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Completion, safety, and efficacy of tuberculosis preventive treatment regimens containing rifampicin or rifapentine: an individual patient data network meta-analysis

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Contributors

NW and DM conceptualised and designed the study, drafted the manuscript, had full access to all the data, and take responsibility for the integrity of the data and accuracy of data analysis. All authors contributed to data acquisition, analysis, or interpretation and critical review of the manuscript. NW performed the statistical analysis. NW, AB, and DM conceptualised data analysis. DM had final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

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Summary

Background—3 months of weekly rifapentine plus isoniazid (3HP) and 4 months of daily rifampicin (4R) are recommended for tuberculosis preventive treatment. As these regimens have not been compared directly, we used individual patient data and network meta-analysis methods to compare completion, safety, and efficacy between 3HP and 4R.

Methods—We conducted a network meta-analysis of individual patient data by searching PubMed for randomised controlled trials (RCTs) published between Jan 1, 2000, and Mar 1, 2019. Eligible studies compared 3HP or 4R to 6 months or 9 months of isoniazid and reported treatment completion, adverse events, or incidence of tuberculosis disease. Deidentified individual patient data from eligible studies were provided by study investigators and outcomes were harmonised. Methods for network meta-analysis were used to generate indirect adjusted risk ratios (aRRs) and risk differences (aRDs) with their 95% CIs.

Findings—We included 17 572 participants from 14 countries in six trials. In the network meta-analysis, treatment completion was higher for people on 3HP than for those on 4R (aRR 1·06 [95% CI 1·02–1·10]; aRD 0·05 [95% CI 0·02–0·07]). For treatment-related adverse events leading to drug discontinuation, risks were higher for 3HP than for 4R for adverse events of any severity (aRR 2·86 [2·12–4·21]; aRD 0·03 [0·02–0·05]) and for grade 3–4 adverse events (aRR 3·46 [2·09–6·17]; aRD 0·02 [0·01–0·03]). Similar increased risks with 3HP were observed with other definitions of adverse events and were consistent across age groups. No difference in the incidence of tuberculosis disease between 3HP and 4R was found.

Interpretation—In the absence of RCTs, our individual patient data network meta-analysis indicates that 3HP provided an increase in treatment completion over 4R, but was associated with a higher risk of adverse events. Although findings should be confirmed, the trade-off between completion and safety must be considered when selecting a regimen for tuberculosis preventive treatment.

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Introduction

Tuberculosis is a substantial global health burden, with nearly 10·6 million reported cases and 1·6 million deaths estimated in 2021.[1] An estimated one-quarter of the global population is living with tuberculosis infection (TBI),[2] of whom 5–10% will develop tuberculosis disease in their lifetime. Hence, treating TBI is essential to meet the goals of the WHO End TB strategy.[3,4]

Historically, WHO has recommended daily isoniazid for 6 or 9 months (6–9H)[5] for tuberculosis preventive treatment. Although these regimens have shown good efficacy, they are associated with poor completion rates[6,7] and significant hepatotoxicity.[8] There is a demand from clinicians and patients for shorter and more tolerable tuberculosis preventive treatment regimens.[5,9,10]

In 2020, the WHO recommended a 3-month regimen of weekly rifapentine plus isoniazid (3HP) and 4 months of daily rifampicin (4R),[2] based on the results of several randomised controlled trials (RCTs) over the past 20 years.[11-15] In the trials supporting these recommendations, compared with mono-isoniazid regimens, 4R had significantly fewer grade 3–5 adverse events, including hepatotoxicity,[11,13] whereas 3HP had lower hepatotoxicity, but higher overall rates of grade 3–4 adverse events and adverse event-related drug discontinuations.[14,16] A meta-analysis concluded that proportions of adverse events with 3HP and 6–9H were similar,[6] while a network meta-analysis of 61 studies found no direct comparisons of 3HP and 4R and little evidence of difference in hepatotoxicity between these two regimens.[17]

As 3HP and 4R have not yet been compared directly in a trial, uncertainty about optimal regimen selection remains. Therefore, we used existing data from completed RCTs to perform a network meta-analysis of individual patient data, to generate and compare indirect estimates of relative treatment completion, safety, and efficacy between 3HP and 4R.

Methods

The protocol for this individual patient data network meta-analysis was registered on PROSPERO (CRD42019124635).

Search strategy and selection criteria

We conducted a structured review of the literature to identify RCTs comparing treatment for TBI, published since 2000 (as we considered that individual-level patient data published earlier would be difficult to locate and obtain). A list of keywords and medical subject headings terms related to TBI, drug regimens, and treatment outcomes were used to search PubMed for RCTs published between Jan 1, 2000, and March 1, 2019 (appendix 3 p 2). In addition, we identified relevant articles from the reference lists of retrieved reports and from previously published reviews.

Eligible RCTs compared either 3HP or 4R to 6H or 9H, were published in peer-reviewed journals, and reported at least one of the following outcomes: treatment completion, treatment-related adverse events, or incidence of tuberculosis disease. We also searched for studies of 3 months of rifampicin plus isoniazid (3HR) but were unable to acquire data for analyses. We included RCTs with participants of all ages who had a documented positive tuberculin skin test or interferon-gamma release assays, or other conditions associated with increased risk of tuberculosis disease. We excluded observational studies, grey literature or unpublished data, and populations where participants were exposed to people with tuberculosis strains resistant to isoniazid or rifampicin, or both drugs.

Authors of all eligible studies were contacted and invited to contribute their deidentified individual-level patient data. Information requested included: (1) baseline characteristics, (2) risk factors and indication for treatment, (3) treatment regimens, and (4) treatment outcomes: treatment completion, adverse events, and incidence of tuberculosis disease (appendix 3 p 3).

To assess comparability of outcomes between studies, we also asked for study protocols and standard operating procedures to determine diagnostic methods and outcome assessments. For treatment completion, we requested participant pill counts and treatment durations. Information was abstracted for adverse events to determine definitions (grading system, investigator defined, etc), attribution to drug, and whether assessed by a blinded, independent committee. For incidence of tuberculosis disease, methods for diagnosis were abstracted including laboratory tests and whether case records were adjudicated by an independent committee. Demographic characteristics and treatment outcomes were harmonised across studies, the accuracy of these procedures was validated by comparing with results reported in the original publications. All adverse events were harmonised according to the grading criteria in the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). The criteria used to describe grading categories of adverse events in other systems were matched to those of the CTCAE, and if discrepant were reassigned a grade to conform to what they would be classified as in the CTCAE (appendix 3 pp 4-14).

Risk of bias was assessed using the Cochrane risk of bias 2 tool[18] for RCTs.

Our outcome of treatment completion was defined as taking more than 80% of the prescribed doses (using pill counts) in 120% of the allowed time, dichotomised into completers or non-completers, and analysed as risks among the entire population of all participants randomly allocated and included in the data sent for our individual patient data analysis (appendix 3 p 15). We analysed adverse event outcomes in the safety population (participants who took ≥1 dose of study drug), which were defined as (1) any treatment-related adverse event (ie, adjudicated to be definitely, possibly, or probably related to study drug) that led to permanent drug discontinuation; and (2) any treatment-related grade 3–4 adverse events that led to permanent drug discontinuation. In secondary analyses of adverse events, we compared the risk of (1) any adverse events that led to permanent drug discontinuation (regardless of relationship to treatment); (2) any grade 3–4 adverse events (regardless of relationship to treatment or drug discontinuation); and (3) treatment-related grade 3–4 adverse events (regardless of effect on drug discontinuation). To assess

our outcome of efficacy for prevention of tuberculosis disease, we estimated the relative incidence rate of all forms of tuberculosis disease, per 1000 person-years of follow-up, by pooling suspected, microbiologically confirmed, or clinically diagnosed tuberculosis disease in the entire population.

Data analysis

The power for each outcome in our network meta-analysis was determined using both traditional and indirect methods as described by Thorlund and Mills[19] (appendix 3 pp 16-17). We determined that we had an adequate number of participants to detect an indirect difference between 3HP and 4R of 13–15% in the proportion of treatment completion with 80% power (0·05 α), using an intraclass correlation coefficient (ICC) of 0·004 calculated from data in included RCTs. For adverse events, based on study ICCs of 0·0005 and the number of participants in the datasets we obtained, we had 80% power (0·05 α) to detect indirect differences in the proportion of adverse events of 1·8–3·1% between 3HP and 4R. Due to inadequate power, all analyses of efficacy for prevention of tuberculosis disease were exploratory.

We conducted a network meta-analysis using individual patient data to estimate indirect treatment effects between 3HP and 4R using the estimates generated from direct analyses with their common comparator of 6–9H. As included studies were few, we pooled those receiving 6H or 9H and assumed clinical equivalence in the absence of trials directly comparing these two treatment durations. The individual patient data network meta-analysis was done in two stages. In the first stage, one-step individual patient data meta-analyses were conducted separately for studies of 3HP compared with 6–9H and for studies of 4R compared with 6–9H to obtain their direct effect estimates. The estimates for direct risk ratios (RRs) were calculated using Poisson regression in generalised linear mixed models (GLMM) with a random intercept for study and a log link, whereas risk differences (RDs) were calculated with a Gaussian distribution and identity link. The estimates for direct incidence rate ratios (IRRs) were calculated using Poisson regression in a GLMM with a random intercept for study, person-time for follow-up incorporated as an offset, and a log link (incidence rate differences [IRD] were estimated as outlined in Bagos and Nikolopoulos).[20] To account for differences between study populations, estimates were adjusted for covariates considered a priori to be important predictors; each outcome was adjusted for different covariates and missing data for categorical variables were included as a not available category (appendix 3 p 18). In our model building diagnostics, we assessed the effect that different specifications of random intercepts and the use of propensity scores (for confounders of adverse events and tuberculosis incidence, as the small number of events limited adjustment sets) had on both model fit and variance. When no substantial differences were observed, the model with simplest interpretation was chosen.

In the second stage, the network meta-analysis of the indirect RRs and RDs between 3HP and 4R were calculated from the estimates of the direct models as log[direct $RR_{3HPvs6–9H}$] − log[direct $RR_{4Rvs6–9H}$] for RRs and [direct $RD_{3HPvs6–9H}$] − [direct $RD_{4Rvs6–9H}$] for RDs (IRRs and IRDs were calculated similarly).[21,22] The 95% CIs were estimated with bootstrap resampling methods on 1000 replications and calculated using the 2·5th and 97·5th

percentiles of the sampling distribution. As methods for assessing heterogeneity of adjusted individual patient data network meta-analysis were not available and few studies were included, this was not assessed statistically. All analyses were conducted using R (version 4.1.2).

We conducted post-hoc sensitivity analyses of treatment completion in the network meta-analysis between 3HP and 4R, stratified by age (<18 compared with ≥18 years of age), age among adults only (<35, 35 to 65, >65 years of age), and HIV status. In addition, we investigated treatment completion only in studies using 9H as the comparator regimen. We analysed differences in treatment-related adverse events that led to permanent drug discontinuation and treatment-related grade 3–4 adverse events that led to permanent drug discontinuation in the network meta-analysis between 3HP and 4R stratified by age (<50 and ≥50 years of age). We also analysed treatment-related grade 3–4 adverse events that led to permanent drug discontinuation in the entire population and per-protocol population (defined as all participants with an adverse event but excluding participants without adverse events who did not complete >80% of prescribed doses).

Role of the funding source

There was no funding source for this study.

Results

The literature search identified datasets from 12 RCTs described in 17 publications,[11-16,23-33] of which six trials described in ten publications[11-16,25,26,29,31] were included: three trials that compared 3HP with 6–9H[12,14-16,25,26,29] and three trials that compared 4R with 6–9H[11,13,31] (figure). Of note, participants of one trial were reported in several publications;[14-16,26,29] we refer to this trial as CDC Study 26. Six trials described in seven publications[23,24,27,28,30,32,33] were not included: of these, data from four trials described in five publications could not be located or were no longer available,[23,24,27,30,33] one trial had no comparator arm of 6–9H,[32] and data from one trial was not included because corresponding authors did not respond.[28]

In total, we included 17 572 participants: 4897 received 3HP, 4055 received 4R, and 8620 received 6–9H. Participants in the included datasets were enrolled in 14 countries in six WHO regions (appendix 3 p 20). In one trial, directly observed therapy (DOT) was used for both 3HP and 9H.[25] In a second trial, DOT was used for both 4R and 6H,[31] but was excluded from completion analyses due to insufficient data obtained to estimate completion. In two trials, DOT was used for 3HP but the comparator arms of 6–9H were self-administered,[12,14] and in the final two trials, 4R and the 9H comparator arms were self-administered.[11,13] The average age of participants was similar across trials with the exception of one trial in a paediatric population,[11] but the proportion with HIV ranged from 0%[11,25,31] to 100%.[12] All three outcomes were available in five trials, whereas only adverse events were available in one published report, but data on the outcome of tuberculosis disease were added to the data provided.[31] Appendix 3 (p 21) presents the study-level descriptions and outcomes of trials excluded from our individual patient data.[23,24,27,28,30,32,33] Study characteristics and outcomes were similar between included

and excluded studies; the majority of excluded studies compared 3HR with 6–9H, with the result that only a single arm of 3HR was in the included studies, which is why this arm was dropped from the analysis.

Overall Cochrane risk of bias 2 assessment indicated some concerns in four data sets, due to absence of blinded outcome assessments in these four trials;[12,14,25,31] and two open-label trials had blinded and independent adjudication of the adverse events (appendix 3 p 19).[11,13]

For the overall population included in the network meta-analysis of 3HP and 4R (table 1), the mean age was 34·9 years, 50·8% were female, and the mean BMI was 25·4 kg/m^2. Age, sex, BMI, and recreational drug use were similar across treatment groups. Most participants were contacts (82·9%), and 68·6% of participants were close contacts (≥4 h per week of contact with a confirmed active tuberculosis case). The prevalence of people living with HIV was 7·2% and was higher in studies of 3HP, whereas antiretroviral therapy use was higher in 4R (49·2%) than in 3HP (1·4%).

In the studies of 3HP compared with 6–9H, the number of participants completing treatment was 3963 (80·9%) of 4897 for those receiving 3HP and 2856 (61·9%) of 4614 for those receiving 6–9H (table 2), resulting in an adjusted RR (aRR) of 1·30 (95% CI 1·24–1·37) and an adjusted RD (aRD) of 0·19 (95% CI 0·17–0·21). In the studies reporting completion of 4R compared with 9H, the number completing treatment was 2828 (73·2%) of 3865 for those receiving 4R and 2270 (59·4%) of 3823 for those receiving 9H, resulting in an aRR of 1·23 (1·17–1·30) and an aRD of 0·14 (0·12–0·16).

In the network meta-analysis of the indirect effect between 3HP and 4R, treatment completion was more likely with 3HP, with an aRR of 1·06 (95% CI 1·02–1·10) and aRD of 0·05 (95% CI 0·02–0·07). When only including studies of 9H as the comparator, the indirect aRR was 1·02 (0·98–1·07) and the aRD was 0·03 (0·00–0·06).

In sensitivity analyses, those younger than 18 years had a higher completion of 3HP than in the entire study population, with indirect aRR between 3HP and 4R of 1·12 (95% CI 1·01–1·23) and aRD of 0·07 (95% CI 0·00–0·15; appendix 3 pp 22-23). In those 18 years and older, the indirect aRR and aRD from the network meta-analysis between 3HP and 4R were similar to those of the overall study population. Completion between 3HP and 4R in those younger than 35 years was similar to that in participants younger than 18 years (aRR 1·09 [1·02–1·15]; aRD 0·07 [0·03–0·11]), but in those aged 35–65 years and older than 65 years, there were no significant differences.

For the 1271 people living with HIV (appendix 3 p 24), treatment completion was substantially higher for those receiving 3HP compared with 4R in indirect network meta-analysis. In those without HIV (n=11 817) differences in treatment completion between 3HP and 4R were similar to that of the overall study population.

Separate specifications of models with random intercept for country with missing category, random slope for treatment effects, or propensity score for adjustment had negligible effect on variance and model fit.

As presented in table 3, the proportion of participants who experienced any treatment-related adverse event that led to permanent drug discontinuation was slightly higher with 3HP than 6–9H, and lower with 4R than 6–9H in direct comparisons. As a result, in the network meta-analysis, 3HP had higher risk than 4R, with an aRR of 2·86 (95% CI 2·12–4·21) and an aRD of 0·03 (95% CI 0·02–0·05). Results were similar for treatment-related grade 3–4 adverse events that led to permanent drug discontinuation, and in the network meta-analysis 3HP had higher risk than 4R, with an aRR of 3·46 (2·09–6·17) and an aRD of 0·02 (0·01–0·03).

For the indirect network meta-analysis stratified by age (appendix 3 pp 25-26), 3HP had greater risk than 4R for both treatment-related adverse events of any grade and grade 3–4 events that led to permanent drug discontinuation, regardless of age category.

Using other definitions of adverse events, differences were similar between 3HP and 4R (appendix 3 p 27). Findings were similar in analyses using the entire population and per-protocol populations (appendix 3 p 28). For rates of adverse events by HIV status, see appendix 3 (p 29).

In direct comparisons, the rate of tuberculosis disease was similar between 3HP and 6–9H, as well as between 4R and 9H (table 4). In the network meta-analysis of the indirect effect, the rate of tuberculosis disease with 3HP was similar to that with 4R, with an aIRR of 1·16 (95% CI 0·40 to 3·58) and an aIRD of 0·8 per 1000 person-years of follow-up (95% CI −2·3 to 7·0).

Discussion

Our network meta-analysis comparing treatment outcomes between 3HP and 4R using individual patient data from six trials with 17 572 participants indicated that people treated with 3HP have about 5% higher treatment completion than those receiving 4R. However, compared with 4R, those treated with 3HP had a 3% higher risk of treatment-related adverse events that led to permanent drug discontinuation and a 2% higher risk of treatment-related grade 3–4 adverse events that led to permanent drug discontinuation. Our results suggest no difference in efficacy for prevention of tuberculosis disease between these regimens, although this analysis was limited by the low number of disease occurrences.

Interpreting treatment completion between 3HP and 4R requires certain considerations. Differences in the regimens compared, including treatment scheduling (3HP taken once a week and 4R taken once a day) and site-level clinical practices, will affect completion. Of note, for analysis of completion, treatment was self-administered in both arms of the included studies of 4R,[11,13] whereas in studies of 3HP, all 3HP arms were under DOT but the comparator (6–9H) could be either self-administered or under DOT.[25] Since DOT might increase treatment completion[32] the structure of the included trials could have differentially affected our analysis of completion favouring 3HP over 4R. Additionally, when excluding the single study using 6H,[12] the difference in completion between 3HP and 4R was no longer significant; we could not distinguish whether this was due to the comparator arm regimen or because all those receiving 6H were people living with HIV.

As only 5–10% of people with TBI will progress to tuberculosis disease, and TBI is an asymptomatic condition, treatment safety is paramount. In this analysis, the risk of adverse events was higher among those who received 3HP compared to 4R, using different definitions of adverse events. We were unable to compare risks of adverse events in paediatric populations because events were too few, but few adverse events and high completion in participants younger than 18 years could indicate better tolerability of all regimens in this age group.

Our study has some limitations to consider. The numbers of people with HIV or other comorbidities (including diabetes or other immunosuppressive conditions) were too few to adequately analyse safety (including drug–drug interactions with antiretroviral therapy) in these important subgroups. Imbalance in antiretroviral therapy availability for people living with HIV between 4R and 3HP adds complexity in comparing outcomes in people living with HIV in our individual patient data, but adverse event rates were actually lower among people living with HIV, whereas the rate of tuberculosis disease was very low in all groups. Overall, we do not think that the low numbers of people living with HIV resulted in biased estimates, but they certainly meant less precision. Hence, further research is needed to assess the relative safety of 3HP and 4R in persons with HIV or other comorbidities. Although our analysis suggests no major difference in efficacy between the two regimens, this analysis was limited because few individuals developed tuberculosis disease. Propensity scores might be inappropriate for prediction of randomly assigned treatment, thus adjusting for between-study differences using variables with substantial missing data (such as renal failure, use of biologics, and immune-suppression other than HIV) was restricted. However, in our model selection we assessed a propensity score that predicted the probability of a participant being in their given study, and no substantial differences were observed between a model with this propensity score and our fully adjusted model. We could not include treatment site or country as random intercepts in our models (although we could include study) as these data were unavailable for a large portion of the population, leading to an underestimation of variance. However, we assessed both fit (using AIC and BIC) and changes in variance between a model fit using a country variable with a missing category specified as a random intercept and our model fit with just a random intercept for study, and we observed no substantial differences. All treatment arms were unblinded in the included trials, and the consequent bias must be considered when interpreting results, notably the ascertainment of adverse events with novel treatments such as 3HP. Additionally, calendar dates were unavailable as the data received were deidentified, precluding assessment of temporal trends within trials.

Despite these limitations, our study has several strengths. This is the first study to combine individual patient data and network meta-analysis approaches to provide adjusted indirect estimates of the relative completion, safety, and efficacy between 3HP and 4R, two treatment regimens that have not been directly compared in a randomised trial. The availability of individual-level patient data from RCTs enabled adjustment for study-level differences and harmonisation of outcomes across studies, resulting in estimates that are more robust to study-level or patient-level differences than those from a traditional aggregate data network meta-analysis. In a previous network meta-analysis using aggregate data,[17] authors were unable to analyse adverse events other than hepatotoxicity. Having access to the individual

patients' data allowed us to harmonise all adverse event outcomes and assess differences between the two regimens using different definitions of adverse events. Furthermore, our sample size and number of events provided adequate power to make precise estimates for comparisons of treatment completion and adverse events for age-stratified analyses, although not for tuberculosis prevention, as noted here.

In the absence of trials directly comparing 3HP and 4R, this individual patient data network meta-analysis from RCTs of tuberculosis preventive treatment provides evidence that 3HP under DOT had significantly higher treatment completion but also significantly higher risks of treatment-related adverse events compared with 4R. This trade-off between completion and risk of adverse events must be considered when deciding the optimal treatment for TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

As this is an analysis of individual patient data shared by contributing authors, they retain the right to review requests for sharing of their data. The data from Prevent TB is publicly accessible; for access contact the Critical Path Institute (C-PATH). For all other data, please contact the corresponding author with all data sharing inquiries.

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Research in context

Evidence before this study

We searched PubMed for randomised controlled trials (RCTs) published in the peer-reviewed literature between Jan 1, 2000, and March 1, 2019 (we did not specify any search limits besides the date range), using variations of the following keywords: latent tuberculosis infection, LTBI, treatment, safety, completion, adherence, activation, adverse events, randomized controlled trials, rifampin, rifamycin, rifapentine, and isoniazid. Historically, WHO has recommended 6 months of isoniazid (6H) for tuberculosis preventive treatment. In 2020, WHO added a recommendation for 3 months of rifapentine plus isoniazid (3HP) and a conditional recommendation for 4 months of rifampicin (4R) for prevention of tuberculosis disease. In RCTs, these shorter regimens showed non-inferior efficacy for prevention of tuberculosis disease and better completion when compared with longer isoniazid regimens. Compared with 9 months of isoniazid (9H), 4R was well tolerated, but trials of 3HP compared with 9H indicated an increased risk of grade 3–4 adverse events in those receiving 3HP. A meta-analysis indicated that 3HP had similar rates of adverse events to 6–9H, but included mostly observational studies, and in a network meta-analysis there was not enough data on hepatotoxicity to allow comparisons between regimens, and no comparisons between 3HP and 4R were reported. As 3HP and 4R have not been directly compared in an RCT, questions remain regarding optimal regimen selection. We conducted this individual patient data network meta-analysis to compare treatment outcomes between 3HP and 4R.

Added value of this study

In the absence of direct head-to-head trials, we were able to generate evidence comparing 3HP with 4R. We showed that 3HP administered under directly observed therapy had a higher proportion of participants completing therapy than did 4R. Of note, we found that a higher proportion of participants had adverse events when treated with 3HP compared with 4R, a finding that was consistent in age subgroups and using different definitions of adverse events. We found no difference in efficacy for prevention of tuberculosis disease between 3HP and 4R.

Implications of all the available evidence

Our findings provide evidence for clinicians to draw on when deciding which shorter regimen to prescribe for tuberculosis preventive treatment. The proportion completing therapy was higher with 3HP, which was administered under directly observed therapy in the clinical trials included in our analysis. The higher risk of serious adverse events associated with 3HP is of importance as safety is paramount for preventive treatments and must be considered in deciding between regimens. The trade-off between treatment completion and risk of adverse events needs to be considered when choosing tuberculosis preventive treatment. Although ideally these findings would be confirmed in RCTs directly comparing 3HP with 4R, such trials would be expensive and time consuming. Evidence from this study might assist clinicians in deciding optimal treatment, which will help to improve efforts to reduce the global burden of tuberculosis disease.

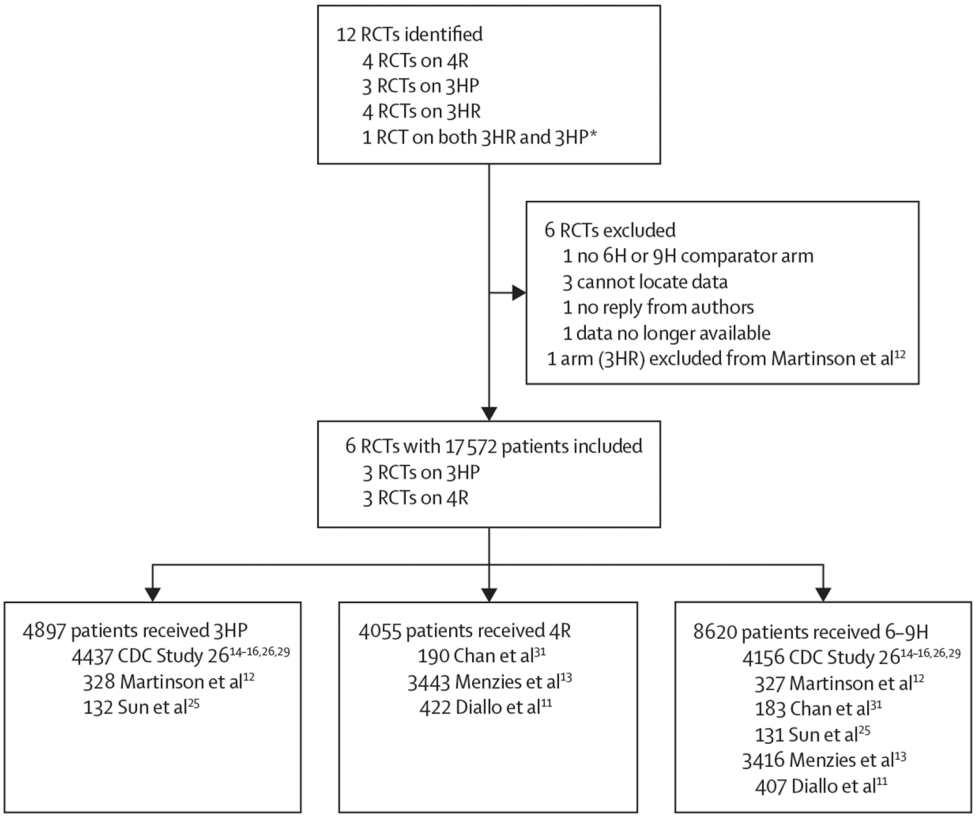

Figure: Study profile

3HP=3 months of rifapentine plus isoniazid. 3HR=3 months of rifampicin plus isoniazid. 4R=4 months of rifampicin. 6–9H=6 to 9 months of isoniazid. RCT=randomised controlled trial. *Martinson et al[12] had both a 3HP and a 3HR arm.

Table 1:

Baseline characteristics of the participants included in the individual patient dataset by treatment received

	3HP (n=4897)	4R (n=4055)	6–9H (n=8620)	Overall (N=17 572)
Sex				
Female	2298 (46·9%)	2224 (54·8%)	4413 (51·2%)	8935 (50·8%)
Male	2598 (53·1%)	1831 (45·2%)	4207 (48·8%)	8636 (49·1%)
NA	1	0	0	1
Age, years	34·8 (15·4)	35·2 (15·7)	34·9 (15·3)	34·9 (15·4)
BMI, kg/m^2	26·7 (6·5)	23·8 (5·5)	25·4 (6·5)	25·4 (6·4)
Diabetes				
No	459 (9·4%)	3937 (97·1%)	4349 (50·5%)	8745 (49·8%)
Yes	1	118 (2·9%)	115 (1·3%)	234 (1·3%)
NA	4437 (90·6%)	0	4156 (48·2%)	8593 (48·9%)
Renal failure				
No	459 (9·4%)	3592 (88·6%)	4010 (46·5%)	8061 (45·9%)
Yes	1	43 (1·1%)	27	71
NA	4437 (90·6%)	420 (10·4%)	4583 (53·2%)	9440 (53·7%)
Contact of active tuberculosis case				
No	1033 (21·1%)	190 (4·7%)	1242 (14·4%)	2465 (14·0%)
Yes	3595 (73·4%)	3865 (95·3%)	7111 (82·5%)	14571 (82·9%)
NA	269 (5·5%)	0	267 (3·1%)	536 (3·1%)
Type of contact with active tuberculosis case				
Not a contact	1033 (21·1%)	190 (4·7%)	1242 (14·4%)	2465 (14·0%)
Casual	0	402 (9·9%)	358 (4·2%)	760 (4·3%)
Close	3518 (71·8%)	2649 (65·3%)	5891 (68·3%)	12 058 (68·6%)
NA	346 (7·1%)	814 (20·1%)	1129 (13·1%)	2289 (13·0%)
Recent converter				
No	2907 (59·4%)	3300 (81·4%)	5936 (68·9%)	12 143 (69·1%)
Yes	1266 (25·9%)	145 (3·6%)	1362 (15·8%)	2773 (15·8%)
NA	724 (14·8%)	610 (15·0%)	1322 (15·3%)	2656 (15·1%)
Biologic use				
No	132 (2·7%)	3129 (77·2%)	3212 (37·3%)	6473 (36·8%)
Yes	0	34 (0·8%)	36	70
NA	4765 (97·3%)	892 (22·0%)	5372 (62·3%)	11 029 (62·8%)
Immune suppression				
No	459 (9·4%)	3809 (93·9%)	4232 (49·1%)	8500 (48·4%)
Yes	1	246 (6·1%)	232 (2·7%)	479 (2·7%)
NA	4437 (90·6%)	0	4156 (48·2%)	8593 (48·9%)
HIV infection				
Negative	2204 (45·0%)	3923 (96·7%)	6063 (70·3%)	12 190 (69·4%)
Positive	510 (10·4%)	132 (3·3%)	629 (7·3%)	1271 (7·2%)
HIV status unknown	2183 (44·6%)	0	1928 (22·4%)	4111 (23·4%)

	3HP (n=4897)	4R (n=4055)	6–9H (n=8620)	Overall (N=17 572)
HIV-positive on antiretroviral therapy	7 (1·4%)	65 (49·2%)	76 (12·1%)	148 (11·6%)
Smoking status				
Never	3365 (68·7%)	2895 (71·4%)	6030 (70·0%)	12 290 (69·9%)
Current	1184 (24·2%)	509 (12·6%)	1601 (18·6%)	3294 (18·7%)
Ever	345 (7·0%)	284 (7·0%)	624 (7·2%)	1253 (7·1%)
NA	3	367 (9·1%)	365 (4·2%)	735 (4·2%)
Alcohol use				
Never	2381 (48·6%)	128 (3·2%)	2278 (26·4%)	4787 (27·2%)
Current	81 (1·7%)	128 (3·2%)	230 (2·7%)	439 (2·5%)
Ever	2050 (41·9%)	8	2014 (23·4%)	4072 (23·2%)
NA	385 (7·9%)	3791 (93·5%)	4098 (47·5%)	8274 (47·1%)
Recreational drug use				
No	4731 (96·6%)	3387 (83·5%)	7809 (90·6%)	15 927 (90·6%)
Yes	157 (3·2%)	57 (1·4%)	198 (2·3%)	412 (2·3%)
NA	9	611 (15·1%)	613 (7·1%)	1233 (7·0%)
TST performed	4632 (94·6%)	4010 (98·9%)	8316 (96·5%)	16 958 (96·5%)
IGRA performed	132 (2·7%)	481 (11·9%)	594 (6·9%)	1207 (6·9%)
Chest x-ray result at baseline				
Normal	4310 (88·0%)	3195 (78·8%)	7230 (83·9%)	14 735 (83·9%)
Abnormal	253 (5·2%)	395 (9·7%)	620 (7·2%)	1268 (7·2%)
Abnormal not tuberculosis	0	306 (7·5%)	300 (3·5%)	606 (3·4%)
NA	334 (6·8%)	159 (3·9%)	470 (5·5%)	963 (5·5%)

Data are n (%) or mean (SD). 3HP=3 months of rifapentine plus isoniazid. 4R=4 months of rifampicin. 6–9H=6 to 9 months of isoniazid. NA=not available. TST=tuberculin skin test. IGRA=interferon-gamma release assay. Close contact defined as 4 h or longer per week of contact with a confirmed active tuberculosis case.

Table 2:

Adjusted risk ratios and risk differences for the comparison of treatment completion between 3HP and 4R

	Completing intervention (3HP or 4R)	Completing comparator (6–9H)	Adjusted risk ratio (95% CI)*	Adjusted risk difference (95% CI)*
3HP *vs* 6–9H, direct individual patient data meta-analysis				
CDC Study 26[14-16,26,29]	3545/4437 (79·9%)	2609/4156 (62·8%)	··	··
Martinson et al[12]	300/328 (91·5%)	143/327 (43·7%)	··	··
Sun et al[25]	118/132 (89·4%)	104/131 (79·4%)	··	··
Total	3963/4897 (80·9%)	2856/4614 (61·9%)	1·30 (1·24–1·37)	0·19 (0·17–0·21)
4R *vs* 6–9H, direct individual patient data meta-analysis				
Menzies et al[13]	2476/3443 (71·9%)	1965/3416 (57·5%)	··	··
Diallo et al[11]	352/422 (83·4%)	305/407 (74·9%)	··	··
Total	2828/3865 (73·2%)	2270/3823 (59·4%)	1·23 (1·17–1·30)	0·14 (0·12–0·16)
3HP *vs* 4R, individual patient data network meta-analysis				
All studies	··	··	1·06 (1·02–1·10)†	0·05 (0·02–0·07)†
9H only‡	··	··	1·02 (0·98–1·07)†	0·03 (0·00–0·06)†

Data are n/N (%), unless otherwise specified. 3HP=3 months of rifapentine plus isoniazid. 4R=4 months of rifampicin. 6–9H=6 to 9 months of isoniazid. *Risk ratios and risk differences adjusted for age, sex, BMI category, diabetes, smoking status, HIV infection, and alcohol use. Note: cannot adjust for contact or close contact, recreational drug use, or use of antiretroviral therapy. †CIs estimated with bootstrap resampling methods on 1000 replications and calculated using the 2·5th and 97·5th percentiles of the sampling distribution. Treatment completion defined as taking >80% of prescribed doses in 120% of the allowed time. ‡Study by Martinson and colleagues[12] removed (only study with 6H arm); no study with 6H arm included for 4R comparison of treatment completion.

Table 3:

Adjusted risk ratios and risk differences for the comparison of the incidence of treatment-related adverse events that led to permanent drug discontinuation between 3HP and 4R in the safety population

	Intervention (3HP or 4R)	Comparator (6–9H)	Adjusted risk ratio (95% CI)*	Adjusted risk difference (95% CI)*
Any treatment-related adverse event that led to permanent drug discontinuation†				
3HP *vs* 6–9H, direct individual patient data meta-analysis				
CDC Study 26[14-16,26,29]	247/4343 (5·7%)	170/4066 (4·2%)	..	..
Martinson et al[12]	0/328	2/326 (0·6%)	..	..
Sun et al[25]	12/132 (9·1%)	7/131 (5·3%)	..	..
Total	259/4803 (5·4%)	179/4523 (4·0%)	1·37 (1·13 to 1·66)	0·01 (0·01 to 0·02)
4R *vs* 6–9H, direct individual patient data meta-analysis				
Chan et al[31]	2/190 (1·1%)	13/183 (7·1%)	..	..
Menzies et al[13]	68/3281 (2·1%)	131/3231 (4·1%)	..	..
Diallo et al[11]	0/420	0/397	..	..
Total	70/3891 (1·8%)	144/3811 (3·8%)	0·48 (0·36 to 0·63)	−0·02 (−0·03 to −0·01)
3HP *vs* 4R, individual patient data network meta-analysis				
All studies	..	..	2·86 (2·12 to 4·21)‡	0·03 (0·02 to 0·05)‡
Treatment-related grade 3 or 4 adverse events that led to permanent drug discontinuation†				
3HP *vs* 6–9H, direct individual patient data meta-analysis				
CDC Study 26[14-16,26,29]	104/4343 (2·4%)	75/4066 (1·8%)	..	..
Martinson et al[12]	0/328	2/326 (1%)	..	..
Sun et al[25]	2/132 (1·5%)	4/131 (3·1%)	..	..
Total	106/4803 (2·2%)	81/4523 (1·8%)	1·24 (0·93 to 1·66)	0·00 (0·00 to 0·01)
4R *vs* 6–9H, direct individual patient data meta-analysis				
Chan et al[31]	2/190 (1·1%)	13/183 (7·1%)	..	..
Menzies et al[13]	29/3281 (0·9%)	72/3231 (2·2%)	..	..
Diallo et al[11]	0/420	0/397	..	..
Total	31/3891 (0·8%)	85/3811 (2·2%)	0·36 (0·24 to 0·54)	−0·01 (−0·02 to −0·01)
3HP *vs* 4R, individual patient data network meta-analysis				
All studies	..	..	3·46 (2·09 to 6·17)‡	0·02 (0·01 to 0·03)‡

Data are n events/N individuals (%), unless otherwise specified. 3HP=3 months of rifapentine plus isoniazid. 4R=4 months of rifampicin. 6–9H=6 to 9 months of isoniazid. *Risk ratios and risk differences adjusted for age, sex, BMI category, and HIV infection. †Judged to be possibly, probably, or definitely related to study drug in primary studies with harmonisation conducted for meta-analysis. ‡CIs estimated with bootstrap resampling methods on 1000 replications and calculated using the 2·5th and 97’5th percentiles of the sampling distribution.

Table 4:

Adjusted incidence rate ratios and incidence rate differences for the comparison of incidence rate of active tuberculosis between 3HP and 4R

	Intervention			Comparator			Adjusted incidence rate ratio (95% CI)*	Adjusted incidence rate difference per 1000 (95% CI)*
	N	Tuberculosis events per person-years	Rate per 1000 person-years	N	Tuberculosis events per person-years	Rate per 1000 person-years		
3HP *vs* 6–9H, direct individual patient data meta-analysis								
CDC Study 26[14-16,26,29]	4437	14/11 326	1	4156	22/10 511	2	..	..
Martinson et al[12]	328	28/1167	24	327	24/1129	21	..	..
Sun et al[25]†	132	0/289	0	131	0/344	0	..	..
Total	4897	42/12 782	3	4614	46/11 984	4	0·84 (0·54 to 1·25)	−0·1 (−0·4 to 0·2)
4R *vs* 9H, direct individual patient data meta-analysis								
Menzies et al[13]	3443	8/7986	1	3416	9/7908	1	..	..
Diallo et al[11]	422	0/546	0	407	2/523	4	..	..
Total	3865	8/8532	1	3823	11/8431	1	0·72 (0·29 to 1·79)	−0·9 (−3·9 to 2·0)
3HP *vs* 4R, individual patient data network meta-analysis								
All studies	..	..	..	..	..	..	1·16 (0·40 to 3·58)‡	0·8 (−2·3 to 7·0)‡

3HP=3 months of rifapentine plus isoniazid. 4R=4 months of rifampicin. 6–9H=6 to 9 months of isoniazid. TST=tuberculin skin test. *Incidence rate ratios and differences adjusted for age, sex, BMI category, HIV infection, and TST size category. †Incidence of tuberculosis not reported in publication, but additional data provided by study authors. ‡CIs estimated with bootstrap resampling methods on 1000 replications and calculated using the 2·5th and 97·5th percentiles of the sampling distribution.