Adverse events in adults with latent tuberculosis infection receiving daily rifampicin or isoniazid: post-hoc safety analysis of two randomised controlled trials

Jonathon R Campbell, Anete Trajman, Victoria J Cook, James C Johnston, Menonli Adjobimey, Rovina Ruslami, Lisa Eisenbeis, Federica Fregonese, Chantal Valiquette, Andrea Benedetti, Dick Menzies

Summary

Background An important problem limiting treatment of latent tuberculosis infection is the occurrence of adverse events with isoniazid. We combined populations from phase 2 and phase 3 open-label, randomised controlled trials, to establish risk factors for adverse events during latent tuberculosis infection treatment.

Methods We did a post-hoc safety analysis based on data from two open-label, randomised controlled trials done in health-care facilities in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea. Participants were consenting adults (aged ≥18 years) with a positive latent tuberculosis infection diagnostic test, indication for treatment, and without contraindications to rifampicin or isoniazid. Patients were centrally randomly assigned 1:1 to 4 months of daily 10 mg/kg rifampicin or 9 months of daily 5 mg/kg isoniazid. The primary outcome evaluated was adverse events (including grade 1–2 rash and all events of grade 3–5) resulting in permanent discontinuation of study medication and judged possibly or probably related to study drug by a masked, independent, three-member adjudication panel (trial registration: NCT00170209; NCT00931736).

Findings Participants were recruited from April 27, 2004, up until Jan 31, 2007 (phase 2), and Oct 1, 2009, up until Dec 31, 2014 (phase 3). The safety populations for each group comprised 3205 individuals receiving isoniazid and 3280 receiving rifampicin. Among those receiving isoniazid, 86 (2·7%) of 3205 had grade 1–2 rash or any grade 3–5 adverse events, more than the 50 (1·5%) of 3280 who had these events with rifampicin (risk difference –1·2%, 95% CI –1·9 to –0·5). Age was associated with adverse events in adults receiving isoniazid. Compared with individuals aged 18–34 years, the adjusted odds ratio (OR) for adverse events was 1·8 (95% CI 1·1–3·0) for individuals aged 35–64 years and 3·0 (1·2–6·8) for individuals aged 65–90 years. With rifampicin, adverse events were associated with inconsistent medication adherence (adjusted OR 2·0, 1·1–3·6) and concomitant medication use (2·8, 1·5–5·2), but not age, with an adjusted OR of 1·1 (0·6–2·1) for individuals aged 35–64 years and 1·7 (0·5–4·7) for individuals aged 65–90 years. One treatment-related death occurred in the isoniazid group.

Interpretation In patients without a contraindication, rifampicin is likely to be the safest latent tuberculosis infection treatment option. With more widespread use of rifampicin, rare, but serious adverse events might be seen. However, within these randomised trials, rifampicin was safer than isoniazid and adverse events were not associated with older age. Therefore, rifampicin should become a primary treatment option for latent tuberculosis infection based on its safety.

Funding Canadian Institutes of Health Research.

Introduction

In the absence of new strategies, tuberculosis elimination will require identification and treatment of a substantial proportion of the 1·7 billion people with latent tuberculosis infection.[1] A key part of WHO's End TB Strategy, latent tuberculosis infection treatment has gained momentum with the goal of initiating treatment in 30 million patients by 2022.[2] Current diagnostics are quite sensitive for latent tuberculosis infection but have poor predictive value in identifying the few individuals who will progress to tuberculosis disease.[3] Therefore, its treatment must be safe above all else.

Yet, safety has been the Achilles heel of latent tuberculosis infection treatment. The risk of adverse events, particularly hepatotoxicity, with most current first-line tuberculosis drugs, are orders of magnitude higher than other drugs routinely used in primary care.[4] Daily isoniazid, the most widely used treatment, was reported to cause fatal hepatotoxicity shortly after its widespread introduction for latent tuberculosis infection in 1971.[5,6] In addition, a 2-month regimen of daily rifampicin and pyrazinamide was recommended in 2000, but this recommendation was withdrawn in 2001[7] after more widespread use led to cases of fatal hepatotoxicity. Despite these concerns, 9 months of daily isoniazid remains the most widely used regimen for latent tuberculosis infection treatment in many high-resource settings.

Lancet Infect Dis 2019

Published Online December 19, 2019 https://doi.org/10.1016/S1473-3099(19)30575-4

See Online/Comment https://doi.org/10.1016/S1473-3099(19)30627-9

Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill International TB Centre, McGill University Health Centre Research Institute (Prof D Menzies MD, J R Campbell PhD, Prof A Trajman MD, C Valiquette CNA, A Benedetti PhD, F Fregonese PhD, J C Johnston MD) **and Department of Epidemiology and Biostatistics** (Prof D Menzies, J R Campbell, A Benedetti), **McGill University, Montréal, QC, Canada; Department of Biomedical Sciences, Division of Pharmacology and Therapy, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia** (Prof R Ruslami MD); **Federal University of Rio de Janeiro, Rio de Janeiro, Brazil** (Prof A Trajman); **Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada** (V J Cook MD, J C Johnston); **Provincial TB Services, British Columbia Centre for Disease Control, Vancouver, BC, Canada** (V J Cook, J C Johnston); **National Hospitalier Universitaire de Pneumo-Phtisiologie, Cotonou, Benin** (M Adjobimey MD); **and University of Alberta, Edmonton, AB, Canada** (L Eisenbeis MSc)

Correspondence to: Prof Dick Menzies, McGill University, Montréal, QC H4A 3S5, Canada **dick.menzies@mcgill.ca**

Research in context

Evidence before this study

Approximately a quarter of the world's population has latent tuberculosis infection. The most common regimen used globally for this indication is daily isoniazid. Age-related hepatotoxicity and a treatment duration of 6–9 months results in suboptimal completion of isoniazid. Shorter rifamycin-based regimens of 3 or 4 months of daily rifampicin and isoniazid and 3 months of weekly isoniazid and rifapentine are just as effective and more often completed, but results of randomised trials of these regimens compared with isoniazid show little or no overall safety benefit. Comparatively, 4 months of daily rifampicin has consistently shown better completion, reduced toxicity, and non-inferior effectiveness to isoniazid across randomised trials and observational studies. A previous network meta-analysis including randomised trials in PubMed, Embase, and Web of Science from database inception to May 8, 2017, has been published. This analysis compared several regimens for latent tuberculosis infection treatment, including 3 or 4 months of daily rifampicin and isoniazid, 3 months of weekly isoniazid and rifapentine, 4 months of daily rifampicin, and isoniazid of various durations, and concluded that 4 months of daily rifampicin was the safest regimen in terms of hepatotoxicity. However, other adverse event types were not evaluated. Previous reports of phase 2 and phase 3 randomised controlled trials of 4 months of daily rifampicin compared with 9 months of daily isoniazid have shown superior safety of rifampicin but did not formally evaluate the timing and risk factors for adverse events. We undertook this detailed safety analysis of these phase 2 and phase 3 randomised controlled trials comparing 4 months of daily rifampicin with 9 months of daily isoniazid to answer these questions.

Added value of this study

We showed that occurrence of grade 1–2 rash or any grade 3–5 adverse event is less frequent with rifampicin than with isoniazid. We also showed that when treating patients with rifampicin, inconsistent medication adherence and concomitant medication use are associated with increased risk of all adverse events. Importantly, grade 3–4 hepatotoxicity was not associated with older age among patients receiving rifampicin—for example, no hepatotoxic events occurred in the 130 patients aged 65 years and older. Among all patients receiving rifampicin, grade 1–4 rash was the most frequent adverse event. These events were associated with patients aged 65 years and older and concomitant medication use—96% of these events occurred within 60 days of starting treatment. Grade 3–4 hepatotoxicity was the most frequent adverse event with isoniazid. 75% of these events occurred within 120 days of starting treatment and were associated with patients aged 35 years and older and pre-treatment alanine aminotransferases concentrations above the upper limit of normal.

Implications of all the available evidence

In patients without a contraindication, rifampicin is probably the safest latent tuberculosis infection treatment option. For prescribing physicians, it is important to stress the importance of consistent medication adherence to patients and to be wary of potential interactions with concomitant medications. On the basis of safety considerations alone, rifampicin should become a primary treatment option for latent tuberculosis infection. As use of this regimen expands, we believe careful surveillance is warranted to confirm that the findings from these randomised trials are consistent even under programmatic conditions. Achieving the ambitious goal set forth by WHO to treat 30 million patients for latent tuberculosis infection by 2022 will be facilitated through use of this short, safe, and effective treatment.

Shorter regimens, such as 3 or 4 months of daily rifampicin and isoniazid[8–12] and 3 months of weekly isoniazid and rifapentine[13,14] have been compared with 6 or 9 months of isoniazid in randomised controlled trials. Although both regimens have similar efficacy, and equal or better completion than 6 or 9 months of daily isoniazid, neither regimen appears to be safer. In a 2007 randomised controlled trial, 4 months of daily rifampicin had superior safety and completion to 9 months of daily isoniazid among 847 adults.[15] A phase 3 randomised controlled trial in 6012 adults showed that 4 months of daily rifampicin was non-inferior to 9 months of daily isoniazid in preventing active tuberculosis and had superior safety, and emergent drug-resistance was not different between study groups.[16]

Considering the recent evidence[15,16] supporting 4 months of daily rifampicin's effectiveness and safety, use among providers prescribing latent tuberculosis infection treatment is expected to increase. To aid provider decision making, a more detailed safety analysis, expanding on previous reports of overall safety, is necessary. Therefore, we analysed the frequency, timing, and risk factors for adverse events in the phase 2 and phase 3 trials, which had compared 4 months of daily rifampicin with 9 months of daily isoniazid.

Methods

Study design and participants

We did a post-hoc safety analysis based on two parallel, open-label, randomised controlled trials, the methods for which have been published previously.[15,16] Briefly, adults aged 18 years or older who gave written consent were enrolled in 17 health-care facilities across nine countries: Australia, Benin, Brazil, Canada (nine centres), Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea. All

patients had an indication for latent tuberculosis infection testing and treatment (eg, contact within past 3 months, HIV-positive) with a documented positive tuberculin skin test or interferon-γ release assay. Patients were assessed clinically pre-treatment, then monthly for the first 4 months during treatment, and every 8 weeks thereafter (if randomly assigned to 9 months of daily isoniazid). Complete blood counts and liver aminotransferases were done pre-treatment and after 1 month of treatment, with subsequent testing done at clinician discretion. Normal values for blood tests were defined on the basis of the ranges provided by the clinical laboratories at each site (appendix p 5). The trials were approved by the Biomedical Clinical Research Ethics Board of the McGill University Health Centre (phase 2: 03-046-BMB-t; phase 3: 09-007-BMBt) and by each centre's responsible ethics committee.

Randomisation and masking

Participants were, via a central computer, randomly assigned 1:1 in blocks of varying length (two to eight) to receive either 4 months (120 doses) of daily rifampicin at a dose of 10 mg/kg (maximum 600 mg) or 9 months (270 doses) of daily isoniazid at a dose of 5 mg/kg (maximum 300 mg). This trial was open-label for the clinical staff, patients, and some investigators. The study principal investigator and data analyst (DM and AB) for the original analysis (published previously) remained masked until analysis was complete. The adjudication panels for adverse events and active tuberculosis were masked to drug assignment during all judgments and were never unmasked.

Procedures

At each visit, patients were questioned and examined for evidence of adverse events, and they were encouraged to report any new symptoms between visits. All staff were trained before the start of the trial regarding recognition, management, and reporting of potential adverse events emerging during treatment. Adverse event reporting, assessment, and grading was standardised and followed a strict protocol.[16] If the treating clinician decided to stop therapy because of a possible treatment-related adverse event, the clinician filed an initial web-based report within 24 h. Symptoms of intolerance that did not warrant treatment cessation or only resulted in temporary pauses (<48 h) in treatment were not reported. Adverse events were collected until 30 days after the end of treatment.

After the adverse event had resolved, the laboratory results, clinical management, patient response to drug withdrawal, and results of drug re-challenge (if unsuccessful) were compiled into a final report. This report was transmitted to an adverse event administrator who ensured the report was masked (by reviewing it to ensure there were no details that would potentially give away which drug the patient was receiving) and then to the principal investigator who ensured it was complete. If necessary, further information was requested from the reporting clinician. The description of the event was then transmitted to an adverse event adjudication panel of three members who had clinical-epidemiological experience and expertise managing tuberculosis. The panel members assessed the events independently and were masked to the study drug. Adverse events were categorised into one of ten types: drug interaction, rash, hepatotoxicity, gastrointestinal intolerance, haematological, pregnancy, dizziness, drug induced pancreatitis, seizure, and other. The panel's judgment of adverse event severity was on the basis of previously published criteria (graded on a scale of 1–5, in which death was grade 5). Grading for hepatotoxicity, was based on guidelines of the American Thoracic Society[17] and for all other adverse events on the National Cancer Institute Common Terminology Criteria for Adverse Events.[18] Relationship to the study drug was judged as none, unlikely, possible, or probable. If individuals with adverse events were hospitalised, these same experts determined if the hospitalisation was indicated for management of the event (yes or no). In the case of panel disagreement, a simple majority was used. If there was no majority, the panel members were asked to independently reassess. Reassessment due to complete difference in opinion was only required once across 310 adverse events that were reviewed by the panel.

See Online for appendix

Outcomes

Only adverse events resulting in permanent treatment cessation and considered possibly or probably related to study medication by the panel were included as outcomes in the statistical analysis. The primary outcome was grade 1–2 rash or grade 3–5 adverse events. We included grade 1–2 rash within our primary outcome as providers are usually hesitant to continue medications if a rash develops, whereas for other mild adverse events, such as grade 1–2 hepatotoxicity, guidelines encourage continuation of treatment as these are generally transient.[17] Secondary outcomes comprised grade 1–4 rash, grade 3–4 hepatotoxicity, grade 3–4 haematological events, and grade 3–5 non-hepatotoxic or non-rash adverse events. The phase 3 trial was designed with identical outcome definitions and ascertainment methods to those used in the phase 2 trial to permit the conduct of the prespecified combined analysis for active tuberculosis. Although not prespecified, these outcome definitions also permitted our combined analysis for adverse events.

Statistical analysis

The sample size for the phase 3 trial[16] was calculated on the basis of efficacy. For the purposes of this analysis, we estimated the power provided by participants recruited for the phase 3 trial for the outcome of grade 1–2 rash or grade 3–5 adverse events based on the results of the phase 2 trial.[15] In the phase 2 trial, 15 (4%) of 418 patients receiving rifampicin and 22 (5%) of 422 patients receiving isoniazid had these events. Assuming this proportion of

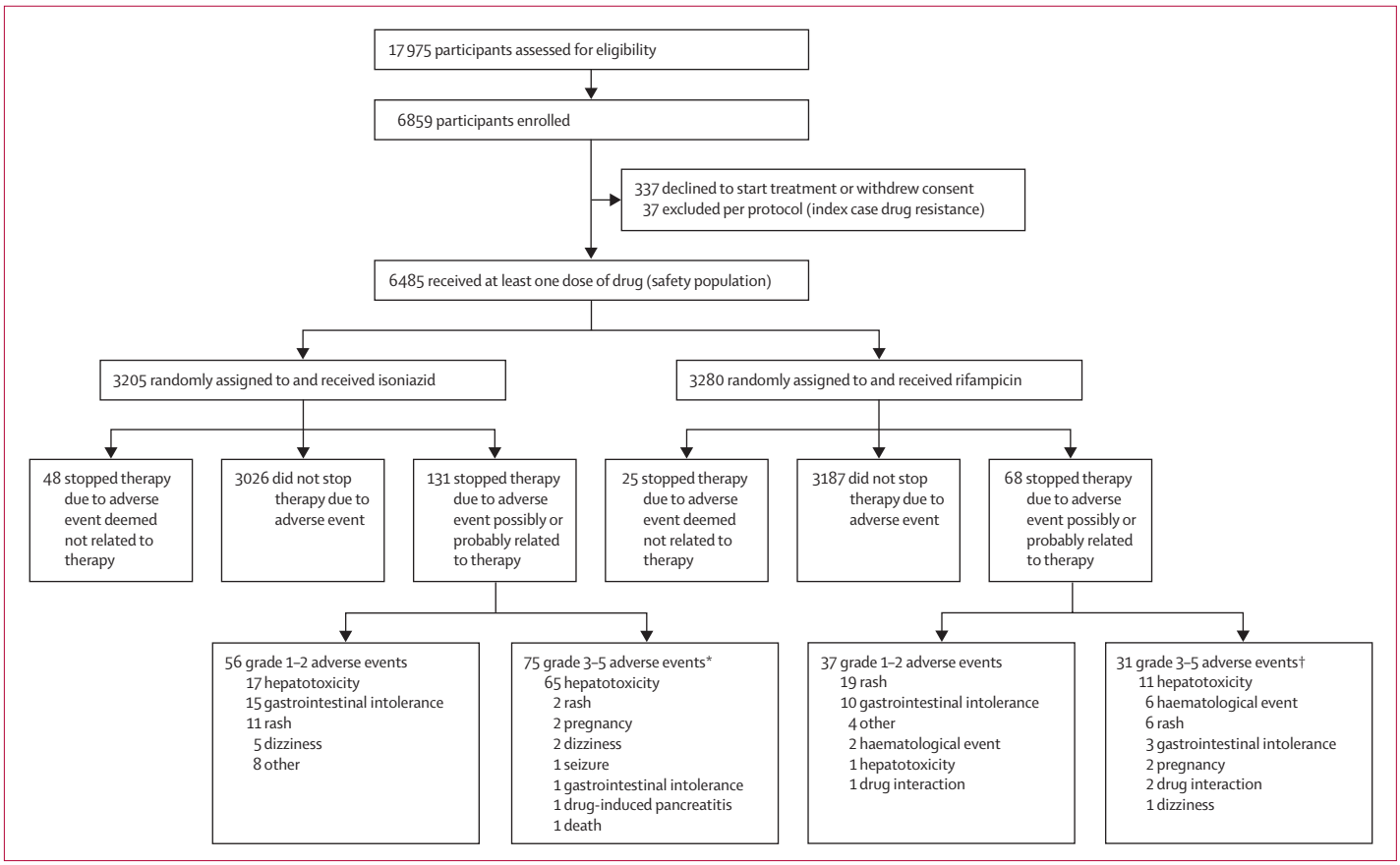

Figure 1: **Trial profile**
*Three hospitalisations comprising two for hepatotoxicity and one for drug-induced pancreatitis. †One hospitalisation due to a haematological event.

events, a sample size of 2800 patients in each group provided a power of 83% to detect a difference with a type I error rate of 5%.

Univariable analysis was done for potential predictors of the primary outcome of grade 1–2 rash or any grade 3–5 adverse event for each treatment group separately. Predictors were selected a priori guided by either the literature (such as age)[17] or by the principle that their identification could permit clinical action. As adverse events were rare, Firth's bias-reduced (penalised likelihood) logistic regression was used with R package logistf (version 1·23).[19] Age at treatment start was considered a categorical variable (18–34, 35–64, and 65–90 years) after examining frequency of adverse events by age group (appendix p 2). Body-mass index was categorically defined as underweight (<18·5 kg/m²), normal (≥18·5 and <25 kg/m²), overweight (≥25 and <30 kg/m²), and obese (≥30 kg/m²). Immune suppression was defined categorically as no immune suppression, or HIV-positive, or non-HIV-related immune suppression (eg, diabetes, renal failure)—HIV was diagnosed either before the study, or during baseline assessment. Alcohol use (never drinks, one drink or less per week, more than one drink per week), smoking history (never smoked, currently smokes, or history of smoking), and concomitant medication use (any, none) at pre-treatment were also considered as potential predictors. Medication consistency was defined as the proportion of days a patient took their medication while on latent tuberculosis infection treatment. This factor was considered clinically meaningful if more than three doses were missed per month and calculated by dividing the number of doses taken by the number of days on treatment at the time of treatment cessation (<90%, ≥90%). In the case of permanent treatment discontinuation occurring on medication rechallenge, treatment cessation was considered the time of initial occurrence—this method reduced the risk of potentially attributing the adverse event to medication inconsistency.

We also evaluated the most common adverse events separately: grade 3–4 hepatotoxicity, grade 1–4 rash, and grade 3–4 haematological events. In the hepatotoxicity analysis, in addition to the predictors above, we included alanine aminotransferase (ALT) tests (dichotomised as normal, or above the upper limit of normal). In the haematological event analysis, we further included white blood cell count and platelet count tests (dichotomised as normal, or less than the lower limit of normal).

	4 months of daily rifampicin (n=3280)	9 months of daily isoniazid (n=3205)
Sex		
Male	1364 (41·6%)	1394 (43·5%)
Female	916 (58·4%)	1811 (56·5%)
Age, years	38·1 (13·7)	38·3 (13·7)
18–34	1489 (45·4%)	1436 (44·8%)
35–64	1661 (50·6%)	1642 (51·2%)
65–90	130 (4·0%)	127 (4·0%)
Body-mass index, kg/m^2	24·7 (5·1)	24·6 (5·1)
Underweight	216 (6·6%)	222 (6·9%)
Normal	1674 (51·0%)	1646 (51·4%)
Overweight	916 (27·9%)	907 (28·3%)
Obese	474 (14·5%)	430 (13·4%)
Country of enrolment		
Australia	120 (3·7%)	108 (3·4%)
Benin	569 (17·4%)	556 (17·4%)
Brazil	467 (14·2%)	473 (14·8%)
Canada	814 (24·8%)	810 (25·3%)
Ghana	185 (5·6%)	180 (5·6%)
Guinea	402 (12·3%)	371 (11·6%)
Indonesia	416 (12·7%)	416 (13·0%)
Saudi Arabia	27 (0·8%)	23 (0·7%)
South Korea	280 (8·5%)	268 (8·4%)
Immune suppression		
HIV-positive	130 (4·0%)	138 (4·3%)
Other immune suppression*	221 (6·7%)	196 (6·1%)
Concomitant medication use†		
Any	763 (23·3%)	735 (22·9%)
None	2517 (76·7%)	2473 (77·1%)
Alcohol use		
Never drinks	2200 (67·1%)	2112 (65·9%)
Has ≤1 drink per week	873 (26·6%)	891 (27·8%)
Has >1 drink per week	207 (6·3%)	202 (6·3%)
Smoking history		
Has never smoked	2496 (76·1%)	2421 (75·5%)
Currently smokes or history of smoking	784 (23·9%)	784 (24·5%)
Medication consistency‡		
<90%	840 (25·6%)	1054 (32·9%)
≥90%	2440 (74·4%)	2151 (67·1%)
ALT concentrations, units per L§		
Pre-treatment ALT	24·5 (14·5)	25·5 (18·6)
Pre-treatment ALT above upper limit of normal	184 (5·6%)	196 (6·1%)
ALT at 1 month	26·5 (19·2)	29·0 (22·4)
ALT at 1 month above upper limit of normal	199 (6·1%)	277 (8·6%)
White blood cell count, ×1000 per µL¶		
Pre-treatment white blood cell count	6·4 (2·0)	6·4 (2·1)
Pre-treatment white blood cell count less than lower limit of normal	438 (13·4%)	424 (13·2%)
White blood cell count at 1 month	5·5 (1·8)	6·2 (2·0)
White blood cell count at 1 month less than lower limit of normal	694 (21·2%)	457 (14·3%)
Platelet count, ×1000 per µL‖		
Pre-treatment platelet count	245·8 (65·1)	247·6 (69·5)
Pre-treatment platelet count less than lower limit of normal	145 (4·4%)	146 (4·6%)
Platelet count at 1 month	223·0 (61·4)	244·6 (68·3)
Platelet count at 1 month less than lower limit of normal	221 (6·7%)	138 (4·31%)

Data are n (%) or mean (SD). ALT=alanine aminotransferase. *Includes immune suppressing medications, diabetes, renal failure, or other physician-defined immune suppressing conditions. †Not included in this count is pyridoxine, which was given to 176 (5·5%) patients receiving 9 months of daily isoniazid and 60 (1·8%) patients receiving 4 months of daily rifampicin—only seven participants (five in the 9 months of daily isoniazid group and two in the 4 months of daily rifampicin group) were HIV-positive. ‡Defined as the proportion of days the patient took a dose of medication while on treatment (doses taken divided by days on treatment). §In the 4 months of daily rifampicin group, pre-treatment ALT concentrations were missing for 36 patients and ALT concentrations at 1 month were missing for 448 patients; in the 9 months of daily isoniazid group, pre-treatment ALT concentrations were missing for 37 patients and ALT concentrations at 1 month were missing for 425 patients. ¶In the 4 months of daily rifampicin group, pre-treatment white blood cell counts were missing for 46 patients and white blood cell counts at 1 month were missing for 494 patients; in the 9 months of daily isoniazid group, pre-treatment white blood cell counts were missing for 59 patients and white blood cell counts at 1 month were missing for 474 patients. ‖In the 4 months of daily rifampicin group, pre-treatment platelet counts were missing for 50 patients and platelet counts at 1 month were missing for 499 patients; in the 9 months of daily isoniazid group, pre-treatment platelet counts were missing for 59 patients and platelet counts at 1 month were missing for 478 patients.

Table 1: **Baseline characteristics**

Patients with missing laboratory data were excluded from these univariable and multivariable analyses as appropriate; however, we also examined including them within a third category of missing.

Multivariable models for each evaluated outcome were created including the covariate of age and all covariates that had $p<0·1$ in univariable analysis. We further explored inclusion of all a priori defined predictors in multivariable models.

Monthly occurrence of grade 3–4 hepatotoxicity, grade 1–4 rash, and grade 3–5 non-hepatotoxic or non-rash adverse events were examined. Further, differences between values of ALT, white blood cells, and platelets at pre-treatment and at 1 month were examined. Differences in blood tests at these timepoints were evaluated via linear mixed models with each patient acting as the cluster using R package lme4 (version 1·1-19).[20] Histograms of blood tests approximated normal distributions for each

	4 months of daily rifampicin (n=3280)	9 months of daily isoniazid (n=3205)	Risk difference per 100 (95% CI)
Any time during treatment			
All adverse events	68 (2·1%)	131 (4·1%)	−2·0 (−2·9 to −1·2)
Primary outcome			
Grade 1–2 rash or any grade 3–5 adverse event	50 (1·5%)	86 (2·7%)	−1·2 (−1·9 to −0·5)
Secondary outcomes			
Grade 3–4 hepatotoxicity	11 (0·3%)	65 (2·0%)	−1·7 (−2·2 to −1·2)
Grade 1–4 rash	25 (0·8%)	13 (0·4%)	0·4 (−0·01 to 0·7)
Grade 3–4 haematological event	6 (0·2%)	0	0·2 (0·04 to 0·3)
Grade 3–5 non-rash or non-hepatotoxicity adverse event	14 (0·4%)	8 (0·2%)	0·2 (−0·1 to 0·5)
Requiring hospitalisation*	1 (0·03%)	3 (0·1%)	−0·1 (−0·2 to 0·1)
Grade 5 death	0	1 (0·03%)	−0·03 (−0·1 to 0·03)
Within first 146 days of treatment†			
All adverse events	68 (2·1%)	114 (3·6%)	−1·5 (−2·3 to −0·7)
Primary outcome			
Grade 1–2 rash or any grade 3–5 adverse event	50 (1·5%)	71 (2·2%)	−0·7 (−1·4 to −0·03)
Secondary outcomes			
Grade 3–4 hepatotoxicity	11 (0·3%)	51 (1·6%)	−1·3 (−1·7 to −0·8)
Grade 1–4 rash	25 (0·8%)	12 (0·4%)	0·4 (0·02 to 0·8)
Grade 3–4 haematological event	6 (0·2%)	0	0·2 (0·04 to 0·3)
Grade 3–5 non-rash or non-hepatotoxicity adverse event	14 (0·4%)	8 (0·2%)	0·2 (−0·1 to 0·5)
Requiring hospitalisation*	1 (0·03%)	3 (0·1%)	−0·1 (−0·2 to 0·1)
Grade 5 death	0 (0%)	1 (0·03%)	−0·03 (−0·1 to 0·03)

Data are n (%) or risk difference per 100 (95% CI). Results are reported by study outcome and time of occurrence. Exact binomial CIs are reported for each risk difference. *Hospitalisations during treatment phase that were judged by the independent adjudication panel to be necessary and possibly or probably related to study drug. †146 days of treatment reported because this was the maximum time allowed to complete rifampicin.

Table 2: **Adverse events judged possibly or probably related to therapy by the adverse event panel**

timepoint—shifts between timepoints were visualised using smoothed density plots.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited from April 27, 2004, up until Jan 31, 2007 (phase 2), and Oct 1, 2009, up until Dec 31, 2014 (phase 3). 6859 patients were randomly assigned—337 declined treatment or withdrew consent and 37 were excluded per protocol due to index case drug resistance. 3280 patients (393 from phase 2, 2887 from phase 3) received at least one dose of rifampicin and 3205 patients (396 from phase 2, 2809 from phase 3) received at least one dose of isoniazid and were included in the safety analysis (figure 1). Patients received treatment for a median of 123 (IQR 119–129) days with rifampicin and a median of 273 (165–288) days with isoniazid. Baseline characteristics for both groups were similar (table 1). Mean age in both groups was 38 years and HIV co-infection was 4%. Patients receiving rifampicin were more likely to take their medication each day (table 1).

Rifampicin was safer than isoniazid (table 2, appendix p 6). The primary outcome of grade 1–2 rash or grade 3–5 adverse events was observed in 50 (1·5%) of 3280 patients receiving rifampicin and 86 (2·7%) of 3205 patients receiving isoniazid with a risk difference of –1·2% (95% CI –1·9 to –0·5). This difference equates to a number needed to harm for rifampicin of 67 and for isoniazid of 37. Rifampicin remained safer than isoniazid even when limiting adverse events to the maximum allowed time of rifampicin treatment (146 days). Age-related incidence of these events was lowest in individuals aged 18–34 years and highest in individuals aged 65 years and older; incidence was similar in age strata explored across individuals aged 35–64 years (appendix p 2). In multivariable analysis, the adjusted odds ratio (OR) of these events increased with age in patients receiving isoniazid (table 3). Age was not associated with these adverse events in patients receiving rifampicin. Rather, concomitant medications (adjusted OR 2·8, 95% CI 1·5–5·2) and taking medication on less than 90% of days (2·0, 1·1–3·6) were associated with these adverse events (table 4).

During treatment, six hospitalisations occurred among patients with an adverse event; four were judged necessary by the review panel. One occurred with rifampicin (haematological, neutropenia), while three occurred with isoniazid (two for hepatotoxicity and one for drug-induced pancreatitis). An individual receiving isoniazid died and it was judged possibly related to isoniazid by two review panel members and not related to isoniazid by one. The individual was a 32-year old woman from a west African site who was asymptomatic at the time of enrolment and randomisation, had normal pre-treatment test results, no history of substance use, no concomitant medications, and no known medical conditions. 4 days after starting treatment, the patient called the clinic with symptoms of fever, physical asthenia, joint pain, chills, and a bitter taste in the mouth. She continued study treatment. She was examined in the clinic 3 days later, at which time the physical exam was normal. The patient was diagnosed with malaria; she continued isoniazid treatment and took artemether, lumefantrine, and calcium that day for her malaria. The next morning the patient died—the patient's family did not permit an autopsy to establish the exact cause of death.

Grade 3–4 hepatotoxicity was the most common adverse event with isoniazid (65 [2·0%] of 3205), with 75% of these events occurring in the first 4 months (appendix pp 3–4). There was a broad shift of ALT concentrations after 1 month of treatment in both treatment groups (figure 2A). ALT concentrations increased in 1558 (56·5%)

	Number	Grade 1–2 rash and all grade 3–5 adverse events*			Grade 3–4 hepatotoxicity*		
		Risk	Univariable estimate OR (95% CI)	Multivariable estimate† adjusted OR (95% CI)	Risk	Univariable estimate OR (95% CI)	Multivariable estimate† adjusted OR (95% CI)
Age, years							
18–34	1436	25 (1·7%)	1 (ref)	1 (ref)	15 (1·0%)	1 (ref)	1 (ref)
35–64	1642	54 (3·3%)	1·9 (1·2–3·1)‡	1·8 (1·1–3·0)	43 (2·6%)	2·5 (1·4–4·6)‡	2·3 (1·3–4·2)
65–90	127	7 (5·5%)	3·5 (1·4–7·6)‡	3·0 (1·2–6·8)	7 (5·5%)	5·7 (2·2–13·5)‡	5·3 (1·9–13·3)
Sex							
Female	1811	48 (2·7%)	1 (ref)	..	33 (1·8%)	1 (ref)	..
Male	1394	38 (2·7%)	1·0 (0·7–1·6)	..	32 (2·3%)	1·3 (0·8–2·1)	..
Body-mass index							
Normal	1646	44 (2·7%)	1 (ref)	..	34 (2·1%)	1 (ref)	..
Underweight	222	11 (2·6%)	0·9 (0·3–2·1)	..	4 (1·8%)	1·0 (0·3–2·4)	..
Overweight	907	26 (2·9%)	1·1 (0·7–1·8)	..	19 (2·1%)	1·0 (0·6–1·8)	..
Obese	430	5 (2·3%)	1·0 (0·5–1·8)	..	8 (1·9%)	0·9 (0·4–1·9)	..
Immune status							
No immune suppression	2871	73 (2·5%)	1 (ref)	..	52 (1·8%)	1 (ref)	1 (ref)
HIV-positive	138	5 (3·6%)	1·6 (0·6–3·5)	..	5 (3·6%)	2·2 (0·8–5·0)	1·9 (0·7–4·5)
Other immune suppression	196	8 (4·1%)	1·7 (0·8–3·4)	..	8 (4·1%)	2·4 (1·1–4·8)‡	1·7 (0·7–3·6)
Alcohol use							
Never drinks	2112	58 (2·8%)	1 (ref)	..	40 (1·9%)	1 (ref)	1 (ref)
≤1 drink per week	891	20 (2·2%)	0·8 (0·5–1·4)	..	17 (1·9%)	1·0 (0·6–1·8)	0·9 (0·5–1·7)
>1 drink per week	202	8 (4·0%)	1·5 (0·7–3·0)	..	8 (4·0%)	2·2 (0·98–4·5)‡	1·8 (0·8–3·7)
Smoking history							
Has never smoked	2421	60 (2·5%)	1 (ref)	..	42 (1·7%)	1 (ref)	1 (ref)
Currently smokes or history of smoking	784	26 (3·3%)	1·4 (0·8–2·1)	..	23 (2·9%)	1·7 (1·02–2·9)‡	1·4 (0·8–2·3)
Medication consistency							
Consistency ≥90%	2151	57 (2·7%)	1 (ref)	..	48 (2·2%)	1 (ref)	..
Consistency <90%	1054	29 (2·8%)	1·1 (0·7–1·6)	..	17 (1·6%)	0·7 (0·4–1·3)	..
Concomitant medications							
None	2470	58 (2·4%)	1 (ref)	1 (ref)	42 (1·7%)	1 (ref)	1 (ref)
Any	735	28 (3·8%)§	1·7 (1·04–2·6)‡	1·3 (0·8–2·2)	23 (3·1%)¶	1·9 (1·1–3·1)‡	1·1 (0·6–2·0)
Pre-treatment ALT test‖							
Normal	2972	..	..	..	56 (1·9%)	1 (ref)	1 (ref)
Above normal	196	..	..	..	9 (4·6%)	2·6 (1·2–5·0)‡	2·6 (1·2–5·0)

Data are n (%) or OR or adjusted OR (95% CI). OR=odds ratio. ACE=angiotensin-converting-enzyme. *Four patients were subsequently diagnosed with hepatitis C and two with hepatitis B in response to their hepatotoxicity. †Multivariable models included age plus covariates that were p<0·1 in univariable analysis. Inclusion of predictors with p<0·05 or all predictors in the multivariable models did not reveal any new associations. ‡p<0·1. §11 patients used ACE inhibitors, three used levothyroxine, two used atopic or allergy medications, two used cholesterol lowering medications, and ten used other medications. ¶Ten patients used ACE inhibitors, two used cholesterol lowering medications, one used levothyroxine, one used atopic or allergy medications, and nine used other medications. ‖Only included in models for grade 3–4 hepatotoxicity and based on normal ranges at each site (appendix p 5). Estimates only include participants for whom data were available (missing, n=37). Inclusion of participants with missing data as a category did not affect estimates and this factor was not associated with hepatotoxicity.

***Table 3*: Risk factors for grade 1–2 rash and all grade 3–5 adverse events attributed to isoniazid and grade 3–4 hepatotoxicity attributed to isoniazid**

of 2757 patients receiving isoniazid and 1379 (49·1%) of 2808 patients receiving rifampicin (p<0·0001). Concentrations at 1 month increased 3·5 units per L (95% CI 1·7–5·4) in patients receiving isoniazid and 1·9 units per L (1·2–2·7) in patients receiving rifampicin, corresponding to ALT concentrations increasing 1·6 units per L (0·5–2·7) more in those taking isoniazid. Future risk of grade 3–4 hepatotoxicity was not better predicted by ALT concentrations at 1 month than pre-treatment ALT in either treatment group (appendix p 7). Pre-treatment ALT above the upper limit of normal was associated with grade 3–4 hepatoxicity in patients receiving isoniazid (adjusted OR 2·6, 95% CI 1·2–5·0). Being aged 35 years or older was also associated with hepatotoxicity in multivariable analysis. Alcohol use, smoking, concomitant medication use, and immune suppression were associated with hepatotoxicity in univariable analysis, but not in multivariable analysis as these were confounded by age

	Number	Grade 1–2 rash and all grade 3–5 adverse events*			Grade 1–4 rash		
		Risk	Univariable estimate OR (95% CI)	Multivariable estimate† adjusted OR (95% CI)	Risk	Univariable estimate OR (95% CI)	Multivariable estimate† adjusted OR (95% CI)
Age, years							
18–34	1489	18 (1·2%)	1 (ref)	1 (ref)	6 (0·4%)	1 (ref)	1 (ref)
35–64	1661	28 (1·7%)	1·4 (0·8–2·5)	1·1 (0·6–2·1)	15 (0·9%)	2·2 (0·9–5·8)†	1·6 (0·6–4·5)
65–90	130	4 (3·1%)	2·8 (0·9–7·4)†	1·7 (0·5–4·7)	4 (3·1%)	8·1 (2·2–27·2)†	4·4 (1·1–16·2)
Sex							
Female	1916	34 (1·8%)	1 (ref)	..	18 (0·9%)	1 (ref)	..
Male	1364	16 (1·2%)	0·7 (0·4–1·2)	..	7 (0·5%)	0·6 (0·2–1·3)	..
Body-mass index							
Normal	1674	24 (1·4%)	1 (ref)	..	14 (0·8%)	1 (ref)	..
Underweight	216	3 (1·4%)	1·1 (0·3–3·0)	..	0 (0%)	0·3 (0–2·0)	..
Overweight	916	16 (1·8%)	1·2 (0·7–2·3)	..	9 (1·0%)	1·2 (0·5–2·7)	..
Obese	474	7 (1·5%)	1·1 (0·4–2·4)	..	2 (0·4%)	0·6 (0·1–2·0)	..
Immune status							
No immune suppression	2929	42 (1·4%)	1 (ref)	1 (ref)	21 (0·7%)	1 (ref)	1 (ref)
HIV-positive	130	1 (0·8%)	0·8 (0·1–3·0)	0·5 (0·1–1·9)	0 (0%)	0·5 (0–3·8)	0·3 (0–2·5)
Other immune suppression	221	7 (3·2%)	2·4 (0·99–4·9)†	1·3 (0·5–2·9)	4 (1·8%)	2·8 (0·9–7·1)†	1·2 (0·3–3·3)
Alcohol use							
Never drinks	2200	31 (1·4%)	1 (ref)	..	17 (0·8%)	1 (ref)	..
≤1 drink per week	873	17 (2·0%)	1·4 (0·8–2·5)	..	7 (0·8%)	1·1 (0·4–2·5)	..
>1 drink per week	207	2 (1·0%)	0·8 (0·2–2·5)	..	1 (0·5%)	0·9 (0·1–3·6)	..
Smoking history							
Has never smoked	2496	42 (1·7%)	1 (ref)	..	21 (0·8%)	1 (ref)	..
Currently smokes or history of smoking	784	8 (1·0%)	0·6 (0·3–1·3)	..	4 (0·5%)	0·7 (0·2–1·7)	..
Medication consistency							
Consistency ≥90%	2440	30 (1·2%)	1 (ref)	1 (ref)	16 (0·7%)	1 (ref)	..
Consistency <90%	840	20 (2·4%)	2·0 (1·1–3·5)†	2·0 (1·1–3·6)	9 (1·1%)	1·7 (0·7–3·7)	..
Concomitant medications							
No	2517	27 (1·1%)	1 (ref)	1 (ref)	12 (0·5%)	1 (ref)	1 (ref)
Yes	763	23 (3·0%)‡	2·9 (1·6–5·0)†	2·8 (1·5–5·2)	13 (1·7%)§	3·6 (1·7–7·9)†	2·9 (1·2–7·1)

Data are n (%) or OR or adjusted OR (95% CI). OR=odds ratio. ACE=angiotensin-converting-enzyme. *One patient was subsequently diagnosed with hepatitis B in response to a haematological adverse event, and another subsequently diagnosed with hepatitis B in response to hepatotoxicity. †p<0·1. ‡Multivariable models included age plus covariates that were p<0·1 in univariable analysis. Inclusion of predictors with p<0·05 or all predictors in the multivariable models did not reveal any new associations. ‡Six patients used ACE inhibitors, four used atopic or allergy medications, one used a cholesterol lowering medication, and 12 used other medications. Two individuals had grade 3 drug interactions—one patient was taking methadone and another patient was taking escitalopram. §Three patients used ACE inhibitors, three used atopic or allergy medications, and seven used other medications.

Table 4: **Risk factors for grade 1–2 rash and all grade 3–5 adverse events attributed to rifampicin and grade 1–4 rash attributed to rifampicin**

(table 3). Possible interaction between pre-treatment ALT and alcohol use was suspected for those receiving isoniazid, but no effect modification was observed (appendix pp 8–9). By contrast with isoniazid, grade 3–4 hepatotoxicity was rare in patients receiving rifampicin (11 [0·3%] of 3280) and risk was similar during each month of treatment (appendix pp 3–4). No examined risk factor was associated with hepatotoxicity in patients receiving rifampicin, although this analysis was limited by the few events (appendix p 10).

In patients receiving rifampicin, 25 (0·8%) of 3280 had grade 1–4 rash, with 64% of events occurring before the end of month 1 and all but one event occurring before the end of month 2 (appendix pp 3–4). Being aged 65–90 years (adjusted OR 4·4, 95% CI 1·1–16·2) and concomitant medication use (2·9, 1·2–7·1) were associated with grade 1–4 rash in patients taking rifampicin in multivariable analysis. Immune suppression was associated with rash in univariable analysis, but not in multivariable analysis, probably confounded by concomitant medication use (table 4). Grade 1–4 rash occurred in 13 (0·4%) of 3205 patients receiving isoniazid—85% of events occurred before the end of month 2. Taking isoniazid on less than 90% of days was associated with rash in univariable analysis (OR 3·2, 95% CI 1·1–9·9), which was consistent in multivariable analysis including age (appendix p 11).

Six (0·2%) of 3280 patients receiving rifampicin stopped treatment due to a grade 3–4 haematological adverse event. No patient receiving isoniazid had this type of adverse event. White blood cell counts decreased after 1 month in both treatment groups (figure 2B). White blood cell counts fell in 1417 (52·5%) of 2697 patients receiving isoniazid and 2033 (73·7%) of 2758 patients receiving rifampicin (p<0·0001). Concentrations at 1 month decreased 183 cells per µL (95% CI 46–319) in patients receiving isoniazid and 835 cells per µL (779–892) in patients receiving rifampicin, corresponding to white blood cell counts decreasing 652 cells per µL (572–733) more in those taking rifampicin.

Platelet counts decreased only in patients receiving rifampicin (figure 2C). Platelet counts fell in 1369 (50·9%) of 2690 patients receiving isoniazid and 2046 (74·4%) of 2749 patients receiving rifampicin (p<0·0001). Concentrations at 1 month decreased 1777 platelets per µL (95% CI −2176 to 5730) in patients receiving isoniazid and 21 400 platelets per µL (19 800 to 23 000) in patients receiving rifampicin, corresponding to platelet counts decreasing 19 621 platelets per µL (17 300 to 21 942) more in those taking rifampicin. Being underweight (adjusted OR 7·8, 95% CI 1·2–50·7) was associated with haematological adverse events but pre-treatment white blood cell counts (3·6, 0·6–16·1) or platelet counts (5·8, 0·6–29·4) less than the lower limit of normal were not (appendix p 12).

Adverse events by study site location and age group and logistic regression for grade 3–5 non-rash or non-hepatotoxic adverse events and for each adverse event including study drug as a predictor are included in the appendix (pp 13–19).

Discussion

This detailed analysis of safety data shows that the incidence of grade 1–2 rash or any grade 3–5 adverse event is 1·2% lower among those receiving 4 months of daily rifampicin than those receiving 9 months of daily isoniazid. For those receiving isoniazid, being aged 35 years or older was the only predictor of these events. Grade 3–4 hepatotoxicity was associated with older age and pre-treatment ALT above the upper limit of normal, independent of alcohol intake. Three-quarters of all cases of hepatotoxicity occurred within the first 4 months of treatment. Among those receiving rifampicin, less consistent medication intake (missing a mean of >3 doses per month) and concomitant medication use, but not older age, were associated with increased odds of grade

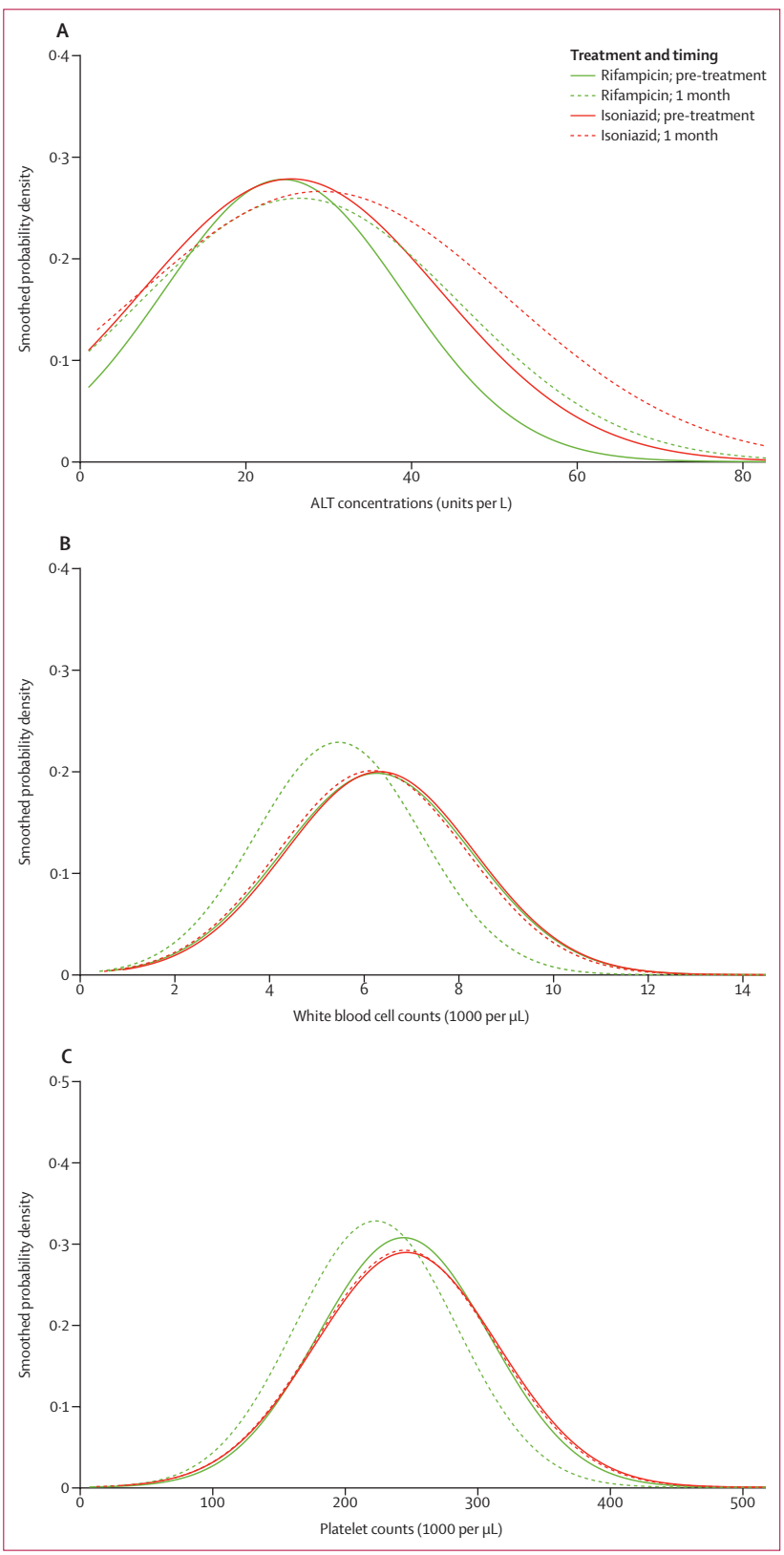

Figure 2: **Comparison of routine blood test results at pre-treatment and month 1**

Smoothed probability densities fit to histograms at pre-treatment and 1 month for ALT (A), white blood cell counts (B), and platelet counts (C) among patients with data at both timepoints. Probability densities were estimated for the histogram of tests at each timepoint using a normal distribution. ALT=alanine aminotransferase.

1–2 rash or any grade 3–5 adverse event. No risk factor was associated with severe hepatotoxicity, although this event was uncommon in patients receiving rifampicin. Being aged 65 years and older and concomitant medication use were associated with greater odds of grade 1–4 rash, two-thirds of which presented in the first month.

Safety, particularly hepatotoxicity, has been a major concern with isoniazid treatment for people aged 65 years and older.[21] This concern is even more prominent as it appears inevitable that patients aged 65 years or older will need to be treated for latent tuberculosis infection to eliminate tuberculosis.[22] Among study participants who were aged 65 years or older, none of the 130 taking rifampicin had grade 3–4 hepatotoxicity, compared with seven (6%) with hepatotoxicity among 127 receiving isoniazid. Rash was the only adverse event among patients receiving rifampicin in this age group. Although few participants were older, this finding points to key manifestations to monitor when prescribing these medications.

Previous meta-analyses have provided evidence that 4 months of daily rifampicin is the safest option for latent tuberculosis infection treatment. Meta-analysis of the 3 or 4 months of daily rifampicin and isoniazid trials showed that this regimen was no safer than isoniazid among high-quality trials, providing indirect evidence that 4 months of daily rifampicin might be safer than 3 or 4 months of daily rifampicin and isoniazid.[23] Additionally, network meta-analysis (not including the phase 3 trial data in our analysis) evaluating hepatotoxicity of eight different treatment options for latent tuberculosis infection concluded that 4 months of daily rifampicin was one of the safest treatment options.[24]

The rates of grade 3–4 hepatotoxicity, and overall discontinuation of study drug in the 9 months of daily isoniazid group were very similar in this analysis to those reported in a large-scale clinical trial evaluating 3 months of weekly isoniazid and rifapentine and 9 months of daily isoniazid published in 2011.[13] The rates of grade 3–4 hepatotoxicity in the 3 months of weekly isoniazid and rifapentine group of that trial were the same as the rates in the 4 months of daily rifampicin group in this analysis (0·3%). However, the overall rate of adverse events that resulted in permanent discontinuation of study therapy in the 2011 trial was 4·9% with 3 months of weekly isoniazid and rifapentine, compared with 2·1% for 4 months of daily rifampicin in our analysis (or 2·8%, if events judged not related to 4 months of daily rifampicin were included). We speculate that this result might be related to the intermittency of the 3 months of weekly isoniazid and rifapentine regimen, given the finding in this study that the incidence of adverse events was higher in those who took rifampicin less consistently. This finding extends observations from older studies of increased adverse events with highly intermittent rifampicin.[25–28] To date, there have not been any direct head-to-head trials comparing 3 months of weekly isoniazid and rifapentine with 4 months of daily rifampicin, but this indirect comparison suggests that 4 months of daily rifampicin could be a safer latent tuberculosis infection treatment option overall. A trial comparing 1 month of daily rifapentine and isoniazid to 9 months of daily isoniazid in individuals who are HIV co-infected showed non-inferiority of 1 month of daily rifapentine and isoniazid for the composite outcome of active tuberculosis and death, with similar incidence (6% *vs* 7%) of serious adverse events in each group.[29] The safety profile of this regimen should be further described in additional trials, including in individuals who are HIV-uninfected.

A possible barrier to uptake of 4 months of daily rifampicin is the fear of propagating rifampicin-resistance through monotherapy of undetected active tuberculosis disease.[30] However, there is good evidence that before initiating therapy, ruling out active tuberculosis using a combination of tuberculosis symptom screening, physical examination, chest radiography, and spontaneous sputum collection is adequate to protect against this risk.[31,32] Within the trials included in our analysis, occurrence of drug resistance was not different between groups: one case of rifampicin-resistant tuberculosis occurred in the 4 months of daily rifampicin group and one case of isoniazid-resistant tuberculosis occurred in the 9 months of daily isoniazid group. Further, a previous meta-analysis of six randomised controlled trials did not detect any increase in rifampicin-resistance among patients receiving rifampicin versus placebo or versus a non-rifamycin-containing regimen.[33] Although occurrence of any form of drug-resistance is undesirable, there is no current evidence to substantiate the fear that latent tuberculosis infection monotherapy will propagate drug-resistance if active tuberculosis disease is ruled out.

Strengths of this study include the standardised methods to assess and grade severity of adverse events. The use of a masked and independent panel should have reduced bias that could influence judgment of severity and attribution of specific adverse events (eg, hepatotoxicity, rash) to study drugs, and minimise possible bias from the open-label design. Furthermore, these results are likely to be generalisable to many different populations, as the trials were done over a number of continents. A substantial proportion of trial participants received treatment in western Africa and southeast Asia, with consistent trends seen between these settings.

Limitations include that the trial was not designed to capture temporary pauses in treatment of less than 48 h or the incidence of minor adverse events that did not require therapy cessation, which might be important to clinicians and patients. The routine blood tests done might not be inclusive of all those available (eg, bilirubin) and were only routinely done pre-treatment and after 1 month of treatment; testing at other times was based on clinician discretion—the open-label design of this study might have influenced clinicians to continue

testing liver aminotransferases in patients receiving isoniazid because of this design. Medication consistency was calculated based on pill counts at each patient visit and could be subject to bias.[34] It is possible patients became inconsistent with their medication because of the onset of symptoms. This trial excluded patients at high-risk of drug-interactions to study medication. The risks of drug interactions with rifamycins are well known[35] and in individuals at risk, it might be safer to prescribe isoniazid. Finally, children were not included in this safety analysis; however, no serious adverse events were observed in our parallel paediatric trial.[36]

In conclusion, 4 months of daily rifampicin appears to be safer than 9 months of daily isoniazid for the treatment of latent tuberculosis infection. Unlike isoniazid, adverse events in patients taking rifampicin do not appear to be age-related, except for the greater likelihood with concomitant medications. Of the currently available regimens for latent tuberculosis infection, we believe that rifampicin is the optimal choice on the basis of safety.

Contributors

JRC and DM had full access to all the data and take responsibility for the integrity of the data and accuracy of data analysis. They were responsible for concept and design, and drafting the manuscript. JRC, AB, AT, and DM were responsible for statistical analysis. All authors were responsible for acquisition, analysis, and interpretation of data, and critical revisions.

Declaration of interests

We declare no competing interests.

Data sharing

The data collected for these trials in the form of deidentified participant data and a data dictionary will be made available on Jan 1, 2020. Investigators wishing to access these data will need to have an approved research proposal and complete a data access agreement. All inquiries should be sent to Dick Menzies (dick.menzies@mcgill.ca).

Acknowledgments

The authors thank Bill Burman, Mike Lauzardo, Rick O'Brien, Marcel Behr, Neil Colman, Eric Rousseau, Yvan Fortier, Mei Xin Ly, Merrin Rutherford, and Norma Tink, as well as all others involved as members of the active tuberculosis review panel, the adverse event review panel, the scientific advisory committee, and trial facilitators, plus the trial staff, tuberculosis care providers, and the participants in all the countries. The trials were supported by grants MCT-44154 (phase 2) and MCT-94831 (phase 3) from the Canadian Institutes of Health Research; the Australian National Health and Medical Research Council supported the portion of the phase 3 trial in Australia. JRC received salary support from the Fonds de recherche du Québec - santé (258907) for this analysis. Portions of this study were presented at the 49th Annual Union World Conference on Lung Health; Oct 26, 2018, The Hague, Netherlands, and the 23rd Annual Conference of The Union-North America Region; Feb 23, 2019; Vancouver, Canada.

References

1 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; **13:** e1002152.

2 Marais B, Zumla A. Advancing global tuberculosis control after the UNGA-HLM. *Lancet* 2018; **392:** 1096–97.

3 Abubakar I, Drobniewski F, Southern J, et al. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. *Lancet Infect Dis* 2018; **18:** 1077–87.

4 Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. *J Antimicrob Chemother* 2011; **66:** 1431–46.

5 Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; **281:** 1014–18.

6 Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis* 1978; **117:** 991–1001.

7 Centers for Disease Control and Prevention (CDC). Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. *MMWR Morb Mortal Wkly Rep* 2001; **50:** 733–35.

8 Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *Am Rev Respir Dis* 1992; **145:** 36–41.

9 Martínez Alfaro E, Solera J, Serna E, et al. Compliance, tolerance and effectiveness of a short chemoprophylaxis regimen for the treatment of tuberculosis. *Med Clin (Barc)* 1998; **111:** 401–04.

10 Martínez Alfaro EM, Cuadra F, Solera J, et al. Evaluation of 2 tuberculosis chemoprophylaxis regimens in patients infected with human immunodeficiency virus. *Med Clin (Barc)* 2000; **115:** 161–65.

11 Rivero A, López-Cortés L, Castillo R, et al. Randomized trial of three regimens to prevent tuberculosis in HIV-infected patients with anergy. *Enferm Infecc Microbiol Clin* 2003; 21: 287–92.

12 Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997; **337:** 801–08.

13 Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365:** 2155–66.

14 Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr* 2015; **169:** 247–55.

15 Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med* 2008; **149:** 689–97.

16 Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med* 2018; **379:** 440–53.

17 Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52.

18 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), v4.0. 2009. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed March 30, 2019).

19 Heinze G, Ploner M. logistf: Firth's Bias-Reduced Logistic Regression (R package version 1.23). 2018 https://CRAN.R-project.org/package=logistf (accessed March 30, 2019).

20 Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *J Stat Softw* 2015; **67:** 1–48.

21 Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. *CMAJ* 2011; **183:** e173–79.

22 Ronald LA, Campbell JR, Rose C, et al. Estimated impact of World Health Organization latent tuberculosis screening guidelines in a low TB incidence region: retrospective cohort study. *Clin Infect Dis* 2019; **69:** 2101–08.

23 Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005; **40:** 670–76.

24 Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med* 2017; **167:** 248–55.

25 Girling DJ, Hitze KL. Adverse reactions to rifampicin. *Bull World Health Organ* 1979; **57:** 45–49.

26 Aquinas M, Allan WGL, Horsfall PAL, et al. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *BMJ* 1972; **1:** 765–71.

27 A controlled trial of daily and intermittent rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis: results up to 30 months. *Tubercle* 1975; **56:** 179–89.

28 Steingart KR, Jotblad S, Robsky K, et al. Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review. *Int J Tuberc Lung Dis* 2011; **15:** 305–16.

29 Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019; **380:** 1001–11.

30 Batt J, Khan K. Responsible use of rifampin for the treatment of latent tuberculosis infection. *CMAJ* 2019; **191:**e678–79.

31 Menzies D, Cook V, Long R, Ruslami R. Re: Responsible use of rifampin for the treatment of latent tuberculosis infection. *CMAJ* 2019; **191:** e678–79.

32 Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* 2006; **12:** 744–51.

33 den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2016; **20:** 1065–71.

34 Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999; **21:** 1074–90.

35 Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. *Arch Intern Med* 2002; **162:** 985–92.

36 Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med* 2018; **379:** 454–63.