

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Study Sites, Investigators, and Additional Contributions (n = number enrolled)

TBTC and IMPAACT Investigators

All sites are Tuberculosis Trials Consortium (TBTC) unless labeled International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT).

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Additional Contributions

Amina Ahmed, MD, Department of Pediatrics, Carolina Medical Center, Charlotte, North Carolina, enrolled participants at her site and contributed to the review and editing of the manuscript.

Constance Benson, MD, Department of Medicine, University of California San Diego, San Diego, California, facilitated the liaison between the National Institute of Allergy and Infectious Diseases, the AIDS Clinical Trials Group Network, the Tuberculosis Trials Consortium, and the Centers for Disease Control and Prevention.

Kenneth G. Castro, MD, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia, provided leadership and support throughout the years of the clinical trial.

Mark Cotton, MD, PhD, Department of Pediatrics, Stellenbosch University, Cape Town, South Africa, John Johnson, MD, Department of Medicine, Case Western Reserve University, Cleveland, Ohio, and Wing-wai Yew, MBBS, FRCP, Hong Kong Tuberculosis, Chest, and Heart Diseases Association, Hong Kong, China, contributed to the evaluation and adjudication of the pediatric participants who developed tuberculosis.

George McSherry, MD, Department of Pediatrics, University of Medicine and Dentistry New Jersey Medical School, Newark, New Jersey, a member of the protocol team, encouraged the inclusion of pediatric participants in the study.

Jeffrey Starke, MD, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, a protocol consultant from the beginning of the study, also contributed to review and editing of the manuscript.

eAppendix 2. Inclusion and Exclusion Criteria

Inclusion criteria

Children and adolescents at high risk for tuberculosis (TB) disease according to age, tuberculin skin test (TST) results, and TB exposure history:

- 1) With history of household or other close contact with person diagnosed with infectious TB disease
 - a) Children ≥ 5 but < 18 years old with a positive TST (≥ 5 mm induration).
 - b) Children ≥ 2 but < 18 years old and HIV-seropositive, regardless of TST reaction size.
 - c) Children ≥ 2 but < 5 years old, regardless of TST reaction size.

- 2) With or without a documented history of close contact to infectious TB
 - a) Children ≥ 5 but < 18 years old with a TST conversion (> 10 mm induration).
 - b) Children ≥ 2 but < 18 years old, HIV-seropositive and TST positive (> 5 mm induration)
 - c) Children ≥ 2 but < 5 years old and TST positive (> 10 mm induration)

Infectious TB disease was defined as *Mycobacterium tuberculosis* sputum-culture positive. Time period allowed between date of household and other contact investigations and enrollment was < 2 years. Close contact was defined as contact with infectious TB patient of > 4 hours in a shared airspace during a one-week period. TST conversion was defined as a change in TST reaction size of ≥ 10 mm within 2 years of a nonreactive test.

Children < 5 years old with a negative initial TST who were close contacts of a culture-confirmed TB case could, at the discretion of the local study investigator, discontinue study treatment if a follow-up TST performed 8-12 weeks after the initial TST was also negative. If treatment was discontinued because of a negative follow-up TST, the child was considered ineligible for the study and follow-up was discontinued.

Exclusion criteria

- Current confirmed culture-positive or clinical TB
- Suspected TB (as defined by the site investigator)
- Tuberculosis resistant to isoniazid (H) or rifampin (R) in the source TB case
- History of treatment for > 14 consecutive days with a rifamycin or > 30 consecutive days with H within the 2 years prior to enrollment.
- History of completing an adequate course of treatment for TB disease or latent TB infection in a child who is HIV-seronegative.
- History of sensitivity/intolerance to H or rifamycins
- Serum aminotransferase aspartate (AST) $> 5x$ upper limit of normal among persons in whom AST is determined
- Pregnant or nursing females
- Children currently receiving or planning to receive antiretroviral therapy (e.g., HIV-1 protease inhibitors, nucleoside or non-nucleoside reverse transcriptase inhibitors, CCR5 inhibitors or integrate inhibitors) in the first 90 days after enrollment.
- Weight < 10.0 kg

eAppendix 3. Randomization: Sequence Generation, Allocation Concealment Mechanism and Implementation

Children in this sub-study received treatment assignments within the parent study and its extension. Allocation was stratified by study site and participant HIV status using unrestricted randomization. In group settings (e.g., households), additional participants in a group could be placed on the same regimen as the first person in that group.

The protocol prescribed the following methods:

Two randomization tables were created by the data center at the beginning of the study and used throughout the study. Each table has 46000 units, numbered from 1-46000. One randomization table was used for all participants not reported at enrollment to be HIV-infected. Another randomization table was used for all participants reported at enrollment to be HIV-infected. HIV testing was not required at enrollment. A block of randomization units was assigned in each table to each site.

All randomization assignments were made at the data center. The data center provided each randomization assignment to site staff at the time of each enrollment, initially by telephone and later through a web application. The enrollment application sequentially recorded use of each “randomization unit,” in documented randomization tables, as each unit was assigned to an LTBI patient enrolled as a study participant; the application did not retain the study ID number of each participant to whom a unit was assigned.

“Eligibility will be confirmed by a telephone call to the TBTC Data Center at CDC. Eligible patients will be randomized to either weekly RPT plus INH x 3 months (3RPT/INH) OR daily INH x 9 months (9INH). Among household close contacts, randomization will occur by household. The first person in the household to enter the study will be randomized to one of the study arms, and all subsequent participants from the same household will receive the same regimen. *[The next two sentences were added to the protocol in Version 05_16_05, to clarify defining characteristics of household members who would be enrolled and treated with the same regimen as the first member of the household, but would not be randomized independently.]* All such participants must sign informed consent prior to randomization of the first person in the household. Any household members subsequently identified who are eligible for the study will be randomized separately. All other participants will be randomized individually. Participants and investigators were not blinded to treatment arm.

eAppendix 4. A Monte Carlo Simulation to test the impact of the imbalance of age and sex between treatment arms

A Monte Carlo simulation was conducted to determine the impact of the age and sex imbalance on the non-inferiority claim of 3HP to 9H. Although there was no observed evidence that age and sex were risk factors for developing TB in the study sample, a higher proportion of males and younger children were enrolled into the 3HP arm than the 9H arm.

A single simulation proceeds as follows. A new sample of 905 observations is drawn, with replacement, from the study sample of 905. For each of these 905 simulated participants, 2 new values are simulated: (1) the age- and sex-specific probability that the simulated participant is assigned to the 3HP arm, using a logistic regression model for assignment to the 3HP arm; and (2) the age- and sex-specific probability that a simulated participant develops TB, using a logistic regression model for developing TB among participants assigned to the 9H arm. These values are combined to produce simulated proportions of TB cases in each arm. For a single simulation, the test statistic is the difference between these estimated proportions. This simulation procedure is repeated with 100,000 pseudo samples, producing a sampling distribution of the test statistic for the difference in TB risk between arms.

Based on 100,000 pseudo samples, the simulation resulted in a mean p-value (0.024) for the null hypothesis that the probability of developing TB in the 3HP arm is more than 0.75% greater than the probability of developing TB in the 9H arm. This result supports the rejection of the null hypothesis at the pre-specified level of 0.025. Thus, the conclusion that 3HP is not inferior to 9H appears to be robust against apparent differences in age and sex between study arms.

eTable. Study Drug Doses of Rifapentine

Weight Range (kg)	Dose (mg)	Dose (mg/kg)
10.0-14.0	300	21.4 - 30.0
14.1-25.0	450	18.0 - 31.9
25.1-32.0	600	18.8 - 23.9
32.1-50.0	750	15.0 - 23.4
>50.0	900	≤18.0

For the 9 month isoniazid self-administered (9H) arm the dose of isoniazid (H) was adjusted for age: those who were ≥12 years of age were prescribed an H dose of 5 mg/kg and those 2-11 years old were prescribed an H dose of 10 mg/kg (for both age groups the doses were rounded to the nearest 50 mg or 100 mg and the maximum daily dose was 300 mg).

For the 3 months of H and rifapentine (P) (3HP) arm the dose of H was adjusted for age: the dose was 15 mg/kg for children ≥12 years old and 25 mg/kg for those 2-11 years (for both age groups the maximum weekly dose was 900 mg). The dose of P given in combination with H was not adjusted for age: children of all ages weighing at least 10 kg, were treated with P doses ranging from 300 mg to 900 mg based on their weight at enrollment and its relationship with a dose-per-weight band table.

Children who could not swallow tablets were administered a slurry of crushed H and P tablets in either a soft food or liquid, starch-based pudding (e.g. commercial chocolate pudding) was particularly recommended and fruit-based carriers were particularly discouraged²³.

eFigure. Enrollment and Treatment Allocation of Children 2–17 Years Old

