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Safety and Efficacy of Rifampin or Isoniazid Among People With *Mycobacterium tuberculosis* Infection and Living With Human Immunodeficiency Virus or Other Health Conditions: Post Hoc Analysis of 2 Randomized Trials

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Background. The safety and efficacy of rifampin among people living with human immunodeficiency virus (PLHIV) or other health conditions is uncertain. We assessed completion, safety, and efficacy of 4 months of rifampin vs 9 months of isoniazid among PLHIV or other health conditions.

Methods. We conducted post hoc analysis of 2 randomized trials that included 6859 adult participants with *Mycobacterium tuberculosis* infection. Participants were randomized 1:1 to 10 mg/kg/d rifampin or 5 mg/kg/d isoniazid. We report completion, drug-related adverse events (AE), and active tuberculosis incidence among people living with HIV; with renal failure or receiving immunosuppressants; using drugs or with hepatitis; with diabetes mellitus; consuming >1 alcoholic drink per week or current/former smokers; and with no health condition.

Results. Overall, 270 (3.9%) people were living with HIV (135 receiving antiretroviral therapy), 2012 (29.3%) had another health condition, and 4577 (66.8%) had no condition. Rifampin was more often or similarly completed to isoniazid in all populations. AEs were less common with rifampin than isoniazid among PLHIV (risk difference, −2.1%; 95% confidence interval [CI], −5.9 to 1.6). This was consistent for others except people with renal failure or on immunosuppressants (2.1%; 95% CI, −7.2 to 11.3). Tuberculosis incidence was similar among people receiving rifampin or isoniazid. Among participants receiving rifampin living with HIV, incidence was comparable to those with no health condition (rate difference, 4.1 per 1000 person-years; 95% CI, −6.4 to 14.7).

Conclusions. Rifampin appears to be safe and as effective as isoniazid across many populations with health conditions, including HIV.

Clinical Trials Registration. NCT00170209; NCT00931736.

Keywords. tuberculosis; comorbidity; HIV; patient-centered care; rifampin.

Treatment of *Mycobacterium tuberculosis* infection is considered essential to eliminate tuberculosis (TB) [1]. The World Health Organization [2] and others [3–6] recommend TB preventive therapy (TPT) for individuals at increased risk for progression to TB. These include close contacts of persons with TB, people living with human immunodeficiency virus (PLHIV), and people with other concomitant health conditions (eg, renal failure or use of immunosuppressing medications, such as tumor necrosis factor-alpha [TNF-α] inhibitors).

Previously, individuals receiving TPT faced prolonged treatment with substantial toxicity involving 9 months of isoniazid (9INH). Presently, rifamycin-based regimens of 3–4 months have emerged as safer alternatives with noninferior efficacy [7]. Three months of once-weekly rifapentine and isoniazid, 3 months of daily isoniazid and rifampin, and 4 months of daily rifampin (4RIF) comprise the current options for rifamycin-based TPT. An updated network meta-analysis in the 2020 guidance from the US Centers for Disease Control and the National Tuberculosis Controllers Association suggests 4RIF is the most effective and safest rifamycin-based option for TPT in adults and children [8]. However, data on safety and efficacy of 4RIF among PLHIV and persons with other health conditions

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have not been reported. These data can support shared decision-making between providers and patients on the appropriateness of 4RIF-based TPT [9] and inform which side effects to be most aware of.

We conducted post hoc analysis of 2 randomized, controlled trials comparing 4RIF to 9INH in adults for completion, safety, and efficacy among PLHIV or with other concomitant health conditions.

METHODS

Design

The trial methods and protocol have been described previously [10–12]. Briefly, they were open-label, parallel, randomized, controlled trials that recruited participants from April 2004 to January 2007 (phase 2; NCT00170209) and October 2009 to December 2014 (phase 3; NCT00931736). Participants were recruited at 17 facilities in 9 countries: Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea. Eligible participants were aged ≥18 years with a positive tuberculin skin test or interferon-gamma release assay and an indication for TPT. Exclusion criteria included participants receiving medications that may interact with isoniazid or rifampin that the treating clinician felt they could not manage, allergy to isoniazid or rifampin, pregnancy, or contact with TB patients whose isolates were resistant to isoniazid and/or rifampin. The McGill University Health Centre Biomedical Clinical Research Ethics Board provided ethical approval for the trials; so too did each center's responsible ethics committee.

Procedures

Eligible participants were block randomized to receive 10 mg/kg (600 mg maximum) of daily rifampin for 4 months or 5 mg/kg (300 mg maximum) of daily isoniazid for 9 months. Participants from the same household were assigned the same regimen if they were randomized in the same week. Participants were assessed at randomization, then every month for the first 4 months and every 2 months thereafter, or more frequently if required. Blood tests for liver transaminases and complete blood counts were routinely done pretreatment and at 1 month, and thereafter as required. All participants were counseled prior to treatment on the importance of limiting alcohol consumption during treatment. Participants had their pills counted to assess adherence and were monitored for presence of active TB symptoms and adverse events at each visit and encouraged to report any symptoms between visits. Adverse events were ascertained through 30 days after treatment cessation; active TB was assessed through 28 months after treatment initiation (via phone calls every 3 months and registry checks).

Outcomes

Identical outcome ascertainment and definitions were used for both trials [11, 12], which permitted pooled analysis. Three outcomes were assessed: completion, safety, and efficacy. The primary completion outcome was per protocol completion in the modified intention-to-treat population, defined as ingestion of ≥80% of doses in ≤120% of the allowed time (ie, 96 doses of rifampin within 146 days; 216 doses of isoniazid within 324 days).

The primary safety outcome was permanent discontinuation of study medication due to any adverse event judged probably or possibly related to the study drug. If a drug was withheld for >48 hours due to an adverse event, an initial report was filed to the coordinating center. When the adverse event resolved, a complete report, blinded to study drug, was sent to the coordinating center. The report was passed to an independent, blinded, 3-member adverse event review panel, which made judgments on the type and grade of adverse event. They used American Thoracic Society guidelines [13] to judge the severity of hepatotoxicity and the National Cancer Institute definitions [14] for all other adverse events. They also judged whether the event was related to the study drug (not at all, unlikely, possibly, or probably).

The primary efficacy outcome was development of microbiologically or clinically diagnosed TB that was judged as probable TB in the modified intention-to-treat population. If TB was suspected, a blinded report was sent to the coordinating center once all investigations and treatment were complete. The report was sent to a different independent, blinded, 3-member TB review panel, which made judgments on whether the diagnosis of TB was probable or unlikely.

Secondary outcomes included completion (≥80% of doses) of therapy ever, any grade 3–5 (serious) adverse events, grade 3–4 hepatotoxicity, grade 1–4 rash, or grade 3–4 hematologic events, and TB rates between people with and without concomitant health conditions.

Statistical Analyses

For this post hoc analysis, we classified participants hierarchically based on concomitant health conditions at the time of treatment initiation (eg, alcohol consumption reflects patient self-reported behavior prior to start of treatment). We grouped certain conditions together a priori based on judgment that TB and adverse event risks were likely to be similar. The ranking of these groups were PLHIV; renal failure or use of TNF-α inhibitors; injection or nonprescription drug use or hepatitis; diabetes mellitus; alcohol consumption of >1 drink per week or current or ex-smoker [10]; and no health condition of interest. Only 1 participant was receiving methotrexate and was classified with the renal failure or use of TNF-α inhibitors group. Participants with multiple conditions were classified in the higher-ranked group.

For outcomes of completion and safety, we calculated the proportion and exact binomial confidence interval using the Clopper-Pearson method [15] of individuals completing

treatment or experiencing an adverse event for both regimens within each subgroup. We conducted post hoc sensitivity analysis separating conditions that were combined (ie, separating participants with renal failure and who used TNF-α inhibitors, separating participants who used injection or nonprescription drugs and participants with hepatitis, and separating participants who smoked and who consumed alcohol) to observe if completion or safety differed among conditions previously grouped together for the primary analysis.

To compare completion and safety, we calculated risk differences and corresponding confidence intervals (CIs) between regimens for each subgroup. Risk differences were calculated using generalized estimating equations [16] with a binomial distribution and identity link, accounting for clustering at the household level. We evaluated age-related risk of adverse events among those with and without any health condition. Age categories evaluated were 18–34 years, 35–44 years, 45–54 years, 55–64 years, and 65–90 years [10]. We further examined time to adverse event among participants with each health condition, stratified by treatment allocation.

For the outcome of efficacy, we calculated active TB rate differences and corresponding CIs between regimens for each subgroup. We then conducted efficacy analyses stratified by regimen. We compared rates of TB between people without any concomitant health condition and PLHIV or people with any non-HIV health condition for each regimen separately. For these analyses, generalized estimating equations with a Poisson distribution and log link were used [17], which accounted for clustering at the household level.

Sample sizes were adequate for the outcomes of completion, safety, and efficacy in the overall trial population, as published previously [11, 12, 18]. We calculated 95% CIs but did not attempt to infer significance for these post hoc subgroup analyses. Statistical analyses were conducted in R (version 3.6.0) using *geepack* (version 1.3–1) [19] and SAS (version 9.4) using Proc Genmod and the NLEstimate macro [17].

RESULTS

Participants

In total, 6859 participants were included in the modified intention-to-treat population of the 2 trials. Of these, 6485 (94.5%) received at least 1 dose of study therapy. The participant flow diagram is detailed in Supplementary Figure 1. Overall, 270 (3.9%) participants were PLHIV, and 135 (50%) were receiving antiretroviral therapy (ART), most commonly efavirenz, zidovudine, and lamivudine. CD4 counts pretreatment were known for 95 (72%) PLHIV receiving rifampin and 100 (72%) PLHIV receiving isoniazid. Median (interquartile range [IQR]) CD4 counts were 600 (474 to 718) cells/mm^3 and 536 (400 to 718) cells/mm^3 for participants receiving rifampin and isoniazid, respectively. Of the remaining participants, 145 (2.1%) had renal failure or were receiving immunosuppressants (TNF-α inhibitors), 110 (1.6%) used injection or nonprescription drugs or had hepatitis, 189 (2.8%) had diabetes mellitus, 1568 (22.9%) consumed >1 alcoholic drink per week or were current or ex-smokers, and 4577 (66.7%) had no concomitant health condition of interest.

Participants with renal failure or who were receiving immunosuppressants or who had diabetes mellitus were older (median age, 52 years) than participants with other concomitant health conditions (median age, 39.5 years) or participants without any condition (median age, 34 years). Participants with diabetes mellitus had the highest median body mass index (27.0 kg/m^2). Participants with a concomitant health condition were more often male (1468/2282; 64.3%) than participants without (1438/4577; 31.4%). This disparity was largely driven by those who consumed alcohol or smoked. Further differences between subgroups are detailed in Table 1.

Completion

Except for PLHIV and participants with renal failure or receiving immunosuppressants, treatment completion was higher among those receiving rifampin compared with those receiving isoniazid (Table 2). This was true when considering both per protocol treatment completion and treatment completion within any timeframe. Per protocol completion with rifampin was very similar across all subgroups (67.9% to 74.2%). Among participants receiving isoniazid, completion was more variable (40.7% to 78.3%) and was lowest among participants with injection or nonprescription drug use or hepatitis. When separating conditions, completion appeared higher among participants receiving TNF-α inhibitors compared with participants with renal failure; findings for other conditions were similar when considered separately as when considered together (Supplementary Table 1).

Safety

Among all participants included in the safety population (Table 3), those receiving rifampin were less likely to permanently stop treatment due to a drug-related adverse event (risk difference, −1.9%; 95% CI, −2.7 to −1.1). Among the 138 PLHIV receiving isoniazid, 5 (3.6%; 95% CI, 1.2% to 8.3%) experienced an adverse event, all grade 3–4 hepatotoxicity. Among the 130 PLHIV receiving rifampin, 2 (1.5%; 95% CI, .2% to 5.4%) experienced adverse events, both drug–drug interactions. One was a grade 1 event that resulted in virological failure of the participant's nevirapine-based ART regimen; the other was a grade 3 event that occurred in a participant not receiving ART but receiving escitalopram who experienced worsening depressive symptoms after beginning rifampin. The risk difference for drug-related adverse events among PLHIV receiving rifampin vs isoniazid was −2.1% (95% CI, −5.9 to 1.6).

Table 1. Characteristics of Participants

Characteristic	Total Population	People Living With Human Immunodeficiency Virus	Renal Failure or Use of Tumor-necrosis Factor-alpha Inhibitors	Injection or Nonprescription Drug Use or Hepatitis	Diabetes Mellitus	Alcohol Use or Smoking History	No Concomitant Health Condition of Interest
Number in modified intention-to-treat population	6859	270[a]	145[b]	110[c]	189	1568[d]	4577
Median age (IQR), y	36 (27 to 48)	38 (32 to 46)	52 (40 to 61)	31 (25 to 44)	52 (45 to 61)	40 (30 to 50)	34 (25 to 45)
Female sex	3953 (57.6)	141 (52.2)	62 (42.8)	24 (21.8)	99 (52.4)	488 (31.1)	3139 (68.6)
Median body mass index (IQR)	24 (21 to 27.1)	25 (22 to 27.7)	24.2 (21 to 27)	22 (20.1 to 25)	27 (24.3 to 31.8)	24 (21 to 27)	23.7 (21 to 27)
Underweight[e]	468 (6.8)	12 (4.4)	4 (2.8)	10 (9.1)	3 (1.6)	85 (5.4)	354 (7.7)
Normal[e]	3524 (51.4)	119 (44.1)	73 (50.3)	68 (61.8)	52 (27.5)	825 (52.6)	2387 (52.2)
Overweight/Obese[e]	2867 (41.8)	139 (51.5)	68 (46.9)	32 (29.1)	134 (70.9)	658 (42)	1836 (40.1)
Country enrolled[f]							
Australia, Canada, Saudi Arabia, South Korea	2609 (38)	19 (7)	122 (84.1)	57 (51.8)	105 (55.6)	659 (42)	1647 (36)
Brazil, Indonesia	1860 (27.1)	135 (50)	22 (15.2)	21 (19.1)	52 (27.5)	631 (40.2)	999 (21.8)
Benin, Ghana, Guinea	2390 (34.8)	116 (43)	1 (0.7)	32 (29.1)	32 (16.9)	278 (17.7)	1931 (42.2)
ALT measured pretreatment	6743 (98.3)	264 (97.8)	145 (100)	107 (97.3)	185 (97.9)	1540 (98.2)	4502 (98.4)
Median ALT pretreatment (IQR)[g]	21 (15 to 33)	22 (15 to 33)	18 (12 to 28)	24 (19 to 34.5)	22 (16 to 32)	22 (16 to 34)	20 (14 to 33)
Above upper limit of normal[g]	404 (6)	17 (6.4)	6 (4.1)	10 (9.3)	14 (7.6)	135 (8.8)	222 (4.9)
WBC measured pretreatment	6709 (97.8)	264 (97.8)	144 (99.3)	107 (97.3)	183 (96.8)	1531 (97.6)	4480 (97.9)
Median WBC pretreatment (IQR)[g]	6.1 (4.9 to 7.6)	5.1 (4.3 to 6.6)	7.1 (5.8 to 8.6)	6.7 (5.2 to 8.1)	6.7 (5.7 to 8.3)	6.7 (5.4 to 8.2)	5.9 (4.8 to 7.2)
Below lower limit of normal[g]	893 (13.3)	56 (21.2)	2 (1.4)	9 (8.4)	13 (7.1)	127 (8.3)	686 (15.3)
Platelets measured pretreatment	6705 (97.8)	264 (97.8)	144 (99.3)	107 (97.3)	183 (96.8)	1533 (97.8)	4474 (97.7)
Median platelets pretreatment (IQR)[g]	242 (201 to 285)	227 (193.5 to 272.2)	247.5 (191 to 296.8)	226 (201.5 to 277)	242 (199.5 to 286.5)	239 (201 to 281)	243 (202 to 287)
Below lower limit of normal[g]	307 (4.6)	17 (6.4)	12 (8.3)	5 (4.7)	6 (3.3)	59 (3.8)	208 (4.6)

Values are n (%) based on modified intention-to-treat population, unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase; IQR, interquartile range; WBC, white blood count.

[a]Includes 135 (50%) receiving antiretroviral therapy (ART; 64 receiving rifampin and 71 receiving isoniazid). These include 87/135 (64%) receiving efavirenz-based ART, 44/135 (33%) receiving nevirapine-based ART, and 4/135 (3%) receiving other forms.

[b]Includes 72/145 (50%) with renal failure, 72/145 (50%) receiving tumor necrosis factor-alpha inhibitors, and 1/145 (<1%) receiving methotrexate.

[c]Includes 98/110 (89%) with injection or nonprescription drug use and 12/110 (11%) with hepatitis.

[d]Includes 1195/1568 (76%) who only smoked, 191/1568 (12%) who only had >1 alcoholic drink per week, and 182/1568 (12%) who did both.

[e]Underweight was defined as <18.5 kg/m^2; normal weight was defined as ≥18.5 kg/m^2 to <25 kg/m^2; overweight or obese was defined as ≥ 25 kg/m^2.

[f]Countries grouped as high-income, middle-income, and countries in sub-Saharan Africa.

[g]Of those with pretreatment measurements and based on local laboratory definitions of normal [10].

Adverse events were most common among participants with renal failure or receiving immunosuppressants. Among these participants, the difference in adverse event risk between rifampin and isoniazid was 2.1% (95% CI, −7.2 to 11.3). Among participants with renal failure or receiving immunosuppressants receiving rifampin, most (75%) events were mild (grade 1–2) in nature; with isoniazid, most (60%) were serious (grade 3–4) hepatotoxicity (Supplementary Tables 2 and 3). Adverse events appeared to be more common among people with diabetes mellitus compared with people without any concomitant health condition when rifampin (3.3%; 95% CI, .7% to 9.3% diabetes vs 2.1%; 95% CI, 1.5% to 2.7% no health condition) or isoniazid (7.3%; 95% CI, 2.7% to 15.2% diabetes vs 3.7%; 95% CI, 2.9% to 4.6% no health condition) was used. For these participants with diabetes, only 1 of 3 events was serious with rifampin (rash), while 4 of 6 were serious with isoniazid (all hepatotoxicity). Among all other subgroups, regimen safety was like that observed in participants without concomitant health conditions. When separating conditions previously grouped together, safety was similar for conditions when considered separately as when considered together (Supplementary Table 1).

Among those receiving rifampin, adverse event risk ranged from 1.6% to 2.8% across all age groups among those without health conditions; age-related risk was similar among those with health conditions, except among those aged ≥65 years, where risk appeared to sharply increase (Figure 1*A*; Supplementary Table 4). Among those receiving isoniazid, risk was generally lower among those without health conditions (2.4% to 6.4% across all age groups) compared with those with health conditions (2.9% to 10.4% across all age groups) but appeared to rise with increasing age for all participants (Figure 1*B*; Supplementary Table 4).

The timing of treatment cessation due to adverse events varied by concomitant health condition (Figure 2). Adverse events were skewed to the first months of treatment for participants who had renal failure, were receiving immunosuppressants, used drugs, or had hepatitis, while risk appeared constant for other groups.

With respect to secondary outcomes, grade 3–4 hepatotoxicity was more frequent among participants receiving isoniazid and tended to occur more often among participants with concomitant health conditions. The outcome of grade 1–4 rash

Table 2. Treatment Completion

	4RIF		9INH		
Outcome	Participants Completing	Percent (95% CI)	Participants Completing	Percent (95% CI)	Percent (95% CI) Risk Difference (4RIF-9INH)
Total population	N = 3443		N = 3416		
Completed treatment per protocol[a]	2411	70.0 (68.5 to 71.6)	1931	56.5 (54.8 to 58.2)	13.0 (10.6 to 15.3)
Completed treatment ever[b]	2671	77.6 (76.1 to 79.0)	2095	61.3 (59.7 to 63.0)	15.6 (13.4 to 17.8)
People living with human immunodeficiency virus	N = 132		N = 138		
Completed treatment per protocol[a]	98	74.2 (65.9 to 81.5)	108	78.3 (70.4 to 84.8)	−4.1 (−14.3 to 6.1)
Completed treatment ever[b]	115	87.1 (80.2 to 92.3)	116	84.1 (76.9 to 89.7)	3.0 (−5.3 to 11.4)
Renal failure or use of tumor necrosis factor-alpha inhibitors	N = 81		N = 64		
Completed treatment per protocol[a]	56	69.1 (57.9 to 78.9)	41	64.1 (51.1 to 75.7)	5.1 (−10.4 to 20.5)
Completed treatment ever[b]	61	75.3 (64.5 to 84.2)	44	68.8 (55.9 to 79.8)	6.6 (−8.2 to 21.3)
Injection or nonprescription drug use or hepatitis	N = 56		N = 54		
Completed treatment per protocol[a]	38	67.9 (54.0 to 79.7)	22	40.7 (27.6 to 55.0)	26.7 (8.5 to 45.0)
Completed treatment ever[b]	46	82.1 (69.6 to 91.1)	24	44.4 (30.9 to 58.6)	37.8 (21.0 to 54.6)
Diabetes mellitus	N = 95		N = 94		
Completed treatment per protocol[a]	65	68.4 (58.1 to 77.6)	50	53.2 (42.6 to 63.6)	15.3 (1.3 to 29.2)
Completed treatment ever[b]	71	74.7 (64.8 to 83.1)	54	57.4 (46.8 to 67.6)	17.4 (4.0 to 30.8)
Alcohol use or smoking history	N = 782		N = 786		
Completed treatment per protocol[a]	531	67.9 (64.5 to 71.2)	422	53.7 (50.1 to 57.2)	14.3 (9.3 to 19.3)
Completed treatment ever[b]	589	75.3 (72.1 to 78.3)	459	58.4 (54.9 to 61.9)	17.3 (12.6 to 22.0)
No concomitant health condition of interest	N = 2297		N = 2280		
Completed treatment per protocol[a]	1623	70.7 (68.7 to 72.5)	1288	56.5 (54.4 to 58.5)	13.5 (10.5 to 16.6)
Completed treatment ever[b]	1789	77.9 (76.1 to 79.6)	1398	61.3 (59.3 to 63.3)	16.2 (13.4 to 19.1)

Exact binomial CIs for proportions calculated using the Clopper-Pearson method. Risk differences and CIs calculated using generalized estimating equations with a binomial distribution and identity link, accounting for clustering at the household level.

Abbreviations: 4RIF, 4 months daily rifampin; 9INH, 9 months daily isoniazid; CI, confidence interval.

[a]Took ≥80% of doses in ≤120% of allowed time.

[b]Took ≥80% of doses in any amount of time.

Table 3. Adverse Events Among Participants Included in the Safety Population

Outcome	4RIF		9INH		
	Participants Experiencing Event	Percent (95% CI)	Participants Experiencing Event	Percent (95% CI)	Percent (95% CI) Risk Difference (4RIF-9INH)
Total safety population	N = 3280		N = 3205		
Any drug-related adverse event	68	2.1 (1.6 to 2.6)	131	4.1 (3.4 to 4.8)	−1.9 (−2.7 to −1.1)
Any drug-related grade 3–5 adverse event	31	0.9 (.6 to 1.3)	75	2.3 (1.8 to 2.9)	−1.3 (−1.9 to −.7)
Drug-related grade 1–4 rash or grade 3–4 hematologic	31	0.9 (.6 to 1.3)	13	0.4 (.2 to .7)	0.5 (.1 to .9)
Drug-related grade 3–4 hepatotoxicity	11	0.3 (.2 to .6)	65	2.0 (1.6 to 2.6)	−1.6 (−2.1 to −1.1)
People living with human immunodeficiency virus	N = 130		N = 138		
Any drug-related adverse event	2	1.5 (.2 to 5.4)	5	3.6 (1.2 to 8.3)	−2.1 (−5.9 to 1.6)
Any drug-related grade 3–5 adverse event	1	0.8 (.0 to 4.2)	5	3.6 (1.2 to 8.3)	−2.9 (−6.3 to .6)
Drug-related grade 1–4 rash or grade 3–4 hematologic	0	0.0 (.0 to 2.8)	0	0.0 (.0 to 2.6)	0.0 (–)
Drug-related grade 3–4 hepatotoxicity	0	0.0 (.0 to 2.8)	5	3.6 (1.2 to 8.3)	−3.6 (−6.7 to −.5)
Renal failure or use of tumor necrosis factor-alpha inhibitors	N = 74		N = 58		
Any drug-related adverse event	8	10.8 (4.8 to 20.2)	5	8.6 (2.9 to 19.0)	2.1 (−7.2 to 11.3)
Any drug-related grade 3–5 adverse event	2	2.7 (.3 to 9.4)	3	5.2 (1.1 to 14.4)	−2.2 (−8.4 to 4.0)
Drug-related grade 1–4 rash or grade 3–4 hematologic	3	4.1 (.8 to 11.4)	0	0.0 (.0 to 6.2)	4.0 (−.4 to 8.6)
Drug-related grade 3–4 hepatotoxicity	1	1.4 (.0 to 7.3)	3	5.2 (1.1 to 14.4)	−3.5 (−9.2 to 2.3)
Injection or nonprescription drug use or hepatitis	N = 54		N = 51		
Any drug-related adverse event–	1	1.9 (.0 to 9.9)	2	3.9 (.5 to 13.5)	−1.9 (−8.1 to 4.2)
Any drug-related grade 3–5 adverse event	1	1.9 (.0 to 9.9)	1	2.0 (.0 to 10.4)	−0.1 (−5.1 to 4.9)
Drug-related grade 1–4 rash or grade 3–4 hematologic	0	0.0 (.0 to 6.6)	0	0.0 (.0 to 7.0)	0.0 (–)
Drug-related grade 3–4 hepatotoxicity	0	0.0 (.0 to 6.6)	1	2.0 (.0 to 10.4)	−2.0 (−5.8 to 1.8)
Diabetes mellitus	N = 91		N = 82		
Any drug-related adverse event	3	3.3 (.7 to 9.3)	6	7.3 (2.7 to 15.2)	−3.2 (−9.2 to 2.8)
Any drug-related grade 3–5 adverse event	1	1.1 (.0 to 6.0)	4	4.9 (1.3 to 12.0)	−3.2 (−7.8 to 1.3)
Drug-related grade 1–4 rash or grade 3–4 hematologic	1	1.1 (.0 to 6.0)	0	0.0 (.0 to 4.4)	1.1 (−1 to 3.2)
Drug-related grade 3–4 hepatotoxicity	0	0.0 (.0 to 4.0)	4	4.9 (1.3 to 12.0)	−4.9 (−9.5 to −.2)
Alcohol use or smoking history	N = 747		N = 740		
Any drug-related adverse event	9	1.2 (.6 to 2.3)	34	4.6 (3.2 to 6.4)	−3.1 (−4.7 to −1.5)
Any drug-related grade 3–5 adverse event	4	0.5 (.1 to 1.4)	22	3.0 (1.9 to 4.5)	−2.2 (−3.5 to −1.0)
Drug-related grade 1–4 rash or grade 3–4 hematologic	5	0.7 (.2 to 1.6)	2	0.3 (.0 to 1.0)	0.4 (−.3 to 1.0)
Drug-related grade 3–4 hepatotoxicity	2	0.3 (.0 to 1.0)	21	2.8 (1.8 to 4.3)	−2.4 (−3.6 to −1.2)
No concomitant health condition of interest	N = 2184		N = 2136		
Any drug-related adverse event	45	2.1 (1.5 to 2.7)	79	3.7 (2.9 to 4.6)	−1.5 (−2.5 to −.6)
Any drug-related grade 3–5 adverse event	22	1.0 (.6 to 1.5)	40	1.9 (1.3 to 2.5)	−0.8 (−1.5 to −.1)
Drug-related grade 1–4 rash or grade 3–4 hematologic	22	1.0 (.6 to 1.5)	11	0.5 (.3 to .9)	0.5 (.0 to 1.0)
Drug-related grade 3–4 hepatotoxicity	8	0.4 (.2 to .7)	31	1.5 (1.0 to 2.1)	−1.0 (−1.6 to −.5)

Drug-related events are those resulting in permanent discontinuation of treatment that were judged possibly or probably related to the study drug. Exact binomial CIs for proportions calculated using the Clopper-Pearson method. Risk differences and CIs calculated using generalized estimating equations with a binomial distribution and identity link, accounting for clustering at the household level. If no events occurred in 1 subgroup, CIs were estimated using exact binomial CIs.

Abbreviations: 4RIF, 4 months daily rifampin; 9INH, 9 months daily isoniazid; CI, confidence interval.

or grade 3–4 hematologic events was more frequent among participants receiving rifampin. No hematologic events occurred among participants with concomitant health conditions. However, rash appeared to occur most commonly among participants receiving rifampin who had renal failure or were taking immunosuppressants (Table 3).

Efficacy

TB occurred in 8 participants receiving rifampin and 9 participants receiving isoniazid. TB risk among all subgroups appeared similar with either drug (Table 4). Among PLHIV, 1 participant receiving rifampin developed TB and 2 participants receiving isoniazid developed TB (rate difference, −4.8 per 1000 person-years; 95% CI, −22.2 to 12.7).

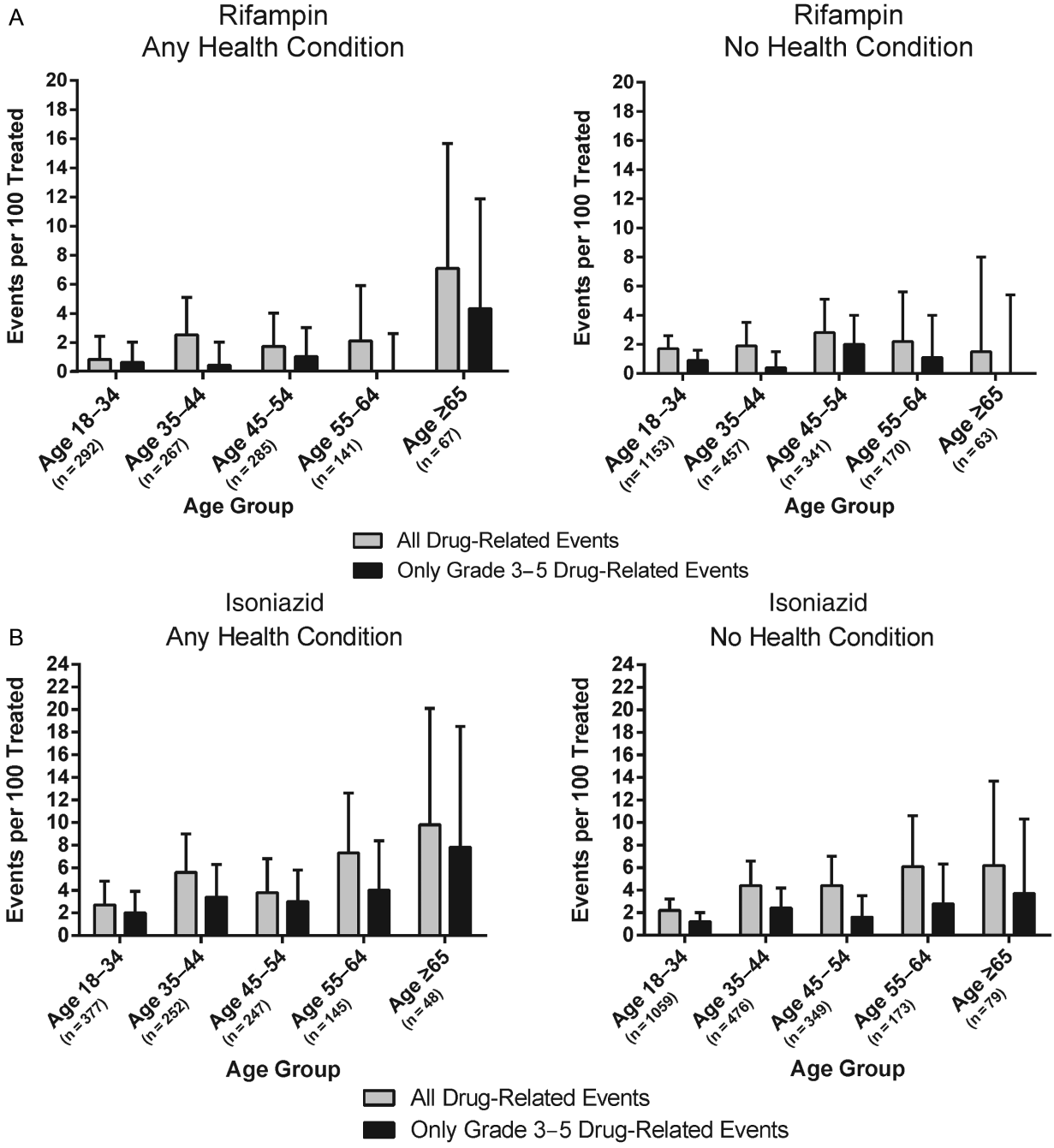

Figure 1. Age-related risk of any drug-related adverse events and serious drug-related adverse events among people without and with health conditions receiving rifampin (*A*) and isoniazid (*B*).

When compared to participants with no concomitant health condition, PLHIV receiving rifampin experienced 4.1 (95% CI, −6.4 to 14.7) more cases of TB per 1000 person-years, while PLHIV receiving isoniazid experienced 8.6 (95% CI, −5.5 to 22.6) more per 1000 person-years (Supplementary Table 5).

DISCUSSION

In this subgroup analysis of participants with and without concomitant health conditions, rifampin appeared to have better completion and safety characteristics than isoniazid across the subgroups analyzed. Rifampin was consistently completed across each group, was well tolerated in nearly all

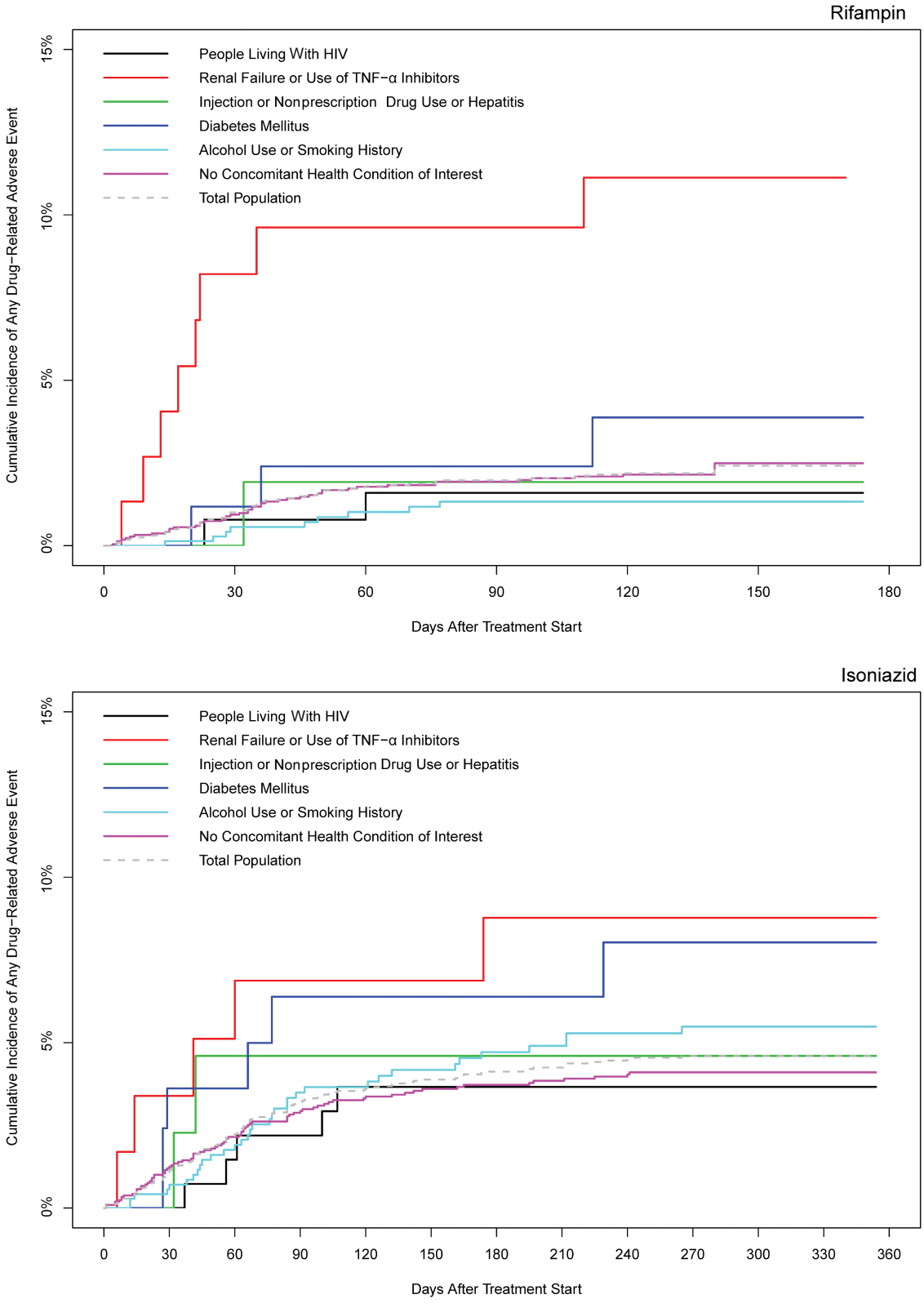

Figure 2. Timing of drug-related adverse events stratified by health condition among people receiving rifampin (*A*) and isoniazid (*B*). Abbreviations: HIV, human immunodeficiency virus; TNF-α, tumor necrosis factor-alpha.

Table 4. Occurrence of Microbiologically or Clinically Diagnosed Tuberculosis Between Treatments in the Modified Intention-to-Treat Population

Outcome	4RIF, n/Person-years of Follow-up	9INH, n/Person-years of Follow-up	Rate Difference (95% Confidence Interval) per 1000 Person-years (4RIF-9INH)
Total population	8/7732	9/7652	−0.1 (−2.3 to 2.2)
People living with HIV	1/298	2/317	−4.8 (−22.2 to 12.7)
Renal failure or use of tumor necrosis factor-alpha inhibitors	0/182	1/145	−6.9 (−20.4 to 6.6)
Injection or nonprescription drug use or hepatitis	1/128	1/115	2.7 (−37.3 to 42.7)
Diabetes mellitus	0/215	0/207	0 (NA)
Alcohol use or smoking history	2/1722[a]	0/1747	1.2 (−.4 to 2.8)
No concomitant health condition of interest	4/5187	5/5121[b]	−0.3 (−2.1 to 1.5)
Any non-HIV concomitant health condition	3/2247	2/2214	0.7 (−2.4 to 3.8)

Rate differences and confidence intervals (CIs) calculated by first using generalized estimating equations with a Poisson distribution and log link, accounting for clustering at the household level, then the NLEstimate macro in SAS software. If no events occurred in 1 subgroup, CIs were estimated using approximate Poisson CIs.

Abbreviations: 4RIF, 4 months daily rifampin; 9INH, 9 months daily isoniazid; HIV, human immunodeficiency virus; NA, Not applicable.

[a]One participant developed rifampin-resistant tuberculosis, as diagnosed by Xpert MTB/RIF; isolate was fully susceptible on traditional phenotypic testing.

[b]One participant developed isoniazid-resistant tuberculosis.

subgroups—and when it was not, most adverse events were mild—and, within the limits of the sample size, did not appear to be less effective in any subgroup. Completion rates for isoniazid were high among PLHIV and people with renal failure or taking immunosuppressants. However, serious hepatotoxicity was relatively common among participants with concomitant health conditions who received isoniazid, including among those where completion rates were high.

This analysis builds on multiple reports of superior safety for rifampin when compared with isoniazid [7, 10–12, 20]. Rifampin remains safe, with low rates of serious adverse events, even in populations with concomitant health conditions. However, a key concern with rifampin use is risk for drug–drug interactions due to its induction of the CYP3A4 enzyme [21, 22]. One of the most common is the potential for rifampin interaction with ART among PLHIV [23]. In our trials, 1 of the 64 PLHIV receiving ART with rifampin experienced virologic failure. This participant was receiving nevirapine-based ART; no participant receiving efavirenz-based ART had virologic failure. No participants included in the trials were receiving dolutegravir-based ART [24]. Some data suggest doubling the dose of dolutegravir during coadministration of rifampin and for two weeks after may be sufficient to overcome any increased clearance caused by CYP3A4 induction [25]. More broadly, rifampin is known to interact with oral anticoagulants, certain antifungals, and oral contraceptives, among others [8]. Participants at risk for these interactions were excluded from our trials, and so isoniazid is likely to be a preferred option for them. Clinical data suggesting fewer drug–drug interactions with other rifamycins (eg, rifapentine, rifabutin) are limited [26].

Estimates of safety with TPT regimens have focused primarily on age-related associations for isoniazid [13, 27]. Consequently, some TPT recommendations suggest caution when administering TPT to individuals aged >35 years [28], >50 years [29], or >65 years [3, 4]. In contrast, our analyses suggest there is no age-related adverse event risk with rifampin among people without concomitant health conditions, with low overall and serious event rates. Rather, risk of adverse events appears to be modulated by concomitant health conditions. Risks of adverse events with rifampin were highest among people with renal failure, receiving immunosuppressants, or with diabetes, which are population groups that tend to be older. Future TPT recommendations should consider both age and concomitant health conditions.

This analysis has several strengths. Most notable are the methods by which active TB and adverse events were ascertained. The use of 3-member, blinded, independent panels to judge possibly subjective outcomes helps limit biases emerging from the open-label study design. The trials enrolled many people with concomitant health conditions, permitting comparison of outcomes across subgroups, which has not previously been done for other rifamycin-based regimens. Finally, trial procedures and drug administration were done as pragmatically as possible to enhance generalizability outside the trial context. This included self-administered therapy assessed by pill counts and frequency of follow-up visits and blood tests reflecting standard practice.

The outcomes of this analysis should be understood in the context of its limitations. Completion of treatment was assessed through pill counting that, although very pragmatic, is subject to bias [30]. Adverse events that did not result in permanent discontinuation of treatment were not captured in the trials; these milder events are still relevant to both patients and providers. Treatment completion, which is a reflection of regimen duration, acceptability, and tolerability, was also better with rifampin; this could indicate the relative impact of these other adverse events among participants. The trials did not enroll participants at risk for drug interactions that providers felt they could not manage; the outcomes of our analysis are therefore not generalizable to this group. We speculate participants treated for health conditions with other medications may have been underrepresented among those enrolled for this reason [31, 32]. When creating subgroups, we grouped certain conditions together. It is possible outcomes may differ between conditions pooled together (eg, between those with hepatitis and those with drug use) and within specific health conditions (eg, between people with diabetes requiring insulin vs oral medications). Our sensitivity analysis separating groups that were

previously grouped together did not highlight important safety differences, including among persons who consumed alcohol and current/former smokers. Owing to small numbers in some subgroups and the POST hoc nature of our analysis, we did not emphasize statistical comparisons. Our observations regarding completion, safety, and efficacy in various subgroups are useful for patients and providers and highlight future areas of research need.

In summary, rifampin appears to be a better option than isoniazid for TPT across many groups with concomitant health conditions, including PLHIV on noninteracting ART regimens. Although sample sizes in some subgroups were small, results were consistent for all health conditions evaluated. We believe rifampin should be considered a first-line treatment option available in all settings for all patients who are candidates for TPT.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. R. C. and D. M. conceptualized the current study. J. R. C. conducted the statistical analyses. H. A., B. B., M. B., V. J. C., R. L., K. S., A. T., and D. M. implemented the trials and collected data. All authors contributed important intellectual content to the study's framing and analysis. J. R. C. wrote the initial draft. All authors provided critical revisions and approved the final submitted version of the manuscript.

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References

1. World Health Organization. WHO end TB strategy. Geneva, Switzerland: World Health Organization, **2014**.
2. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva, Switzerland: World Health Organization, **2018**.
3. Public Health Agency of Canada. Canadian tuberculosis standards: 7th edition. Ottawa (ON): Government of Canada, **2014**.
4. National Institute for Health and Care Excellence. Tuberculosis: guidance and guidelines. London (UK): National Institute for Health and Care Excellence, **2016**.
5. Australian Government Department of Health. CDNA national guidelines for public health units—management of TB. Canberra: Australian Government Department of Health, **2015**.
6. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep **2000**; 49:1–51.
7. 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.
8. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep **2020**; 69:1–11.
9. Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. BMJ **2020**; 368:m549.
10. Campbell JR, Trajman A, Cook VJ, et al. Adverse events in adults with latent tuberculosis infection receiving daily rifampicin or isoniazid: post-hoc safety analysis of two randomised controlled trials. Lancet Infect Dis **2020**; 20:318–29.
11. 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.
12. 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.
13. Saukkonen JJ, Cohn DL, Jasmer RM, et al; American Thoracic Society Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med **2006**; 174:935–52.
14. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), v4.0. **2009**. Available at: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 20 March 2020.
15. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika **1934**; 26:404–13.
16. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol **2003**; 157:364–75.
17. SAS Institute. Estimating nonlinear combinations of model parameters. Available at: https://support.sas.com/kb/58/775.html. Accessed 20 March 2020.
18. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. Am J Respir Crit Care Med **2004**; 170:445–9.
19. Højsgaard S, Halekoh U, Yan J. The R package geepack for generalized estimating equations. J Stat Softw **2005**; 15:1–11.
20. Ronald LA, FitzGerald JM, Bartlett-Esquilant G, et al. Treatment with isoniazid or rifampin for latent tuberculosis infection: population-based study of hepatotoxicity, completion, and costs. Eur Respir J **2020**. doi:10.1183/13993003.02048-2019
21. Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. Arch Intern Med **2002**; 162:985–92.
22. Baciewicz AM, Self TH. Rifampin drug interactions. Arch Intern Med **1984**; 144:1667–71.
23. Semvua HH, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aarnoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. Ther Drug Monit **2015**; 37:22–32.
24. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. Geneva, Switzerland: World Health Organization, **2018**. Available at: http://www.who.int/hiv/pub/guidelines/ARV2018update/en/. Accessed 20 March 2020.
25. Dooley KE, Kaplan R, Mwelase N, et al; International Study of Patients with HIV on Rifampicin ING study group. Dolutegravir-based antiretroviral therapy for patients coinfected with tuberculosis and human immunodeficiency virus: a multicenter, noncomparative, open-label, randomized trial. Clin Infect Dis **2020**; 70:549–56.
26. Williamson B, Dooley KE, Zhang Y, Back DJ, Owen A. Induction of influx and efflux transporters and cytochrome P450 3A4 in primary human hepatocytes by rifampin, rifabutin, and rifapentine. Antimicrob Agents Chemother **2013**; 57:6366–9.
27. 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.
28. Stockholm SSR. Prover som ingår i en hälsoundersökning. Sweden: Public Health Agency of Sweden, **2019**. Available at: https://vardgivarguiden.se/globalassets/kunskapsstod/smittskydd/asyl-halsoundersokning/tester-som-ingar-i-en-halsoundersokning.pdf. Accessed 20 March 2020.
29. Queensland Health. Management of latent tuberculosis in adults: guideline. Australia: Queensland Health, **2016**.
30. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther **1999**; 21:1074–90.
31. Parker K, Wong J. Is polypharmacy an increasing burden in chronic kidney disease? The German experience. Clin Kidney J **2019**; 12:659–62.
32. Edelman EJ, Rentsch CT, Justice AC. Polypharmacy in HIV: recent insights and future directions. Curr Opin HIV AIDS **2020**; 15:126–33.