| Author, YearTrial NameN | Drug, Dose x Duration (N) | DC Due to AEs,N (%) | Hepatotoxicity,N (%) | Mortality From Hepatotoxicity,N (%) | Gastrointestinal,N (%) | Other Specific AEs,N (%)a |
| --- | --- | --- | --- | --- | --- | --- |
| Menzies, 2004143116 | RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months; up to 20 weeks, if needed, depending on missed doses (58)INH 5 mg/kg, up to 300 mg/day x 9 months; up to 43 weeks, if needed, depending on missed doses (58) | 2 (3.4)8 (13.8)RR: 0.25 (95% CI, 0.1 to 1.1) | 0 (0)3 (5.2)Drug-induced hepatitis after 74, 105, and 137 doses of INH | 0 (0)0 (0) | Severe nausea and vomiting: 4 (3.4)b | Other overall AEs2 (3.4)5 (8.6)Calculated RR: 0.40 (95% CI, 0.08 to 1.98)Persistent debilitating fatigue: 2 (1.7)Rash: 1 (0.8)c |
| Menzies, 2008133847 | RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months (420)INH 5 mg/kg, up to 300 mg/day x 9 months (427) | Among protocol-adherent:16 (3.8)24 (5.6)Subtotal for any grade 3 or 4 AEd-h7 (1.7)17 (4.0)RD: -2.3% (95% CI, -5.0 to -0.1)Subtotal for any grade 1 or 2 AE:i-m9 (2.1)7 (1.6)RD: 1% (95% CI, 1.0 to 3.0) | Grade 3 or 4 hepatotoxicityd3 (0.7)16 (3.7)RD: -3.1% (95% CI, -5.0 to -1.0) | 0 (0)0 (0) | Minor AEs reported “similar” between groupsGI intolerance (grade 1 or 2 AE):l1 (0.2)2 (0.5)Calculated RR: 0.51 (95% CI, 0.05 to 5.59) | Hematologic (grade 3 or 4 AE):d2 (0.5)1 (0.2)Calculated RR: 2.0. (95% CI, 0.19 to 22.34)Drug interaction (grade 3 or 4 AE):h1 (0.2)0 (0)Calculated RR: 3.05 (95% CI, 0.13 to 74.66)Rash (grade 3 or 4 AE)e1 (0.2)0 (0)Calculated RR: 3.05 (95% CI, 0.13 to 74.66)Rash (grade 1 or 2 AE)j8 (1.9)5 (1.2)Calculated RR: 1.63 (95% CI, 0.54 to 4.93) |
| Sterling, 2011134oPREVENT TB6,886 | RPT 900 mg + INH 900 mg/week x 12 weeks (3,556)INH 300 mg/day x 36 weeks (3,330) | DC due to adverse drug reaction:186 (5.2)136 (4.1)Calculated RR: 1.28 (95% CI, 1.03 to 1.59) | Grade 3 toxicity:p176 (4.9)184 (5.5)Calculated RR: 0.90 (95% CI, 0.73 to 1.10)Grade 4 toxicity:p 34 (1.0)35 (1.1)Calculated RR for Grade 3 or 4 toxicity: 0.90 (95% CI, 0.75 to 1.08)  | Grade 5 (death): 30 (0.8)34 (1.0)Calculated RR: 0.83 (95% CI, 0.51 to 1.35) | NR | Possible hypersensitivity: 146 (4.1)17 (0.5)Calculated RR: 8.04 (95% CI, 4.88 to 13.26) |
| Thompson, 1982135IUAT27,830 | INH 300 mg x 12 weeks (6,956)NH 300 mg x 24 weeks (6,965)INH 300 mg x 52 weeks (6,919)Placebo (6,990) | Overall DC:INH (8.1)Placebo (5.8)147Due to AEs (GI distress, liver disease, or gallbladder disease):INH (1.8)Placebo (1.2)147DC due to liver disease:INH (0.4)Placebo (0.1)147 | Hepatitis:INH 99q (0.5)Placebo 7 (0.1)Cumulative excess hepatitis rates per 1000 cases for INH:12 weeks: 2.5 24 weeks: 3.6 52 weeks: 5.2 Calculated number of cases:12 weeks: 2424 weeks: 3252 weeks: 43Hepatitis cases prevented per 1000 persons by reducing duration of INH from 52 weeks to:24 weeks: 1.612 weeks: 2.7 | 2 (0.03)0 (0.00)1 (0.01)0 (0.00)0.14 per 1,000 persons receiving INH0 cases in placebo group.Calculated RR: 2.35 (95% CI, 0.12 to 45.46) | GI distress resulting in stopping:INH (1.2)Placebo (0.9)147Calculated RR: 1.33 (95% CI, 1.01 to 1.75) | Gallbladder disease resulting in stopping: INH (0.2)Placebo (0.2) |
| White, 2012144364 | RIF 600 mg/day x 4 months; up to 6 months, if needed, depending on missed doses for a total of 120 doses (180)INH 900 mg 2x/week x 9 months; up to 12 months, if needed, depending on missed doses for a total of 76 doses (184) | 2 (1.1)0 (0) | Grade 3 for LFT was AST or ALT >5.0–10.0 times ULN ≥3 elevated LFT:8 (4.4)21 (11.4) | 0 (0)0 (0) | GI 16 (9) 9 (10) Calculated RR: 1.82 (95% CI, 0.82 to 4.01) | Other AEscRash/pruritus 16 (9) 12 (6) Calculated RR: 1.36 (95% CI, 0.66 to 2.80)Central nervous system 6 (3)20 (11) Calculated RR: 0.31 (95% CI, 0.13 to 0.75)Allergic reaction 1 (1) 0 (0) Calculated RR: 3.07 (95% CI, 0.13 to 74.78)Othere 13 (7)14 (8) Calculated RR: 0.95 (95% CI, 0.46 to 1.96) |

a No studies reported peripheral neuropathy or development of drug-resistant TB outcomes.

b Other adverse events not presented by drug regimen, but for entire population.

c Categories are not mutually exclusive; participants could experience symptoms in more than one body system category. Therefore, the number and percentage represent the number of participants and the percentage of the study group or total that had an adverse event in the category.

d Liver aminotransferase levels that increased to 5 to 10 or 3 to 10 times the upper limit of normal in the presence of compatible symptoms met criteria for grade 3 hepatotoxicity, whereas those that exceeded 10 times the upper limit of normal met criteria for grade 4 toxicity.

e Criteria for a grade 3 rash is a rash that affects 100% of body surface area or mucus membranes, conjunctivae are affected, vital signs are abnormal (fever or low blood pressure), or there is wheezing.

f Neutrophil counts <1.00 to 0.50 x 109 cells/L or platelet counts <50 to 25 x 109 cells/L met the criteria for grade 3 hematologic effects, whereas neutrophil counts that exceeded 0.50 x 109 cells/L or platelet counts greater than 25 x 109 cells/L met the criteria for grade 4.

g Protracted nausea and vomiting or severe abdominal pain that disrupts daily life (for example, cannot sleep), severe diarrhea (more than 5 bowel movements per day) met the criteria for a grade 3 gastrointestinal adverse event.

h Under drug interaction grade 3, drug interaction was noted and therapy was modified repeatedly but eventually successful; patient did not have any untoward clinical effect, and LTBI therapy was continued. Under grade 4, care providers unable to adjust therapy successfully to achieve therapeutic effects; LTBI therapy was discontinued.

i Liver aminotransferase levels that increased to 1 to 3 times the upper limit of normal in the presence of symptoms suggestive of hepatotoxicity (nausea, anorexia, vomiting, fatigue, abdominal pain) met criteria for grade 1, whereas levels 1 to 5 times the upper limit of normal with no symptoms met criteria for grade 2 toxicity.

j Criteria for a grade 1 rash involves itching only or limited to limbs, trunk, or face only; no abnormality of vital signs and no mucosal or conjunctival involvement. Grade 2 rash affects limbs and trunk or more than 50% of total body surface area or rash is confluent in areas.

k Neutrophil levels <1.50 to 1.00 x 109 cells/L or platelet counts <100 to 50 x 109 cells/L met the criteria for grades 1-2.

l Some stomach upset with nausea or loss of appetite, but no vomiting and no change in bowel habits met that criteria for a grade 1 gastrointestinal adverse event.

m Under drug interaction grade 1, a potential drug interaction was noted, but no change in therapy was required and neither short- nor long-term effect detected. Under grade 2, a potential drug interaction was noted, but after an initial change in therapy, no further problems and therapy did not have to be changed.

n Data extracted from supplemental data provided by personal communication source for eligible study subgroup (HIV-negative subjects with IGRA or TST confirmation).

o Other category includes symptoms such as appetite loss, muscle/body pain, fatigue, weight loss, malaise, cold symptoms, change of urine color, fever, and eye redness.

p Common toxicity criteria version 2.0. Bethesda, MD: Cancer Therapy Evaluation Program, 1999 (<http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf>).

q The total number of hepatotoxicity cases among isoniazid patients was calculated based on the cumulative excess hepatitis rates per 1000 cases for INH presented in the paper.

**Abbreviations:** AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; DC=discontinuation; GI=gastrointestinal; INH=isoniazid; LFT=liver function test; N=sample size; NR=not reported; RD=risk difference; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis; ULN=upper limit of normal.