 2013.</p>
Outcomes	<p><u>Primary outcomes</u></p> <ul style="list-style-type: none"> • Rates of active TB (diagnosed by a combination of clinical, mycobacterial, and radiological criteria). <p><u>Secondary outcomes</u></p> <ul style="list-style-type: none"> • TB-related deaths • All-cause death • Incidence of drug-resistant TB including MDR-TB and XDR-TB • Adherence to treatment (as defined by the study authors) <p><u>Adverse events</u></p> <ul style="list-style-type: none"> • Serious adverse events (as defined by the study authors based on clinical as well as laboratory criteria) • Drug-related deaths • Hepatotoxicity (severity based on standard classifications, or as described in the trial report) • Adverse events requiring treatment discontinuation • Other adverse events (including skin rash, nausea or vomiting, diarrhoea, epigastric pain, fatigue or malaise, dizziness, headache, fever or chills, arthralgia, peripheral neuropathy, anorexia/weight loss, insomnia, pruritus, and dysmenorrhoea). 	<p><u>Primary outcomes</u></p> <p>Five trials reported on the development of active TB. The trial in children did not report the method used to diagnose active TB. The two trials in adults with silicosis used bacteriological and radiological assessments and active case finding over five years after treatment completion (unpublished data at five years from one trial was provided to review authors by trial authors). One trial of rifampicin plus pyrazinamide did not provide criteria used for the diagnosis of active TB or the duration of follow up, and had unequal ascertainment periods due to premature termination of the trial. The ongoing trial of rifapentine supplemented active follow-up of participants in US and Canada with passive follow-up of national US and Canadian TB databases. The authors of the trial in prisoners provided unpublished data on follow-up by active case finding (clinical, X-ray; sputum culture) for three years. It was unclear if all trials used procedures that strictly adhered to currently accepted criteria to diagnose TB.</p> <p>Of the remaining four trials, one evaluated efficacy by evaluating the diameter of induration produced by the tuberculin skin test (TST) following the course of treatment and at follow-up time points; this data was excluded from meta-analysis. Efficacy was not a stated objective in the other three trials.</p> <p><u>Secondary outcomes</u></p> <p>Some trials reported TB-related deaths and non-TB deaths, while one provided data for all-cause deaths. Three trials reported the development of drug-resistant TB including MDR-TB; none of the trials reported XDR-TB. All the trials reported on adherence to treatment (measured in different ways).</p> <p><u>Adverse events</u></p> <p>All trials reported adverse events, serious adverse events, and treatment-limiting adverse events.</p>

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What were the effects of rifampicin (3 to 4 months) compared to isoniazid (6 to 9 months) for preventing active TB in HIV-negative people?

Five trials (published from 1992 to 2012) compared these regimens, though efficacy was evaluated in only one 1992 trial. The occurrence of TB over five years of follow-up did not differ significantly in this one small trial in adults with silicosis (312 participants; *very low quality evidence*). However, more people in the five trials completed the shorter course (RR 1.19, 95% CI 1.01 to 1.30; 1768 participants; *moderate quality evidence*). Treatment-limiting adverse events were not significantly different (four trials, 1674 participants; *very low quality evidence*), but rifampicin caused less hepatotoxicity (RR 0.12, 95% CI 0.05 to 0.30; four trials, 1674 participants; *moderate quality evidence*). (Table 1)

What were the effects of rifampicin plus isoniazid (3 months) compared to isoniazid (6 to 9 months) for preventing active TB in HIV-negative people?

The 1992 silicosis trial did not detect a difference between people receiving rifampicin plus INH compared to INH alone for occurrence of active TB (one trial, 328 participants; *very low quality evidence*). Adherence was similar in this and a 1998 trial in people without silicosis (two trials, 524 participants; *high quality evidence*). No difference was detected for treatment-limiting adverse events (two trials, 536 participants; *low quality evidence*), or hepatotoxicity (two trials, 536 participants; *low quality evidence*). (Table 2)

What were the effects of rifampicin plus pyrazinamide (2 months) compared to isoniazid (6 months) for preventing active TB in HIV-negative people?

Three small trials published in 1994, 2003, and 2005 compared these two regimens, and two reported a low occurrence of active TB, with no statistically significant differences between treatment regimens (two trials, 176 participants; *very low quality evidence*) though, apart from one child from the 1994 trial, these data on active TB were from the 2003 trial in adults with silicosis. Adherence with both regimens was low with no statistically significant differences (four trials, 700 participants; *very low quality evidence*). However, people receiving rifampicin plus pyrazinamide had more treatment-limiting adverse events (RR 3.61, 95% CI 1.82 to 7.19; two trials, 368 participants; *high quality evidence*), and hepatotoxicity (RR 4.59, 95% CI 2.14 to 9.85; three trials, 540 participants; *moderate quality evidence*). (Summary of findings table available in the Cochrane review).

What were the effects of rifapentine plus isoniazid weekly for 3 months (12 doses) compared to isoniazid daily for 9 months (270 doses) for preventing active TB in HIV-negative people with LTBI?

A large trial conducted from 2001 to 2008 among close contacts of TB in the USA, Canada, Brazil and Spain found directly observed weekly treatment to be non-inferior to nine months self-administered INH for the incidence of active TB (0.2% vs 0.4%, RR 0.44, 95% CI 0.18 to 1.07, one trial, 7731 participants; *moderate quality evidence*). The directly-observed, shorter regimen had higher treatment completion (82% vs 69%, RR 1.19, 95% CI 1.16 to 1.22, *moderate quality evidence*), and less hepatotoxicity (0.4% versus 2.4%; RR 0.16, 95% CI 0.10 to 0.27; *high quality evidence*), though treatment-limiting adverse events were more frequent (4.9% versus 3.7%; RR 1.32, 95% CI 1.07 to 1.64 *moderate quality evidence*). (Table 3).

What were the conclusions of the review?

This Cochrane review concluded that: "Trials to date of shortened prophylactic regimens using rifampicin alone have not demonstrated higher rates of active TB when compared to longer regimens with INH. Treatment completion is probably higher and adverse events may be fewer with shorter rifampicin regimens. Shortened regimens of rifampicin with INH may offer no advantage over longer INH regimens. Rifampicin combined with pyrazinamide is associated with more adverse events. 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".

What were the assessments of the overall quality of the evidence?

The review authors assessed the overall quality of evidence for the primary outcomes using the GRADE approach (Tables 1–3). In this approach, evidence from randomized controlled studies is initially graded as high and downgraded by one or two levels on five domains, after full consideration of: any limitations in the design of the studies, the directness (or applicability) of the evidence, the consistency, and precision of the results, and the possibility of publication bias. This results in an assessment of the quality of a body of evidence as *high*, *moderate*, *low*, or *very low*. A GRADE quality level of '*high*' reflects confidence that the true effect lies close to that of the estimate of the effect for an outcome, and further research is unlikely to alter these results. A judgement of '*moderate*' quality indicates that the true effect is likely to be close to the estimate of the effect, but acknowledges the possibility that it is substantially different, and that further studies could alter the estimates. '*Low*' and '*very low*' quality evidence limit our confidence in the effect estimate.

The evidence for the efficacy and for treatment-limiting adverse events of shortened prophylactic regimens of rifampicin versus INH in LTBI was downgraded to '*very low*' quality. Evidence graded as '*moderate*' quality for adherence and for hepatotoxicity suggests reasonable confidence in the estimates of better adherence and less frequent liver toxicity with rifampicin mono-therapy compared to INH (Table 1). The overall quality of evidence for all outcomes in the comparison of rifampicin plus INH versus INH alone was graded '*low*' to '*very low*', except for adherence where '*high quality*' evidence indicates confidence in the estimates that adherence was not significantly different with the two treatment regimens (Table 2). The overall quality of the evidence indicating no significant difference with rifampicin plus pyrazinamide versus INH for preventing active TB and for adherence was graded '*low*' or '*very low*'; but the evidence for

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safety outcomes was graded 'moderate' to 'high quality' (Summary table available in the Cochrane review). The evidence of the non-inferiority of a shortened course of *weekly rifapentine plus INH versus nine months of INH* in preventing active TB was judged to be of 'moderate' quality; the main factor limiting full confidence in this estimate was the uncertainty in generalising this result from settings with low- to moderate-TB incidence (North America, Europe and Brazil), to settings with higher TB incidence (Africa, China, India), and the limited data available to date regarding the effects of the weekly combination treatment in children (Table 3).

Strengths and limitations

The review followed the standard methods used in Cochrane Reviews and no important limitations were detected.

The duration of follow-up in the included trials ranged from two years in the trial in children, to three to five years in most of the trials in adults, when the risk of developing active TB is likely to be the highest. Since these trials were conducted in low- to moderate-TB transmission settings, and in largely HIV-negative populations, the risk of re-infection as opposed to reactivation is likely to have been low. However, data for the development of active TB with rifampicin mono-therapy was reported only in three trials included the review and more evidence on the efficacy of rifampicin (three to four months) compared to standard INH regimens in adults and in children, particularly from high TB burden countries, would be required before it is considered as a routine alternative to, or replacement for, standard INH prophylaxis in people with LTBI. There was also some variability in these trials regarding the diagnosis of LTBI, documenting adherence, the definitions used to diagnose active TB, and in determining the incidence of hepatotoxicity. The data for children is from only one trial with a total sample size of 100. The trials included in the review excluded pregnant and lactating women, malnourished children, and children below two years of age, and this review does not provide evidence for the efficacy and safety of rifampicin in these vulnerable groups to inform clinical practice or policy.

The effects of the intermittent rifapentine-INH combination regimen in high TB burden countries in Africa; and in China and India, also need to be evaluated before its widespread use outside low TB burden countries can be envisaged. Data are also insufficient to confirm or refute the efficacy and safety of rifapentine in young children below 12 years.

Did the results and conclusions of the review differ from other reviews on this topic?

For the comparison of *rifampicin versus INH*, the results of the Cochrane review are in agreement with that of an earlier meta-analysis of four studies (two of which were retrospective) that concluded that four months of treatment with rifampicin was associated with about half the non-completion rate of nine months of INH treatment and 12% the risk of hepatotoxicity.¹ However, the findings of this review differ from guidance provided by the National Institute for Clinical Excellence (NICE) that does not mention four months of rifampicin as an effective alternative to INH, but instead recommends either six months of INH or three months of rifampicin and INH for adults and children not known to have HIV infection.² In contrast, four months of rifampicin is recommended by the Centers for Disease Control (CDC), while the rifampicin plus INH combination finds no place in the CDC guidelines.³ This Cochrane review found that the liver toxicity of the combination of rifampicin plus INH was around 5% and similar to that seen with INH; and there was no advantage with the combination over INH alone in treatment completion rates. Rifampicin alone for three to four months has better adherence and less hepatotoxicity than INH, and though the data available from trials completed to date do not provide sufficient high quality evidence regarding the relative efficacy of the two regimens, there was no evidence that shorter rifampicin regimens resulted in more people with active TB compared to longer INH regimens.

The evidence for the effects of *rifampicin plus INH versus INH alone* were similar to those in another Cochrane review of preventing active TB in HIV-positive people with LTBI,⁴ and a non-Cochrane review that included trials in people with LTBI irrespective of the HIV status of the participants.⁵

Regarding the comparison of *rifampicin plus pyrazinamide versus INH alone*, the conclusions in a non-Cochrane review⁶ that rifampicin plus pyrazinamide was associated with a significantly higher risk of severe hepatotoxicity and severe adverse events among HIV-negative people, are in agreement with the conclusions in this Cochrane review, as are the results of another Cochrane review that evaluated this combination among HIV-positive people.⁴

The CDC currently recommends *rifapentine plus INH* given as 12 weekly doses with DOT as an alternative treatment regimen to standard INH in preventing active TB in otherwise healthy HIV-negative people above 12 years of age with LTBI; in HIV-positive people who are not on antiretroviral agents; and also in people who are less likely to complete a six or nine-month course of INH, where 12 supervised weekly doses may confer practical advantages.³ The present Cochrane review concluded that since no data from low-income, high TB burden countries are available for weekly rifapentine plus INH, it may be difficult to extrapolate the otherwise high quality evidence from the single trial done in high-income, low-transmission settings to settings where DOT may not be feasible, or practical, given resource constraints; and where re-infection rates are likely to be higher.

What further research is required?

Three ongoing trials identified in the Cochrane review are evaluating the efficacy of rifampicin (four months) compared to INH (nine months) in preventing active TB among adults and children with LTBI in low-, middle- and high-income countries. The trial of weekly rifapentine is also ongoing and on completion will provide additional data on its efficacy, safety, and tolerability in approximately 454

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additional young children to complement the currently insufficient evidence for children with this combination. Another ongoing, open-label, three-armed, RCT in the US is examining 12 weekly doses of rifapentine 900 mg plus INH 900 mg DOT over three months versus self-administered rifapentine plus INH 12-dose regimen, or self-administered rifapentine plus INH 12 doses with weekly mobile phone short messaging system (SMS) reminders, in 1000 adults.

This review indicated areas where further research is warranted:

1. Trials evaluating adherence to preventive rifampicin-containing treatments for LTBI from low- and middle-income, high TB incidence countries;
2. Trials comparing intermittent rifampicin, or rifabutin (another rifamycin drug), or self-administered INH plus daily rifapentine, with standard INH prophylaxis in HIV-negative people with LTBI;
3. Pharmacovigilance for adverse events and resistance to rifamycins when these regimens become more widely used;
4. Cost-effectiveness studies based on actual efficacy estimates of the rifamycin regimens in comparison with longer INH regimens based on more recent evidence from trials; and incorporating local cost variations for drugs and for monitoring, and variations in monitoring schedules, when used in clinical practice.
5. Implementation research exploring approaches for active case finding and to enhance adherence.

What are the implications of the review for public health?

1. Summary of the evidence from this Cochrane review:

- a. Four months of rifampicin and the standard INH treatment of six or nine months may not differ in preventing progression to active TB in HIV-negative people with LTBI. Rifampicin probably increases adherence and treatment completion compared to INH in adults. While it is uncertain if treatment-limiting adverse events are any different, rifampicin probably results in significantly less hepatotoxicity in adults (0.2%–1.5%) than INH (5%). No instances of rifampicin resistance were observed in 40 people who developed active TB while on rifampicin in the included trials.
- b. No benefit in preventing progression to active TB, increasing adherence, or reducing the frequency of treatment-limiting adverse events and hepatotoxicity was detected when INH was added to rifampicin for three months compared to treatment with INH alone for six to nine months. This indicates that rifampicin plus INH combination treatment may not be a better alternative to INH alone (or rifampicin alone) for people with LTBI.
- c. Rifampicin plus pyrazinamide for two months may not differ from INH for six months in preventing active TB in HIV-negative people with LTBI, or in treatment completion compared to INH, in spite of the shorter treatment duration. This drug combination also probably increases the risk of hepatotoxicity in adults, and increases the incidence of treatment-limiting adverse events. These attributes are not consistent with those required of a public health intervention for preventing active TB in people with LTBI.
- d. Twelve doses of rifapentine plus INH administered weekly by DOT over three months is probably an effective and safer alternative to INH given for nine months in HIV-negative people at risk, though more data on the safety of the combination in adults (particularly the risk of hepatotoxicity in women), as well as in children are needed. One case of rifapentine resistance was observed in an HIV-positive individual who had low CD4 counts, though none were observed in HIV-negative people who developed active TB. The effects of this intermittent regimen in high TB burden countries need to be evaluated before its widespread use outside low TB burden countries commences.

2. Implications for resource-constrained settings:

- a. The results from the trials in this Cochrane review that were conducted in high- and middle-income countries may not yield the same effect estimates in high TB burden countries in Africa and Asia (particularly China and India) where re-infection rates are likely to be higher and co-morbid conditions that impair effectiveness such as nutritional and micronutrient deficiencies, are also higher.
- b. Another barrier to the uptake of four months of rifampicin in treating LTBI is the fear of inadvertent treatment of active TB leading to the development of rifampicin resistance, or the emergence of rifampicin resistance if rifampicin were to be more widely used for treating LTBI. The diagnosis of TB and of rifampicin resistance in adults may be accurately done using molecular techniques, though this may not be as accurate in children.⁷ While the trials in this review did not reveal that anyone given rifampicin developed resistance, rifampicin resistance does occasionally occur in the context of LTBI prophylaxis particularly in immuno-compromised people; thus, careful selection of people with LTBI for rifampicin prophylaxis would be necessary.
- c. Ensuring compliance would also be important if four months of rifampicin were to become standard treatment for LTBI, as interrupted courses of treatment would increase the potential for the emergence of widespread resistance to rifampicin.
- d. The included trials differed regarding health systems arrangements and the delivery of care, such as the availability of resources to provide DOT effectively, that may differ from those in low-income countries where treatment of active TB is a priority; and the availability of adequate resources that can be diverted, or the political will to ensure DOT for LTBI prophylaxis, is likely to be low. While the relative advantage in treatment completion and safety with the shorter rifampicin regimen over INH is likely to be seen even in low-income countries, these pragmatic concerns may limit the applicability of the evidence from this review to resource-constrained countries with a high TB burden.

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- e. Another factor that would influence the uptake of shorter rifampicin regimens over the standard nine months of INH in guidelines and policy is resource use and resource costs. While this review did not directly address economic outcomes, some data provided in the review from two of the included studies and other sources referenced in the review indicate that four months of rifampicin is likely to be cost saving than nine months of INH, while preventing more cases of TB reactivation, if its efficacy was 69–75% or greater. However, the data for efficacy was from the 1992 trial in adults with silicosis and more recent evidence would be required to confirm this impression. Modelling studies referenced in the Cochrane review have also confirmed the cost-effectiveness of weekly rifapentine plus INH for three months versus nine months of INH. However, the actual experience with this combination in real world settings outside a clinical trial is limited and the results of a formal cost-effectiveness exercise in the ongoing rifapentine plus INH trial are awaited.
- f. While these limitations in applicability may suggest that the benefits of rifampicin mono-therapy may be of limited value for TB control programmes in low- and middle-income countries (LMICs), the authors of the review clarified in a video-interview⁸ that three to four months of rifampicin mono-therapy could be considered as an alternative to six months of INH in specific populations at higher risk of developing active TB, such as the categories of immune-compromised people at high risk of developing active TB, young children in contact with an adult with TB, healthcare professionals who fulfil criteria for LTBI, and in those with resistance to INH; once active TB has been ruled out in them. The authors also caution against the misuse of rifampicin in order to prevent the emergence of rifampicin resistant organisms, and suggest that its use in the treatment of LTBI and for active TB should be effectively regulated.

Declaration of interest

TDS is an editor with the Cochrane Infectious Diseases Group, and was involved with the editorial process of this Cochrane review. PT is a one of the authors of this Cochrane review and a programme partner of the Effective Healthcare Research Consortium.

Conflicts of interest

All authors have none to declare.

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