NEJM Evidence

Published August 22, 2023
NEJM Evid 2023; 2 (9)
DOI: 10.1056/EVIDoa2300054

ORIGINAL ARTICLE

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

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Abstract

BACKGROUND Shorter but effective tuberculosis treatment regimens would be of value to the tuberculosis treatment community. High-dose rifampicin has been associated with more rapid and secure lung sterilization and may enable shorter tuberculosis treatment regimens.

METHODS We randomly assigned adults who were given a diagnosis of rifampicin-susceptible pulmonary tuberculosis to a 6-month control regimen, a similar 4-month regimen of rifampicin at 1200 mg/d (study regimen 1 [SR1]), or a 4-month regimen of rifampicin at 1800 mg/d (study regimen 2 [SR2]). Sputum specimens were collected at regular intervals. The primary end point was a composite of treatment failure and relapse in participants who were sputum smear positive at baseline. The noninferiority margin was 8 percentage points. Using a sequence of ordered hypotheses, noninferiority of SR2 was tested first.

RESULTS Between January 2017 and December 2020, 672 patients were enrolled in six countries, including 191 in the control group, 192 in the SR1 group, and 195 in the SR2 group. Noninferiority was not shown. Favorable responses rates were 93, 90, and 87% in the control, SR1, and SR2 groups, respectively, for a country-adjusted absolute risk difference of 6.3 percentage points (90% confidence interval, 1.1 to 11.5) comparing SR2 with the control group. The proportions of participants experiencing a grade 3 or 4 adverse event were 4.0, 4.5, and 4.4% in the control, SR1, and SR2 groups, respectively.

A complete list of investigators in the RIFASHORT Study Group is provided in the Supplementary Appendix, available at evidence.nejm.org.

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CONCLUSIONS Four-month high-dose rifampicin regimens did not have dose-limiting toxicities or side effects but failed to meet noninferiority criteria compared with the standard 6-month control regimen for treatment of pulmonary tuberculosis. (Funded by the MRC/Wellcome Trust/DFID Joint Global Health Trials Scheme; ClinicalTrials.gov number, NCT02581527.)

Introduction

Worldwide, an estimated 10 million people develop tuberculosis each year, and 1.4 million die of the disease.[1] The fact that a cure is not always achieved in routine treatment may, in part, be because of patients not adhering to the current 6-month regimen recommended by the World Health Organization. Reducing treatment to 4 months may improve adherence and increase treatment completion and cure rates. In addition, reducing the duration of treatment may lessen the inconvenience and economic costs of treatment for patients.[2]

Rifampicin is the cornerstone of current therapy because of its ability to kill not only the *Mycobacterium tuberculosis* (MTB) undergoing rapid metabolism but also the persistent mycobacteria believed to be responsible for most relapses.[3] The current standard dose of rifampicin (10 mg/kg) is the minimally effective dose historically selected on the basis of pharmacokinetic variables, toxicity concerns, and cost considerations.[4] However, subsequent animal model studies have shown that high-dose rifampicin leads to more rapid sterilization and in particular, a dose-dependent eradication of persistent mycobacteria,[5] allowing for shorter treatment duration without relapse.[5-9] Furthermore, randomized, controlled trials in patients receiving higher doses of rifampicin (15 to 35 mg/kg) have indicated higher culture conversion rates with no increase in serious adverse events.[10-18]

Rifapentine has also been evaluated for the treatment of pulmonary tuberculosis. In a recent trial conducted by the Centers for Disease Control and Prevention Tuberculosis Trials Consortium (TBTC) and the National Institutes of Health acquired immunodeficiency syndrome (AIDS) Clinical Trials Group (TBTC Study 31/A5349), a 4-month regimen containing daily rifapentine (at 1200 mg) and moxifloxacin met noninferiority criteria, with outcomes comparable with those of the standard 6-month regimen.[19] However, rifampicin has some significant advantages over rifapentine, including lower protein binding and better distribution into cavitary contents.[20] Furthermore, rifampicin is inexpensive, universally available, and used by national programs, suggesting that few barriers would exist to implementation if a 4-month rifampicin-based regimen proved effective.

Thus, the objective of the Randomised Trial to Evaluate Toxicity and Efficacy of 1200 mg and 1800 mg Rifampicin for Pulmonary Tuberculosis (RIFASHORT) was to evaluate the efficacy and safety of a higher dose of rifampicin at either 1200 or 1800 mg/d. The goal was to accumulate evidence supporting its use for more rapid and secure sterilization of the lungs and a reduction in treatment duration to 4 months.

Methods

TRIAL OVERSIGHT

This open-label, phase 3, randomized, controlled, noninferiority trial was performed within the framework of International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis. The trial was sponsored and implemented by St. George's, University of London, with statistical analysis by the London School of Hygiene and Tropical Medicine in collaboration with institutions in sub-Saharan Africa, South America, and South Asia. The trial protocol (Supplementary Protocol) was approved by the London School of Hygiene and Tropical Medicine Research Ethics Committee, as well as institutional and national ethics and regulatory authorities representing all participating sites and countries. Written informed consent was obtained from participants. An independent data monitoring committee oversaw the trial. The trial funder, suppliers, and drug manufacturers had no role in the trial design, data collection, analysis, interpretation, or manuscript presentation.

PARTICIPANTS

Participants were recruited from three African sites (University of Botswana, Gaborone, Botswana; Epicentre, Mbarara, Uganda; and Hospital National Ignace Deen, Conakry, Guinea); two sites in South Asia (German Nepal TB Project/Nepal Anti TB Association, Kathmandu, Nepal

and Aga Khan University Hospital, Karachi, Pakistan); and one site in South America (Hospital Nacional Dos de Mayo, Lima, Peru).

Eligible participants were those given a new diagnosis (by using sputum Xpert MTB/RIF nucleic acid amplification assay) of drug-susceptible pulmonary tuberculosis, who were 18 years or older, and who had undergone no more than 1 week of treatment. Human immunodeficiency virus (HIV)–positive individuals, those with preexisting liver disease (i.e., alanine transaminase level greater than five times the upper limit of normal), those with creatinine clearance levels of less than 30 ml/min, and those with diabetes mellitus were ineligible to participate.

Participants were excluded from efficacy analyses after randomization if they were found to have drug resistance to rifampicin and/or isoniazid (according to GenoType MTBDR line probe assays [Hain Lifescience] or direct susceptibility testing). Complete eligibility criteria are provided in the trial protocol.

RANDOMIZATION AND TREATMENT

Participants were randomly assigned in a 1:1:1 ratio, stratified according to site, to one of three regimens: the control regimen, study regimen 1 (SR1), and study regimen 2 (SR2). A randomized allocation sequence was generated for each trial center using blocks of varying size. Sealed opaque envelopes containing the treatment allocation slips were held by the pharmacist or nurse at each site. Staff at St. George's and participating laboratories were unaware of treatment assignment throughout the trial.

The control regimen was the World Health Organization–recommended standard 6-month treatment for drug-susceptible pulmonary tuberculosis. This regimen consisted of daily rifampicin (10 mg/kg) and isoniazid, with ethambutol and pyrazinamide for the first 2 months. SR1 consisted of 4 months of rifampicin at a daily dose of 1200 mg and isoniazid, with ethambutol and pyrazinamide for 2 months; SR2 was identical to SR1 but with rifampicin at a daily dose of 1800 mg. Treatment was administered 7 days per week and was monitored as noted in the following section. Additional details are provided in the protocol and in the Supplementary Appendix.

TRIAL PROCEDURES

Participants were followed up for 18 months from randomization, apart from those recruited in the final 6 months of recruitment. In the final 6 months of recruitment, follow-up was decreased on a monthly basis until, in the final month, follow-up was for a minimum of 12 months to prolong the enrollment period of the trial.[21]

Participants were monitored and samples were collected according to the assessment schedule (Table S6 in the Supplementary Appendix). Blood samples were collected for biochemical analysis, including liver function tests every 2 weeks for the first 6 weeks and monthly thereafter until 1 month posttreatment. Sputum samples were collected monthly from 2 to 12 months and then at 15 and 18 months. Standard mycobacteriology procedures at all trial sites were performed according to trial guidelines (bacteriologic guidelines are in the Supplementary Protocol, available with this article at evidence.nejm.org), which included sputum Xpert MTB/RIF or Xpert MTB/RIF Ultra (when this became available at sites) nucleic acid amplification tests, smear microscopy, and mycobacterial cultures on solid media using Lowenstein–Jensen or Ogawa slants prepared or commercially sourced according to the site's usual practice. Drug susceptibility testing was performed for isoniazid and rifampicin on *M. tuberculosis* isolates at baseline and on any positive cultures after week 8. For patients in whom tuberculosis recurred, all positive cultures were shipped to St. George's, where cultures were regrown and DNA was extracted. Whole-genome sequencing was performed to distinguish between relapse and a reinfection.[22] Exogenous reinfection was identified if the number of single-nucleotide polymorphism differences between pretreatment and posttreatment isolates was greater than 100.

Adherence to trial medication was monitored through directly observed therapy supervised in the clinic and at home by a domiciliary treatment monitor. A time allowance was in place for making up missed doses within 2 weeks of completing the intensive phase of treatment and within 4 weeks of completing the continuation phase. In addition, an allowance was made for treatment extension for participants following the hepatotoxicity drug reintroduction schedule in the protocol. In such cases, the end point review committee determined whether adequate treatment had been taken. Details of the definition of adequate treatment are reported in the statistical analysis plan (Supplementary Protocol).

Baseline chest radiography images were read centrally and categorized on the basis of the extent of disease and cavitation (Supplementary Appendix) by an independent

expert at St. George's Hospital who was blinded to the allocated treatment.

ANALYSIS POPULATIONS

The primary efficacy analysis followed the modified intention-to-treat (mITT) principle common in trials of tuberculosis therapy, whereby late exclusions because of drug resistance are removed from the analysis set. The primary analysis set included all participants who were microscopy positive, defined as positive on culture and sputum smear at baseline (mITT-M). Given the increasing use of Xpert MTB/RIF nucleic acid amplification assays for the diagnosis of tuberculosis, we also recruited participants who were Xpert MTB/RIF positive but microscopy smear negative, and to increase the generalizability of the findings, we defined a secondary analysis population including all participants who were Xpert MTB/RIF positive (mITT-All). Two further per-protocol (PP) secondary analysis sets were defined (PP-M and PP-All). The PP analysis sets differ from mITT in that any participant who did not complete an adequate course of treatment because of loss to follow-up or withdrawal was considered unassessable. Safety was assessed in all randomized participants receiving at least one dose of treatment. Full details of the analysis populations are given in the statistical analysis plan (Supplementary Protocol).

PRIMARY OUTCOME

The primary efficacy outcome was the proportion of patients who were baseline sputum smear positive with an unfavorable composite outcome measured by the end of follow-up. This period was 18 months for the majority of participants (83.6%), between 12 and 18 months for 14.3%, and a minimum of 12 months for 2.1%. Unfavorable outcomes were defined as any of the following: death during the treatment phase or posttreatment death in which tuberculosis was considered a plausible cause by the end point review committee; loss to follow-up during the treatment phase; participant withdrawal during treatment; permanent change in treatment because of an adverse event; two consecutive positive findings on culture after completing treatment; or retreatment. Participants attending the final trial visit having maintained culture-negative status, not otherwise classified as unfavorable, were classified as having a favorable outcome. Participants who were lost to follow-up or withdrew from the trial while culture negative, those who died after completing treatment with no plausible link to tuberculosis, and those with evidence of exogenous reinfection were classified as unassessable. These definitions are consistent with those used in prior trials.[23,24] Full details are given in the protocol and statistical analysis plan (Supplementary Protocol).

The primary safety outcome was the proportion of patients who experienced a grade 3 or 4 adverse event (defined by using the Division of AIDS 2017 Adverse Event grading criteria) up to 1 month after treatment completion. On-site and remote laboratory monitoring ensured completeness of reporting.

SECONDARY OUTCOMES

Secondary outcomes included PP analysis of the primary efficacy outcome (PP-M), primary efficacy outcome in the inclusive trial populations (mITT-All and PP-All), and time-to-event analyses of the primary efficacy outcome (mITT-M and PP-M); sputum culture conversion status at 8 and 12 weeks from randomization and time to culture conversion (mITT-M and PP-M); and the proportion of participants who experienced an adverse event of any grade (safety).

SUBGROUP ANALYSIS

We also prespecified a subgroup analysis of the primary outcome among participants with and without cavitation on chest radiography at baseline, according to baseline sputum smear grade, and according to baseline quantitative Xpert/MTB line probe assay. Subgroup analysis on the basis of the quantitative Xpert/MTB cycle threshold (C_T) excluded those with the lowest 10% of C_T values (indicating those with the highest organism load). This was a pragmatic decision on the basis of the distribution of C_T values, with the aim of identifying a subgroup that excluded only a minority of the population. Full details are available in the statistical analysis plan (Supplementary Protocol).

STATISTICAL ANALYSIS

Assuming a proportion of participants with an unfavorable outcome in the control regimen of 7% and that up to 20% of participants who were randomly assigned might be late exclusions or unassessable because of drug resistance or loss to follow-up, we calculated that a sample size of 654 patients who were microscopy smear positive, Xpert MTB/RIF positive, and rifampicin susceptible (218 per group) would provide a minimum of 525 evaluable participants; this would give 90% power to test the hypothesis that SR2 was noninferior to control, and it included a noninferiority margin of 8 percentage points and a one-sided significance level of 0.05. For the primary outcome, to

control the family-wise type I error rate, a fixed sequence of ordered hypotheses was used. Noninferiority of SR2 was tested first, with noninferiority of SR1 formally tested only if SR2 exhibited noninferiority to the control group. Because randomization was stratified according to trial site, all statistical analyses include adjustment for the site. Full details of the sample size parameters and justification of the margin of noninferiority are described in the statistical analysis plan (Supplementary Protocol).

Results

TRIAL POPULATION

Between January 2017 and December 2020, a total of 672 participants were randomly assigned to treatment across trial sites in Uganda (n=224), Guinea (n=175), Peru (n=119), Nepal (n=70), Botswana (n=54), and Pakistan (n=30). In total, 224, 223, and 225 participants were assigned to the control regimen, SR1, and SR2, respectively. All randomized participants received at least one dose of trial medication and the treatment to which they were allocated. Across groups, 12 participants assigned to the control group, 11 assigned to SR1, and 13 assigned to SR2 fulfilled the late exclusion criteria; 29 of these 36 were because of baseline drug resistance (Fig. 1). After removal of late exclusions, 212 participants were included in each trial group for the mITT-All population. Twenty-one participants assigned to the control group, 20 assigned to SR1, and 17 assigned to SR2 had no documented positive smear or culture result at baseline and were excluded from the primary mITT-M population. The mITT-M population included 191 participants in the control group (including 4 unassessable outcomes), 192 in SR1 (6 unassessable), and 195 in SR2 (9 unassessable).

Baseline characteristics of participants were similar in the three groups (the mITT-M population in Table 1 and Table S1, and the safety population in Table S2) and are broadly reflective of the global population with tuberculosis. A notable exception is that the trial population excluded participants with HIV and diabetes (Table S7).

Adherence to trial medication was consistent across groups; between 88 and 90% of participants were recorded as taking all doses of trial medication in each of the trial groups. Among participants who completed the trial with a favorable outcome, adherence was universally excellent, with more than 98% recorded as taking all doses in each trial group. Consequently, no such participants were excluded from the PP analysis because of not receiving adequate treatment.

PRIMARY OUTCOME

Comparing SR2 with the control group, noninferiority was not shown. In the primary mITT-M population, an unfavorable outcome occurred in 13.4% (n=25) of participants in SR2 and 7.0% (n=13) in the control group for an adjusted absolute risk difference of 6.3 percentage points (90% confidence interval [CI], 1.1 to 11.5; hypothesis test of noninferiority, P=0.30) (Figs. 2 and 3 and Table 2). According to the fixed sequence of ordered hypotheses, formal noninferiority testing of SR1 was not performed. An unfavorable outcome occurred in 10.2% (n=19) of participants in SR1 for an adjusted absolute risk difference of 3.1 percentage points (90% CI, –1.6 to 7.9) compared with the control group.

The reasons for unfavorable outcome are shown in Table 2. Eight more participants withdrew during the treatment phase or had a change of treatment because of adverse events in SR2 than in SR1 or the control group. SR1 and SR2 had the same number of culture-confirmed relapses, which was more than in the control group.

SECONDARY OUTCOMES

Results comparing SR2 and SR1 versus the control group in the secondary analysis populations of mITT-All and the PP populations PP-M and PP-All were similar to those seen in the primary outcome analysis (Fig. 2 and Table S3). The time from randomization to an unfavorable outcome is shown in Figure 3 for the primary analysis population (mITT-M) and in Figure S2 for the PP-M population. Week 8 culture conversion was 158 (85.9%) of 184, 166 (92.7%) of 179, and 164 (90.1%) of 182 for the control group, SR1, and SR2, respectively. Week 12 culture conversion was 182 (98.4%) of 185, 180 (97.8%) of 184, and 184 (98.4%) of 187 for the control group, SR1, and SR2 (Table 2).

SUBGROUP ANALYSIS

Prespecified subgroup analyses were performed for the primary analysis population (mITT-M). In subgroups excluding those with the most severe disease at baseline, the unfavorable outcome rates for SR1 were close to those of the control group. Specifically, excluding those with far

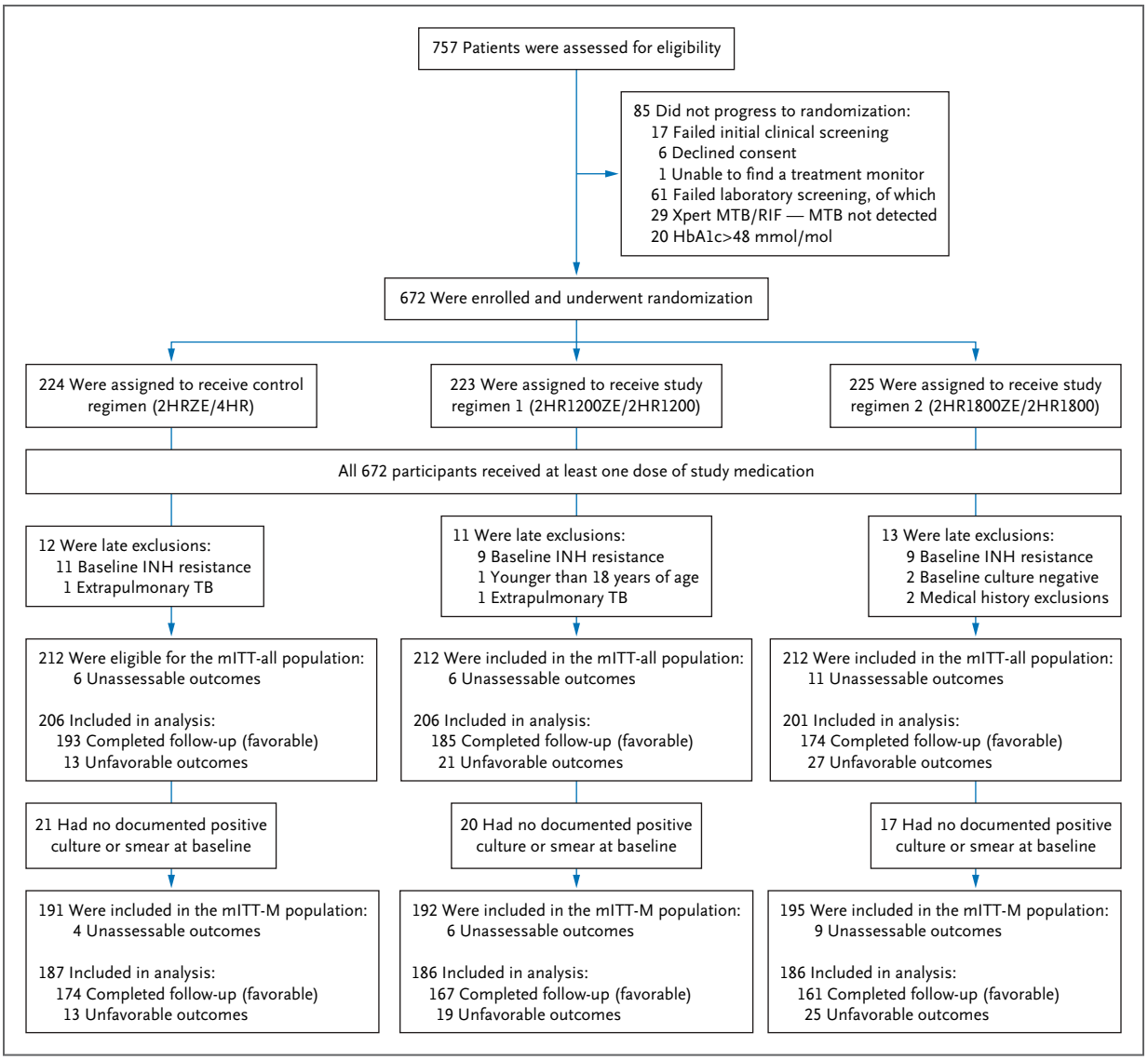

Figure 1. Screening, Randomization, and Analysis Populations (CONSORT).

Participants may have had more than one reason for exclusion. CONSORT denotes Consolidated Standards of Reporting Trials; E, ethambutol; H, isoniazid; HbA1c, glycosylated hemoglobin; INH, isoniazid; mITT, modified intention-to-treat; mITT-M, modified intention-to-treat microscopy positive; MTB, *Mycobacterium tuberculosis*; R, rifampicin; RIF, rifampicin; TB, tuberculosis; and Z, pyrazinamide.

advanced disease and cavitation on chest radiography, an unfavorable outcome occurred in 4.4% (4 of 91) of participants in SR1 and 4.5% (4 of 88) in the control group, giving an adjusted risk difference of –0.3 percentage points (90% CI, –5.4 to 4.9) (Fig. S4). Excluding the lowest 10th percentile on baseline semiquantitative Xpert C_T, an unfavorable outcome occurred in 8.9% (15 of 169) of participants in SR1 and 7.3% (12 of 165) in the control group, giving an adjusted risk difference of 1.6 percentage points (90% CI, –3.2 to 6.5). Results for those with far advanced disease on chest radiography are presented in Figure S5.

POST HOC ANALYSIS

In a post hoc analysis of the primary outcome adjusted for site, age, and baseline lung grading on chest radiograph, the comparison of SR2 and the control group produced an adjusted risk difference of 3.6 percentage points (90% CI,

Table 1. Baseline Characteristics of the Participants (Modified Intention-to-Treat Microscopy Positive Population).*			
Characteristic	**Control (n=191)**	**Study Regimen 1 (n=192)**	**Study Regimen 2 (n=195)**
Age, yr — median (IQR)	29.0 (23.0–38.0)	29.0 (22.0–36.0)	28.0 (23.0–43.0)
Age, yr — no. (%)			
18–24	57 (29.8)	64 (33.3)	72 (36.9)
25–34	73 (38.2)	69 (35.9)	53 (27.2)
>34	61 (31.9)	59 (30.7)	70 (35.9)
Weight, kg — median (IQR)	52.2 (47.0–57.7)	51.9 (46.8–58.1)	52.6 (48.0–58.0)
BMI — median (IQR)	18.4 (16.9–20.2)	18.6 (16.9–20.8)	18.8 (17.0–21.0)
Female sex — no. (%)	54 (28.3)	41 (21.4)	49 (25.1)
Ethnicity — no. (%)			
African	136 (71.2)	133 (69.3)	134 (68.7)
Hispanic	1 (0.5)	2 (1.0)	1 (0.5)
Mixed	32 (16.8)	34 (17.7)	36 (18.5)
Indigenous (South American)	1 (0.5)	1 (0.5)	0 (0.0)
Asian	21 (11.0)	22 (11.5)	24 (12.3)
Smoking status — no. (%)			
Current	47 (24.6)	33 (17.2)	36 (18.5)
Former	15 (7.9)	15 (7.8)	17 (8.7)
Never	129 (67.5)	144 (75.0)	142 (72.8)
CXR cavitation — no. (%)			
Unreadable/unknown	0	1 (0.5)	1 (0.5)
Yes	165 (86.4)	174 (90.6)	174 (89.2)
No	26 (13.6)	17 (8.9)	20 (10.3)
CXR grading — no. (%)			
Unreadable/unknown	3 (1.6)	1 (0.5)	3 (1.5)
Normal or minimal disease	3 (1.6)	4 (2.1)	4 (2.1)
Moderately advanced disease	86 (45.0)	88 (45.8)	85 (43.6)
Far advanced disease	99 (51.8)	99 (51.6)	103 (52.8)
Sputum smear grading — no. (%)			
+ or scanty	68 (35.6)	77 (40.1)	81 (41.5)
++	52 (27.2)	41 (21.4)	49 (25.1)
+++	71 (37.2)	74 (38.5)	65 (33.3)

* The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. CXR denotes chest radiography; and IQR, interquartile range.

–1.7 to 9.0); the comparison of SR1 and the control group produced an adjusted risk difference of 3.0 percentage points (90% CI, –1.8 to 7.8) (Fig. S1).

SAFETY AND ADVERSE EVENTS

The proportions of participants experiencing a grade 3 or 4 adverse event were 4.0, 4.5, and 4.4% in the control group, SR1, and SR2, respectively (Table 3). There were three serious adverse events (1.3%) in each group. Five (2.2%) deaths occurred in total in the control group, eight (3.6%) occurred in SR1, and three (1.3%) occurred in SR2. Six posttreatment deaths were determined to be unrelated to tuberculosis or tuberculosis treatment by the independent end point review committee (two in the control group, one in SR1, and three in SR2). There were more cases of a grade 4 alanine transaminase rise or a grade 3 or 4 increase in bilirubin in SR2 than in SR1 or the control group, although the proportion of participants with such increases was low. Additional details of liver injury events are presented in Table S5. A complete list of adverse events leading to a change in allocated trial treatment is presented in Table S4.

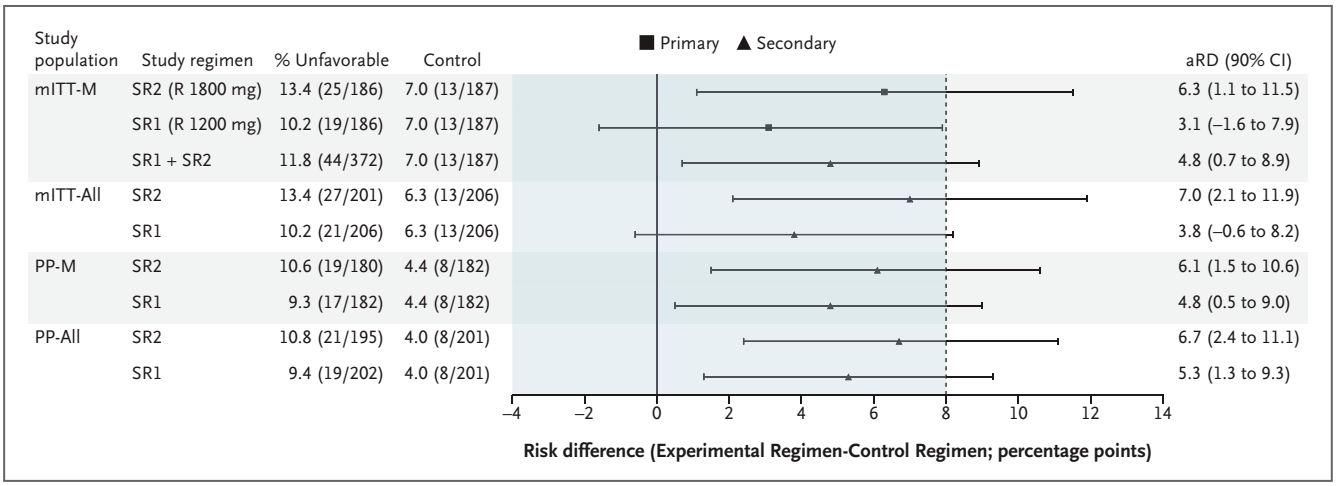

Figure 2. Differences from the Control Regimen in Unfavorable Outcome Rates (90% Confidence Intervals [CIs]).

Closed squares indicate primary outcome analyses, closed triangles indicate secondary outcome analyses, and the dashed vertical line indicates the prespecified 8 percentage point noninferiority margin. Formal testing of the noninferiority hypothesis for study regimen 2 (SR2) in the mITT-M population yields a P value of 0.30. aRD denotes adjusted risk difference; mITT, modified intention-to-treat; mITT-M, modified intention-to-treat microscopy positive; PP, per protocol; PP-M, per protocol microscopy positive; R, rifampicin; and SR1, study regimen 1.

Discussion

The trial did not identify a treatment regimen that was noninferior to the control regimen according to our predefined criteria. The primary outcome favorable response rates were 93, 90, and 87% in the control, SR1, and SR2 groups, respectively.

Although comparisons across trials should be made with caution, the response rates were generally higher and risk differences from the control group were generally lower

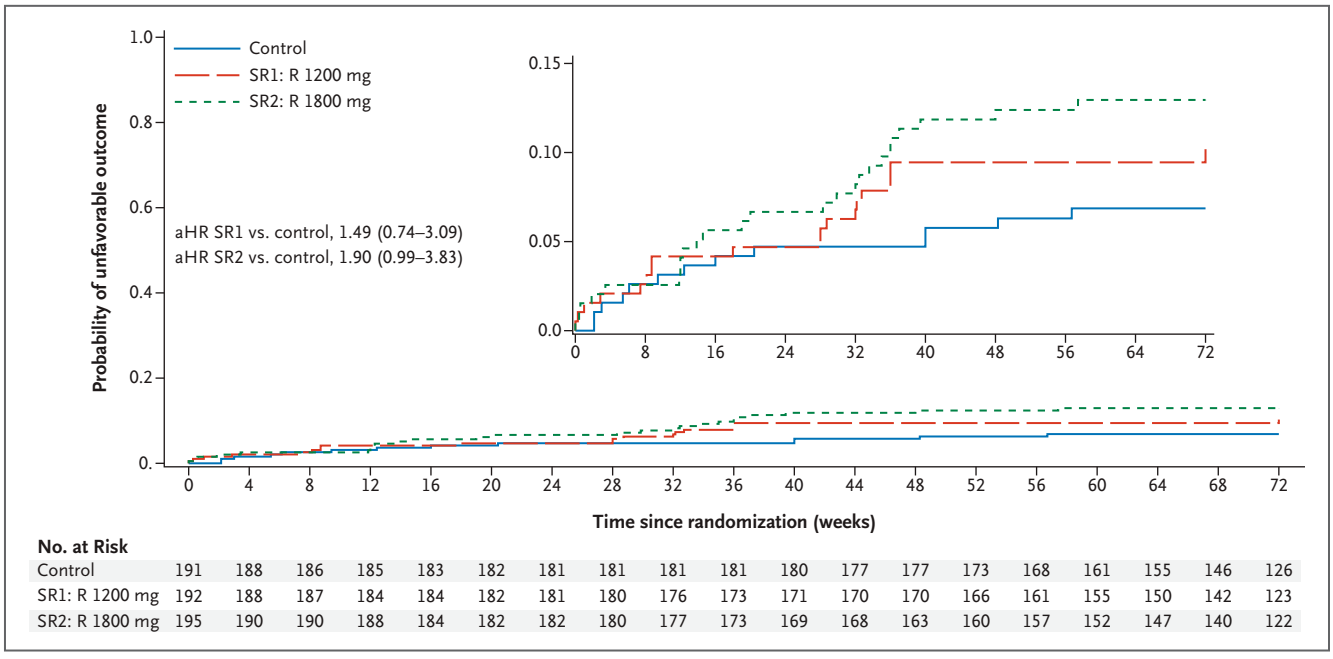

Figure 3. Kaplan–Meier Time to Unfavorable Outcome for the Primary mITT-M Population.

The inset shows the same data on an enlarged y axis. aHR denotes adjusted hazard ratio; mITT-M, modified intention-to-treat microscopy positive; R, rifampicin; SR1, study regimen 1; and SR2, study regimen 2.

Table 2. Primary and Key Secondary Outcome Analyses.*

mITT-M Primary Analysis Assessable Outcomes	Control (n=187)	Study Regimen 1 (n=186)	Study Regimen 2 (n=186)
Favorable			
Participants with outcome — no. (%)	174 (93.0)	167 (89.8)	161 (86.6)
Unfavorable			
Participants with outcome — no. (%)	13 (7.0)	19 (10.2)	25 (13.4)
Adjusted percentage point difference from control (90% CI)		3.1 (–1.6 to 7.9)	6.3 (1.1 to 11.5)
Reasons for unfavorable outcome			
Death during the treatment phase	3 (1.6)	4 (2.2)	0
Posttreatment death, TB a plausible cause	0	1 (0.5)	0
Lost to follow-up during the treatment phase	2 (1.1)	0	1 (0.5)
Withdrew from the trial during the treatment phase†	3 (1.6)	2 (1.1)	5 (2.7)
Change in treatment because of adverse event‡	1 (0.5)	2 (1.1)	7 (3.8)
Two consecutive positive cultures after completing treatment	2 (1.1)	9 (4.8)	9 (4.8)
Retreated for TB because of clinical signs and symptoms without 2 consecutive positive cultures	2 (1.1)	1 (0.5)	3 (1.6)
Unassessable outcomes	4	6	9
Posttreatment death deemed unrelated to TB or treatment	2	1	2
Posttreatment LTFU when culture negative	1	3	5
Evidence of exogenous TB reinfection	0	1	2
Withdrawal during the treatment phase when culture negative	1	0	0
Posttreatment withdrawal when culture negative	0	1	0
Secondary analysis outcomes			
Confirmed culture conversion from positive to negative — n/N (%)			
8 weeks from randomization	158/184 (85.9)	166/179 (92.7)	164/182 (90.1)
12 weeks from randomization	182/185 (98.4)	180/184 (97.8)	184/187 (98.4)

* CI denotes confidence interval; LTFU, lost to follow-up; mITT-M, modified intention-to-treat microscopy positive; and TB, tuberculosis.

† Reasons for withdrawal during the treatment phase are as follows: control, three moved home address; study regimen 1, one unhappy with the allocated regimen and one moved home address; study regimen 2, two concerned about high-dose treatment, one unhappy with the allocated regimen, one concerned about high-dose treatment exacerbating a preexisting medical condition, and one moved home address.

‡ All changes in treatment because of adverse events involved high liver transaminase levels or jaundice, except for one patient in study regimen 1, whose changes in treatment were because of depression. These events are described in Table S4.

than seen in previously tested 4-month regimens in the RIFAQUIN (high-dose rifapentine with moxifloxacin for pulmonary tuberculosis), REMox (four-month moxifloxacin-based regimens for drug-sensitive tuberculosis), and OFLOTUB (a four-month gatifloxacin-containing regimen for treating tuberculosis) trials.[23-25] Notably, our results (Fig. 2 and Fig. S1) are similar to the results seen in the 4-month high-dose rifapentine (without moxifloxacin) group in the recent TBTC Study 31/A5349 trial,[19] with the assessable population results for that group (percentage point difference from control, 4.6) representing a similar analytical approach to that used in the current trial. The data suggest that our trial participants had disease severity at least comparable with that in these other trials; cavitation was seen in 87% of participants in RIFASHORT, and it was seen in 73, 72, 65, and 51% of participants in the TBTC Study 31/A5349, REMOX, RIFAQUIN, and OFLOTUB trials, respectively. High-grade (3+) sputum smears were seen in 33% in RIFASHORT and 27% in TBTC Study 31/A5349.

In the current study, the 1200 mg/d rifampicin group was associated with marginally fewer hepatic adverse events than the 1800 mg/d rifampicin group. However, the rates of adverse events and hepatic events were less than 5%, and events were reversible, meaning that these data do not eliminate the clinical equipoise needed for the continued trial of rifampicin doses of 1800 mg/d and higher; such trials are ongoing in tuberculous meningitis and tuberculosis in advanced HIV disease.[26-28] The slight increase in hepatic events in the 1800 mg/d group may explain some of the apparent difference in efficacy between doses, with

Table 3. Laboratory-Defined and Clinical Adverse Events According to Treatment Group.*

Participants Experiencing	Control (n=224)	Study Regimen 1 (n=223)	Study Regimen 2 (n=225)
Primary safety outcome			
Grade 3 or 4 adverse event — no. (%)	9 (4.0)	10 (4.5)	10 (4.4)
Percentage point difference from control (95% CI)		0.5 (–3.3 to 4.2)	0.4 (–3.3 to 4.2)
Secondary safety outcome			
Grade 1–4 adverse event — no. (%)	120 (53.6)	109 (48.9)	115 (51.1)
Percentage point difference from control (95% CI)		–4.7 (–13.9 to 4.6)	–2.5 (–11.7 to 6.8)
Other safety outcomes — no. (%)			
Serious adverse event	3 (1.3)	3 (1.3)	3 (1.3)
Notifiable adverse event	10 (4.5)	13 (5.8)	13 (5.8)
Notifiable adverse event, excluding pregnancy	6 (2.7)	11 (4.9)	13 (5.8)
Death	5 (2.2)	8 (3.6)	3 (1.3)
Hepatotoxicity outcomes			
ALT>180 U/l (5×ULN, grade 3) — no. (%)	3 (1.3)	7 (3.1)	7 (3.1)
ALT>360 U/l (10×ULN, grade 4) — no. (%)	2 (0.9)	1 (0.4)	4 (1.8)
Grade 3/4 ALT results, U/l — median (IQR; max)	387 (237–511; 511)	212 (189–350; 449)	377 (332–450; 942)
Total bilirubin >3 mg/dl (2.6×ULN, grade 3) — no. (%)	1 (0.4)	1 (0.4)	6 (2.7)
Total bilirubin >6 mg/dl (5×ULN, grade 4) — no. (%)	1 (0.4)	0	3 (1.3)
Grade 3/4 total bilirubin results, mg/dl — median (IQR; max)	12.1	3.2	5.4 (4.1–9.4; 29.5)
Satisfies Hy's law (ALT>3×ULN and total bilirubin >2×ULN) — no. (%)	0	1 (0.4)	2† (0.9)

* ALT denotes alanine aminotransferase; CI, confidence interval; IQR, interquartile range; Max, maximum; and ULN, upper limit of normal.

† Two additional participants met the ALT and total bilirubin criteria for Hy's law; however, both were positive for hepatitis B surface antigen, meaning that Hy's law was not satisfied. These events are described in Table S5.

more unfavorable outcomes in the 1800 mg/d group resulting from treatment change because of adverse events and withdrawal during treatment. In analyses adjusted by factors known to be associated with outcome (site, age, lung grading, and sex), the risk difference results were more similar comparing the 1200 and 1800 mg doses, suggesting that some of the underperformance of the 1800 mg/d group and both experimental groups may be explained by small differences in baseline characteristics (Fig. S1). In addition, in those patients with advanced disease on chest radiography, results slightly favored the 1800 mg/d dose over the 1200 mg/d dose (Fig. S5).

In the 1200 and 1800 mg/d groups, culture-confirmed relapses were the same, and culture conversion was similar at 2 and 3 months. In both experimental groups, culture conversion was higher at 2 months than in the control group, and culture-confirmed relapse rates (4.8% in both the 1200 and 1800 mg groups) were less than the 12% seen in historical 4-month regimens using rifampicin at 10 mg/kg.[29] Of note, given a median weight of participants of 52 kg, 1800 mg/d was equivalent to 35 mg/kg/d or more for one half of all participants, a dosing level associated with more rapid bactericidal activity and culture conversion in prior clinical studies.[13,15]

In subgroup analyses excluding those with the most severe disease, results for the 1200 mg/d regimen were close to those for the control group, including among 90% of the trial population without the lowest Xpert C_T values at baseline. These data support a simple stratified approach to treatment. C_T is available wherever GeneXpert is used, and it could be used to identify the 10% of patients with the highest organism load for 6 months of therapy.

Limitations of the current trial include the fact that we did not include participants with HIV infection or diabetes. When the trial was designed, antiretroviral therapy frequently included efavirenz, and the degree of interaction between efavirenz and high-dose rifampicin was uncertain. With dolutegravir-based antiretroviral therapy, significant drug interaction is no longer an issue, and planned follow-up studies will include participants with HIV and diabetes to maximize generalizability. In addition, we did not collect individual-level rifampicin pharmacokinetic data. Analyses of the TBTC Study 31/A5349

trial showed the importance of individual-level rifapentine exposure.[19] We used solid media for sputum cultures, available across all trial sites, and where available, mycobacteria growth indicator tube cultures. Our trial was a pragmatic trial across low- and middle-income country settings, and pharmacokinetic assessments and creation of new mycobacterial growth indicator tube culture facilities were not possible with our resources. Finally, it is possible that some initial concerns regarding the higher dose may have prompted earlier treatment changes than would otherwise have occurred in participants on the higher dose; however, this seems to have been a possibility in only one case.

In conclusion, 4-month regimens including high-dose rifampicin were associated with few adverse events but did not meet noninferiority criteria. Efficacy results were closely in line with those of the high-dose rifapentine-alone group of TBTC Study 31/A5349. Ongoing studies are planned, incorporating moxifloxacin and simple stratification of treatment duration according to C_T.

Disclosures

Supported by a grant (MR/N006127/1) through the MRC/Wellcome Trust/DFID Joint Global Health Trials Scheme. This work was also funded by the Aga Khan Foundation.

Author disclosures and other supplementary materials are available at evidence.nejm.org.

We thank all trial participants, their families, and caregivers as well as the clinical, laboratory, and administrative staff at all the sites who were not directly involved in the trial; Gerry Davis, Andrew Nunn, and Payam Nahid for serving on the data and safety monitoring committee; and Peter Godfrey-Faussett, Alwin Mwinga, Patrick Phillips, and Andrew Vernon for serving on the trial steering committee.

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References

1. World Health Organization. Global Tuberculosis Report 2020. October 15, 2020 (https://www.who.int/publications/i/item/9789240013131).
2. Gomez GB, Dowdy DW, Bastos ML, et al. Cost and cost-effectiveness of tuberculosis treatment shortening: a model-based analysis. BMC Infect Dis 2016;16:726. DOI: 10.1186/s12879-016-2064-3.
3. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. Int J Tuberc Lung Dis 2000;4:796-806.
4. van Ingen J, Aarnoutse RE, Donald PR, et al. Why do we use 600 mg of rifampicin in tuberculosis treatment? Clin Infect Dis 2011;52:e194-e199. DOI: 10.1093/cid/cir184.
5. Liu Y, Pertinez H, Ortega-Muro F, et al. Optimal doses of rifampicin in the standard drug regimen to shorten tuberculosis treatment duration and reduce relapse by eradicating persistent bacteria. J Antimicrob Chemother 2018;73:724-731. DOI: 10.1093/jac/dkx467.
6. Jayaram R, Gaonkar S, Kaur P, et al. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. Antimicrob Agents Chemother 2003;47:2118-2124. DOI: 10.1128/AAC.47.7.2118-2124.2003.
7. Rosenthal IM, Tasneen R, Peloquin CA, et al. Dose-ranging comparison of rifampin and rifapentine in two pathologically distinct murine models of tuberculosis. Antimicrob Agents Chemother 2012;56:4331-4340. DOI: 10.1128/AAC.00912-12.
8. de Steenwinkel JEM, Aarnoutse RE, de Knegt GJ, et al. Optimization of the rifampin dosage to improve the therapeutic efficacy in tuberculosis treatment using a murine model. Am J Respir Crit Care Med 2013;187:1127-1134. DOI: 10.1164/rccm.201207-1210OC.
9. Hu Y, Liu A, Ortega-Muro F, Alameda-Martin L, Mitchison D, Coates A. High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rate in vitro and in vivo. Front Microbiol 2015;6:641. DOI: 10.3389/fmicb.2015.00641.
10. Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. Antimicrob Agents Chemother 2007;51:2994-2996. DOI: 10.1128/AAC.01474-06.
11. Ruslami R, Nijland HMJ, Alisjahbana B, Parwati I, van Crevel R, Aarnoutse RE. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. Antimicrob Agents Chemother 2007;51:2546-2551. DOI: 10.1128/AAC.01550-06.

12. 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;15:305-316.

13. Boeree MJ, Diacon AH, Dawson R, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med 2015;191:1058-1065. DOI: 10.1164/rccm.201407-1264OC.

14. Jindani A, Borgulya G, de Patiño IW, et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. Int J Tuberc Lung Dis 2016;20:832-838. DOI: 10.5588/ijtld.15.0577.

15. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. Lancet Infect Dis 2017;17:39-49. DOI: 10.1016/S1473-3099(16)30274-2.

16. Aarnoutse RE, Kibiki GS, Reither K, et al. Pharmacokinetics, tolerability, and bacteriological response of rifampin administered at 600, 900, and 1,200 milligrams daily in patients with pulmonary tuberculosis. Antimicrob Agents Chemother 2017;61:e01054-e17. DOI: 10.1128/AAC.01054-17.

17. Svensson EM, Svensson RJ, te Brake LHM, et al. The potential for treatment shortening with higher rifampicin doses: relating drug exposure to treatment response in patients with pulmonary tuberculosis. Clin Infect Dis 2018;67:34-41. DOI: 10.1093/cid/ciy026.

18. Velásquez GE, Brooks MB, Coit JM, et al. Efficacy and safety of high-dose rifampin in pulmonary tuberculosis. A randomized controlled trial. Am J Respir Crit Care Med 2018;198:657-666. DOI: 10.1164/rccm.201712-2524OC.

19. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med 2021;384:1705-1718. DOI: 10.1056/NEJMoa2033400.

20. Alfarisi O, Alghamdi WA, Al-Shaer MH, Dooley KE, Peloquin CA. Rifampin vs. rifapentine: what is the preferred rifamycin for tuberculosis? Expert Rev Clin Pharmacol 2017;10:1027-1036. DOI: 10.1080/17512433.2017.1366311.

21. Nunn AJ, Phillips PP, Mitchison DA. Timing of relapse in short-course chemotherapy trials for tuberculosis. Int J Tuberc Lung Dis 2010;14:241-242.

22. Witney AA, Bateson AL, Jindani A, et al. Use of whole-genome sequencing to distinguish relapse from reinfection in a completed tuberculosis clinical trial. BMC Med 2017;15:71. DOI: 10.1186/s12916-017-0834-4.

23. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med 2014;371:1599-1608. DOI: 10.1056/NEJMoa1314210.

24. Merle CSC, Sismanidis C, Sow OB, et al. A pivotal registration phase III, multicenter, randomized tuberculosis controlled trial: design issues and lessons learnt from the Gatifloxacin for TB (OFLOTUB) project. Trials 2012;13:61. DOI: 10.1186/1745-6215-13-61.

25. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 2014;371:1577-1587. DOI: 10.1056/NEJMoa1407426.

26. ISRCTN Registry. HARVEST trial — improving outcomes from TB meningitis with high-dose oral rifampicin. June 23, 2022 (https://www.isrctn.com/ISRCTN15668391).

27. ClinicalTrials.gov. Testing new strategies for patients hospitalised with HIV-associated disseminated tuberculosis (NEW-STRAT TB). March 31, 2022 (https://clinicaltrials.gov/ct2/show/NCT04951986).

28. ClinicalTrials.gov. Intensified tuberculosis treatment to reduce the mortality of patients with tuberculous meningitis (INTENSE-TBM). August 2, 2023 (https://clinicaltrials.gov/ct2/show/NCT04145258?id=NCT04145258&draw=2&rank=1).

29. Fox W. Whither short-course chemotherapy? Br J Dis Chest 1981;75:331-357. DOI: 10.1016/0007-0971(81)90022-X.